

Under-prescription of direct oral anticoagulants for treatment of non-valvular atrial fibrillation and venous thromboembolism in the COVID-19 lockdown period

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During the COVID-19 lockdown period, care of non-communicable diseases was limited due to difficulties in accessing services, population concerns about infectious risk in healthcare facilities, and relocation of healthcare resources to assist patients with COVID-19.¹ Few studies so far have focused on the effect of the lockdown on medication prescriptions to treat non-COVID-19 conditions.

Direct oral anticoagulants (DOACs) are commonly used medications for stroke prevention in non-valvular atrial fibrillation (NVAf) and for the treatment and prevention of venous thromboembolism (VTE). We hypothesized that access to care for patients with these conditions might have been limited during the lockdown, leading to a reduction in new prescriptions of DOACs. Therefore, the aim of this retrospective, cross-sectional study was to assess new prescriptions of DOACs during the lockdown period (March–May 2020) and in the post-lockdown period (June–July 2020) and compare them with what is expected based on time series forecasts.

The Italian Medicines Agency (AIFA) monitors prescriptions of DOACs through a web-based monitoring registry.² Prescription of DOACs in hospitalized patients are not monitored with this registry. New prescriptions observed from June 2013 to July 2020 were measured by analysing data from the registry. Estimates of new prescriptions during March–July 2020 were calculated based on time series

forecasts, computed using seasonal Arima models estimated on historical data from June 2013 to February 2020 on monthly aggregated data. All statistical analyses were performed using R version 3.6.1 and figures were obtained using ggplot2.³ Time series analysis was performed using the Arima function of R base library and the forecast package for predictions.⁴

From June 2013 to July 2020, the registry collected data on 1 515 629 new DOACs prescriptions, including 1 312 214 (86.6%) new prescriptions for NVAf and 203 415 (13.4%) for VTE. *Figure 1* presents observed and estimated numbers of new prescriptions of DOACs for NVAf and VTE from 2016 up to July 2020. New DOACs prescriptions progressively increased over time, with seasonal variations due to periodical reduction in the summer period. In the lockdown period, between March and May 2020, the number of new prescriptions declined substantially. After the lockdown period, in June and July 2020, this number increased for both conditions.

The upper panel of *Table 1* presents estimates based on time series forecasts and observed number of new DOACs prescriptions for NVAf by age group in the period between March and July 2020. Overall, the number of new prescriptions largely declined during the lockdown period as compared with what was forecasted (–34.8%), reaching a negative peak in April (–58.9%). In the post-lockdown

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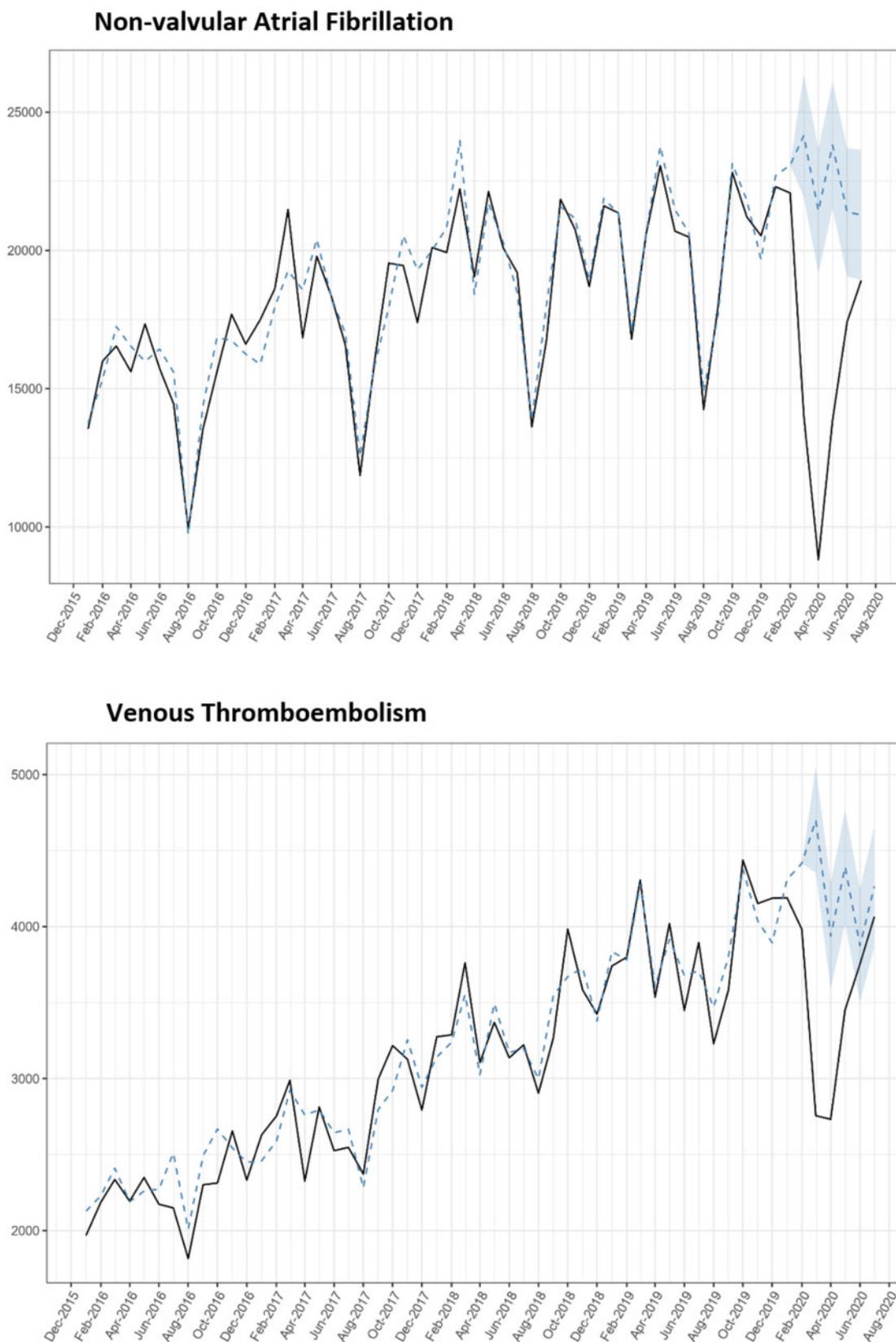


Figure I Temporal trend in new prescriptions of non-vitamin K oral anticoagulants for treatment of non-valvular atrial fibrillation (upper panel) and venous thromboembolism (lower panel) from 2016 up to July 2020. Observed values are represented as a black coloured continuous line, while estimates are represented as a dashed light-blue line. Confidence intervals for March–July estimates are represented as a light-blue area.

Table 1 Monthly estimated and observed new prescriptions of non-vitamin K oral anticoagulants for treatment of non-valvular atrial fibrillation and venous thromboembolism by age group

Month	Treatment of non-valvular atrial fibrillation						Treatment of venous thromboembolism					
	Estimated	Observed	Δ (95%CI)	Estimated	Observed	Δ	Estimated	Observed	Δ	Estimated	Observed	Δ
Overall				<65 years			65–74 years			75 years or older		
March	24 151	14 024	-41.9%	2339	1531	-34.5%	5783	3368	-41.8%	16 085	9125	-43.3%
April	21 427	8811	-58.9%	1894	1052	-44.5%	5100	2147	-57.9%	14 417	5612	-61.1%
May	23 807	13 852	-41.8%	2073	1454	-29.9%	5586	3314	-40.7%	16 172	9084	-43.8%
June	21 382	17 414	-18.6%	1878	1787	-4.8%	5032	3994	-20.6%	14 514	11 633	-19.9%
July	21 288	18 914	-11.2%	1921	1918	-0.2%	5039	4363	-13.4%	14 331	12 633	-11.8%
March–July	112 055	73 015	-34.8%	10 105	7742	-23.4%	26 540	17 186	-35.2%	75 519	48 087	-36.3%
Overall				<65 years			65–74 years			75 years or older		
March	4701	2756	-41.4%	1461	969	-33.7%	1124	676	-39.9%	2134	1111	-47.9%
April	3938	2732	-30.6%	1234	1163	-5.8%	964	684	-29.1%	1764	885	-49.8%
May	4394	3453	-21.4%	1426	1314	-7.9%	1062	791	-25.5%	1914	1348	-29.6%
June	3875	3753	-3.1%	1290	1298	+0.6%	938	920	-1.9%	1681	1535	-8.7%
July	4265	4065	-4.7%	1426	1479	+3.7%	1008	926	-8.1%	1843	1660	-9.9%
March–July	21 172	16 759	-20.8%	6838	6223	-9.0%	5096	3997	-21.6%	9336	6539	-30.0%

Rows identifying months characterized by the lockdown period are in grey.

period there was a less consistent decline in the number of new prescriptions (June -18.6% and July -11.2%). Large differences were observed across age groups, with the largest reduction in number of prescriptions in the March–July period observed in the population aged 65–74 years (-35.2%) and 75 years or older (-36.3%). The lower panel of [Table 1](#) presents the estimated and observed number of new DOACs prescriptions for VTE by age group in the period between March and July 2020. A substantial decrease was observed in the number of new prescriptions as compared with what was forecasted (-20.8%), with a negative peak in March (-41.4%). Persons aged 75 years or older had the largest decrease in new prescriptions (-30.0%). The population aged <65 years had the lowest decrease (-9.0%) and the number of observed new prescriptions in this age group in the post-lockdown period (June and July) was very closed to the forecasted numbers.

The decline in use of DOACs shown by this study can be explained by different factors. First, the diagnosis of conditions requiring the use of DOACs might have declined during the COVID-19 lockdown period.⁵ Second, patients may have experienced difficulties in accessing healthcare services during the lockdown period or may have avoided contact with healthcare services due to increased risk and fear of contracting COVID-19.⁶ In addition, in the lockdown period healthcare resources were relocated to assist patients with COVID-19 and appointments or visits for conditions different from COVID-19 were often postponed.¹

Older adults experienced a larger decline in use of DOACs as compared with younger adults. The presence of physical, psychological, and social problems in older adults and possible concerns about the severe consequences of COVID-19 may have increased difficulties in accessing healthcare services during the lockdown period.^{6,7}

Study limitations relate to the fact that the registry only collects data on DOACs but information on other anticoagulants (i.e. warfarin) is not collected. Data from AIFA show that prescription of warfarin was not modified in March–April 2020 as compared with January–February 2020, suggesting that reduction in new DOACs prescription was not compensated by an increment in use of other anticoagulants.⁸ Data on prescriptions in hospitalized patients are not covered by the registry. Indeed, in patients with atrial fibrillation, hospitalization is associated with an increase in DOACs initiation, but hospitalizations due to this condition declined in the lockdown period as compared with 2019.⁹ In addition, new prescriptions of DOACs in hospitalized patients are tracked in the registry when the patient is discharged to the community. For these reasons, it is unlikely that the lack of data on in-hospital prescriptions might have influenced our findings. Furthermore, an increase of VTE and cardiovascular events has been shown in COVID-19 hospitalized patients and this may have led to an overestimation of DOACs prescriptions for this specific condition during the lockdown period.¹⁰ In addition, occurrence of embolic events related to under-prescription of DOACs was not examined in this study. Finally, from July 2020, compilation of the web-based monitoring registry was no longer mandatory. Thus, the present analysis cannot be extended to the second half of 2020.

In conclusion, this study suggests that the COVID-19 epidemic might have caused relevant indirect health consequences due to the undertreatment of potentially life-threatening conditions, including NVAf and VTE. DOACs under-prescription seems more pronounced in older adults probably due to increased difficulties in accessing healthcare services during the lockdown period.

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