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Impact of the COVID-19 pandemic in a cohort of anticoagulant users: a descriptive drug utilization study based on data from the Tuscany Healthcare administrative database

Responsible parties

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BACKGROUND

Anticoagulants drugs, such as vitamin K antagonist (VKA) and direct oral anticoagulants (DOACs) are widely used to prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and to treat patients with venous thromboembolism (VTE).

Patients treated with VKAs should be continuously monitored because of high instability of PT (Prothrombin time) INR (International Normalized Ratio). Several factors can influence PT-INR, in particular vitamin K metabolism, diet, fasting, co-medication, and liver impairment. The aforementioned factors could make more challenging for clinicians to maintain VKAs at the desired therapeutic range in those patients.

The rapid spread all over the world of the SARS-COV-2 forced all healthcare professionals to urgently reconsider the management of patients requiring continuing access to healthcare services. Therefore, deciding whether to offer, postpone or stop a treatment has become a crucial dilemma for several clinicians, particularly oncologists, neurologist and cardiologist (Passaro, 2020).

Regarding the management of patients treated with VKAs, *Poli et al*. (Poli, 2020) provided general rules/suggestions to adopt during COVID-19 pandemic period, in particular considerations on the prolongation of INR controls between 4 and 8 weeks. Moreover, the same authors suggested:

- to reorganize during the reopening phases the procedures of PT-INR monitoring for patients treated with VKAs and not reached during lockdown;
- to switch from VKAs to DOACs for those who showed stable levels of PT-INR.

To the best of our knowledge, there is still no evidence on the impact of COVID-19 pandemic in the management of patients under anticoagulants treatment. Therefore, we aim to conduct a time-trend analysis in the period 01/01/2019-30/06/2020 in order to observe:

1. Possible changes in prevalence and incidence of VKAs and DOACs use potentially associated with COVID-19 pandemic
2. Possible changes in the secular trends of switch from VKAs to DOACs potentially associated with COVID-19 pandemic

METHODS

Study design

This is a descriptive drug utilization study based on Tuscany's healthcare administrative databases.

Study population

Subjects having at least one dispensing of VKAs (ATC code: B01AA) or DOACs [Apixaban (B01AF02); Rivaroxaban (B01AF01); Edoxaban (B01AF03); Dabigatran (B01AE07)] between 1st of January 2019 and 30th June 2020 will be included.

Covariates

The following demographic characteristics will be reported within the study cohort: (1) Gender (Male Vs Female); (2) Age (mean + standard deviation); (3) Age group: (18-65, 65-74, ≥75).

Treatment episodes

Consecutive VKAs or DOACs dispensing dates will be converted into treatment episodes of uninterrupted use. From the date of dispensing, the exposure to VKAs or DOACs will be calculated by adding 30 days for each package being issued. The end date of a treatment episode will be set at the end of the duration of the last VKAs or DOACs dispensing with no other new subsequent corresponding VKAs or DOACs being dispensed within three months.

Study Outcomes

In this study the following definitions will be considered:

- *Prevalent users* i.e. patients claimed at least one dispensing of VKA or DOAC in the observed period; the users will be considered prevalent for the entire period covered by the treatment episode.
- *Incident users* i.e. patients treated with VKA or DOAC in the observed period with no use of anticoagulants in the three months prior to the date of dispensing;

Prevalent VKA users will be considered as:

- *Switchers* if they will receive a DOAC prescription before the end of supply of the current prescription or within three months after the end of the treatment episode;
- *Interrupters* if no new prescription of VKA or DOAC will be issued within three months after the end of treatment episode.

Statistical analysis

Prevalent/incident users, switchers and interrupters will be calculated on a weekly basis during the entire observation period. However, to evaluate the effect of COVID-19 pandemic prescribing patterns of VKAs/DOACs before and after the 9th of March 2020, which is the date of the official lockdown, an interrupted time series (ITS) analysis will be carried out using the abovementioned date as cut-off point to detect whether or not this public health intervention had a significantly greater effect than any underlying trend. Regression analysis will be used to define the trends of each proportion in pre- and post-implementation periods. The angle between the trends will be calculated for the two periods to provide insights into the impact of the implementation.

Prevalence and incidence

Prevalence and incidence will be calculated as number of prevalent/incident divided by the number of inhabitants during the observed period. For this analysis, the number of inhabitants resident in Tuscany the 1st of January of each calendar year will be assumed as constant during the study period and it will be used as the denominator to calculate prevalence/incidence of use. Results will be presented as number of users per 1,000 inhabitants. The analyses will be stratified by gender, age, and individual DOAC.

Number of switch overtime

In this analysis a dynamic cohort will be considered. This will allow a continuous enrolment of prevalent VKAS users. The date of DOAC dispensing dose will be considered as the date of switch. The results will be shown as number of switchers divided by the number of VKAs users in the corresponding period. The analysis will be descriptive in nature, although an ITS analysis will be carried out to confirm the potential impact of COVID-19 pandemic as described in the previous paragraph.

Dummy tables and figure

Figure 1. Prevalence trend of DOACs and VKA users between Jan 2019 and June 2020.
X axis: time in weeks
Y axis: Prevalence per 1,000 inhabitants
The figure will show 2 lines:
a) Red line VKA users;
b) Blue line DOACs users

Figure 2. Time series analysis: Incidence of DOACs and VKA new users between Jan 2019 and June 2020.
X axis: time in weeks
Y axis: Incidence per 1,000 inhabitants
Interruption point (9-03-2020)
The figure will show 2 lines:
a) Red line VKA new users;
b) Blue line DOACs new users

Figure 3. Time series analysis: Incidence of DOACs and VKA new users between Jan 2019 and June 2020, stratified by age.

Figure 4. Time series analysis: Incidence of DOACs and VKA new users between Jan 2019 and June 2020, stratified by sex.

Figure 5. Time series analysis: Switch from VKA to DOAC between Jan 2019 and June 2020.
X axis: time in weeks
Y axis: number of switchers
Interruption point (9-03-2020)

Dataset

Variable	Note
IDUNI	Id_Paz
Prevalent	Yes/No
Incident	Yes/No
Start_of treatment episode	Date
End_date of treatment episode	Date
Incident	Yes/No
Prevalent	Yes/No
Type_AC	VKA/DOAC
Switcher	Yes/No
Date_switch	Date
Date of cohort exit	Date

Reference

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