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Direct oral anticoagulant plasma levels striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents. The Cremona experience

Running title: Severe COVID-19 syndrome and direct oral anticoagulant

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Background

- Antiviral drugs are administered in patients with severe COVID-19 respiratory syndrome (SARS-CoV-2), including those treated with direct oral anticoagulants (DOACs).
- Concomitant administration of antiviral agents has the potential to increase their plasma concentration.
- A series of patients managed in the Cremona Thrombosis Center were admitted at Cremona Hospital for SARS-CoV-2 and started antiviral drugs without stopping DOAC therapy.

AIM of the study

- To compare DOAC plasma levels in patients admitted to Cremona Hospital for severe SARS-CoV2 respiratory syndrome, and treated with antiviral agents, with those recorded in the same patients at the Thrombosis Center before hospitalization.

Methods

- All consecutive patients on DOACs were candidates for administration of antiviral agents (lopinavir, ritonavir or darunavir).
- Plasma samples for DOAC measurement were collected 2-4 days after starting antiviral treatment, at 12 hours from the last dose intake in patients on dabigatran and apixaban, and at 24 hours in those on rivaroxaban and edoxaban.
- For each patient, C-trough DOAC level , expressed as ng/mL, was compared with the one measured before hospitalization.

Results

- Of the 1039 patients hospitalized between February 22th and March 15th 2020 with SARSCoV-2 and candidates for antiviral therapy, 32 were on treatment with a DOAC.
- DOAC was stopped in 20, and continued in the remaining 12.
- On average, C-trough levels were 6.14 times higher during hospitalization than in pre-hospitalization period.

Table 1. Main clinical characteristics and C-trough DOAC levels in the cohort of patients

Number	Age	Sex	Clinical indication	DOAC	Dose mg/day	Antiviral drugs	C-trough (ng/mL) Pre-hospitalization	C-trough (ng/mL) In-hospital	Δ %
1	86	M	NVAF	dabigatran	110 x 2	lopinavir/ritonavir	54	221	+309.3
2	89	F	NVAF	apixaban	2.5 x 2	lopinavir/ritonavir	71	420	+491.5
3	74	M	NVAF	apixaban	5 x 2	darunavir/ritonavir	112	185	+65.2
4	69	F	NVAF	apixaban	5 x 2	lopinavir/ritonavir	85	326	+283.5
5	77	M	VTE	apixaban	5 x 2	darunavir/ritonavir	78	142	+82
6	73	M	NVAF	apixaban	5 x 2	lopinavir/ritonavir	92	163	+77.2
7	80	F	NVAF	edoxaban	60	lopinavir/ritonavir	102	473	+363.7
8	89	M	NVAF	edoxaban	30	darunavir/ritonavir	25	112	+348
9	85	M	NVAF	edoxaban	30	darunavir/ritonavir	11	71	+545.5
10	82	M	NVAF	rivaroxaban	15	lopinavir/ritonavir	12	143	+1091.7
11	77	M	NVAF	rivaroxaban	20	lopinavir/ritonavir	16	505	+3056.2
12	79	F	NVAF	rivaroxaban	15	lopinavir/ritonavir	13	99	+661.5

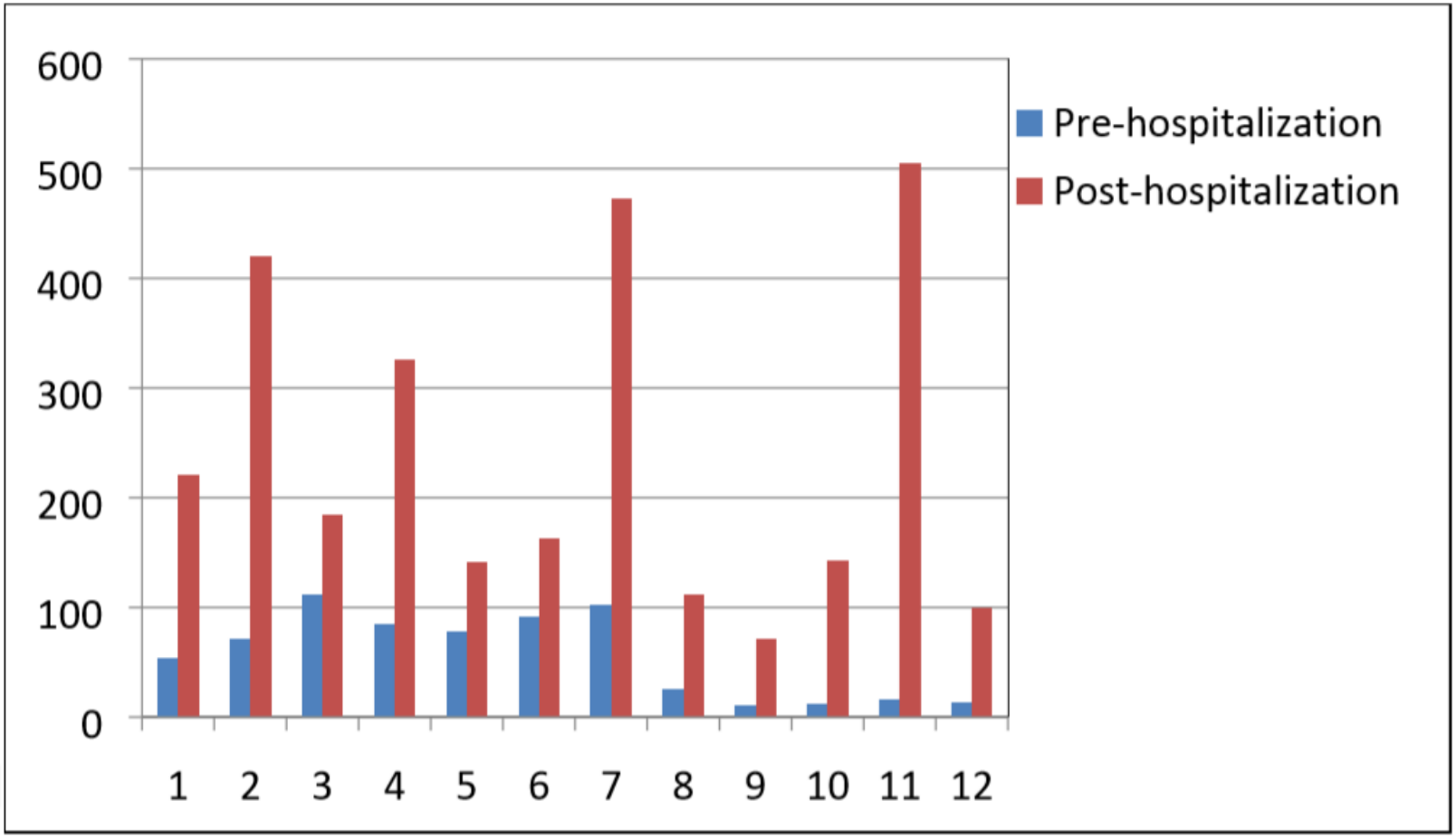

Fig.1: Changes in C-trough plasma levels, expressed as ng/mL, between pre- and in-hospital , in the twelve patients observed.

Conclusions

- DOAC patients treated with antiviral drugs show an alarming increase in DOAC plasma levels.
- In order to prevent bleeding complications, physicians should consider withholding DOACs from patients with SARS-CoV-2 and replacing them with alternative parenteral antithrombotic strategies for as long as antiviral agents are deemed necessary and until discharge.