LETTER TO THE EDITOR

Bleeding prevalence in COVID-19 patients receiving intensive antithrombotic prophylaxis

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Published online: 14 August 2020
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To the editor

In-hospital patients with severe acute respiratory syndrome coronavirus 2-induced disease (COVID-19) have a high risk of thrombosis [1–4]. Pharmacological thromboprophylaxis is strongly encouraged, and several experts even suggest the use of high-dose prophylaxis or full anticoagulation for patients with severe disease at low risk of bleeding, but up to now, data on safety of this approach are lacking [1, 5–8].

Here, we report observational single-center prevalence of major bleeding events (ISTH definition, Table S1) in patients with COVID-19 receiving intensive thromboprophylaxis [9]. We included all consecutive adult patients with laboratory-proven COVID-19 treated between April 1st and May 6th 2020 at the Hospital La Carità, Locarno, Switzerland. On April 1st 2020, we have implemented the following intensive thromboprophylaxis scheme: Patients with COVID-19 with an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m² received subcutaneous enoxaparin twice daily (BID) at a dose of 40 mg (< 80 kg), or 60 mg (≥ 80 kg) for a minimum of 14 days (dose level 1). Dose escalation to 60 mg BID (< 80 kg), or 80 mg BID (≥ 80 kg) was discussed if D-dimer levels increased during follow-up > 2.0 mg/L, irrespective of the presence of thromboembolic complications (dose level 2). Patients with COVID-19 with an eGFR < 30 ml/min/1.73 m² received subcutaneous UFH at a dose of 5000 IU three times a day in the regular ward, or continuous intravenous UFH in the intensive care unit (ICU) with a target anti-Xa activity of 0.3–0.5 U/ml. The study was approved by the Ethical Committee Ticino, Switzerland (2020-00838 RIF.CE 3621).

A total of 270 inpatients with confirmed COVID-19 were eligible for this analysis. 22 (8.2%) patients received regular thromboprophylaxis with once daily enoxaparin 40 mg or UFH 5000 IU two times a day, 183 (67.8%) patients received the intensified thromboprophylaxis, and 65 (24%) patients had full anticoagulation (Table 1). Of the 65 patients with therapeutic anticoagulation, 20

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11239-020-02244-y) contains supplementary material, which is available to authorized users.

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Table 1 Characteristics of patients with COVID-19 with and without major bleedings

| Characteristic                                      | COVID-19 patients without major bleedings | COVID-19 patients with major bleedings | p-value* |
|---------------------------------------------------|-------------------------------------------|---------------------------------------|----------|
| **Age (years)**                                   | 70.28 (22–96)                             | 73.89 (59–88)                         | 0.17     |
| Male sex (%)                                      | 157 (61.3)                                | 9 (64.3)                              | 0.83     |
| Time from first symptoms to hospital admission (days) | 6 (0–45)                                  | 6.5 (0–18)                            | 0.62     |
| Comorbidities (%)                                 | 194 (75.8)                                | 14 (100)                              | 0.04     |
| Cardiovascular disease (%)                        | 102 (39.8)                                | 7 (50)                                |          |
| Diabetes mellitus (%)                             | 55 (21)                                   | 4 (28.6)                              |          |
| Arterial hypertension (%)                         | 128 (50)                                  | 9 (64.3)                              |          |
| Pulmonary disease (%)                             | 55 (21.5)                                 | 5 (35.7)                              |          |
| Chronic renal failure (%)                         | 31 (12.6)                                 | 2 (14.3)                              |          |
| Malignancy (%)                                    | 18 (7.1)                                  | 1 (7.1)                               |          |
| Immunosuppression (%)                             | 21 (8.2)                                  | 2 (14.3)                              |          |
| **COVID-19 clinical syndrome (%)**, WHO definition [15] |                                      |                                       | 0.093    |
| Mild illness                                      | 13 (5.1)                                  | 0 (0)                                 |          |
| Pneumonia                                         | 27 (10.5)                                 | 0 (0)                                 |          |
| Severe Pneumonia                                  | 114 (44.5)                                | 4 (28.6)                              |          |
| Mild ARDS                                         | 13 (5.1)                                  | 1 (7.1)                               |          |
| Moderate ARDS                                     | 21 (8.2)                                  | 4 (28.6)                              |          |
| Severe ARDS                                       | 68 (26.6)                                 | 5 (35.7)                              |          |
| **COVID therapy protocol (%)**                    |                                          |                                       |          |
| Hydroxychloroquine                                | 56 (21.9)                                 | 6 (42.9)                              | 0.1      |
| Lopinavir + ritonavir                             | 40 (15.6)                                 | 6 (42.9)                              | 0.02     |
| Remdesivir                                        | 26 (10.2)                                 | 2 (14.6)                              | 0.65     |
| **Antithrombotic drug (%)**                       |                                          |                                       | 0.26     |
| UFH                                               | 39 (15.3)                                 | 5 (35.7)                              |          |
| LMWH                                              | 201 (78.5)                                | 9 (64.3)                              |          |
| DOAC                                              | 8 (3.1)                                   | 0                                     |          |
| VKA                                               | 8 (3.1)                                   | 0                                     |          |
| **Antithrombotic strategy**                       |                                          |                                       | < 0.01   |
| Regular prophylaxis                               | 22 (8.6)                                  | 0                                     |          |
| Intensive prophylaxis (dose level 1)              | 151 (59)                                  | 2 (14.3)                              |          |
| Intensive prophylaxis (dose level 2)              | 29 (11.3)                                 | 1 (7.1)                               |          |
| Full anticoagulation                              | 54 (21.1)                                 | 11 (78.6)                             |          |
| Dose intensification of the antithrombotic strategy during inpatient treatment (%) | 65 (25.4)                                 | 8 (57.1)                              | 0.03     |
| ICU treatment (%)                                 | 65 (26.9)                                 | 11 (78.6)                             | < 0.01   |
| Mortality (%)                                     | 40 (15.6)                                 | 6 (42.9)                              | 0.02     |

WHO World Health Organization, ARDS acute respiratory distress syndrome, UFH unfractionated heparin, LMWH low molecular weight heparin, DOAC direct oral anticoagulant, VKA vitamin K antagonist, OD once daily, BID two times per day, TID three times per day, INR international normalized ratio, anti-Xa anti-activated coagulation factor X activity, ICU intensive care unit

* Groups were compared by Chi², Fisher’s exact test or ANOVA, as appropriate

†Median (range)

‡Severe ARDS includes deaths attributed to not otherwise specified ARDS

§Regular prophylaxis = enoxaparin 40 mg OD or subcutaneous UFH 5000 UI BID if eGFR < 30 ml/min/1.73 m². Intensive prophylaxis (dose level 1) = subcutaneous enoxaparin 40 mg BID (< 80 kg), or 60 mg BID (≥ 80 kg), if eGFR < 30 ml/min/1.73 m² subcutaneous UFH 5000 IU, TID in the regular ward, and continuous intravenous UFH in the ICU (target anti-Xa ≤ 0.4 U/ml), Intensive prophylaxis (dose level 2) = subcutaneous enoxaparin 60 mg BID (< 80 kg), or 80 mg BID (≥ 80 kg), if eGFR < 30 ml/min/1.73 m² continuous intravenous UFH (target anti-Xa 0.3–0.5 U/ml), Full anticoagulation = weight adapted enoxaparin, continuous intravenous UFH (anti-Xa 0.3–0.7 U/ml), standard dose DOAC, or VKA with a target INR of 2.5 (±0.5)
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Funding
No funding source involved.

Data availability
Original data can be requested by contacting the corresponding author.

Compliance with ethical standards

Conflict of interest
D. Rossi reports grants and personal fees from Abbvie, grants and personal fees from Janssen, grants and personal fees from Gilead, grants and personal fees from AstraZeneca, personal fees from Verastem, personal fees from Loxo, grants from Celsiustedia, during the conduct of the study; B. Gerber reports grants and personal fees from Pfizer; personal fees and funding for accredited continuing medical education from Sanofi and Alnylam, during the conduct of the study; funding for accredited continuing medical education program from Axonlab, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Janssen, Mitsubishi Tanabe Pharma, NovoNordisk, Octapharma, Takeda, Sanofi, SOBI; non-financial support from Axonlab and Thermo Fisher from outside the submitted work; All other authors report no conflict of interest related to this study.

Ethical approval
The study was approved by the Ethical Committee Ticino, Switzerland (2020-0038 RIF.CE 3621).

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