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Letter to the Editors-in-Chief

Anti-Xa monitoring improves low-molecular-weight heparin effectiveness in patients with SARS-CoV-2 infection

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To the Editor,

A worryingly increased incidence of thrombotic events has been reported among patients suffering from COVID-19 despite standard antithrombotic prophylaxis [1]. This observation came along with more recent alerts regarding extremely high prevalence of SARS-CoV-2-positive patients admitted in intensive care units (ICU) failing to achieve the target inhibition of the activated factor X (anti-Xa): 95–100% compared to 27% in internal wards [2,3]. These findings can be explained by several coagulopathy and pro-thrombotic mechanisms induced by SARS-CoV-2 that lead to heparin resistance and decreased recovery of anti-Xa activity [3–5]. Furthermore, the increased factor VIII levels induced by the infection proved to be able to alter aPTT results, so that other authors have prompt hypothesized a better and promising application of anti-Xa assessment in monitoring the downstream heparin activity in COVID-19 [5]. Nevertheless, to date real-life evidence of any clinical benefit from this approach for COVID-19 management is missing and this laboratory test can be relatively expensive and not routinely manageable. To support anti-Xa monitoring in routine clinical management of COVID-19 further questions have to be addressed. Is heparin effectiveness a matter of doses or timing? Do we have to target higher anti-Xa ranges compared to those validated in surgical and standard prophylaxis? Do we have to monitor intensively anti-Xa levels due to the frequent and different alterations that may characterize the different phases of SARS-CoV-2 infection?

We have retrospectively collected and reviewed data from SARS-CoV-2-positive patients admitted to and dead/discharged from our sub-intensive unit of Infectious Diseases (Amedeo di Savoia hospital, Torino, Italy) between March–May 2020 to assess whether the application of a clinically driven anti-Xa monitoring may have associated with the disease outcomes: deaths from overall causes, COVID-19-related deaths and thrombotic events.

All the included patients were treated with low-molecular-weight heparin (LMWH) doses adjusted for renal function and body weight and underwent at least one anti-Xa measurement, while further determinations were clinically driven. We have excluded patients with previous admissions for COVID-19 in other hospitals, thrombotic events preceding the admission, low platelets count (< 100,000 cells/μL) and severe renal impairment (eGFR < 30 mL/min). Peak Anti-Xa levels were assessed through a chromogenic assay (Anti-Xa STA-Liquid; STAGO, Asnieres-sur-Seine, France) in citrate plasma withdrawn 4 h post-LMWH administration. Once-daily LMWH (enoxaparin or parnaparin) was administered at 6 a.m. to allow for the blood sampling during the morning shift (10 a.m.). Twice daily LMWH (enoxaparin) was administered at 6 a.m. and 6 p.m. Anti-Xa target values were 0.3–0.7 and 0.7–1.2 IU/mL for prophylactic and therapeutic use, respectively. While our therapeutic target range is in line with the most commonly suggested in literature [6], the adopted prophylactic target range slightly differs from the more commonly suggested 0.2–0.5 UI/mL [6,7]. Since some authors have suggested adopting higher target values of anti-Xa for LMWH prophylaxis when patients are characterized by significantly higher risk of thrombosis [8], we set our prophylactic target range at 0.3–0.7 UI/mL to be safely and certainly above the lower target limit of 0.2 usually recommended and not to exceed the threshold of 0.8, that has been linked to increased bleeding risks [6,9]. Nonparametric tests were performed. Data are presented as median (95% confidence interval).

56 patients were included: 64.3% were male; the median age, BMI and serum creatinine were 67 years (59–80), 24.5 (21.9–26.5) and 1.0 mg/dL (0.86–1.22), respectively. 12 patients underwent CPAP, 10 refused it and required mask ventilation with reservoir, while the others were on wall-oxygen (maximum FiO2 0.6). At admission, 49 patients (87.5%) were on once-daily prophylactic enoxaparin (44 patients; median 4000 IU/dose [4000–6000]) or parnaparin (5 patients; median 4000 IU/dose [4000–4000]), while 7 patients (12.5%) were on twice daily enoxaparin (median 6000 IU/dose [4000–6000]) due to atrial fibrillation. The median times from COVID-19 onset to LMWH start and to hospitalisation were 8 (4–11) and 6 days (3–9), respectively. 3 pulmonary emboli, 1 deep vein thrombosis and 1 retinal vein occlusion were observed and 9 deaths occurred. Among the latter, 5 were directly attributable to COVID-19 (1 pulmonary embolus, 3 respiratory failure due to severe viral pneumonia, 1 hypoxic myocardial infarction); no major bleeding was observed.

Anti-Xa activity was measured 126 times (38 patients had at least 2 measurements). 52 determinations (41.3%) were out of the target range (38 below and 14 above). The median first and second anti-Xa levels

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were 0.4 (0.3–0.6) and 0.5 IU/mL (0.3–0.6), respectively. 30 (53.6%) and 13 patients (34.2%) did not reach the target range at the first (39.3% below and 14.3% above) and second assessment (28.9% below and 5.3% above), respectively. LMWH doses were changed 39 times: 34 (87.2%) based on the anti-Xa results, while 5 times due to clinical indications or suspicions. eGFR significantly deteriorated in 8 patients, but in none this associated with anti-Xa alterations.

Patients with an available anti-Xa assessment within 72 h from LMWH prescription presented a lower overall mortality (6.4% vs 28.0%, OR 0.18 [0.033–0.95], p 0.031) compared to those tested later. Having the first anti-Xa measurement within the target range per se was not associated with none of the outcomes, as well as no association was observed between absolute LMWH doses and any of the clinical outcomes. The pragmatic anti-Xa-based approach represented by maintaining LMWH doses when first anti-Xa result was within the target or immediately modifying the dose accordingly associated with a lower risk of subsequent thrombotic events compared to not modifying LMWH doses due to competing clinical indications or waiting for a second anti-Xa assessment as confirmation (2.6% vs 23.5%, OR 0.086 [0.009–0.84], p 0.034).

After adjusting for the worst values of the arterial oxygen partial pressure to fractional inspired oxygen ratio and of IL-6 zenith during the hospitalisation, for age and for treatments (corticosteroids, antivirals and/or immune-modulants), the prompt correction of LMWH doses according to the first anti-Xa measurement (if needed) independently associated with a lower risk of COVID-19-related deaths (aOR 0.040 [0.002–0.90], p 0.043).

In our small sample of SARS-CoV-2-positive patients admitted to our sub-intensive ward, we have observed a significantly elevated prevalence of patients failing to achieve an effective anti-Xa activity (41.3%); this value sits in between the prevalence previously reported in ICU and normal wards [2,3], leading to hypothesize a positive correlation between the disease severity and hampered heparin effectiveness.

Secondly, rather than with the absolute LMWH doses or with single in-target anti-Xa assessments, we have observed a favourable association between immediate changes of LMWH dose, if needed, after repeated evaluations of anti-Xa activity and the positive clinical outcomes related to COVID-19: a lower risk of thrombotic events and of SARS-CoV-2-related deaths. This approach was based on standard prophylactic LMWH doses adjusted for renal function and body weight and having a higher prophylactic range as reference target of anti-Xa activity: 0.3–0.7 IU/mL instead of 0.2–0.5 IU/mL, which is more commonly used in other clinical conditions. These findings represent the first evidence of a potential clinical usefulness of anti-Xa-based LMWH use and of a candidate prophylactic target range in COVID-19, suggesting that patients with COVID-19 may undergo LMWH prophylaxis targeting higher values of anti-Xa levels compared to the traditional ones. If confirmed, the data may endorse the application of this laboratory tool in ICU as well as in general and sub-intensive wards such as ours.

This is a routine clinical practice snapshot where blood testing and management were not based on an orderly study protocol and the sample size limited adjustments for significant variables. Moreover, the adopted higher prophylactic anti-Xa target range may limit potential comparisons with future studies and may have led to an overestimation of the prevalence of patients not in the advisable range.

Randomized studies on larger and different populations are urgently required to confirm any improvement in LMWH effectiveness provided by anti-Xa monitoring and to detail its best application in COVID-19 pandemic, possibly assessing the most effective and safest range of anti-Xa levels to be targeted, as well as the timing of the measurement and the interpretation of the activity during the different phases of the disease course.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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