Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

The hazard of fondaparinux in non-critically ill patients with COVID-19: Retrospective controlled study versus enoxaparin

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Dear Editors-in-Chief,

COVID-19 (acronym of COronaVIrus Disease 2019) is an infectious respiratory disease, responsible for a worldwide pandemic, with a high rate of venous and arterial thrombotic complications. These complications have recently been reported to occur in patients with COVID-19 disease regardless of the use of prophylactic doses of low-molecular-weight heparin (LMWH) [1,2]. Although their incidence is higher in the most severe patients, it has been reported to be substantial also in those with less severe disease [1,3,4].

Fondaparinux, an indirect inhibitor of factor Xa that is injected subcutaneously and is highly effective for protection against VTE in admitted medical patients [5], was found to be more effective than and as safe as LMWH in high-risk surgical patients, such as candidates to major orthopedic surgery [6]. These findings are consistent with those achieved by several oral inhibitors of factor Xa not only in major but also in minor orthopedic surgery of the legs [6–8]. Unlike oral Xa inhibitors, fondaparinux does not interfere with antiviral drugs, and, therefore, it qualifies as a potential candidate to replace LMWH for prevention of thrombotic complications in high-risk patients, such as those admitted to medical departments because of a non-severe COVID-19 infectious disease. Surprisingly enough, this drug has not been investigated yet in this clinical setting.

Accordingly, we decided to retrieve the medical charts of non-critically ill COVID-19 patients admitted to seven medical departments in the Northern Italy during the current pandemic, and to compare the incidence of venous and arterial thrombotic complications, as well as that of major and clinically relevant bleeding complications between patients allocated to prophylactic doses of enoxaparin and those given prophylactic doses of fondaparinux. Patients who for any reason did not receive antithrombotic prophylaxis were excluded, as were those who were prescribed (sub)therapeutic doses of either drug. As the two drugs are both registered for this purpose, and are freely available in the Italian Institutions, their use was largely dependent on the drug availability.

As there was no systematical search for thrombotic complications, only symptomatic events were investigated and recorded. We pointed at the development of clinically symptomatic and objectively confirmed deep vein thrombosis (DVT) of the extremities and/or pulmonary embolism (PE), and at the development of acute arterial cardiovascular disorders. Major and clinically relevant bleeding complications were defined according to the ISTH classification. Only events occurring during the administration of prophylactic doses of either drug were computed. All-cause mortality was also recorded, as was the clinical deterioration requiring admission to Intensive Care Units. Given the retrospective nature of the study, pointing at the analysis of clinical charts that had been de-identified, the need for patients consent was waived by the Ethical Board of the participating centers.

Of the 380 patients who had been admitted to the seven medical departments because of non-critically ill COVID-19 patients, 12 were excluded because of lack of antithrombotic drugs, 15 because of ongoing anticoagulation, and 45 because of the administration of sub (therapeutic) doses of LMWH or fondaparinux. Accordingly, 308 patients were available for the comparison between standard prophylactic doses of either drug: 4000 units of enoxaparin and 2.5 mg of fondaparinux once daily, which were generally reduced to 2000 units and 1.5 mg, respectively, in patients with severe renal failure. Of these patients, 160 had been treated with enoxaparin and 148 with fondaparinux.

Table 1 shows the main baseline demographic and clinical characteristics of the recruited patients, which were all fully comparable between the two study groups. To this purpose, the Student *t*-test and

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Table 1
Main baseline demographic and clinical characteristics of the recruited patients.

	LMWH (n = 160)	Fondaparinux (n = 148)	*P*-value
Age (mean ± SD)	65 ± 18	64 ± 16	0.84
Males	87 (54.4)	86 (58.1)	0.91
Obesity (BMI ≥ 30)	27 (16.9)	22 (14.9)	0.96
One or more risk factors for venous thrombosis*	18 (11.2)	12 (8.1)	0.35
One or more risk factors for arterial thrombosis^	91 (56.9)	88 (59.5)	0.65
Severe renal failure (creatinine clearance < 30 ml/min)§	5 (3.1)	3 (2.0)	0.55
PPS° (mean ± SD)	5.1 ± 1.4	4.9 ± 1.3	0.88
Baseline D-Dimer ≥2 times the cutoff value	35 (21.9)	32 (21.6)	0.95

Values in parentheses are percentages unless otherwise indicated.
* Cancer, recent trauma or surgery, hormonal treatment, already known thrombophilia, previous VTE.
^ Heavy smoking, diabetes, blood hypertension, hyperlipemia, symptomatic atherosclerosis.
§ Requiring the use of lower doses of either drug.
° Padua Prediction Score (≥4 in all admitted patients) [10].

the chi-square test with Yates correction were adopted for comparison of continuous and categorical variables, respectively. The duration of treatment was similar in the two groups: 16.9 ± 8.3 days among enoxaparin and 17.2 ± 6.6 days among fondaparinux recipients ($P = 0.80$). They had received a comparable pharmacological treatment for their infectious disease in terms of antiviral, antibiotic and anti-inflammatory drugs. The number of patients who deteriorated clinically, thus requiring admission to Intensive Care Units was similar (6 among enoxaparin and 4 among fondaparinux recipients), as was the number of patients who died (8 and 7, respectively). Except for two patients who died because of acute coronary syndrome (one in each group), in all other cases the death was attributed to disease-related complications.

A similarly proportion of clinically symptomatic and objectively confirmed venous or arterial thrombotic complications was shown in the two study groups: 5 episodes (3.1%) in the enoxaparin group (1 proximal leg DVT, 1 proximal arm DVT, 1 PE, 1 ischemic stroke and 1 fatal coronary syndrome), and 4 (2.7%) in the fondaparinux group (1 proximal leg DVT, 1 PE, 1 fatal and 1 non-fatal coronary syndrome) ($P = 0.83$). In contrast, the rate of major or clinically relevant bleeding complications was remarkably higher (7/148, 4.7%) in patients treated with fondaparinux than in those (1/160, 0.6%) allocated to enoxaparin ($P = 0.03$). Details of bleeding complications are shown in Table 2. No bleeding was fatal. All of them led to discontinuation of thromboprophylaxis.

Although selection bias is likely to have occurred, because of the lack of a randomized allocation to the treatment groups, our conclusions are plausible, because of the full comparability in the baseline and clinical characteristics of the recruited patients. In addition, an identical approach was used to identify and classify the thrombotic and hemorrhagic complications according to widely accepted definitions.

While the rate of clinically symptomatic and objectively confirmed venous or arterial thrombotic complications was similar in the two study groups, that of major or clinically relevant bleeding complications was remarkably higher among fondaparinux recipients. The hemorrhagic potential of fondaparinux in low, prophylactic doses was somewhat unexpected, as it contrasts with that seen in other medical

Table 2
Severity and timing of bleeding complications in the recruited patients.

Type of bleeding	Severity of bleeding	Timing of bleeding (days)
Enoxaparin		
Gastrointestinal	MB	8
Fondaparinux		
Retroperitoneal	MB	10
Retroperitoneal	MB	11
Gastrointestinal	MB	20
Gastrointestinal	MB	21
Epistaxis	CRNMB	10
Epistaxis	CRNMB	11
Epistaxis	CRNMB	17

MB = major bleeding; CRNMB = clinically relevant non major bleeding.

[5] and surgical settings [6]. It was found to mirror that of (sub)therapeutic doses of LMWH in the same clinical scenario [9]. A potential explanation is the frailty of patients, such as those admitted because of a COVID-19 infection, who are on average old and with additional comorbidities, thus more vulnerable when treated with a more potent antithrombotic drug, which in addition possesses a much longer half-life and a higher risk of accumulation (potentially dangerous in patients with infection-related renal impairment).

Based on our study results, the use of fondaparinux in place of LMWH in patients with non-critically ill COVID-19 infectious disease should be discouraged. Whether these conclusions apply to patients with a more severe disease remains to be demonstrated.

Declaration of competing interest

Nothing to disclose.

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