ESC European Society of Cardiology
European Heart Journal (2020) **0**, 1–3
doi:10.1093/eurheartj/ehaa553

EDITORIAL

COVID-19 and pulmonary embolism: an unwanted alliance

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This editorial refers to 'Pulmonary embolism in COVID-19 patients: a French multicentre cohort study', by C. Flauvel *et al.*, doi:10.1093/eurheartj/ehaa500.

After having terrorized the world with an unprecedented spread of potentially fatal infection, COVID-19 has also initiated a second pandemic. By this I mean the flood of information offered by online scientific publications multiplied by their often distorted echoes in the lay press and media. Some articles are accepted on the day of submission, and on the same day posted as open access web publications. They are in turn immediately cited by similar web publications. Confusion is great, as we are faced mostly with case series or retrospective observational trials far from methodologically perfect and therefore often providing inconsistent and potentially harmful information. The army used to call casualties suffering from such confusion on a battlefield victims of 'friendly fire'

This frantic activity is caused—though not justified—by an urgent need to better understand the pathogen and the disease in order to come up with some evidence-based preventive and management solutions. Such solutions are so far lacking if we don't count social isolation and masks, a symbol that will always remind us of the year 2020.

While COVID-19 primarily affects our respiratory systems, it is the cardiovascular system which so far has provided the most clinically relevant data regarding the effectiveness and safety of potential management strategies; sometimes conflicting, but at least indicating directions for further research, as in the case of efficacy of antimalaria drugs vs. their risk of fatal arrhythmia

The study published by our French colleagues in this issue of the *European Heart Journal*, while again observational, provided some new and reinforced previously reported data.[1] These data may help to limit one of the recently recognized cardiovascular complications of COVID-19 infection, complications which may have a significant influence on morbidity and mortality, i.e. pulmonary embolism (PE).

Anticoagulants again? Yes, because symptomatic COVID-19 patients seem to be prone to develop clots in their pulmonary arteries. Do they come, as is usually the case, from systemic veins? Probably,[2] though intrapulmonary thrombosis induced by local inflammation and disturbed haemostasis may contribute to this process.[3]

However, not pathogenesis but risk factors and prevention of PE are in the spotlight of the 24 French centres which contributed to this trial performed under the formal auspices of the French Cardiac Society (NCT04344327).[1] The investigators focused on COVID-19 patients who at admission did not qualify for intensive care unit (ICU) admission. Furthermore, they excluded from the analysis those patients in whom CT angiography was not performed. Consequently, the 1240 patients that remained in the trial represented a preselected subgroup of COVID-19 patients: symptomatic though initially stable, but at some point during hospitalization requiring contrast-enhanced CT. It was offered to patients when unenhanced chest imaging could not explain the severity of their respiratory insufficiency. Based on CT angiography, 103 out of 1240 (8.3%) patients were ultimately diagnosed with PE. This is a relatively low prevalence, when compared with previously reported series, probably due to exclusion of the most severely ill COVID-19 patients, who required ICU care already at admission. In one of the most cited early series, deep-vein thrombosis (DVT) was found—when specifically searched for—in a frightening proportion of 69% (18 out of 26) mechanically ventilated COVID-19 patients, with PE confirmed in 6/26 (23%).[2] In those patients, standard prophylaxis was futile and even therapeutic anticoagulation already present at admission was only partly effective in preventing venous thrombo-embolism (VTE). Indeed, all six cases of PE occurred in patients who were fully anticoagulated.[2] Also a larger series from three Dutch hospitals and another single-centre study from Milan reported similarly high PE incidence in their ICU patients despite at least a prophylactic dose anticoagulation.[3–5] Such a high prevalence of PE led to concepts suggesting a COVID-19–PE 'alliance' as the main cause of mortality during the current pandemic requiring intensive preventive parenteral anticoagulation.

So far indications for prophylaxis in COVID-19 infection have been supported mostly by data collected from severely ill ICU patients. The French study extended our knowledge to those patients who were initially stable. As already suggested by others,[5]

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.
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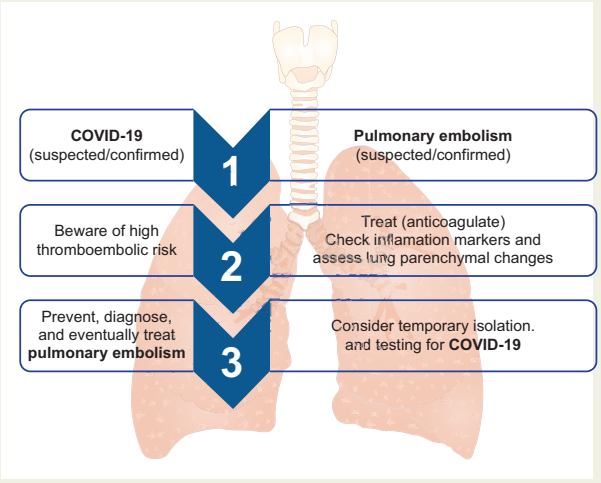

Figure 1 COVID-19 and pulmonary embolism – an unwanted alliance. Suggested general management strategies.

the prevalence of PE in this population was much lower, though still more linked to the intensity of infection as assessed by C-reactive protein (CRP), than to usual conditions known to predispose to VTE—such as age, obesity, history of VTE, or cancer. Of note, the mobility of COVID-19-positive patients is invariably restricted, if not due to symptoms certainly for isolation purposes.

Beyond CRP, only a few other factors correlated at multivariate analysis with the presence of PE in hospitalized COVID-19 patients: male gender—hardly modifiable—delay from initial symptoms to admission, and finally anticoagulation introduced prior to diagnosis of PE. Both chronic oral and in-hospital parenteral prophylactic anticoagulation were associated with lower incidence of PE. Moreover, higher prevalence of PE found in patients with longer time from initial symptoms to admission could be interpreted as reflecting delayed introduction of parenteral VTE prophylaxis, further highlighting its clinical relevance.

Taken together, existing evidence,[6] emerging expert opinions,[7] and the results of the current trial all suggest immediate initiation of prophylactic anticoagulation in all hospitalized patients with COVID-19, regardless of the presence or absence of usual risk factors or of results of VTE risk scores. Moreover, in contrast to, for example, cancer patients, COVID-19 patients seem to represent relatively safe candidates for anticoagulation.[5] Regretably, data on bleeding complications were not revealed by the authors of the current trial. Also, assessment of effectiveness and safety of doubling the dose of primary prophylaxis, or reaching therapeutic doses for preventive reasons as suggested by some recent papers,[3] was impossible due to the low number of patients in such subgroups.

Apart from data on risk factors and the incidence of PE, the French trial offers relatively scarce information on the in-hospital course of enrolled patients. Strangely, no signal for increased mortality has been associated with intrapulmonary clots detected on CT angiography. While patients diagnosed as having PE were more often transferred to ICUs and treated with mechanical ventilation, their survival seemed not to be affected by this potentially fatal complication. We do not know what the distribution and volume of thrombi found on CT angiography were. However, 32 out of 103 patients were classified as having PE with high risk of early death according to prognostic stratification recommended by recent ESC Guidelines based on haemodynamic instability, right ventricular dysfunction, and positive troponin test. No information was provided on how those critically ill patients were managed. Only nine deaths among 103 patients with COVID-19 complicated by PE, classified as high risk in 1/3 of cases, seems a remarkable management success. In another large retrospective series of 2773 individuals hospitalized with COVID-19, in whom 28% received systemic anticoagulation and 14% were intubated, mortality was 22.5% in those anticoagulated and 22.8% in non-anticoagulated patients.[8] Only intubated patients benefited from anticoagulation, with mortality of 29% compared with 63%, in those who were not anticoagulated. Bleeding risk was negligible and not significantly increased by anticoagulation.

Despite knowledge gaps and lack of randomized controlled trials, there is little doubt that antithrombotic VTE protection should be recommended for hospitalized COVID-19 patients to reduce morbidity and mortality regardless of the presence or absence of classical risk factors for VTE. Whether the dose should be higher than usually recommended for prevention,[3,8] whether we should adjust the doses to the objectively assessed level of heparin resistance,[9] whether there is any role for new anticoagulants, and whether we should be concerned about drug interactions[7,10] remain to be resolved by future prospective trials.

However, there is also the other side of the coin. In view of the obvious association between COVID-19 and PE, how should we manage our usual patients with suspected PE during the expected second wave of the pandemic? Such patients often present in the Emergency Department with increased body temperature, cough, malaise, dyspnoea, hypoxaemia, and non-specific parenchymal changes on chest imaging. PCR tests require time and are not fully sensitive. Even in the current trial, 15% of patients with intrapulmonary clots were diagnosed with COVID-19 infection based on chest imaging without PCR confirmation.[1] Should we suspect COVID-19 in every patient with apparently idiopathic PE just as we always consider them for occult cancer? Implementation of cumbersome individual and institutional preventive procedures would delay and jeopardize diagnosis and management of PE, which remains the third most common cause of cardiovascular deaths even without COVID-19 infection. Whichever approach is taken, it is important to remember a prophetic recommendation from the 2019 ESC Guidelines issued before the global community was hit by COVID-19: 'Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress'[11] maybe just adding to it 'and/or while COVID-19 preventive measures are being implemented'.

Conflict of interest: A.T. has received lecture and consultancy honoraria from Bayer and Pfizer outside the submitted work.

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