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

Protective effect of oral anticoagulant drugs in atrial fibrillation patients admitted for COVID-19: Results from the CORIST study

Coagulopathy is an independent predictor of poor outcome in Coronavirus Disease of 2019 (COVID-19) patients [1]. Endothelial dysfunction, hypercoagulability, and platelet activation are initially induced by direct endothelial injury and then sustained by a systemic inflammatory response to the viral infection predisposing to an increased risk of arterial and venous thrombosis [2]. High rates of venous thromboembolic events in hospitalized COVID-19 patients have been consistently reported in a number of observational studies [3] and routine thromboprophylaxis with low molecular weight heparin (LMWH) is recommended for this high risk population [4]. A greater protective effect from the use of LMWH has been hypothesized and is currently evaluated in randomized controlled trials. Since early endothelial injury leading to microvascular pulmonary thrombosis is possibly associated with poor clinical outcomes in patients with respiratory failure caused by interstitial pneumonia, it can also be hypothesized that COVID-19 patients already receiving therapeutic anticoagulation at the time of the infection may be protected from adverse outcomes as compared to non-treated patients. To explore this hypothesis, we compared the rates of in-hospital adverse outcomes between COVID-19 patients with atrial fibrillation (AF) who were receiving oral anticoagulant drugs for stroke or systemic embolism prevention at the time of hospital admission and COVID-19 patients with AF not receiving oral anticoagulation at the time of admission using the database of the CORIST study.

CORIST is a large retrospective observational study of patients hospitalized with laboratory-confirmed SARS-CoV-2 infection in 34 Italian hospitals carried out between February 19th and May 23rd 2020. The study was approved by all local Ethics Committees. Clinical data were abstracted from electronic medical records or charts and gathered through a centralized database. Information on baseline characteristics, previous and current drug lists, medical history and comorbidities, and clinical outcomes during hospitalization was collected. Adverse outcome was defined by the composite of severe pneumonia, or acute respiratory distress syndrome (ARDS), or death. Logistic regression analysis was used to estimate the association between the use of oral anticoagulant drugs before admission and the occurrence of severe outcomes. Analysis was first adjusted for age, sex, and heparin use after admission and then additionally for history of acute myocardial infarction, diabetes, hypertension, cancer, chronic obstructive pulmonary disease, renal function and C reactive protein at hospital entry. This analysis was then repeated using death as the only outcome and then separating patients on vitamin K antagonists (VKAs) and patients on direct oral anticoagulants (DOACs). Finally, because the use of statins may also have an impact on clinical outcomes in these patients, all analyses were repeated comparing statins users and non-users at the time of admission.

We included 4396 patients who were hospitalized with confirmed SARS-CoV-2 infection who either died or had been discharged or were still in hospital as of June 30, 2020. AF was known in 154 (3.5%) of admitted patients, 43 patients (28%) were receiving oral anticoagulant drugs at the time of hospitalization, 22 on VKAs and 21 on DOACs; 21 patients were on statins. Of the 4242 patients without AF, 2143 (50.5%) had an adverse outcome, 766 died (18.1%). Data on adverse outcome events and mortality in patients with AF according to anticoagulant and statin treatment are reported in Table 1.

When the analysis was conducted according to the type of anticoagulation, 12 of 22 on VKAs had an adverse outcome event (54.6%) compared to 10 of 21 on DOACs (47.6%). As compared to untreated patients with AF, the odds ratio for the adverse outcome adjusted for age, sex, and use of heparin after hospital admission was 0.82 (0.28 to 2.38) for patients on VKAs and 0.64 (0.23 to 1.81) for patients on DOACs.

The results of this analysis from a large, retrospective, observational study suggest that patients with AF admitted to hospital because of COVID-19 could be at higher risk of adverse outcomes as well as mortality alone as compared to patients without AF and that the use of oral anticoagulants before admission may have a protective effect in this population, with a non-significant 62% reduction of mortality. A non-significant trend toward fewer adverse events was observed in patients treated with DOACs as compared to patients with VKAs, but numbers are too limited to allow any meaningful conclusion. Few patients with AF were on statins and no signs of potential protective effect were observed.

Patients affected by chronic cardiac diseases, including AF, are at increased risk of mortality when hospitalized for COVID-19 [5]. This increased risk may be explained by older age and higher number of comorbidities, as compared to the general population of COVID-19 patients, but also by a greater propensity to both venous and arterial thrombosis. Chronic use of oral anticoagulants, which is recommended for most patients with AF, may have protected these patients from the early onset of thrombosis at the pulmonary arteries and from pulmonary embolism and, thus, reduced the risk of adverse outcomes and mortality. Our results are consistent with the results of a large population-based study of elderly patients [6]. In this study patients on chronic oral anticoagulant therapy had a significantly lower mortality rate during hospitalization for COVID-19 than patients not receiving oral anticoagulation. Of note, mortality rates in non-anticoagulated versus anticoagulated patients (32% and 26%, respectively) were similar to those reported in our study (Table 1). This effect was not observed in another study from the United States [7]. In this study, however, mortality rates were much higher in the two groups of patients on anticoagulant or antiplatelet treatment than in controls, suggesting that the populations compared may have been different from those compared in

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Table 1
Adverse outcome in patients with and without atrial fibrillation and according to oral anticoagulant or statins therapy.

Patients	N	Event	%	OR (1) (95% CI)	OR (2)	OR (3)
Composite endpoint						
No AF	4242	2143	50.5			
AF and no OAT	111	65	58.6	-1-	-1-	-1-
AF on OAT	43	22	51.2	0.74 (0.37 to 1.50)	0.83 (0.38 to 1.81)	0.74 (0.32 to 1.70)
AF and no statins	92	46	50.0	-1-	-1-	-1-
AF on statins	21	15	71.4	2.50 (0.89 to 7.01)	2.43 (0.85 to 6.93)	2.91 (0.89 to 9.49)
Death						
No AF	4233	766	18.1			
AF and no OAT	110	39	35.5	-1-	-1-	-1-
AF on OAT	43	10	23.3	0.55 (0.25 to 1.24)	0.47 (0.19 to 1.15)	0.38 (0.14 to 1.02)
AF and no statins	91	26	28.6	-1-	-1-	-1-
AF on statins	21	8	38.1	1.54 (0.57 to 4.14)	1.40 (0.49 to 3.97)	1.48 (0.43 to 5.05)

OR (1): unadjusted odds ratio; OR (2): odds ratio adjusted for OAT, statins, age, sex and heparin use after hospital admission; OR (3): odds ratio adjusted for OAT, statins, age, sex, heparin, history of acute myocardial infarction, diabetes, hypertension, cancer, chronic obstructive pulmonary disease, renal function and C reactive protein. AF Atrial fibrillation; OAT oral anticoagulant therapy. Statins use was missed for 41 patients with AF.

our study limited to AF patients with and without anticoagulation. Protective effect on mortality was also reported with the use of heparin, mainly at prophylactic doses, in the CORIST study [8]. In this retrospective observational study, 70% COVID-19 patients received heparin during hospitalization and had a 40% lower risk of mortality compared to patients not treated with heparin [8]. Thus, the issue on whether anticoagulation should be administered at prophylactic or therapeutic doses remains open. Preliminary findings from a large NIH multiplatform, adaptive-design trial that included 3 randomized controlled trials (REMAP-CAP, ATTACC, and ACTIV-4A) suggest that full dose anticoagulation with heparin is superior to standard prophylactic dose anticoagulation in reducing the need for organ support in moderately ill hospitalized COVID-19 patients, but not in severely ill patients requiring intensive care unit level of care (NIH press releases December 21, 2020 and January 22, 2021).

While awaiting for the final results of these studies, a few hypotheses should be made. Full dose anticoagulation may be effective in preventing early microthrombotic events at a local level as well as venous thromboembolism, thus reducing adverse outcomes during hospitalization, if timely started. This is suggested by the results of this study and by the study by Denas et al. [6], but also by the preliminary findings from the NIH multiplatform, where full dose anticoagulation was effective when administered within 72 h of hospital admission in patients with moderate severity of disease (and more effective than prophylactic dose anticoagulation), but not in patients already presenting with high severity of disease. The protective effect of anticoagulant drugs may not only depend on the time of initiation and on the dose, but also on the anticoagulant type. In this study, we observed a trend toward lower rates of adverse outcomes in patients receiving DOACs than in patients on VKAs. In addition to the prevention of pulmonary artery thrombosis, some anticoagulant drugs may also have an antiviral effect by inhibiting SARS-CoV-2 fusion, as suggested by preliminary findings [9]. In particular, it has been suggested that factor Xa and factor IIa, both serine proteases, might have a role in the cleavage of SARS spike protein [10]. For instance, factor Xa expression by cells co-expressing ACE2 may favor local cleavage of spike protein into spike protein 1 and spike protein 2 upon virus binding to its receptor [11]. Thus, factor Xa inhibition may reduce cleavage of spike protein and cell entry by SARS-Cov2 virus. This interesting mechanism may, at least partially, explain better protection by DOACs with respect to VKAs.

This study has several limitations that need to be acknowledged. First, using retrospective analysis of electronic medical records we cannot exclude that some diagnoses of AF may have been missed. However, the prevalence of AF in our study (3.5%) is similar to the expected prevalence in the general population with a similar mean age (67 years). Second, the proportion of patients with AF receiving oral anticoagulant drugs at the time of admission was lower than expected, and we cannot exclude that in some patients anticoagulation was stopped only few days before admission, after the onset of symptoms, and replaced with prophylactic LMWH. This practice is not uncommon and should be avoided in the absence of contraindications to oral anticoagulation. Third, information on anticoagulant drugs was collected at hospital admission and we cannot exclude that full therapeutic doses were subsequently started during hospitalization. However, the aim of our study was to assess the protective effect of therapeutic anticoagulation taken at the time of the infection.

In conclusion, patients with AF hospitalized for COVID-19 are at high risk of adverse outcomes. A non-significant trend toward a lower risk of mortality was observed in patients on oral anticoagulants prior to hospital admission. These findings from a retrospective study can only be considered as hypothesis generating.

Declaration of competing interest

Dr. Ageno reports grants and personal fees from Bayer, personal fees from BMS/Pfizer, personal fees from Daiichi Sankyo, personal fees from Aspen, personal fees from Portola, personal fees from Janssen, personal fees from Sanofi, outside the submitted work.

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