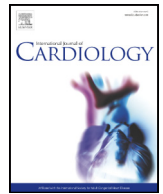




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## Editorial

## Does anticoagulation reduce mortality in patients with atrial fibrillation who later developed a COVID-19 infection?



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Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is associated with a hypercoagulable state that increases the risk of venous and arterial thromboembolic complications [1,2]. Despite anticoagulant therapy, these thromboembolic complications occurred in up to 69% in critically ill mechanically ventilated patients and post-mortem examinations have identified both macrovascular and microvascular thrombosis that may contribute to organ failure, multisystem injury and death, and clotting of circuits and vascular access have been well described in COVID-19-infected patients [1,2]. Thus, prophylactic and therapeutic antithrombotic therapy is recommended for hospitalized patients with COVID-19 to reduce morbidity and mortality regardless of the presence/absence of classical risk factors [1]. However, in the absence of randomized controlled trials or prospective data, the optimal prevention and treatment of thrombosis in COVID-19 remains uncertain and present evidence, mainly derived from retrospective studies (Table 1), is contradictory [3–6].

In this issue of the International Journal of Cardiology, Denas et al. [7] used a novel approach to obtain information on the effect of anticoagulation on COVID-19 morbidity and mortality. They retrospectively reviewed all elderly patients ( $\geq 65$  years) from the Veneto Region with confirmed positive SARS-Covid-2 infection but, very smartly, compared patients who received chronic anticoagulation for atrial fibrillation (AF) with those who did not. Interestingly, AF is present in 10–36% in COVID-19 patients [8]. This high prevalence may be related to the observed increase in plasma angiotensin converting enzyme 2 (ACE2) activity, which is more marked in patients with persistent AF, and the presence of a systemic inflammatory response syndrome; both effects led to atrial electrical and structural remodelling, i.e. the arrhythmogenic substrate that increased susceptibility to AF [9,10].

Denas et al enrolled 4,697 patients (Table 1) after excluding those with mechanical heart valves, diagnosed mitral stenosis, venous thromboembolism or other indications for anticoagulation. To compensate for bias due to non-random allocation of potential covariates among COVID-19 patients, propensity scores were calculated using a logistic regression model, adjusting for multiple covariates. The propensity score

matching yielded 559 patients per arm. Anticoagulated patients were older, presented more comorbidities, required more frequently hospital admissions and had higher all-cause and in-hospital mortality. Study outcomes, including hospital admission and intensive care unit admission, were similar in the two cohorts, but all-cause mortality was significantly lower among anticoagulated patients (26.5% vs. 32.2%;  $P=0.036$ ). On time to event analysis, however, a non-significant toward reduction in all-cause mortality was observed among anticoagulated patients ( $P=0.054$ ). Thus, the present study suggests that among elderly patients with COVID-19, those on chronic oral anticoagulant treatment for AF seem to be at lower risk of all-cause mortality compared to their propensity score matched counterpart not on anticoagulant treatment. Nevertheless, the lower mortality observed in anticoagulated patients needs to be confirmed in further prospective randomized studies.

This study has some limitations, mainly due to its observational retrospective nature. Furthermore, authors did not take into account the anticoagulation that the patients received while in the intensive care unit or the influence of in-hospital interventions which might have affected the outcomes. Additionally, and even when a number of factors were included in their propensity score matching, they have missed some factors (i.e. illness severity) that could impact mortality, need for mechanical ventilation, or hospitalization. The finding that prediagnosis AC was not associated with a decreased rate of hospitalization, suggests that anticoagulation did not protect against development of severe COVID-19 disease. However, it has been hypothesized that if thrombotic complications are more a feature of later-stage disease, it is possible that administration of anticoagulation therapy early in the disease course may fail to detect later benefit [4].

In conclusion, further prospective randomized trials, are urgently needed to assess the efficacy and safety of anticoagulant therapy, determine the optimal dose and course of prophylactic and therapeutic anticoagulation and identify those hospitalized patients with COVID-19 in whom this therapy confers a greater survival benefit. The results of several ongoing clinical trials (see [clinicaltrials.gov](https://clinicaltrials.gov)) will shed light on these questions for which there is still no answer.

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**Table 1**  
Retrospective clinical trials that studied the association between anticoagulation therapy and outcomes in patients with COVID-19.

Reference	Patients (n)	Treatment	Primary end points	Outcomes
Tang et al., 2020 [3]	449, severe COVID-19	94 received LMWH (40–60 mg enoxaparin/day); 5 received UFH (10,000–15,000 U/day) 350 without heparin treatment or treatment for <7 days	28-day mortality..	No difference in 28-day mortality between heparin users and non-users. 28-day mortality of heparin users was lower than nonusers in patients with SIC score $\geq 4$ (40.0% vs 64.2%, $P = 0.029$ ), or D-dimer $>3 \mu\text{g/mL}$ (32.8% vs 52.4%, $P = 0.017$ ).
Tremblay et al., 2020 [4]	3772 hospitalized and ambulatory patients	AC ( $n = 241$ ), antiplatelet therapy ( $n = 672$ ), or not receiving AC or antiplatelet therapy ( $n = 2859$ ) at the time of COVID-19 diagnosis	All-cause mortality.	There was no statistically significant difference in survival, mechanical ventilation, and hospital admission in the AC vs no-AC/antiplatelet groups
Paranje et al., 2020 [5]	2773 hospitalized patients	AC therapy was not described	Association between administration of in-hospital AC and survival	No difference on in-hospital mortality for patients treated with AC or who did not receive AC treatment Significant reduction in in-hospital mortality between patients who received and who did not receive AC treatment (29.1% vs 62.7%)
Nadkarni et al., 2020 [6]	4389 hospitalized patients	No AC ( $n = 1530$ ). Prophylactic AC ( $n = 1959$ ): 941 on LMWH, 445 on UFH. Therapeutic AC ( $n = 900$ ): 227 on LMWH, 235 on UFH	In-hospital mortality	Compared with no AC, therapeutic AC and prophylactic AC were associated with lower in-hospital mortality (aHR: 0.53 and 0.50, respectively; both $P < 0.001$ ), and intubation (0.69 and 0.72, respectively; both $P = 0.002$ ). When initiated $\leq 48$ h from admission, there was no significant differences between therapeutic versus prophylactic AC
Denas et al., 2020 [7]	4697 patients: 651 AC patients and 4046 non-AC patients	269 on vitamin K antagonists, 138 on rivaroxaban, 116 on apixaban, 70 on edoxaban, and 58 on dabigatran	Hospital admission, ICU admission and all-cause mortality	Hospital admission and ICU admission were similar in the two cohorts; all-cause mortality was significantly lower among anticoagulated patients (26.5% vs. 32.2%; $P = 0.036$ )

AC: anticoagulant. aHR: adjusted hazard ratio. ICU: intensive care unit; LMWH: low molecular weight heparin. SIC: sepsis-induced coagulopathy. UFH: unfractionated heparin. ULN: upper limit of normal.

## Declaration of Competing Interest

Dr. Tamargo reports no conflicts of interest.

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## References

- [1] B. Bikdeli, M.V. Madhavan, D. Jimenez, T. Chuich, I. Dreyfus, E. Driggin, et al, for the Global COVID-19 Thrombosis Collaborative Group, COVID-19 and thrombotic or thromboembolic disease implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review, *J. Am. Coll. Cardiol.* 75 (2020) 2950–2973.
- [2] J.M. Connors, J.H. Levy, COVID-19 and its implications for thrombosis and anticoagulation, *Blood* 135 (2020) 2033–2040.
- [3] N. Tang, H. Bai, X. Chen, J. Gong, D. Li, Z. Sun, Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, *J. Thromb. Haemost.* 18 (2020) 1094–1099.
- [4] D. Tremblay, M. van Gerwen, M. Alsen, S. Thibaud, A. Kessler, S. Venugopal, et al., Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study, *Blood* 136 (2020) 144–147.
- [5] I. Paranje, V. Fuster, A. Lala, A. Russak, B.S. Glicksberg, M.A. Levin, et al., Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19, *J. Am. Coll. Cardiol.* 76 (2020) 122–124.
- [6] G.N. Nadkarni, A. Lala, E. Bagiella, H.L. Chang, P.R. Moreno, E. Pujadas, et al., Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19, *J. Am. Coll. Cardiol.* 76 (2020) 1815–1826.
- [7] G. Denas, N. Gennaro, E. Ferroni, U. Fedeli, G. Lorenzoni, D. Gregori, et al., Reduction in all-cause mortality in COVID-19 patients on chronic oral anticoagulation: a population-based propensity score matched study, *Int. J. Cardiol.* (2020) (in press).
- [8] F. Sanchis-Gomar, C. Perez-Quilis, C.J. Lavie, Should atrial fibrillation be considered a cardiovascular risk factor for a worse prognosis in COVID-19 patients? *Eur. Heart J.* 41 (2020) 3092–3093.
- [9] G.Y. Lip, L. Fauchier, S.B. Freedman, I. Van Gelder, A. Natale, C. Gianni, et al., Atrial fibrillation, *Nat. Rev. Dis. Primers* 2 (2016) 16016.
- [10] T.E. Walters, J.M. Kalman, S.K. Patel, M. Mearns, E. Velkoska, L.M. Burrell, Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling, *Europace* 19 (2017) 1280–1287.