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The effect of previous oral anticoagulant use on clinical outcomes in COVID-19: A systematic review and meta-analysis

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ABSTRACT

Data on the prognosis of patients treated with oral anticoagulation (OAC) prior to hospital admission for COVID-19 remains controversial and insufficient. Therefore, we endeavored to perform a systematic review and meta-analysis to evaluate the effect of chronic use of OAC prior to the diagnosis of COVID-19 on intensive care unit (ICU) admission and mortality. An electronic search of the Pubmed, Embase, Cochrane library databases was conducted. Meta-analysis and statistical analyses were completed with using the RevMan 5.3 and Stata 12.0. A total of 13 articles representing data from 1,266,231 participants were included in this study. The meta-analysis of unadjusted results showed no decrease in mortality (OR = 1.31, 95% CI: 0.99 to 1.73, P = 0.059) or ICU admission rate (OR = 0.71, 95% CI: 0.29 to 1.77, P = 0.46) in COVID-19 patients with prior OAC therapy at hospital admission compared to patients without prior use of OAC. Moreover, the meta-analysis of adjusted results showed no decrease in mortality (OR = 1.08, 95% CI: 0.90 to 1.30, P = 0.415) or ICU admission (OR = 1.50, 95% CI: 0.72 to 3.12, P = 0.284) in patients with prior OAC use compared to patients without previous OAC use. In conclusion, the results of this study revealed that the use of OAC prior to hospital admission appeared to be ineffective in reducing the risk of intensive care need and mortality in COVID-19 patients. Randomized controlled trials are needed to evaluate and optimize the use of OAC in COVID-19 infection.

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patients on oral anticoagulation before admission for COVID-19; (4) availability of a risk ratio (RR) with 95% confidence intervals (CI) for overall survival or relevant clinical events from which it could be calculated. We excluded studies if they were abstracts, conferences, editorials, or reviews. All decisions in terms of eligibility were made according to pre-specified selection criteria. Any differing decision was resolved by a third investigator.

Two main investigators (YW and JZ) independently extracted the data and reached a consensus on all items. The following items were extracted from each study if available: name of the first author; study design, country, number of participants, age of patients, number of male and female participants, type of oral anticoagulation therapy, and outcomes of interest. The endpoint was the effect of chronic oral anticoagulation on rates of ICU admission and mortality of COVID-19.

### Table 1 - Characteristics of included studies

| Study            | Country       | Study design | Sample size | Age | Sex | Oral anticoagulation therapy used | Outcomes                                      |
|------------------|---------------|--------------|-------------|-----|-----|-----------------------------------|-----------------------------------------------|
| Arachchilage     | United Kingdom| Retrospective| 5883        | NR  | NR  | DOACs (rivaroxaban 20 mg, 15 mg or 10 mg daily, apixaban 5 mg or 2.5 mg daily or edoxaban 30 mg or 60 mg daily, dabigatran 110 mg bd or 150 mg bd) or warfarin | Mortality, thrombosis, major bleeding, multi-organ failure |
| Aslan Denas      | Turkey        | Retrospective| 1710        | (67–81)| 61  | DOAC (dabigatran, apixaban, edoxaban, dabigatran) | Mortality, need for ICU admission, hospital admission, all-cause mortality |
| Flam             | Denmark       | Retrospective| 496,277     | NR  | NR  | DOAC (dabigatran, apixaban, rivaroxaban, DOAC) | Hospital admission for COVID-19, ICU admission or death due to COVID-19 |
| Fröhlich         | Germany       | Retrospective| 6637        | NR  | NR  | VKA, DOAC                         | All-cause mortality, need for non-invasive ventilation, ECMO, ARDS |
| Fumagalli Iaccarino | Italy       | Retrospective| 806         | NR  | NR  | VKA, DOAC                         | Mortality, ICU admission, combined hard events |
| Gülcü Rieder     | Turkey Germany| Retrospective| 5575        | NR  | NR  | Warfarin, DOAC (rivaroxaban, apixaban, edoxaban, dabigatran etexilate) | Mortality, All-cause mortality, thrombotic events, intracerebral bleeding, death or thrombotic event, death or intracerebral bleeding |
| Russo Caravaca a | Italy         | Retrospective| 467         | NR  | NR  | NOACs or VKAs                    | All-cause mortality, all-cause mortality or any thromboembolic event, renal failure, respiratory insufficiency, systemic inflammatory response syndrome, heart failure, sepsis |
| Caravaca b Spain | Spain        | Retrospective| 1002        | NR  | NR  | NOACs or VKAs                    | ICU admission, ARDS, all-cause mortality, hospital length of stay, non-invasive ventilation |
| Schiavone        | Italy         | Retrospective| 844         | NR  | NR  | NOACs or VKAs                    | Mortality, thrombosis, major bleeding, multi-organ failure |

DOAC: direct-acting oral anticoagulants; NOAC: novel oral anticoagulants; VKA: vitamin K antagonists; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; VTE: venous thromboembolism; ICH: intracranial hemorrhage; TIA: transient ischemic attack; SE: systemic embolism; ICU: intensive care unit.
hospitalized patients. Most studies reported that OAC treatment was continued in patients using OAC as long as no clinical condition developed that would limit its use. However, in one study by Gülcü et al. [16], parenteral anticoagulation treatments were given at therapeutic doses to patients who had previously used DOAC. Of note, the in-hospital discontinuation of OAC was considered an exclusion criterion in the Russo et al. [19] study to avoid bias deriving from the out-of-range therapeutic periods caused by in-hospital anticoagulation treatment switching or discontinuation. The characteristics of the study are demonstrated in Table 1. The overall quality of included studies was high, with NOS scores ≥7. The quality of the included articles is assessed and displayed in Table S1. The meta-analysis of unadjusted results showed no decrease in mortality (OR = 1.31, 95% CI: 0.99 to 1.73, \(P = 0.059\); \(I^2 = 94.6\%\)) (Fig. 1A) or ICU admission rate (OR = 0.71, 95% CI: 0.29 to 1.77, \(P = 0.46\); \(I^2 = 97\%\)) (Fig. 1B) in COVID-19 patients with prior OAC therapy at hospital admission compared to patients without prior use of OAC. Moreover, the meta-analysis of adjusted results showed no lower risk of mortality (OR = 1.08, 95% CI: 0.90 to 1.30, \(P = 0.415\); \(I^2 = 75.5\%\)) (Fig. 1C) or ICU admission (OR = 1.50, 95% CI: 0.72 to 3.12, \(P = 0.284\); \(I^2 = 74.7\%\)) (Fig. 1D) in patients with prior OAC use compared to patients without previous OAC use. The subgroup analysis based on countries significantly reduced the heterogeneity but did not significantly alter the overall results. Additionally, sensitivity analyses by omitting each study at a time did not significantly change the results either.

The current systematic review and meta-analysis revealed that OAC use prior to admission was not associated with lower risks of mortality or ICU admission. This finding could be explained by the fact that patients on OAC therapy are older, more susceptible to COVID-19 complications, and have more comorbidities. In addition, comorbid diseases and advanced age are associated with morbidity and mortality in COVID-19 infection. Thus, those patients should be hospitalized and followed up more closely after the diagnosis of COVID-19 infection. Akiyama et al. indicated that microvascular thrombosis rather than classical pulmonary embolism could lead to hypoperfusion in COVID-19 infection. Thus, directly acting oral anticoagulants (DOAC) therapy has no protective effect on leukocyte-related thrombosis and prevention of severe COVID-19 infection [21,22]. In addition, recent evidence associated the use of heparin and low-molecular-weight heparin (LMWH) with various non-anticoagulant effects, including antiviral, anti-inflammatory/immunomodulatory properties [23,24]. Anti-inflammatory properties of heparin, inhibition of NF-κB transcription factor can potentially reduce the activation of inflammatory molecules and regulate the expression and production of proinflammatory cytokines, chemokines, and adhesion molecules [25]. The antiviral and anti-inflammatory/immunomodulatory effects indicated a potential role of heparin and LMWH in the treatment of COVID-19 infection [26]. Due to a certain proportion of patients who previously took OAC switching their in-hospital antithrombotic treatment to heparin following the local attending physician criteria, parenteral anticoagulant therapy may be a serious confounding factor on outcomes. Our results should be interpreted with caution. All of the studies included were retrospective in design, which could be subject to selection bias and potential confounders. Data on duration, type, the dose of OAC, and other clinical outcomes were insufficient in most incorporated studies; hence, they cannot be further analyzed. In conclusion, the results of this study revealed that the use of OAC prior to hospital admission appeared to be ineffective in reducing the risk of intensive care need and mortality in COVID-19 patients. Randomized controlled trials are needed to evaluate and optimize the use of OAC in the course of the COVID-19.

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Declaration of Competing Interest

None.

References

[1] Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.

[2] Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. Circulation. 2020;141(20):1648–55. https://doi.org/10.1161/CIRCULATIONAHA.120.046928.

[3] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18:1412–4. https://doi.org/10.1111/jth.14830.

[4] Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrari P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan. Italy Thromb Res. 2020;187:109–14. https://doi.org/10.1016/j.thromres.2020.108291.

[5] Kruse JM, Magomedov A, Kurreck A, Munch FH, Koerner R, Kamhieh-Milz J, et al. Direct-acting oral anticoagulants use prior to COVID-19 diagnosis and associations with mortality among hospitalized patients with COVID-19. Thromb Res. 2021;191:9–14. https://doi.org/10.1016/j.thromres.2021.06.014.

[6] Hunt BJ, De Paula EV, McIntlock C, Dumantepe M. Prophylactic anticoagulation for patients in hospital with COVID-19. BMJ. 2021;372:m2487. https://doi.org/10.1136/bmj.m2487.

[7] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18:1094–9. https://doi.org/10.1111/jth.14817.

[8] Arachchilage DJ, Rajakaruna I, Zain O, Thambiah CC, Nicolson PLR, Roberts LN, et al. Clinical outcomes and the impact of prior oral anticoagulant use in patients with coronavirus disease 2019 admitted to hospitals in the UK – a multicentre observational study. Br J Haematol. 2021. https://doi.org/10.1111/bjh.17787. [Online ahead of print].

[9] Aslan B, Akyüz A, İşık F, Çap M, İnci Ü, Kaya I, et al. The effect of chronic DOAC treatment on clinical outcomes of hospitalized patients with COVID-19. Int J Clin Pract. 2021;75(9):e14467. https://doi.org/10.1111/ijcp.14467. [Epub 2021 Jun 22].

[10] Caravaca JMR, Buckley BJR, Harrison SL, Eynulayeva EF, Underhill P, Marin F, et al. Direct-acting oral anticoagulants use prior to COVID-19 diagnosis and associations with 30-day clinical outcomes. Thromb Res. 2021;205:1–7. https://doi.org/10.1016/j.thromres.2021.06.014.

[11] Caravaca JMR, Gil IJN, Vivas D, Llamas MCV, Urbiarri A, Muñoz VMB, et al. Clinical profile and prognosis in patients on oral anticoagulation before admission for COVID-19. Eur J Clin Invest. 2021;51(1):e13436. https://doi.org/10.1111/eci.13436.

[12] Denis G, Gennaro N, Ferroni E, Fedeli U, Lorenzoni G, Gregori D, 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. 2021;315(2):266–9. https://doi.org/10.1016/j.jcin.2020.12.024.

[13] Flm B, Wintzell V, Ludvigsön JF, Martensson J, Pasternak B. Direct oral anticoagulant use and risk of severe COVID-19. J Intern Med. 2021;289(3):411–9. https://doi.org/10.1111/j.1323-8286.2021.02658.x.

[14] Fröhlich GM, Jeschke E, Eichler U, Thiele H, Alharrari I, Reinthaler M, et al. Impact of oral anticoagulation on clinical outcomes of COVID-19: a nationwide cohort study of hospitalized patients in Germany. Clin Res Cardiol. 2021;110(7):1041–50. https://doi.org/10.1007/s00392-020-02178-3.

[15] Fumagalli S, Trevisan C, Signore SD, Pelagalli G, Volpato S, Garei P, et al. COVID-19 and atrial fibrillation in older patients: does Oral anticoagulant therapy provide a survival benefit?—an insight from the GeroCovid registry. Thromb Haemost. 2021. https://doi.org/10.1055/a-1503-3875. Online ahead of print.

[16] Gülcü O, Aksakal E, Aydenir S, Doğan R, Sarac I, Aydin SS, et al. Association between previous anticoagulant use and mortality among hospitalized patients with COVID-19. J Thromb Thrombolysis. 2021;1–8. https://doi.org/10.1007/s11239-021-02489-1. [Online ahead of print.]

[17] Iaccarino G, Grassi G, Borghi C, Grassi D, Mancusi C, Muiesan ML, et al. Preexisting oral anticoagulant therapy ameliorates prognosis in hospitalized COVID-19 patients. Front Cardiovasc Med. 2021;8:633878. https://doi.org/10.3389/fcvm.2021.633878. [eCollection 2021].

[18] Rieder M, Gauchel N, Kaier K, Jakob C, Borgmann S, Claessen AY, et al. Pre-medication with oral anticoagulants is associated with better outcomes in a large multinational COVID-19 cohort with cardiovascular comorbidities. Clin Res Cardiol. 2021:1–11. https://doi.org/10.1007/s00392-021-01939-3. [Online ahead of print.]

[19] Russo V, Bottino R, D'Andrea A, Silverio A, Maio MD, Golino P, et al. Cardiovascular drugs Therapy. Chronic oral anticoagulation and clinical outcome in hospitalized COVID-19 patients; 2021; 1–8. https://doi.org/10.1055/s-00392-021-07194-y [Online ahead of print].

[20] Schiavone M, Gasperetti A, Mancone M, Curnis A, Mascioli G, Mitacchione G, et al. Oral anticoagulation and clinical outcomes in COVID-19: an Italian multicenter experience. Int J Cardiol. 2021;325:276–80. https://doi.org/10.1016/j.ijcard.2020.05.054.

[21] Akıyama S, Hamdeh S, Micic D, Sakuraba A. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. Correspondence Ann Rheum Dis. 2020. https://doi.org/10.1136/annrheumdis-2020-218946. annrheumdis-2020-218946. [Online ahead of print].

[22] Grenese E, Ferrarioli G. The pathogenesis of microthrombi in COVID-19 can not be controlled by DOAC: NETosis should be the target. J Intern Med. 2021;289(3):420–1. https://doi.org/10.1111/jim.13378.

[23] Litov L, Petkov P, Rangelov M, Ilieva N, Lilkova E, Todorova N, et al. Molecular mechanism of the anti-inflammatory action of heparin. Int J Mol Sci. 2021;22:10730. https://doi.org/10.3390/ijms221910730.

[24] Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Antiinflammatory effects of heparin and its derivatives: a systematic review. Adv Pharmacol Sci. 2015.; https://doi.org/10.1155/2015/906586.

[25] Litov L, Petkov P, Rangelov M, Ilieva N, Lilkova E, Todorova N, et al. Molecular mechanism of the anti-inflammatory action of heparin. Int J Mol Sci. 2021;22:10730. https://doi.org/10.3390/ijms221910730.

[26] Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Antiinflammatory effects of heparin and its derivatives: a systematic review. Adv Pharmacol Sci. 2015.;507151.

[27] Antonio V, Francesco F. Low molecular weight heparin, anti-inflammatory/ immunoregulatory and antiviral effects, a short update. Cardiovasc Drugs Ther. 2021;1–5. https://doi.org/10.1007/s10557-021-07251-6. [Online ahead of print].

[28] Huppensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. Am J Physiol Lung Cell Mol Physiol. 2020;319:L211–7.