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Original Article

The effect of oral anticoagulant use before visit for patients with COVID-19 on mortality: A meta-analysis

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Abstract

Objectives: Anticoagulants have been used as therapeutic or prophylactic agents in COVID-19 and seem to be more beneficial. However, the advantage of oral anticoagulant (OAC) consumption before visit in lowering mortality in COVID-19 patients remains debatable. This meta-analysis aimed to evaluate the effect of OAC use before visit on mortality using the hazard ratio (HR) to estimate the effect of time-to-event endpoints. **Materials and Methods:** We conducted a literature search in the PubMed and ProQuest databases for any studies comparing groups consuming OAC to no-OAC before visit for mortality in patients with COVID-19. We calculated the overall HRs and their variances across the studies using the random-effects model to obtain pooled estimates. **Results:** We included 12 studies which had sample sizes ranging from 70 to 459,402 patients. A meta-analysis comparing OAC therapy and non-OAC consumption in COVID-19 patients before visit revealed no decrease in all-cause mortality (HR = 0.92, 95% confidence interval [CI]: 0.83–1.02, P = 0.12; I^2 = 68%). However, subgroup analysis of laboratory-confirmed populations revealed that OAC use before visit had a beneficial effect on mortality (HR = 0.84, 95% CI: 0.73–0.98, P = 0.02; I^2 = 56%). **Conclusion:** The use of OAC before visit had no beneficial effect on all-cause mortality in COVID-19 patients.

Keywords: *Anticoagulation, COVID-19, Direct oral anticoagulant, Mortality, Oral anticoagulant*

Introduction

COVID-19 has contributed a substantial quantity of mortality. Patients with COVID-19 might also fall into a hypercoagulable state, resulting in an increased rate of thrombotic and thromboembolic events [1]. Anticoagulants have been used as therapeutic or prophylactic agents in COVID-19 and seem to be more beneficial [2]. However, the advantage of oral anticoagulant (OAC) consumption in COVID-19 patients before visit remains debatable in lowering mortality.

There has been already a meta-analysis from China comparing the effect of chronic OAC consumption on mortality in COVID-19 using the odds ratio (OR) [3]. In this meta-analysis, we aimed to evaluate the effect of OAC use before visit on all-cause mortality using the hazard ratio (HR) to estimate the effect of time-to-event endpoints. HR displayed useful statistics about how the rate of mortality is modified by OAC consumption before visit compared with the control group.

Materials and methods

We selected studies involving COVID-19 patients who were on OAC before their visit. The included studies measured the mortality rate as an outcome. Any trials not comparing the OAC to non-OAC groups, not expressing the mortality rate difference as HR, or having incomplete data should be excluded.

We conducted a literature search on PubMed and ProQuest databases on March 1, 2022. We performed the following search strategy: ("coronavirus" OR "sars-cov2" OR "covid") AND ("oral anticoagulation" OR "oral anticoagulant") in abstract/title AND "mortality" in text. Additional records were identified from the references of the included articles. The titles and abstracts of every record from the retrieved studies obtained by applying the above search strategies were checked independently by two reviewers against the inclusion criteria.

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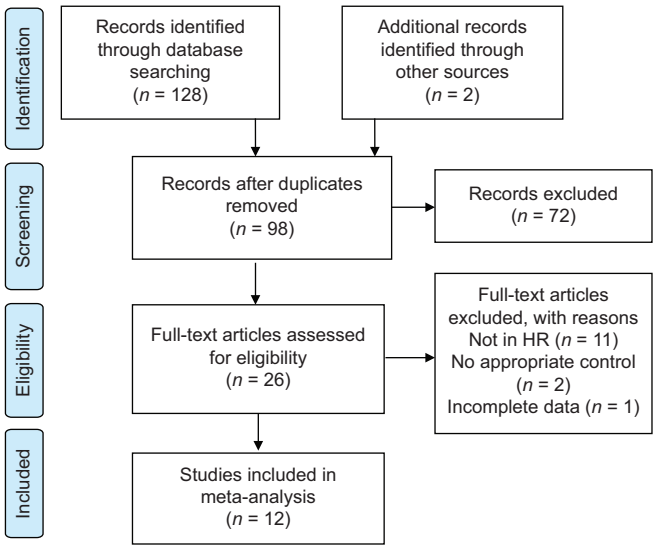

Figure 1: PRISMA flow diagram of this study

Subsequently, the full papers that potentially met the inclusion/exclusion criteria were reviewed by two investigators for final inclusion. The first author was the referee if there was any disputed study.

Pooled results on all-cause mortality were expressed as HRs with 95% confidence intervals (CI) by calculating the overall HRs and their variance across the studies. We only pooled HR data in the propensity score matching (PSM) study or adjusted multivariate-HR in the study without PSM. We estimated the observed and expected events (O-E events) and the variance of the natural logarithm of the HR and CI using the formula provided by Tierney *et al*. [4].

Two authors independently assessed the methodological quality assessment using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies National Institute of Health. Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI) (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). The statistical package Review Manager 5.3 (RevMan 5.3) provided by the Cochrane Collaboration was used to analyze the data. A fixed-effects model and Peto OR were used for the analysis. We evaluated between-study heterogeneity using the I^2 statistic. A sensitivity analysis was performed using the leave-one-out method. We performed a subgroup analysis based on admission status.

Results

After searching the literature, we found 85 articles in PubMed and 43 in the ProQuest database [Figure 1]. Two studies were retrieved from the references of the included articles. Then, we retrieved 26 full-text articles and excluded 14. The reasons for exclusion were that the result was not expressed in HR, the data were incomplete, and there was no appropriate control. Finally, 12 studies were included [5-16].

The baseline characteristics are shown in Table 1. The sample sizes of the included studies ranged from 70 to 459,402. The region came mostly from Europe, with one study from Asia and one from the United States. Most of the included studies had a retrospective design. Hospitalized and laboratory-confirmed patients were the predominant population, with five studies each, and the remaining were emergency visit patients. All studies involved direct OAC, including rivaroxaban, apixaban, edoxaban, and dabigatran. Enoxaparin was used in only one study [12]. Only two studies did not consider warfarin [10,14].

We assessed all studies' quality based on NHLBI quality assessment resulting in good and fair methodology qualities in all included studies [Table 1]. None of the studies was seriously flawed. The analyses were rigorous, and the conclusions drawn by the studies were credible. All studies assessed exposure before outcome measurement. However, all studies did not provide a sample size justification, power description, or variance and effect estimates.

The meta-analysis comparing OAC therapy and non-OAC consumption in COVID-19 patients before visit revealed no decrease in all-cause mortality (HR = 0.92, 95% CI: 0.83–1.02, P = 0.12; I^2 = 68%) [Figure 2a]. A similar result was shown if we only pooled data from PSM studies (HR = 0.97, 95% CI: 0.85–1.11, P = 0.69; I^2 = 71%) [Figure 2b]. Analysis of the study using adjusted multivariate HR also showed similar results (HR = 0.95, 95% CI: 0.87–1.04, P = 0.29; I^2 = 71%) [Figure 2c].

Sensitivity analysis showed the same result without improvement in heterogeneity (HR = 0.95, 95% CI: 0.85–1.05, P = 0.30; I^2 = 61%). Analysis of the hospital admission and emergency department visit subgroup reported similar results to the total group [Figure 3]. However, subgroup analysis of laboratory-confirmed populations revealed that OAC use before visit had a beneficial effect on mortality (HR = 0.84, 95% CI: 0.73–0.98, P = 0.02; I^2 = 56%).

Discussion

The main finding of this meta-analysis was that consumption of OAC before visit had no benefit in reducing all-cause mortality in patients with COVID-19. This was similar to the findings of a previous meta-analysis that used pooled data of OR [3]. Analysis using HR in this meta-analysis provided how OAC use before admission changes the mortality rates and not just determines if there is an association between OAC use before admission and mortality. This showed that the risk of an individual in the OAC group was similar to that of an individual in the non-OAC group at any given time interval.

It was suspected that patients taking OAC before visit had a higher risk of mortality due to comorbidities and advancing age. However, this meta-analysis suggested that there was no difference in mortality between patients on OACs versus those without OACs before visit when compared in an adjusted multivariate analysis or in a PSM analysis. This analysis was corrected for confounding effects, such as underlying comorbidities and advancing age. However, it was not possible to perform complete matching for all conditions, such as atrial fibrillation with or without stroke, history of venous thromboembolism, and mechanical heart valves.

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Table 1: Baseline characteristic of the included studies

First author	Country	Registry	Year	Study design	Population	Sample size	Sex (%)	Age (years)	OAC agent	Outcome	Study quality
Arachchillage	UK	UK NHS trusts	2020	Retrospective and prospective	Hospital admission	5883	Male 55.2	74 (56-84)	DOAC, VKA	No difference in mortality [aHR: 1.05 (95% CI 0.93-1.19); *P*=0.15]	Good
Buenen	Netherlands	Bernhoven Hospital, Uden	2020	Prospective	Emergency department visit	497	Male 64	72	DOAC, VKA	Reduction in risk for mortality [aHR: 0.64 (95% CI 0.42-0.96); *P*=0.03]	Fair
Chocron	French	Critical COVID-19, France	2020	Retrospective	Hospital admission	2878	Male 57.9	66.63±16.96	DOAC, VKA	Reduction in risk for mortality [aHR: 0.70 (95% CI 0.55-0.88); *P*=0.003]	Good
Covino	Italy	An urban teaching hospital	2020	Prospective	Emergency department visit	2666	Male 50	84 (81-87)	DOAC, VKA	Increased risk of mortality [aHR: 1.56 (95% CI: 0.78-3.12); *P*=0.208]	Good
Denas	Italy	Veneto Region	2020	Retrospective	Laboratory confirmed	4697	Male 50.1	≥65	DOAC, VKA	Reduction in risk for mortality [PSM-HR: 0.81 (95% CI: 0.65-1.01); *P*=0.054]	Fair
Flam	Sweden	Nationwide Swedish Register	2020	Retrospective	Laboratory confirmed	459,402	Male 65.6	73.6±7.6	DOAC	No difference in mortality [aHR: 0.91 (95% CI: 0.70-1.18)]	Good
Gulcu	Turkey	No information	2020	Retrospective	Hospital admission	5575	Male 50.2	64 (51-74)	DOAC, VKA	Reduction in risk for mortality [aHR: 0.62 (95% CI: 0.42–0.92), *P*=0.03]	Fair
Hozayen	USA	M Health Fairview system	2020	Prospective	Laboratory confirmed	6195	Male 43	50.68±22.15	DOAC, VKA, enoxaparin	No difference in mortality [aHR: 0.88 (95% CI 0.50–1.52); *P*=0.64]	Good
Rivera-caravaca	Ecuador, Germany, Italy, Spain	HOPE Registry	2020	Retrospective	Hospital admission	1002	Male 60.9	81.5 (75-87)	DOAC, VKA	Increased risk of mortality [PSM-HR: 1.53 (95% CI: 1.08-2.16)]	Good
Rossi	Italy	Policlinico of Modena Hospital	2020	Retrospective	Laboratory confirmed	70	Male 50	79 (70-92)	DOAC	Reduction in risk for mortality [aHR: 0.38 (95% CI: 0.17-0.58)]	Fair
Russo	Italy	Six Italian Hospitals	2020	Retrospective	Hospital admission	427	Male 63	67±14	DOAC, VKA	No difference in mortality [aHR: 1.07 (95% CI: 0.66-1.73)]	Fair
Tremblay	USA	New York City health system	2020	Retrospective	Laboratory confirmed	3772	Male 54.8	56.6±18.2	DOAC, VKA	No difference in mortality [PSM-HR: 1.21 (95% CI: 0.75-1.95); *P*=0.37]	Fair

OAC: Oral anticoagulant, DOAC: Direct OAC, VKA: Vitamin K antagonists, aHR: Adjusted hazard ratio, CI: Confidence interval, IQR: Interquartile range, PSM: Propensity score matching

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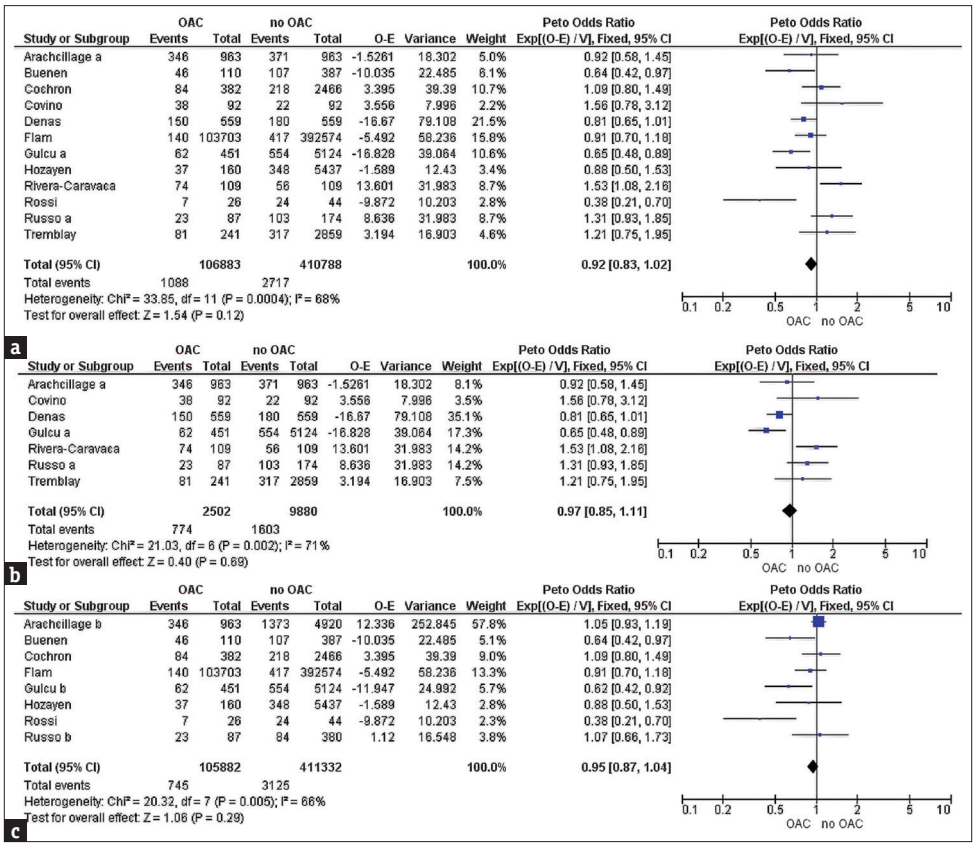

Figure 2: Forest plot in all included studies (a). Forest plot in PSM studies (b). Forest plot in adjusted multivariate studies (c)

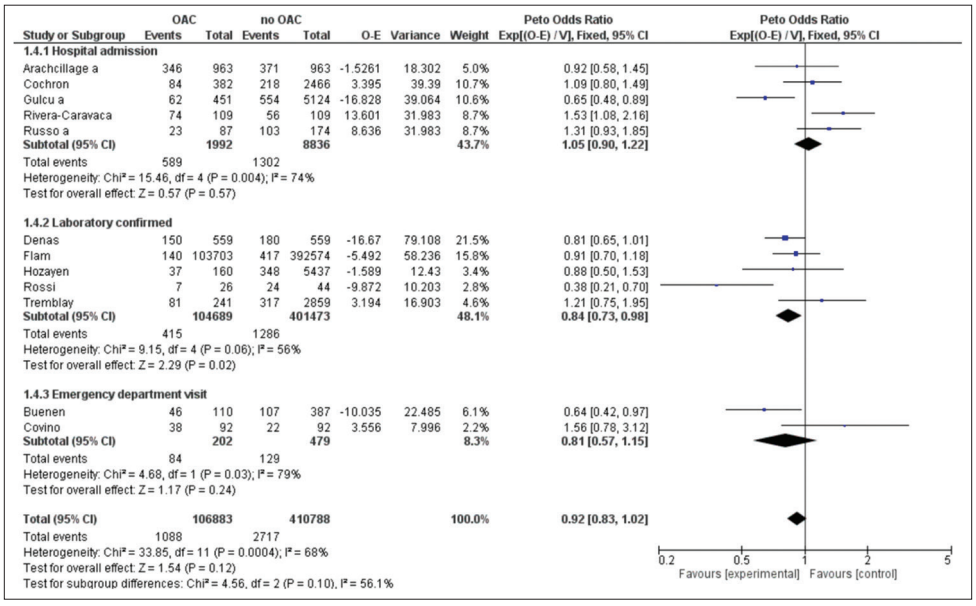

Figure 3: Forest plot in subgroup analysis based on admission status

Thrombosis characterized by increased D-dimer levels in patients with COVID-19 were associated with increased risk of mortality [17,18]. It has been postulated that systemic inflammation and activation of the complement system contribute to the hypercoagulable condition and dysfunction of the endothelium, leading to microvascular thrombosis and consequent increased risk of mortality in COVID-19 [19,20]. Because it has no anti-inflammatory properties, OAC has no effect on the mortality of patients with COVID-19. It differs from heparin in that it can potentially reduce the activation of inflammatory responses [21].

Different results were observed in the subgroup analysis of the laboratory-confirmed patient population. This population

comprised most outpatients. This finding suggests that patients not requiring admission for COVID-19 might benefit from chronic OAC consumption before contracting COVID-19. One report demonstrated that anticoagulation in the early phase of COVID-19 may be beneficial in selected patients [22].

This study has a few limitations. First, heterogeneity was significantly high. We included not only various populations from outpatients to inpatients but also various comorbidities. Most of the included studies were also prospective studies; therefore, they lacked control on cofactors that may affect the outcome. Second, the included studies did not control for the duration of OAC before admission, duration, or the dose regimen of anticoagulation during admission, which could have been a confounding bias. Later, there were probably more studies that not included in our meta-analysis as we have only used two databases.

Conclusion

This meta-analysis revealed that OAC use before visit had no beneficial effect on the all-cause mortality of COVID-19 patients. This analysis corrected for confounding effects such as underlying comorbidities and advancing age because it pooled data only from PSM or adjusted multivariate studies. Patients at risk of thrombovenous events should continue anticoagulation because outpatients may benefit from chronic anticoagulation if they contract COVID-19.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Conflicts of interest

There are no conflicts of interest.

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