



# Knowledge Gaps for Prophylactic Use of Antithrombotic Agents in Patients with COVID-19: Insights into New SARS-CoV-2 Variants, Vaccination Status, and Emerging Oral Antivirals

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## Abstract

Data suggest that coronavirus disease 2019 (COVID-19) results in a prothrombotic state leading to arterial and venous thromboses. Vaccination, novel antiviral drugs, and emerging variants have changed the course of the disease in many ways; however, their effects on the incidence of thrombotic events and the efficacy of preventative antithrombotic agents have not been yet evaluated. A systematic search was conducted to identify studies reported on the incidence of thrombotic events based on vaccination status, use of novel antiviral drugs, and emerging viral variants. Similarly, we screened the ongoing/published randomized trials of preventative antithrombotic therapy in any COVID-19 population to assess whether subgroup-specific results were reported based on any of these variants. Upon searching a total of 3,451 records, only one entry fulfilled the inclusion criteria of our systematic review, which was a self-controlled case series on 29,121,633 vaccinated individuals, the incidence rate ratio of thrombotic complication after breakthrough infection was 13.86 (95% confidence interval [CI]: 12.76–15.05)

## Keywords

- ▶ thromboembolism
- ▶ anticoagulation
- ▶ SARS-CoV-2
- ▶ vaccination
- ▶ COVID-19

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compared with 1.10 (95% CI: 1.02–1.18) during the 28-day postvaccination. In conclusion, although the mortality benefit of mass vaccination and the early promising results of the new antiviral therapies are well known, we were unable to find clinical evidence on whether vaccination, the use of novel antiviral agents, and emerging viral variants have affected the incidence rate of thrombotic events or impacted the efficacy of prophylactic antithrombotic therapy in patients with COVID-19. Analyses from existing trials and large-scale registries can provide interim knowledge and any findings of relevance should be incorporated in the design of future trials.

## Introduction

The hypercoagulable state and the inflammatory response are considered among the main etiologies of the severe acute lung injury, multiorgan failure, and fatality of coronavirus disease 2019 (COVID-19).<sup>1,2</sup> The higher intensity of this thromboinflammation compared with other forms of sepsis<sup>3,4</sup> persuaded several investigators to suggest a high-intensity prophylactic antithrombotic regimen.<sup>5–7</sup> However, mixed results have been reported by randomized clinical trials testing different prophylactic antithrombotic regimens,<sup>7–9</sup> and intensification of anticoagulation has appeared beneficial only in noncritically ill hospitalized patients who received heparin-based regimens<sup>10–12</sup>; other confirmatory trials are underway.

Uncertainties exist about whether the extent of the evidence generated early during the pandemic can be extrapolated to the current understanding of epidemiology of the disease or practice of preventive antithrombotic therapy. There are three important interval changes: mass vaccination in many countries, use of emerging antiviral agents, and the emergence of new viral variants which may have a different risk for disease severity, including potential impact on the development of thrombotic events. Reductions in disease severity and mortality rates were reported among individuals who ultimately contract the disease postvaccination, compared with the unvaccinated patients.<sup>13,14</sup> However, it remains unknown whether vaccination impacts the rates of micro- and macro-thrombosis as the consequence of COVID-19, or whether it impacts the efficacy or safety of antithrombotic therapies. Nirmatrelvir/ritonavir and molnupiravir are two antiviral regimens which decreased hospitalization and mortality when given orally over 5 days in symptomatic SARS-CoV-2-infected outpatients.<sup>15,16</sup> However, their beneficial effect on thrombotic risk remains to be elucidated. Similarly, the thrombogenicity of new COVID-19 variants has been poorly investigated. The Delta (B.1.617.2) variant creates a more aggressive immune invasion and potentially more intense thromboinflammatory response compared with other variants.<sup>17</sup> On the contrary, the Omicron (B.1.1.529) variant, despite increased transmissibility, caused a decreased severity of the disease among infected population.<sup>18</sup> Whether these factors may affect thrombotic events warrants further investigation.

In this review, we aimed to elaborate the possible knowledge gaps and assess the impact of evolving changes in

patients with COVID-19 (the impact of vaccination, new SARS-CoV-2 variants, and novel antivirals) on the incidence of thrombotic complications and the effect of prophylactic antithrombotic regimen.

## Methods

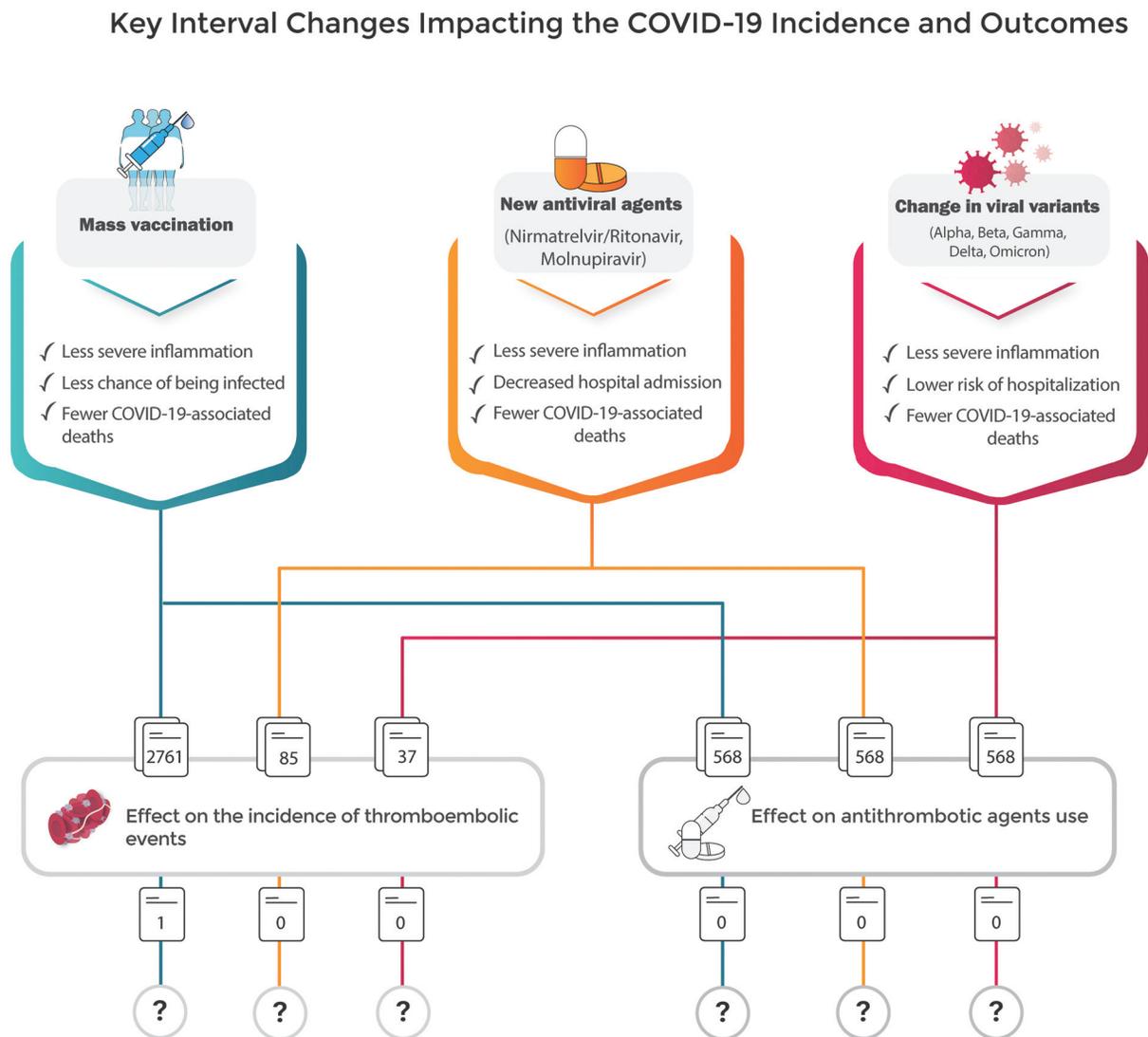
We searched for evidence on whether the incidence of thrombotic events associated with SARS-CoV-2 infection could be influenced by the three variables of vaccination, emerging variants, and the newly approved antivirals (last updated February 2022). MEDLINE was searched for national/multinational registries for the mentioned objective. Additionally, we conducted a systematic search through clinicaltrials.gov and MEDLINE to identify the ongoing or terminated/published COVID-19-related randomized controlled trials (RCTs) with at least one arm of anticoagulation, antiplatelet, or thrombolytic regimen, in which the interactions of vaccination status, emerging variants, or newly approved antiviral agents were evaluated with the investigated antithrombotic regimen.

The results were then independently screened by two reviewers (K.M. and N.K.R.) to tease out studies where vaccinated population, patients contaminated/afflicted with new SARS-CoV-2 variants, or those treated with newly approved antiviral agents were analyzed or reported as a separate subgroup.

The search syntaxes, PRISMA flowcharts, and checklists of our systematic searches are available in **►Supplementary Figs. S1 and S2** (available in the online version)..

## Results

The preliminary result of our systematic search returned 2,761, 85, and 37 entries on potential impact of vaccination, emerging variants, and newly approved antivirals on the incidence of thrombotic events associated with COVID-19, respectively, of which only one entry fulfilled the inclusion criteria.<sup>19</sup> Also, for evaluating the interaction between antithrombotic regimen and any of our three variables (SARS-CoV-2 variants, vaccination status, or newly approved antivirals), in terminated or ongoing RCTs, 568 records were initially screened in which we found no entries that could satisfy the inclusion criteria of our research question regarding the interaction of these variables, and the antithrombotic regimen used in treatment of COVID-19 (**►Fig. 1**).



**Fig. 1** Possible mechanism of three variables of vaccination, novel antivirals and new variants, and risk of thrombosis associated with COVID-19. Mass vaccination, new antiviral agents, and changes in viral variants may affect the risk of COVID-19-associated thromboembolic events or antithrombotic agents used. Ritonavir-boosted medications can interact with direct-acting oral anticoagulants (DOACs)—potentially relevant to consider when DOACs are used. Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gama (P.1), and Omicron (B.1.1.529) variants are different in terms of severity, risk of hospitalization, or mortality.

The only relevant entry is a self-controlled case series conducted in the United Kingdom using national data of 29,121,633 vaccinated individuals, that was aimed to compare the increased incidence rate of thrombotic events after three different exposures of ChAdOx1nCoV-19 or the BNT162b2 mRNA vaccines and a positive SARS-CoV-2 test result between the baseline unexposed (i.e., at least 28 days before the exposure) and exposed (i.e., 28 day after vaccination or SARS-CoV-2 infection) periods. Incidence rates of thrombotic events were increased by both exposures (vaccination and breakthrough infection). However, the 28-day incidence of thrombotic events after a positive SARS-CoV-2 test (i.e., breakthrough infection) was higher compared with those after vaccination (incidence rate ratio of 1.10, 95% CI: 1.02–1.18 in 8–14 days after the ChAdOx1 nCoV-19 vaccine vs. 13.78, 95% CI: 12.66–14.99 in 8–14 days after a positive SARS-CoV-2 test).<sup>19</sup>

## Discussion

### Vaccines and Prophylactic Antithrombotic Regimens in COVID-19

Vaccinated patients have not been enrolled in the vast majority of completed and published randomized trials of preventative antithrombotic therapy in COVID-19. Only one vaccinated patient existed among 657 patients recruited in Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE (ACTIV-4B) trial, which tested low-intensity and full-intensity doses of apixaban, aspirin 81 mg/daily, or placebo in patients with COVID-19 managed as an outpatient setting.<sup>20</sup> Our systematic search showed that vaccinated populations are not at least defined as a prespecified subgroup in newly designed trials.

Vaccines prevent initial virus proliferation in case of exposure or if the initial step is failed and restrict the ongoing proliferation, thereby resulting in decreased viral load and

consequently less severe form of the diseases.<sup>21–23</sup> It can be hypothesized that the less-severe form of the disease might have a different risk of thromboinflammation, and thereby a distinct risk/benefit profile for prophylactic antithrombotic therapy (►Fig. 1). Such a hypothesis has not been, to our knowledge, tested yet.

### Thrombotic Risk of Vaccines

Vaccination itself can be associated with uncommon but potentially serious thromboembolic events. Vaccine-induced immune thrombotic thrombocytopenia is a rare but rapidly devastating complication with an incidence rate of 1 per 100,000 to 250,000 of vaccinated population,<sup>24</sup> mostly observed with ChadOx1 nCoV-19/AZD1222 and Ad26.COV2. S vaccines and most patients were diagnosed between day 5 to 30 postvaccination.<sup>25</sup> In a retrospective cohort study (recently published—after submission of this manuscript), the adjusted risk of acute myocardial infarction (AMI) and ischemic stroke that occurred 31 to 120 days after COVID-19 diagnosis was significantly lower in fully vaccinated patients compared with unvaccinated patients for both AMI (adjusted hazard ratio [aHR]: 0.48; 95% confidence interval [CI]: 0.25–0.94) and ischemic stroke (aHR: 0.40; 95% CI: 0.26–0.63).<sup>26</sup> Another retrospective review (recently published) described an approximately 30% lower incidence of objectively confirmed pulmonary embolism in Delta and Omicron variant-infected symptomatic patients compared with the ancestral SARS-CoV-2 strain. COVID-19-associated pulmonary embolism was reported to be 2.75-fold higher in unvaccinated patients during the Delta and Omicron periods ( $p = 0.02$ ) compared with vaccinated or recovered patients.<sup>27</sup>

### New SARS-COV-2 Variants

SARS-CoV-2 variants including the B.1.351 (Beta), P.1 (Gamma, formerly named B.1.1.28.1), B.1.617.2 (Delta), and B.1.1.529 (Omicron) are distinctive based on their transmissibility and disease severity.<sup>28</sup> Severity of the disease may be translated to more complications, including thrombotic events, which has not been evaluated in previous studies.

### Novel Antiviral Agents

Protease inhibitor use could be a risk factor for venous thrombosis, presumably in association with abnormalities in platelets or endothelial function.<sup>29–31</sup> Compared with placebo, nirmatrelvir/ritonavir reduces hospital admissions and mortality of COVID-19 patients who are at high risk of severe illness.<sup>32</sup> Molnupiravir is a novel nucleoside analog antiviral agent with potent activity against SARS-CoV-2. In a phase 3, double-blind, randomized, placebo-controlled study, efficacy and safety of treatment with molnupiravir started within 5 days after the onset of signs or symptoms in nonhospitalized, unvaccinated adults with mild-to-moderate, laboratory-confirmed COVID-19 and at least one risk factor for severe COVID-19 illness was compared with placebo. Risk of hospitalization for any cause or death through day 29 was lower with molnupiravir than with placebo (7.3 vs. 14.1%; difference: –6.8 percentage points; 95% CI: –11.3 to –2.4;  $p = 0.001$ ).<sup>33</sup> Possibility of thromboembolism fol-

lowing mild infection in these patients is not investigated, as it is not still clear if these drugs can mitigate the hypercoagulability state (►Fig. 1).

## Perspectives of the Review

Thrombotic complications were reported as one of the main features of COVID-19,<sup>34</sup> necessitating the application of a high-intensity prophylactic strategy in specific clinical scenarios.<sup>9</sup> Numerous guidelines existed on the use of antithrombotic agents in patient with COVID-19.<sup>35–40</sup> With the mass vaccination and its success on the global disease burden along with the improved availability of emerging therapeutic strategies with promising short-term results/benefits,<sup>41–44</sup> it can be anticipated that the incidence of thromboembolism will be reduced,<sup>27</sup> which is the main complication of COVID-19 even in long term.<sup>45</sup> However, the reported impact of these factors has thus far limited to hospitalization and mortality, whereas their effect on thrombotic complication remains uncertain. Future well-designed studies are needed to better elucidate the effect of mass vaccination, novel antiviral agent, and emergent virus variants on the incidence rate of thrombotic events and the use of antithrombotic agents to further reduce this complication.

### Disclosures

Dr. B.B. reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters.

Dr G.Y.H.L.: consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally.

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