Accepted Manuscript online: 2022-10-07 Article published online: 2022-12-30

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

Azita H. Talasaz[1,2] Parham Sadeghipour[3,4] Kasra Mehdizadeh[3] Niloofar Khoshnam Rad[1] Behnood Bikdeli[5,6,7,8] Gregory Y. H. Lip[9,10] Job Harenberg[11,12]

[1] Department of Clinical Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Pharmacotherapy and Outcome Sciences, Virginia Commonwealth University, Richmond, Virginia, United States
[3] Cardiovascular Intervention Research Center, Rajaie Cardiovascular, Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
[4] Clinical Trial Center, Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, Iran
[5] Cardiovascular Medicine Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States
[6] Thrombosis Research Group, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States
[7] Yale/YNHH Center for Outcomes Research and Evaluation (CORE), New Haven, Connecticut, United States
[8] Cardiovascular Research Foundation (CRF), New York, New York, United States
[9] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom
[10] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[11] Ruprecht Karls University, Heidelberg, Germany
[12] Ruperto Carola University of Heidelberg, Heidelberg, Germany

Address for correspondence Azita H. Talasaz, PharmD, BCPS, BCCP, Department of Clinical Pharmacy, Tehran University of Medical Sciences, 16 Azar St., Tehran, Iran (e-mail: a-talasaz@tums.ac.ir).

Job Harenberg, MD, Department of Medicine, DOASENSE GmbH, Waldhofer Strasse 102, 69123 Heidelberg, Germany (e-mail: j.harenberg@doasense.de).

Thromb Haemost 2023;123:186–191.

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

Note: The review process for this paper was fully handled by Christian Weber, Editor-in-Chief.

received
June 7, 2022
accepted after revision
August 20, 2022
accepted manuscript online
October 7, 2022
article published online
December 30, 2022

DOI https://doi.org/10.1055/a-1956-9641.
ISSN 0340-6245.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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).[1,2] The higher intensity of this thromboinflammation compared with other forms of sepsis[3,4] persuaded several investigators to suggest a high-intensity prophylactic antithrombotic regimen.[5–7] However, mixed results have been reported by randomized clinical trials testing different prophylactic antithrombotic regimens,[7–9] and intensification of anticoagulation has appeared beneficial only in noncritically ill hospitalized patients who received heparin-based regimens[10–12]; 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.[13,14] 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.[15,16] 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.[17] On the contrary, the Omicron (B.1.1.529) variant, despite increased transmissibility, caused a decreased severity of the disease among infected population.[18] 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.[19] 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**).

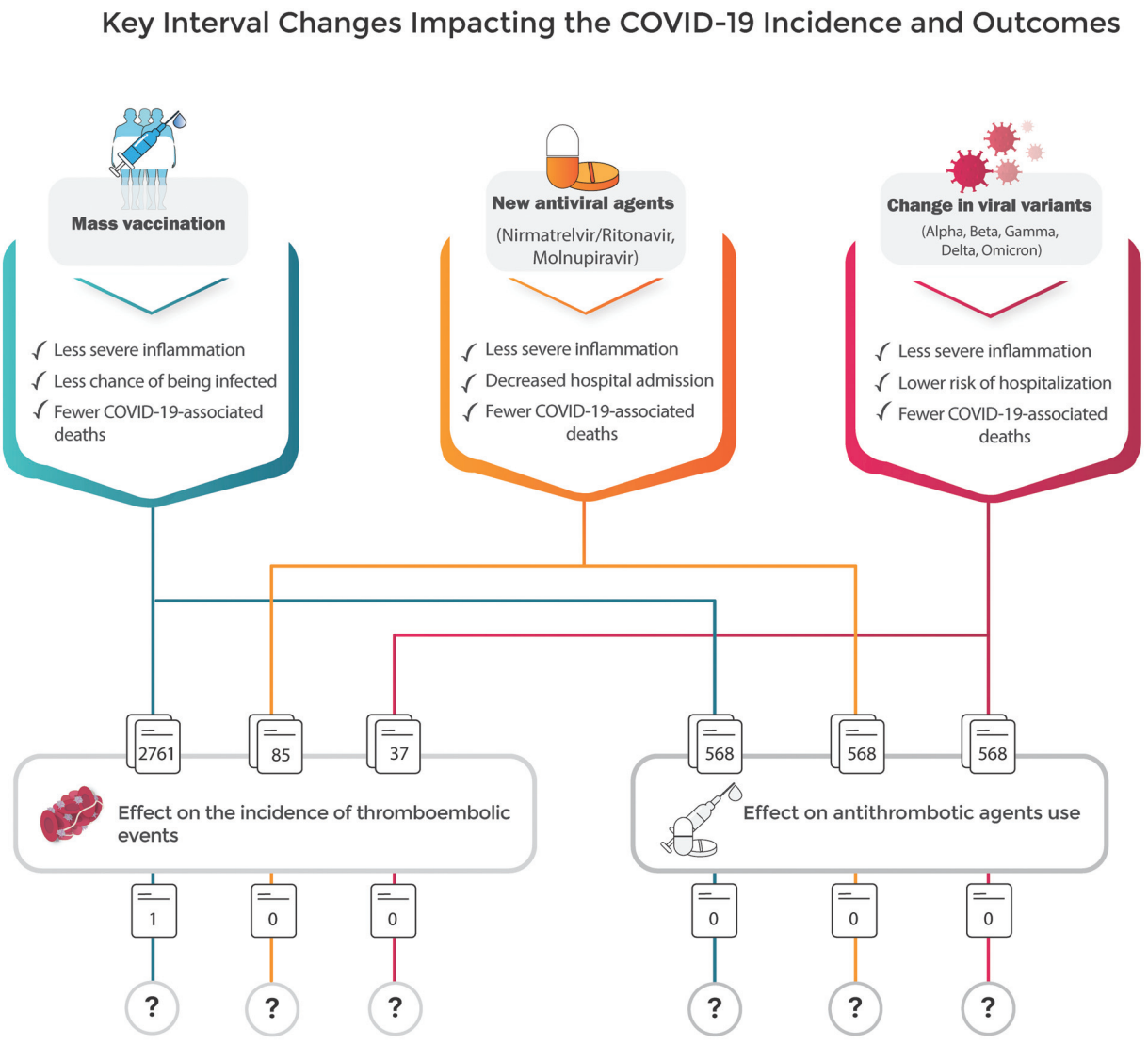

Fig. 1 Possible mechanism of three variables of vaccination, novel antivirals and new variants, and risk of thrombosis associated with COVID-19. Mass vaccination, new antiviral agents, and changes in viral variants may affect the risk of COVID-19-associated thromboembolic events or antithrombotic agents 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).[19]

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.[20] 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.[21–23] 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,[24] mostly observed with ChadOx1 nCoV-19/AZD1222 and Ad26.COV2.S vaccines and most patients were diagnosed between day 5 to 30 postvaccination.[25] 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).[26] 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.[27]

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.[28] 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.[29–31] Compared with placebo, nirmatrelvir/ritonavir reduces hospital admissions and mortality of COVID-19 patients who are at high risk of severe illness.[32] 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; $p = 0.001$).[33] Possibility of thromboembolism following 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,[34] necessitating the application of a high-intensity prophylactic strategy in specific clinical scenarios.[9] Numerous guidelines existed on the use of antithrombotic agents in patient with COVID-19.[35–40] 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,[41–44] it can be anticipated that the incidence of thromboembolism will be reduced,[27] which is the main complication of COVID-19 even in long term.[45] 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.

Dr J.H.: founder and managing director of DOASENSE GmbH.

All other authors report no relevant disclosures.

Funding

Dr. B.B. is supported by the Scott Schoen and Nancy Adams IGNITE Award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital and a Career Development Award from the American Heart Association and VIVA Physicians (#938814).

References

1 Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135(23):2033–2040
2 Barale C, Melchionda E, Morotti A, Russo I. Prothrombotic phenotype in COVID-19: focus on platelets. Int J Mol Sci 2021;22(24):13638
3 Helms J, Tacquard C, Severac F, et al; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis) High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46(06):1089–1098
4 McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol 2020;2(07):e437–e445

5 Lu YF, Pan LY, Zhang W-W, et al. A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. Int J Infect Dis 2020;100:34–41
6 Talasaz AH, Sadeghipour P, Kakavand H, et al. Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC state-of-the-art review. J Am Coll Cardiol 2021;77(15):1903–1921
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(05):1094–1099
8 Sholzberg M, Tang GH, Rahhal H, et al; RAPID trial investigators. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. BMJ 2021;375:n2400
9 Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76(01):122–124
10 Lawler PR, Goligher EC, Berger JS, et al; ATTACC Investigators ACTIV-4a Investigators REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 2021;385(09):790–802
11 Goligher EC, Bradbury CA, McVerry BJ, et al; REMAP-CAP Investigators ACTIV-4a Investigators ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med 2021;385(09):777–789
12 Sadeghipour P, Talasaz AH, Rashidi F, et al; INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA 2021;325(16):1620–1630
13 Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA 2021;326(01):35–45
14 Tenforde MW, Self WH, Adams K, et al; Influenza and Other Viruses in the Acutely Ill (IVY) Network. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA 2021;326(20):2043–2054
15 Wang Z, Yang L. In the age of Omicron variant: Paxlovid raises new hopes of COVID-19 recovery. J Med Virol 2022;94(05):1766–1767
16 Caraco Y, Crofoot GE, Moncada PA, et al. Phase 2/3 trial of molnupiravir for treatment of Covid-19 in nonhospitalized adults. NEJM Evid 2021;1(02). doi: https://doi.org/10.1056/EVIDoa2100043
17 Tian D, Sun Y, Zhou J, Ye Q. The global epidemic of the SARS-CoV-2 delta variant, key spike mutations and immune escape. Front Immunol 2021;12:751778
18 Abdullah F, Myers J, Basu D, et al. Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in Tshwane, South Africa. Int J Infect Dis 2022;116:38–42
19 Hippisley-Cox J, Patone M, Mei XW, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ 2021;374:n1931
20 Connors JM, Brooks MM, Sciurba FC, et al; ACTIV-4B Investigators. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. JAMA 2021;326(17):1703–1712
21 Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol 2021;21(08):475–484
22 Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 2021;397(10287):1819–1829
23 Bahl A, Johnson S, Maine G, et al. Vaccination reduces need for emergency care in breakthrough COVID-19 infections: a multicenter cohort study. Lancet Reg Health Am 2021;4:100065
24 Rizk JG, Gupta A, Sardar P, et al. Clinical characteristics and pharmacological management of COVID-19 vaccine-induced immune thrombotic thrombocytopenia with cerebral venous sinus thrombosis: a review. JAMA Cardiol 2021;6(12):1451–1460
25 Cines DB, Bussel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. N Engl J Med 2021;384(23):2254–2256
26 Kim YE, Huh K, Park YJ, Peck KR, Jung J. Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19 infection. JAMA 2022;328(09):887–889
27 Law N, Chan J, Kelly C, Auffermann WF, Dunn DP. Incidence of pulmonary embolism in COVID-19 infection in the ED: ancestral, Delta, Omicron variants and vaccines. Emerg Radiol 2022;29(04):625–629
28 Tao K, Tzou PL, Nouhin J, et al. The biological and clinical significance of emerging SARS-CoV-2 variants. Nat Rev Genet 2021;22(12):757–773
29 Durand M, Sinyavskaya L, Jin YL, Tremblay CL, Ducruet T, Laskine M. Incidence of venous thromboembolism in patients living with HIV: a cohort study. AIDS Patient Care STDS 2019;33(11):455–458
30 Matta F, Yaekoub AY, Stein PD. Human immunodeficiency virus infection and risk of venous thromboembolism. Am J Med Sci 2008;336(05):402–406
31 Bibas M, Biava G, Antinori A. HIV infection as a permanent, acquired risk factor for VTE. Nat Rev Cardiol 2014;11(06):321
32 Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. BMJ 2021;375(2713):n2713
33 Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al; MOVe-OUT Study Group. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2022;386(06):509–520
34 Bikdeli B, Madhavan MV, Jimenez D, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. 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 2020;75(23):2950–2973
35 Kyriakoulis KG, Kollias A, Kyriakoulis IG, et al. Thromboprophylaxis in patients with COVID-19: systematic review of National and International Clinical Guidance reports. Curr Vasc Pharmacol 2022;20(01):96–110
36 Gerotziafas GT, Catalano M, Colgan MP, et al; Scientific Reviewer Committee. Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: position paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. Thromb Haemost 2020;120(12):1597–1628
37 Spyropoulos AC, Goldin M, Giannis D, et al; HEP-COVID Investigators. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. JAMA Intern Med 2021;181(12):1612–1620

38 Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis 2020;50(01):72–81
39 Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021; 5(03):872–888
40 Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: July 2021 update on postdischarge thromboprophylaxis. Blood Adv 2022;6(02): 664–671
41 van de Veerdonk FL, Giamarellos-Bourboulis E, Pickkers P, et al. A guide to immunotherapy for COVID-19. Nat Med 2022;28(01):39–50
42 Alexander PE, Armstrong R, Fareed G, et al. Early multidrug treatment of SARS-CoV-2 infection (COVID-19) and reduced mortality among nursing home (or outpatient/ambulatory) residents. Med Hypotheses 2021;153:110622
43 Wen W, Chen C, Tang J, et al. Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine and Paxlovid) for COVID-19:a meta-analysis. Ann Med 2022;54(01): 516–523
44 Davidson M, Menon S, Chaimani A, et al. Interleukin-1 blocking agents for treating COVID-19. Cochrane Database Syst Rev 2022;1 (01):CD015308
45 Munblit D, Nicholson TR, Needham DM, et al. Studying the post-COVID-19 condition: research challenges, strategies, and importance of Core Outcome Set development. BMC Med 2022;20 (01):50