# Recent Updates on COVID-19 Associated Strokes

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**ABSTRACT:** The SARS-CoV-2 virus is primarily a respiratory virus, but, as it spread worldwide, it became apparent that there are multiple extrapulmonary manifestations. Reports arose of young and otherwise healthy patients presenting to emergency departments with large-vessel occlusions. Because of a rapidly evolving pandemic, conflicting data sometimes arose regarding the impact of the pandemic on strokes. COVID-19 can induce a hypercoagulable and a proinflammatory state through the interactions with the ACE-2 receptor. These mechanisms may lead to the strokes, both ischemic and hemorrhagic, that are seen in this infection. Strokes, in conjunction with COVID-19 infection, tended to be more disabling and portended a higher mortality. Treatment of these strokes was challenging, as emergency departments were strained with the high burden of COVID-19 admissions. Finally, vaccines against COVID-19 were widely administered, and their potential to cause stroke as an adverse event are discussed. This article will provide an in depth review of the recent updates about the incidence, epidemiology, pathophysiology, clinical presentation and treatment of strokes that are associated with COVID-19.

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## Introduction

The COVID-19 infection is caused by SARS-CoV-2. Due to the global spread of the disease, it was classified as a pandemic and global public health emergency between March 11, 2020 and May 5, 2023, eventually causing over 770 million confirmed infections and over 6.9 million deaths.[1] COVID-19 is a respiratory virus with a similar syndrome to the flu, but as more cases arose, it became evident that there are multiple extrapulmonary manifestations. Some of these symptoms can be mild, such as diarrhea or headache,[2] but serious neurological manifestations like cerebrovascular accidents (CVA), including acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH), have been reported. These adverse cerebrovascular events have also been observed to occur post-COVID-19 vaccination.

Throughout the COVID-19 pandemic, diagnoses and hospitalizations due to AIS varied, with a sharp decline occurring at the onset. A recent meta-analysis found a 26% decrease throughout the pandemic compared to pre-pandemic levels.[3] Despite this decrease, the severity and mortality from AIS increased significantly among those admitted.[4] While this merits further research, it has been postulated that fear of possible exposure to COVID-19, decreased recognition of mild cases of AIS, and the reduction in other contagious viral infections like influenza, which are known to increase the risk of AIS, contributed to this trend.[4,5]

The incidence of AIS in COVID-19 patients is difficult to quantify due to the heterogeneity of published literature. Some meta-analyses have shown an incidence of between 0.9% and 2.8% in COVID-19-positive patients.[6-8] According to the authors, this difference in incidence could be due to differences in viral strains, hospital practices with prescribing anticoagulant prophylaxis, and vaccine administrations.

ICH in COVID-19 patients is different from ICH in non-COVID-19 patients in that COVID-related ICH is lobar, multifocal, and associated with anticoagulation. The pooled incidence of ICH was 0.4%, but its mortality rate is 54%, showing that this is another severe cerebrovascular complication of COVID-19.[9]

Though rare, the co-occurrence of COVID-19 and AIS is often severe and more frequent in younger individuals and men.[8,9] A high proportion of cryptogenic strokes were also seen.[7] Conversely, Qureshi et al found a higher percentage of AIS and COVID-19 infection among older adults and African Americans. These patients were twice more likely at risk of death and discharge to a destination other than home.[10] The risk of arterial thromboembolism (ATE) in COVID-19 patients was found to be elevated in older patients, those with hypertension, and those with pre-existing diabetes, which is in concordance with risk factors in the general population.[11]

In this review, we will explore the pathophysiology, presentation, and treatment of AIS in the setting of COVID-19 infection and vaccine-related complications, and describe the recent literature in a concise and accessible fashion

## Pathophysiology and Prognosis

COVID-19 induced stroke has multiple pathophysiological pathways: (i) immune-mediated hypercoagulability, (ii) decreased activation of the alternative renin-angiotensin-aldosterone-

system (RAAS) pathway, (iii) cardiac embolism, and (iv) intracranial thrombus formation.[12]

(I) Endothelial and cardiac cells express the angiotensin converting enzyme-2 (ACE-2) receptor through which SARS-CoV-2 enters the cell. After entering, replicating, and releasing into the circulatory system, an inflammatory cascade is initiated that includes the release of neutrophil extracellular traps (NETs) and a cytokine storm both locally and systemically. The NETs stimulate the extrinsic coagulation pathway. Thus, a hypercoagulable state is generated which is further enhanced via complement activation.[13] The cytokine storm activates the endothelium which, in turn, activates the coagulation pathway adding to the hypercoagulability.[12] Additionally, COVID-19 infection of the endothelium leads to the destruction of the glycocalyx thus furthering the hypercoagulability. The glycocalyx is a coating of the endothelium which normally acts to inhibit leukocyte recruitment via covering leukocyte adhesion receptors and activating antithrombin via heparan sulfates.[14] Thrombus formation ensues and can lead to systemic embolism, pulmonary embolism, or ischemic stroke.[13] These thrombi can originate in the heart, lungs, brain, or microvasculature where ACE2 is expressed.[15]

(II) ACE-2 cleaves AngiotensinII to Angiotensin[1-7] which activates Mas and AT2 receptors promoting vasodilation and anti-inflammation.[15] Additionally, ACE-2 reduces platelet aggregation and NO release while Ang[1-7] inhibits adhesion and migration of leukocytes.[13] When the SARS-CoV-2 inhibits ACE-2, AngII is not converted and activates the AT1 receptor, promoting opposite effects: vasoconstriction and inflammation.[15] This, along with the hypercoagulable state, presents a higher chance of thromboembolism and ischemic stroke.

(III) Cardiac dysfunction may result from direct invasion of SARS-CoV-2 in cardiac tissue or from myocardial infarction induced by the infection. Dysfunction and hypercoagulability can lead to stasis and thrombus formation within the heart. Thus, there is a high risk of cardiac thrombus formation and embolization leading to ischemic stroke.[16]

(IV) Activation of cell adhesion molecules and the recruitment of monocytes, macrophages and neutrophils occurs within the cerebral blood vessels. Extravasation ensues and SARS-CoV-2 indirectly bypasses the blood-brain barrier (BBB) via virus-infected immune cells. Directly, SARS-CoV-2 spike protein (S1) has been shown to activate RhoA, a regulator of the endothelial cytoskeleton and tight junctions. Activation leads to increased vascular permeability and BBB disruption.[17] This leads to endothelial activation, disruption of the blood-brain barrier, and increased inflammatory activity in the brain. Thrombosis and thromboembolism ensue from the hypercoagulable state which directly causes hypoperfusion of brain tissue and ischemic stroke (Figure 1).[18]

Additionally, there seems to be a higher risk of COVID-induced coagulation in males with an estimated 71.9% of COVID-19 related ischemic strokes in male patients.[19] In rats, high 17β-estradiol was shown to reduce the systemic proinflammatory cytokines produced during acute lung injury.[20] This may explain the high prevalence for the male sex. In conclusion, immune-mediated hypercoagulability, dysregulation of the alternative RAAS pathway, cardiac embolism, and intracranial thrombus formation all contribute to the pathophysiology of COVID-induced stroke which can be even further exacerbated by the hypoxia caused by pneumonia.[12]

## Acute Ischemic Stroke

The concern for AIS in the setting of COVID-19 infection arose because of initial reports of large vessel occlusion (LVO) in younger patients.[21] The potential cardiac injury and the hypercoagulability discussed earlier likely lead to the formation of these embolic manifestations. These instances of AIS contrast with the classic risk factors for AIS such as hypertension, older age and diabetes which lead to endothelial damage that is worsened by the inflammation induced by COVID-19 infection. As more time progressed, it was found that patients with more severe COVID-19 were more likely than those with non-severe COVID-19 to experience an ATE.[11] Additionally, the combination of COVID-19 and AIS worsened the outcomes of AIS compared to COVID-19 negative patients with AIS. COVID-19 patients were more likely to die in the hospital, less likely to be discharged home, and more likely to have significant impairment after discharge.[22]

## Treatment

This increase in morbidity and the variability of presentation of COVID-19 presented a challenge to emergency providers throughout the world. The pandemic strained the access to critical infrastructure in AIS management and created a transmission risk for the first responders and stroke teams.[23] Pre-hospital care was significantly affected with a meta-analysis of international studies showing an increase in the pre-hospital interval (the time from emergency medical services (EMS) activation until arrival at the hospital). These differences were especially prevalent when stratified into high COVID-19 disease burdened hospitals versus low disease burden.[24]

Systematic reviews and meta-analyses did not show a significant increase in door to needle (DTN) or door to groin (DTG) times, though some of the studies did show an overall increase.[25] Hospitals likely optimized their infection control

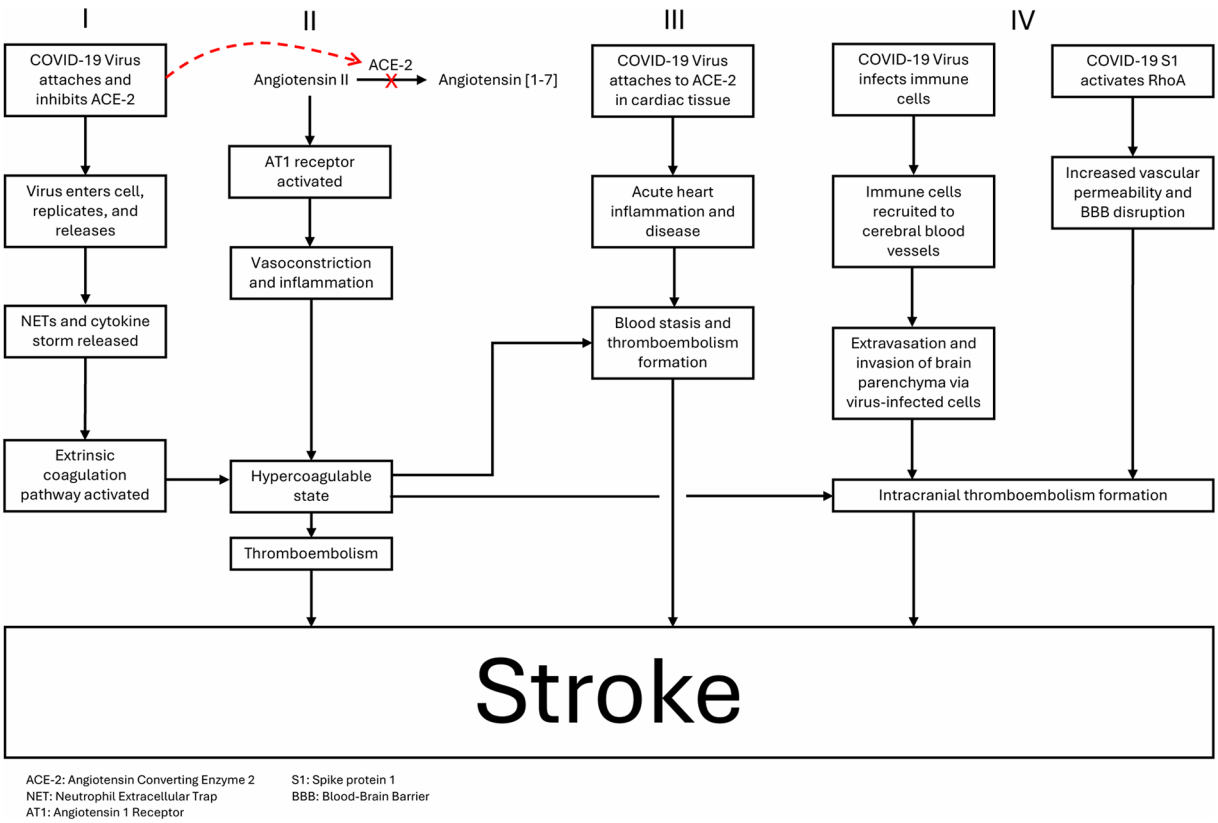


**Figure 1.** Schematic representation of the multiple implicated mechanisms of COVID-19 induced strokes.

systems with their AIS responses, which, unfortunately also may have contributed to the increased pre-hospital interval.[24] A statistically significant increase in last known well (LKW) time was found, however. Avoidance behaviors and shelter in place orders likely contributed to the increase in LKW time, and may contribute to the increased severity of AIS that were treated.[4] Patients may have hesitated in activating EMS until their symptoms became more severe. Additionally, infrastructure strains and an overwhelmed medical system could have led to these delays.

Mechanical thrombectomy (MT) or thrombolysis are the foundations of initial AIS treatment. Multiple reviews showed that there was a slight increase in mortality following thrombectomy in COVID-19 positive patients when compared to COVID-19 negative patients[26] and that there is an increased risk of ICH in COVID-19 positive stroke patients.[27] A national registry also showed that COVID-19 infection was an independent risk factor for increased mortality following thrombectomy.[28] However, this could be due to these patients having an underlying severe COVID-19 infection, leading to these poorer outcomes. The increase in LKW during the pandemic could also have contributed to the decreased utilization of these therapeutic measures. Re-occlusion following MT in LVO stroke patients was also noted in the COVID-19 positive AIS population. This unique situation was treated in a single institution study with dual antiplatelet therapy including intraprocedural aspirin and cangrelor.[29]

For patients who were already hospitalized with severe COVID-19, the risk for ATE was highest in the acute phase of illness.[30] This leads to the question of prevention of these ATE outside of the standard hospital precautions, such as sequential compression devices (SCDs). The SARS-COV-ATE risk assessment tool was preliminarily found to be efficacious in predicting patients who may suffer from an ATE during hospitalization. This model considered age, race, hypertension status, inflammatory serum markers, and electrolyte abnormalities.[31] It is not yet known whether this assessment tool can be combined with prophylactic measures to help prevent ATE in future patient populations. A Cochrane Review of low to high dose anticoagulants for patients hospitalized with COVID-19 showed that any dose of anticoagulation may reduce all-cause mortality, but there is poor evidence to support this. Patients should be anticoagulated in the acute phase of COVID-19 with caution, because of the increased risk of hemorrhagic stroke in these patients, especially after thrombolytic therapy.[32]

## Relationship With Vaccines

Over 80% (270 227 181) of the United States population have received at least one dose of the COVID-19 vaccine, with the highest level (95%) of vaccine uptake seen among older adults ages 65 and over.[33] Currently, three COVID-19 vaccines are widely used in the United States: Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Novavax

(NVX-CoV2373). BNT162b2 and mRNA-1273 are lipid nanoparticle-formulated mRNA vaccines encoding full-length spike SARS-COV-2 RNA. Novavax (NVX-CoV2373) is a recombinant protein-based vaccine encoding full-length spike SARS-COV-2 RNA and Matrix M adjuvant.[34] These genetic materials produce antigens, which elicit a strong antigen-specific immune response once introduced into the human genome. Johnson and Johnson's (Ad26.COV2.S) COVID-19 vaccine is a recombinant, replication-noncompetent adenovirus serotype 26 (Ad26) vector that contains genes for producing SARS-CoV-2 spike protein. The Ad26 viral vector delivers the SARS-COV-2 genome to humans, which the body recognizes and mounts an immune response.[34] In December 2021, the Advisory Committee on Immunization Practices recommended mRNA vaccine use over Ad26.COV2.S in adults ages 18 years and older, except for those with contraindications to mRNA or protein-based vaccines. This recommendation came amidst the discovery of multiple adverse effects (Thrombosis with Thrombocytopenia syndrome and Guillain-Barre Syndrome) associated with the adenovirus vector vaccine.[35]

A significant body of literature reports AIS and ICH post-COVID-19 vaccination. These adverse events are linked to vaccine-induced thrombotic thrombocytopenia (VITT), a phenomenon proposed to have a similar mechanism to heparin-induced thrombocytopenia involving platelet-activated factor 4 (PAF-4), which triggers thrombosis whenever VITT associated PAF-4 antibodies binds heparin receptors.[36-38] A retrospective cohort study showed a significant cumulative incidence of thrombotic events 12 per 10 000 (95% CI: 9, 17; $P = .022$) within 30 days of COVID-19 vaccination.[39] These events were higher 15 per 10 000 (95% CI: 11, 21; $P = .0099$) among older adults. Most patients with post-vaccination thrombosis also had thrombocytopenia, positive D-Dimer, and PAF-4 assay.[36-38]

AIS is encountered following the administration of the COVID-19 vaccination. In a study involving 29 918 participants, 36 subjects who received COVID-19 vaccine developed at least one thromboembolic event (TE). Nine of these subjects with TE had a stroke.[39] Another study found multiple confirmed cases of ischemic strokes resulting from VITT post-COVID-19 vaccination.[38] Though these events are rare, they are often fatal. A case series reported an ischemic stroke in an older woman a few hours after receiving her first dose of the mRNA vaccine, and a cerebellar ischemic stroke was reported in a young woman within a few days of receiving the viral vector COVID-19 vaccine.[40]

More recently, an increased risk of acute ischemic stroke post-COVID-19 vaccination has been reported among individuals with co-existing COVID-19 infection at the time of vaccination. Nahab et al demonstrated an increased risk of ischemic stroke with Ad26.COV2.S, mRNA-1273, and BNT162b2 within 21 days of receiving the first COVID-19 vaccine shot. Their study revealed that individuals who received Ad26.COV2.S were more at risk (57%) of ischemic strokes than those who got BNT162b2.[41] In addition, a recent registry based cohort study that included over 4 million individuals who got the mRNA vaccine identified cerebrovascular events among 0.05% of their study population after 28 days post-vaccination. Of these, over 80% were ischemic strokes, 13% intracerebral hemorrhage, and 5% subarachnoid hemorrhage.[42] Booster doses of the COVID-19 vaccine have also been found to be associated with AIS. Ihle-Hansen et al[43] in their case report, examined right posterior inferior cerebellar artery stroke in a young man 2 days post-vaccination with the third dose (booster) of the BNT162b2 vaccine.

Though extremely rare, a systematic review has demonstrated intracerebral and subarachnoid hemorrhage (SAH) following Ad26.COV2.[37] Some case reports have also confirmed cases of ICH post-COVID-19 vaccination. One report showed a left basal ganglia hematoma in an older woman within 3 days of mRNA-1273 vaccination (first dose).[42] Another revealed a left frontal lobe hemorrhage along with SAH in a middle-aged man, with new onset seizures, unremitting headaches, and neck pain 8 days post-COVID-19 vaccination (mRNA-1273, second dose).[43] Another case report also confirmed a right temporal lobe hemorrhage in a middle-aged woman with left hemiparesis, loss of consciousness, and anisocoria within 48 hours of COVID-19 vaccination (BNT162b2, first dose).[44] Most reported cases of ICH were vastly due to AstraZeneca (ChAdOx1 nCoV-1), which is currently not approved for use in the United States.

COVID-19 vaccine recipients with persistent headaches and symptoms of thrombocytopenia with no history of heparin exposure need immediate investigation for VITT.[37] Early diagnosis and prompt initiation of treatment in patients with VITT are of utmost importance in the prevention of these rare but potentially fatal cerebrovascular complications.

## Conclusion

Cerebrovascular accidents associated with COVID-19 have proven to be a substantial and devastating outcome of infection. These strokes tend to be more devastating than CVA not associated with COVID-19, being more likely to lead to disability or death. These strokes are often caused by a hypercoagulable state caused by infection with COVID-19, changing the demographics of those who are affected. Medical systems around the world were strained with the burden of COVID-19 but admissions due to AIS decreased, and there was an increase in prehospital time in AIS patients. It is not known if the COVID-19 vaccine provides a protective benefit against AIS in those who receive it, but unfortunately, CVA and a prothrombotic state have been rarely associated with receiving the vaccine.

## Author Contributions

All authors contributed equally to the planning and writing of this manuscript.

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