

# Thrombosis in pre- and post-vaccination phase of COVID-19

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## KEYWORDS

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Acute infections may be complicated by thrombosis occurring in the venous and arterial circulation. This may be observed in patients with community-acquired pneumonia (CAP) and also in patients with coronavirus 2019 (COVID-19), that is a pandemic characterized by severe acute respiratory syndrome (SARS-CoV-2) needing mechanical ventilation and intensive care unit treatment. However, the type and rate of thrombosis can vary according to the cause of pneumonia as is more frequently complicated by arterial thrombosis in CAP, while an equal incidence of venous and arterial thrombosis occurs in SARS-CoV-2. The mechanisms of disease are overall platelet-related in CAP while activation of both platelets and clotting system is implicated in the pathogenesis of thrombosis in SARS-CoV-2; this finding could imply a different therapeutic approach of the two settings. Thrombosis may also occur in subjects vaccinated against SARS-CoV-2 even if its incidence is not so high (1/100 000); this rare effect occurs more prevalently in young women, is independent from known risk factors of thrombosis, is caused by antibodies against platelet PF4 and is counteracted by treatment with immunoglobulin and glucocorticoids.

## Introduction

Coronavirus 2019 (COVID-19) is a pandemic characterized by severe acute respiratory syndrome (SARS-CoV-2) needing mechanical ventilation and intensive care unit (ICU) treatment. SARS-CoV-2 is characterized by high mortality rate, which is related not solely to lung disease but also to disease localized in other organs, such as heart, kidney, and cerebellum.<sup>1</sup> Thrombosis is among the most important and frequent complication of SARS-CoV-2 and is a strong predictor of survival. Accordingly, clinical studies in COVID-19 demonstrated an early occurrence of venous and arterial thromboembolism coincidentally with a hypercoagulation state, as depicted by elevated plasma levels of D-dimer.<sup>2</sup> This finding is consistent with previous reports in

patients with community-acquired pneumonia (CAP), which is prevalently caused by viruses, and is among the commonest cause of hospitalization for pneumonia. Interestingly, CAP share similar complications compared to SARS-CoV-2, as shown by the fact that CAP may experience thrombosis in the acute phase of the disease, suggesting that pneumonia *per se* may be a trigger for hypercoagulation.<sup>3</sup> The thrombotic features of the two settings are, however, different as CAP is prevalently complicated by arterial thrombosis while SARS-CoV-2 is complicated by thrombosis in both venous and arterial circulation. Furthermore, the incidence rate of thrombosis is much higher in SARS-CoV-2 compared to CAP suggesting that a different mechanism of disease occurs in the two settings. The higher predisposition to thrombosis by SARS-CoV-2 is also highlighted by the thrombotic complication, which may rarely occur in the general population undergoing

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vaccination against SARS-CoV-2.<sup>3</sup> These findings raise important issues as to whether the pathophysiology of thrombosis is similar in the pre- and post-vaccination phase of SARS-CoV-2 or a different mechanism is responsible for the thrombosis feature. Thus, the aim of this review is to compare the thrombotic features of CAP and SARS-CoV-2, analyse potential differences in the mechanism of the disease of the two settings and assess a potential relationship between thrombotic complications occurring in the pre- and post-vaccination phase of COVID-19.

## Thrombosis features of CAP and SARS-CoV-2

Corrales-Medina *et al.*<sup>4</sup> have been the first to show a relationship between CAP and thrombosis; using CK-MB as biomarker of myocardial necrosis, they reported, in fact, that myocardial (MI) infarction may occur in roughly 4% of patients during the intra-hospital stay. Using serum Troponin as biomarker of myocardial necrosis, our group supported and extended this finding by reporting that MI may occur in about 10% of CAP patients, underscored the peculiarity of MI feature in CAP as.<sup>3</sup>

As platelets play a key role in the pathogenesis of MI and stroke, previous studies evaluated if the marker of platelet activation can be detected in CAP. Globally considered, the study showed elevated markers of *in vivo* platelet activation such as plasma P-selection and CD40 Ligand (CD40L) and suggested over-biosynthesis of platelet Thromboxane (Tx)B<sub>2</sub>, as a potential mechanism. In a recent meta-analysis of 10 cohort studies including roughly 700 000 patients with sepsis, revealing that aspirin may reduce admission to ICU or mortality. Taken together, these findings indicate that CAP is associated with platelet activation but the extent to which antiplatelet treatment can lower MI and stroke remain to be ascertained.

As for the CAP, SARS-CoV-2 is also complicated by thrombosis, but the incidence rate is quite higher. Several observational studies demonstrated that thrombosis occurs during the hospitalization stay in roughly 20% of patients and may occur with an equivalent incidence in both arterial and venous circulation. MI, stroke, and peripheral embolism are the prevalent clinical feature of arterial thrombosis, while deep venous thrombosis, superficial venous thrombosis, and pulmonary embolism are the most frequent feature of venous thrombosis.<sup>3</sup>

Thrombotic complications are inconsistently associated with the changes of laboratory clotting time, such as aPTT and PT or low platelet count, while the elevation of D-dimer, a marker of hyperfibrinolysis, is a typical laboratory feature of SARS-CoV-2. The elevation of D-dimer has been considered a marker of hyper-coagulation status and, thereby, a mirror of the thrombotic events occurring in SARS-CoV-2.<sup>2</sup> Changes of D-dimer were more marked in patients with severe disease such as those needing ICU and significantly associated with poor survival, it is still to be clarified, however, the extent to which elevation of D-dimer may be predictive of thrombosis and, thereby, potentially usable for thrombosis prevention. In addition to clotting activation, patients with SARS-CoV-2 show changes of platelet activation with over-biosynthesis of TxB<sub>2</sub>,

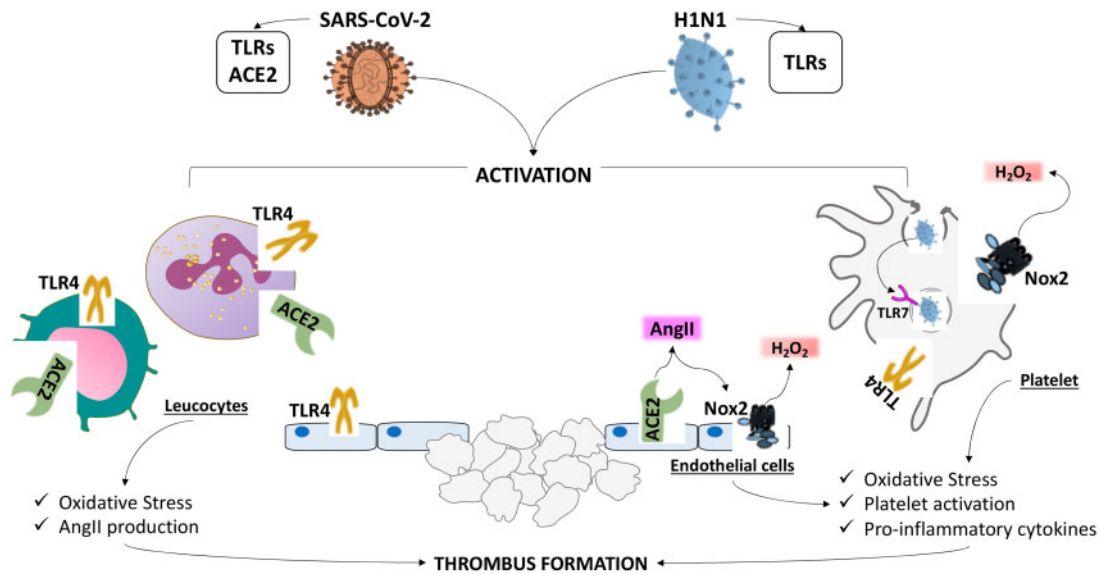
which has been reported to be significantly associated with thrombosis. For this reason, SARS-CoV-2 seems to be different from CAP as both clotting system and platelet function are over-activated and potentially contribute to thrombosis.<sup>3</sup>

## Mechanism of the disease

As CAP is prevalently due to influenza A RNA virus, a direct platelet interaction between influenza virus and platelets could be a putative mechanism. Thus, influenza A virus particles are detectable within platelets and can mediate platelet aggregation and C3 release-dependent neutrophil-DNA release via Toll-like receptor 7 (TLR7). Furthermore, in animal model of mice infected with the H1N1 virus anti-platelet drugs such as the COX1 inhibitor aspirin or the antagonist of the P<sub>2</sub>Y<sub>12</sub> platelet receptor clopidogrel were able to inhibit virus-induced platelet activation.

The role of Toll-like receptors (TLRs) in the pathogenesis of thrombosis by rRNA viruses have been demonstrated by Zhao *et al.* and Choudhury *et al.* showing that SARS-CoV-2 uses TLR4 to activate cells implicated in the thrombotic process, such as monocytes and leucocytes. The deleterious effects of SARS-CoV-2 binding to TLRs are likely related to up-regulation of Nox2, the most important cellular producer of reactive oxidant species (ROS), resulting in endosomal hydrogen peroxide generation. Nox2 is a key enzyme of the innate immune system, which, intriguingly, shifts endothelial cells and platelets to a prothrombotic profile. In patients affected by chronic granulomatous disease, a rare disease characterized by hereditary deficiency of Nox2, arterial vasoconstriction is lowered and platelets are less prone to promote thrombus growth. Analysis of circulating levels of soluble Nox2, which is a marker of Nox2 activation by blood cells including platelets and leucocytes, revealed that Nox2 activation occurs not only in CAP but also in COVID-19. In the case of COVID-19, the virus entry into the cells may occur by its binding to angiotensin-converting enzyme 2 (ACE2) upon its Spike protein cleavage by a serine protease, i.e. TMPRSS2. COVID-19 RNA has been detected in platelets and endothelial cells from patients with severe and non-severe COVID-19 but it is still unclear if this occurs via the Spike protein-ACE2 axis (*Figure 1*) as not all agree that platelets and endothelial cells express ACE2. Assuming, however, that spike protein binding and entry into human cells occurs via ACE2, this would result in surface ACE2 expression down-regulation and loss of function with ensuing angiotensin II (AngII) up-regulation as ACE2 degrades Ang II to Ang 1-7. The increase of Ang II could have potentially deleterious effects on both platelets and endothelial cells as Ang II is a pro-oxidant molecule via NOx2 up-regulation. Of note, Nox2 is more activated in patients with COVID-19 vs. controls, in severe vs. non severe disease and in patients experiencing thrombotic events<sup>3</sup> (*Figure 1*).

In alternative to this mechanism, RNA viruses could activate platelets when antibodies opsonize viral particles and interact with platelet FcγRIIA; however, they would be expected to work at later stage of the disease, thereby



**Figure 1** Mechanisms of thrombosis in COVID-19 and CAP patients. SARS-CoV-2 and H1N1 by Toll-like receptors (TLRs) activate cells implicated in the thrombotic process such as leucocytes, platelets and endothelial cells. Upon binding to TLRs up-regulation of Nox2, the most important cellular producer of reactive oxidant species (ROS), resulting in hydrogen peroxide generation, may occur. In the case of COVID-19 patients, the virus entry into the cells may occur also by its binding to angiotensin-converting enzyme 2 (ACE2) with ensuing loss of function and angiotensin II (AngII)/Nox2 up-regulation.

their potential impact on platelet activation and thrombosis in patients with COVID-19 needs to be elucidated.<sup>3</sup>

Finally, platelet activation can occur via overproduction of inflammatory pro-aggregating cytokines, which are, in fact, elevated in COVID-19. In accordance with this, incubation of endothelial cells or platelets with plasma from COVID-19 or with specific cytokines such as IL-6, promoted a prothrombotic profile (*Table 1*).

Taken together, these data indicate that in patients with pneumonia by RNA viruses a shift to a prothrombotic profile can be detected in both platelets and endothelial cells. The mechanism of disease may include more than one cellular pathways, which may act at different phase of the disease.<sup>3</sup> Thus, the complexity of this phenomenon requires further study for a better comprehension of the disease mechanism and for a more appropriate anti-thrombotic therapy.

### Prevalence and mechanisms of vaccine-induced thrombosis

With the increasing use of anti-SARS-CoV-2 vaccines to reduce the diffusion of COVID-19 and its related complications, side effects occurring after vaccination have been described. In the phase 1/2 study from the Oxford COVID vaccine Trial Group,<sup>5</sup> which included 1077 participants, of whom 543 were randomly assigned to receive ChAdOx1 nCoV-19 (AZD1222), the median age was 35 years and nearly 50% were female. Fatigue (70%) and headache (68%) were the most commonly reported systemic reactions, followed by muscle ache (60%) malaise (61%), chills (56%), and feeling feverish (51%). Transient neutropenia was also reported, but no changes of platelet count or thrombotic events were reported.

Since then, few case reports have been published reporting the onset of thrombosis after ChAdOx1 nCoV-19<sup>6</sup> and AD26.COV2.S vaccine<sup>7</sup> (*Table 1*).

The majority of these thromboses were at cerebral site, were characterized by a moderate-severe fall in the platelet count in all patients and occurred within 2-3 weeks from the first dose.<sup>6</sup> Thrombosis occurred more prevalently in young women aged approximately  $\leq 50$  years and were not associated with thrombophilia or other risk factor for thrombosis; the European Medicine Agency (EMA) evaluated in 1 over 125 000 the incidence of thrombosis.<sup>1</sup> Thus, the term of vaccine-induced thrombotic thrombocytopenia (VITT) has been proposed to describe this condition.

Given its clinical and biochemical characteristics, the mechanism responsible for VITT has been thought to be similar to that occurring with the heparin-induced thrombocytopenia (HIT). Indeed, HIT is characterized by a platelet count ( $< 150 \times 10^9/L$ ) or a relative decline of 30-50% from baseline values. Thrombocytopenia is usually moderate ( $50-70 \times 10^9/L$ ) and not causing bleeding complications.<sup>1</sup> Thrombosis associated with thrombocytopenia typically occur after 5-15 days after heparin (mostly unfractionated) administration, and primarily affect venous circulation.

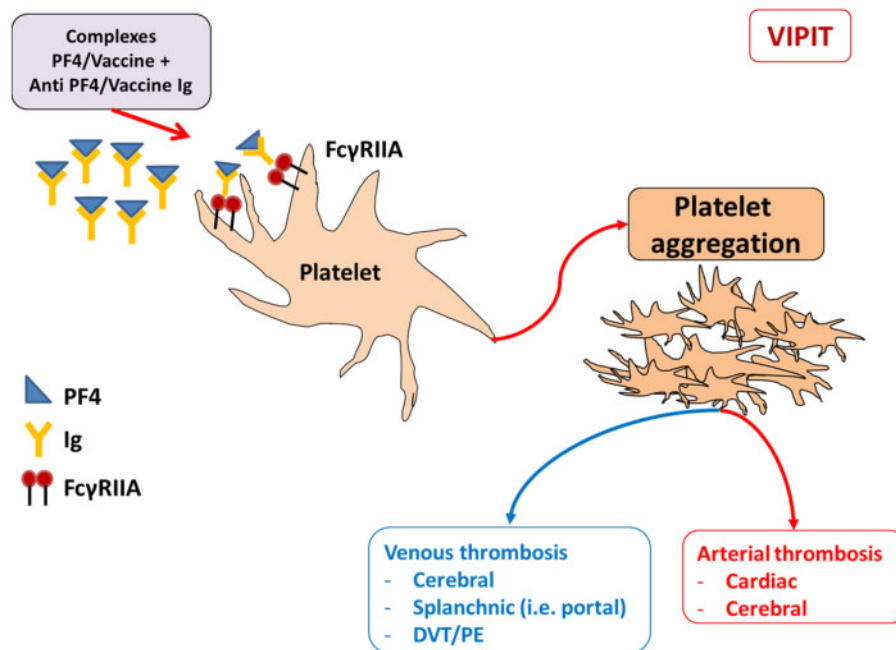
The diagnosis of HIT is confirmed by the presence of anti-Platelet Factor 4 (PF4)/heparin complexes antibodies. In the case of VITT, the production of anti-PF4 antibodies seems to be unrelated from heparin exposure, as it may occur in other clinical conditions. Platelet count, HIT enzyme-linked immunosorbent assay (ELISA), and platelet activation tests in the presence of serum from vaccinated patients have been suggested as laboratory work-up for VITT diagnosis even if there is disagreement regarding

**Table 1** Case series of patients with vaccine-related thrombosis

Author/year	Number of patients	Age, years	Sex, % female	Type of vaccine	Site of thrombosis
Schultz (2021) <sup>6</sup>	5	32-54	80	ChAdOx1 nCoV-19	4 CVT and 1 PVT, left hepatic vein, splenic vein, azygos vein, hemiazygos vein, and several basivertebral veins
See (2021) <sup>7</sup>	12	18-59	100	Ad26.COVS.5 COVID-19	CVT
Greinacher (2021) <sup>11</sup>	11	22-49	82	ChAdOx1 nCov-19	9 CVT, 3 had splanchnic-vein thrombosis, 3 PE, and 4 had other thromboses <sup>a</sup>
Vayne (2021) <sup>9</sup>	11	44	NA	ChAdOx1 nCov-19	6 CVT, 5 had splanchnic vein thrombosis
Scully (2021) <sup>8</sup>	23	21-77	52	ChAdOx1 nCov-19	15 CVT, 6 PE/DVT, 3 PVT <sup>a</sup>
Wolf (2021) <sup>12</sup>	3	22-46	100	ChAdOx1 nCoV-19	Intracranial venous sinus thrombosis
Pottgard (2021) <sup>13</sup>	148 792 in Denmark 132 472 in Norway	18-65	80 in Denmark 78 in Norway	ChAdOx1 nCoV-19	52 cardiac events 27 cerebrovascular events 59 VTE: 7 CVT, 21 PE, 22 DVT Splanchnic thrombosis <5 CVT
Castelli (2021) <sup>14</sup>	1	20-50	0	ChAdOx1 nCoV-19	CVT

CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; PE, pulmonary embolism; PVT, portal vein thrombosis; VTE, venous thromboembolism.

<sup>a</sup>Patients had one or more thrombosis.



**Figure 2** Mechanism of VIPIT. Vaccines against SAR-CoV-2 promote the formation of anti-PF4/polyanionic antibodies, which may activate platelets through the Fcγ-receptor IIA (FcγRIIA).

the sensitivity of the HIT assay<sup>8,9</sup>; conversely, the use of PF4-polyvinyl sulphonate provided results consistent with the autoimmune origin of the disease.<sup>8,9</sup> It seems, therefore, that for reasons still unknown, vaccines against SAR-CoV-2 promotes the formation of anti-PF4/polyanionic antibodies, which may activate platelets through the Fcγ-receptor IIA (FcγRIIA) (Figure 2). For this reason, high-dose

intravenous immunoglobulin (1 g/kg) and glucocorticoids (1 mg/kg) have been suggested as a therapy for VITT.<sup>10</sup>

## Conclusions

The data here reported show that thrombosis may occur in SAR-CoV-2 patients and, very rarely, in subjects vaccinated

against SAR-CoV-2. The underlying mechanism are apparently different as in the first case the thrombotic process seems to be related to the interplay between the S protein and intracellular pathways promoting platelet and clotting activation; this sequence of events requires the use of anti-coagulant which are usually give as prophylactic doses. Conversely, VIPIT is an autoimmune disease associated with thrombocytopenia and platelet-related thrombosis occurring in unusual sites, where antibodies against platelet PF4 play a major role, thereby needing an immunosuppressive therapy. Further study is, however, necessary to better elucidate the mechanism of disease.

**Conflict of interest:** none declared.

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