GTH
Gesellschaft
für Thrombose- und
Hämostaseforschung
e.V.

GTH Geschäftsstelle
Haus der Verbände Köln
Gertrudenstr. 9
50667 Köln / Germany

mail@gth-online.org
www.gth-online.org

Important note for patients
We are unable to provide patient counseling and ask that you refrain from inquiring about potential health risks associated with vaccination with the AstraZeneca vaccine. Please contact your treating physician or a coagulation center. Thank you!

Cologne, 03/29/2021

Updated GTH statement on vaccination with the AstraZeneca COVID-19 vaccine, as of March 29, 2021

On Friday, March 19, 2021, vaccinations with the COVID-19 vaccine from AstraZeneca were resumed in Germany. The Paul Ehrlich Institute (PEI) had previously reported on 13 cases of sinus or cerebral vein thrombosis with > 1.6 million AstraZeneca COVID-19 vaccine doses administered. The thromboses occurred 4–16 days after vaccination with the AstraZeneca COVID-19 vaccine in twelve women and one man aged 20–63 years. The patients also had thrombocytopenia, which suggests an immunological event as the cause of the tendency to thrombosis. However, thrombotic events may not exclusively present as intracranial thrombosis but also manifest at other locations or vascular beds.
An important pathomechanism has meanwhile been clarified within the Society of Thrombosis and Haemostasis Research (GTH) under the leadership of the Greifswald working group around Andreas Greinacher. The vaccination is likely to induce the formation of antibodies against platelet antigens as part of the inflammatory reaction and immune stimulation. Depending on or independently of heparin, these antibodies subsequently cause massive platelet activation via the Fc receptor in analogy to heparin-induced thrombocytopenia (HIT). This mechanism (HIT mimicry) could be demonstrated in four patients with a sinus / cerebral vein thrombosis after vaccination with the AstraZeneca COVID-19 vaccine in Andreas Greinacher's laboratory in cooperation with other GTH members. As with classical HIT, these antibodies appear 4–16 days after vaccination. This pathomechanism does not rule out that the sinus / cerebral vein thromboses after vaccination with the AstraZeneca COVID-19 vaccine also have other causes. However, the identified mechanism forms the basis for the following statements and recommendations by the GTH:

- On a population basis, the positive effects of vaccination with the AstraZeneca COVID-19 vaccine outweigh the negative effects, so that the resumption of vaccinations in Germany with this vaccine is to be welcomed.
- According to the current state of knowledge, there is no evidence that thromboses at typical locations (i.e., leg vein thrombosis, pulmonary embolism) are more common after vaccination with the AstraZeneca COVID-19 vaccine than in the age-matched general population.
- Due to the immunogenesis of thromboses in intracranial veins or other (atypical) locations, patients with a positive history of thrombosis and / or known thrombophilia do not have an increased risk of developing this specific and very rare complication after vaccination with the AstraZeneca COVID-19 vaccine.
- Flu-like symptoms such as joint and muscle pain or headache that persist for 1–2 days after vaccination are a common side effect and not a cause for concern.
- In the event of side effects that persist or recur > 3 days after vaccination (e.g., dizziness; headache; visual disturbances; nausea / vomiting; shortness of breath; acute pain in chest, abdomen, or extremities), further medical diagnostics should be carried out to clarify a thrombosis.
- Important examinations include, in particular, complete blood count analysis with determination of platelet count, blood smear, D-dimers and, whenever indicated, further imaging studies (e.g., cMRI, ultrasound, CT of chest / abdomen).
- In the event of thrombocytopenia and / or evidence of thrombosis, testing for pathophysiologically relevant antibodies should be carried out regardless of previous exposure to heparin. The first test in the diagnostic algorithm is a screening test for heparin-induced thrombocytopenia (HIT), which is based on the immunological detection of antibodies against the platelet factor 4 (PF4) / heparin complex.
    - In case this test is negative, an HIT-like specific immunological cause of thrombosis / thrombocytopenia can be ruled out. Importantly, based on preliminary findings from different laboratories, the fully automated, latex immunoturbidimetric assay (LIA) HemosIL® HIT-Ab$_{(PF4\text{-}H)}$ should not be used as a screening test, because this assay may yield false negative results with regard to the presence of pathophysiologically relevant antibodies.
    - In case this test is positive, a classical HIPA assay (HIPA, heparin-induced platelet activation) or SRA (serotonin-release assay) should be ordered as a functional confirmatory test. These two assays detect pathophysiologically relevant antibodies, which activate platelets dependent on (typical HIT) or independent of exogenous heparin (autoimmune HIT). A positive test result in the absence of previous heparin exposure thus establishes the diagnosis of autoimmune HIT.

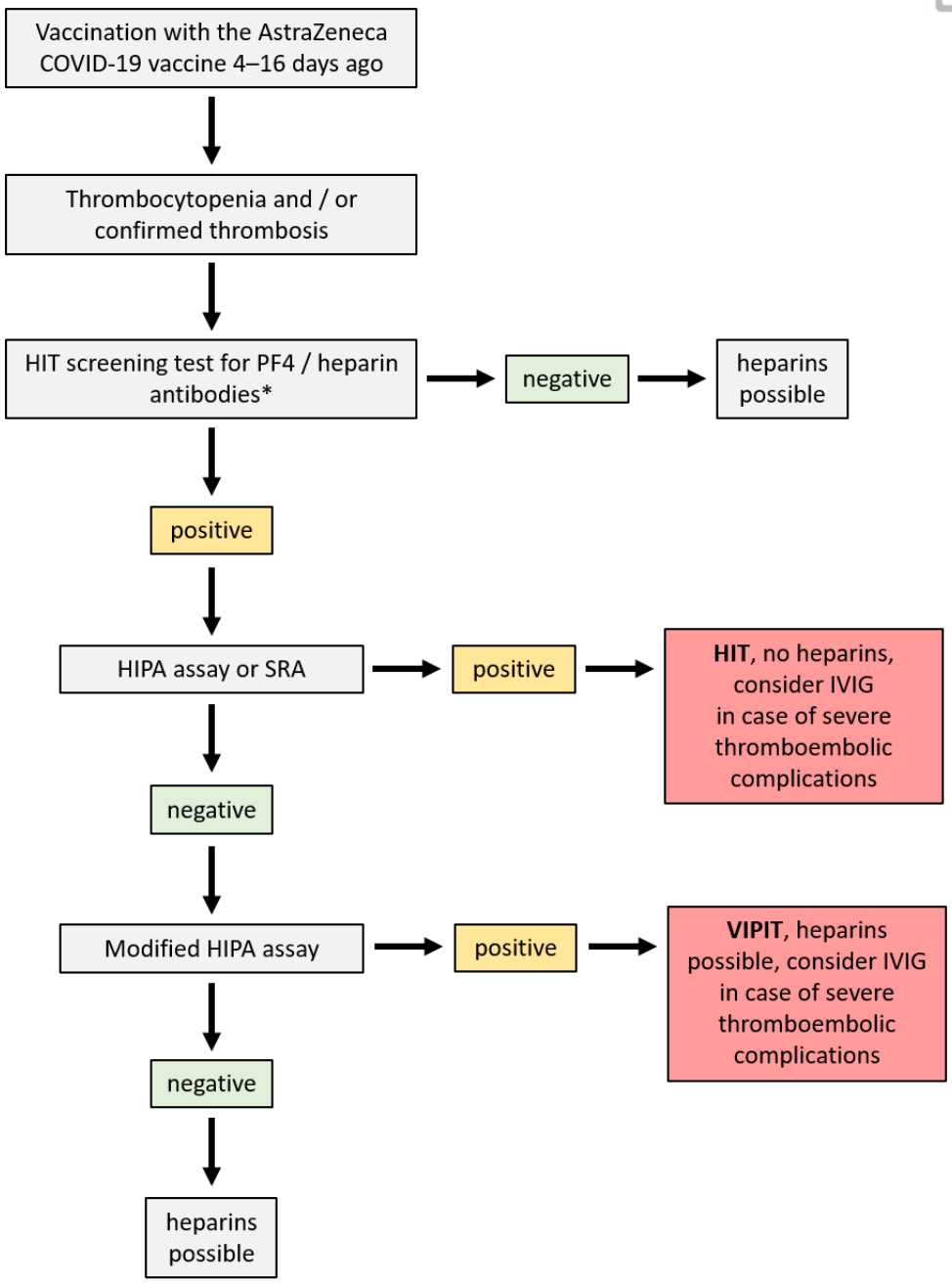
- In case the classical HIPA (or SRA) does not confirm (autoimmune) HIT, a modified HIPA assay should be ordered. This assay has recently been established in Andreas Greinacher's laboratory in Greifswald and detects pathophysiologically relevant antibodies, which display a reaction pattern different from that observed in (autoimmune) HIT (personal communication). Thus, a positive test result establishes the diagnosis of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT).

- Until (autoimmune) HIT is ruled out as the cause of acute thrombocytopenia / thrombosis, if the clinical situation, availability and experience permit, anticoagulation with heparins should be avoided and alternative, HIT-compatible anticoagulants should be used. These anticoagulants include danaparoid, argatroban, direct oral anticoagulants (DOACs), and possibly fondaparinux. Regarding the use of fondaparinux, treatment of acute thrombosis > 4 days following vaccination with the AstraZeneca COVID-19 vaccine must be differentiated from pharmacological thromboprophylaxis during the early phase following vaccination, which is characterized by activation of inflammatory, immunostimulatory signalling pathways and during which administration of fondaparinux may, at least theoretically, foster the production of platelet-activating antibodies (see below).
- In patients with confirmed (autoimmune) HIT or VIPIT and critical thromboses such as sinus / cerebral or splanchnic vein thrombosis, the prothrombotic pathomechanism can very likely be interrupted by administration of high-dose intravenous immunoglobulins (IVIG), e.g., at a dose of 1 g per kg of body weight daily on two consecutive days. Anticoagulation will still be necessary to treat the thrombosis. While heparins are contraindicated in (autoimmune) HIT, parenteral anticoagulation with heparins is possible in confirmed VIPIT.
- Diagnostics for HIT / VIPIT should be ordered prior to the administration of IVIG, since high-dose immunoglobulins may lead to false negative test results.
- Routine pharmacological thromboprophylaxis with anticoagulants or antiplatelet agents to prevent (atypically located) thrombosis resulting from the specific immunological response following vaccination with the AstraZeneca COVID-19 vaccine is not indicated.
  - Patients receiving oral anticoagulation (OAC) for, e.g., atrial fibrillation or venous thromboembolism (VTE), should continue OAC during and after vaccination.
  - In patients with no indication for OAC who are at significant risk of VTE based on dispositional risk factors, pharmacological thromboprophylaxis over several days may be indicated on an individual basis in case of severe flu-like symptoms with fever and immobilisation (AWMF S3 guideline VTE prophylaxis).
  - Since pathophysiologically relevant HIT-like antibodies have been described in association with the specific immunological response following vaccination with the AstraZeneca COVID-19 vaccine, the authors advise against the use of low-molecular-weight heparin or fondaparinux in this situation. According to the current state of knowledge, it cannot be safely ruled out that such parenteral anticoagulants foster the production of platelet-activating antibodies.

- In addition to general measures (e.g., exercise, fluid replacement, compression stockings), prophylactic dosages of direct oral anticoagulants (DOACs), such as rivaroxaban 10 mg once daily or apixaban 2.5 mg twice daily, maybe be considered as an alternative on an off-label basis.

- Regardless of (autoimmune) HIT and VIPIT test results, alternative causes of thrombocytopenia and / or thrombosis must be considered and further clarified accordingly. These include, for example, thrombotic microangiopathies such as immune thrombotic-thrombocytopenic purpura (iTTP) or atypical haemolytic-uraemic syndrome (aHUS), antiphospholipid syndrome, paroxysmal nocturnal haemoglobinuria and underlying malignant (haematological) diseases.

The guidance statements provided here may need an update upon availability of further evidence. Every reader is therefore advised to stay updated with the latest literature on this topic.



Diagnostic and therapeutic algorithm in patients with thrombocytopenia / thrombosis following vaccination with the AstraZeneca COVID-19 vaccine

* The LIA HemosIL® HIT-Ab$_{(PF4-H)}$ should not be used as a screening test due to the possibility of false negative results with regard to the detection of pathophysiologically relevant antibodies.

With friendly recommendation

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Chairman and Director

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Institute of Experimental Haematology and Transfusion Medicine

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Bernd Pötzsch

Stv. Leiter
Institute of Experimental Haematology and Transfusion Medicine

University Clinic Bonn AöR

Prof. Dr. med.
Andreas Greinacher

Leiter der Abteilung Transfusionsmedizin am Institut für Immunologie und Transfusionsmedizin

Universitätsmedizin Greifswald