World Health Organization

Updated Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)

EMA virtual Workshop on TTS

Dr. Rita Helfand (WHO GACVS)

27 June 2022

March 11, 2021 – Denmark Pauses use of AstraZeneca (AZ) Vaccine

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Background of developing TTS Guidance

- March and April 2021:
  - TTS reported in patients vaccinated with the Oxford-AstraZeneca ChAdOx1-S and Johnson & Johnson (J&J) Janssen Ad26.COV2-S COVID-19 vaccines.
    - Both non-replicant adenovirus vector-based vaccines

- National and international bodies concluded there was **a plausible causal link** based upon:
  - proximate **temporal association** with vaccination
  - an **increase in observed rates** when compared with expected baseline rates, **for cerebral venous sinus thrombosis** (CVST)
  - the presence of **simultaneous multiple thromboses in some patients**, unusual sites and extent of thrombosis
  - the presence of **thrombocytopenia and anti-platelet factor 4 antibodies** (anti-PF4)
  - **higher mortality rate** than that reported mortality rates of the same thrombosis in non-vaccinated patients

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GACVS SC Review and recommendations

- **Thrombosis with Thrombocytopenia Syndrome (TTS)**
  - In April 2021, GACVS subcommittee met and reviewed the safety data related to TTS followed by vaccinations of COVID-19 vaccines (AZ COVID-19 vaccine)
  - **GACVS SC issued the Interim statement** of the COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety on AstraZeneca COVID-19 vaccine
  - https://www.who.int/news/item/07-04-2021-interim-statement-of-the-covid-19-subcommittee-of-the-who-global-advisory-committee-on-vaccine-safety
  - AS suggested in the GACVS subcommittee's interim statement, WHO convened a **committee of clinical experts including haematologists and other specialists for advice on clinical diagnosis and case management**.
    - Based on the work of this expert group, on **19 July 2021 WHO published an interim Emergency Guideline** on the detection and clinical case management of TTS following CoVID-19 vaccination.

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Thrombosis with Thrombocytopenia Syndrome

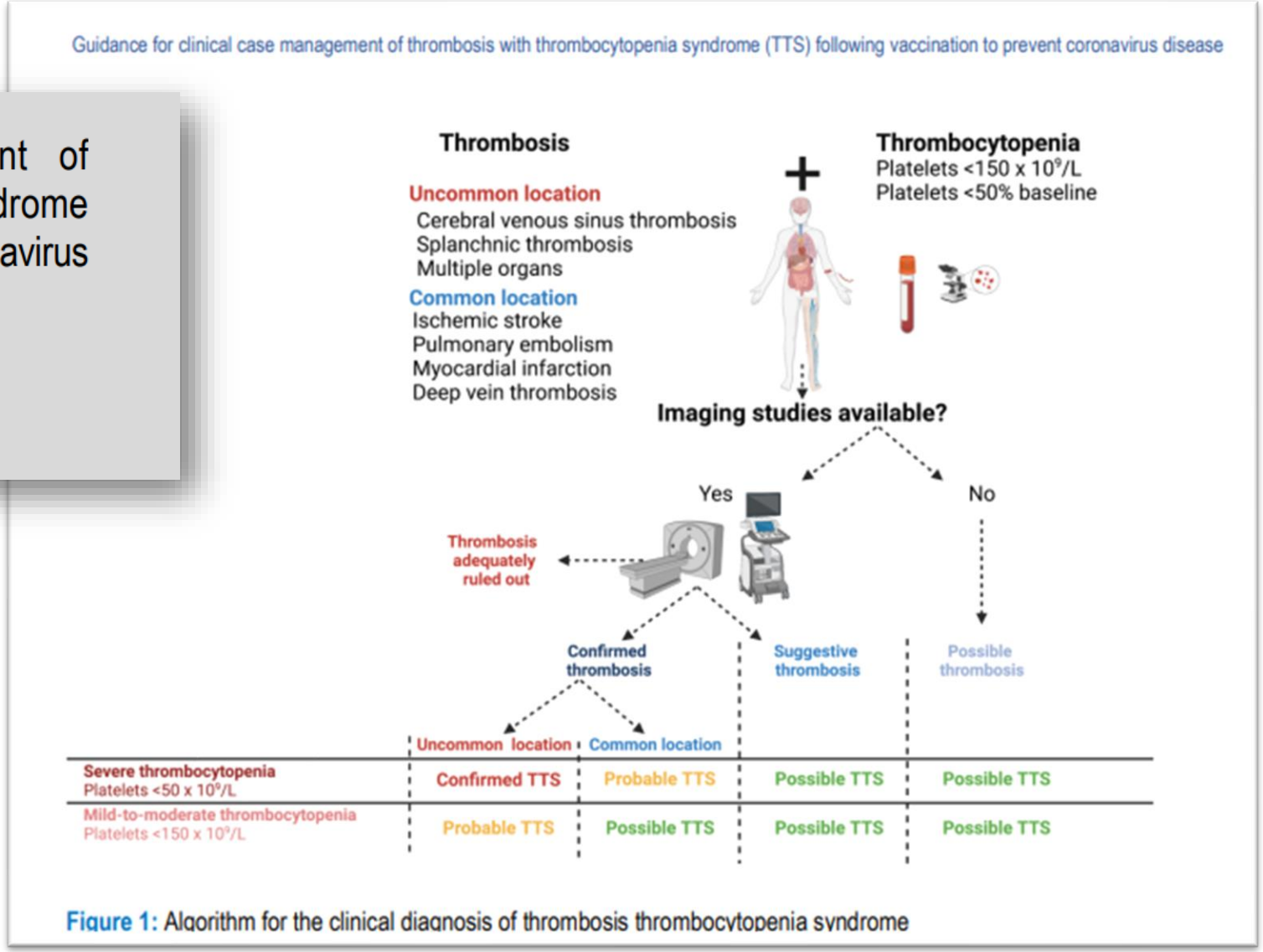
World Health Organization

Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)

Interim guidance

19 July 2021

- The purpose of the document is to provide guidance on the recognition and clinical management of thrombosis with thrombocytopenia syndrome (TTS), following vaccination.
- This syndrome has received different names, including vaccine-induced immune thrombotic thrombocytopenia (VIITT), vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), and vaccine-induced thrombotic thrombocytopenia (VITT).



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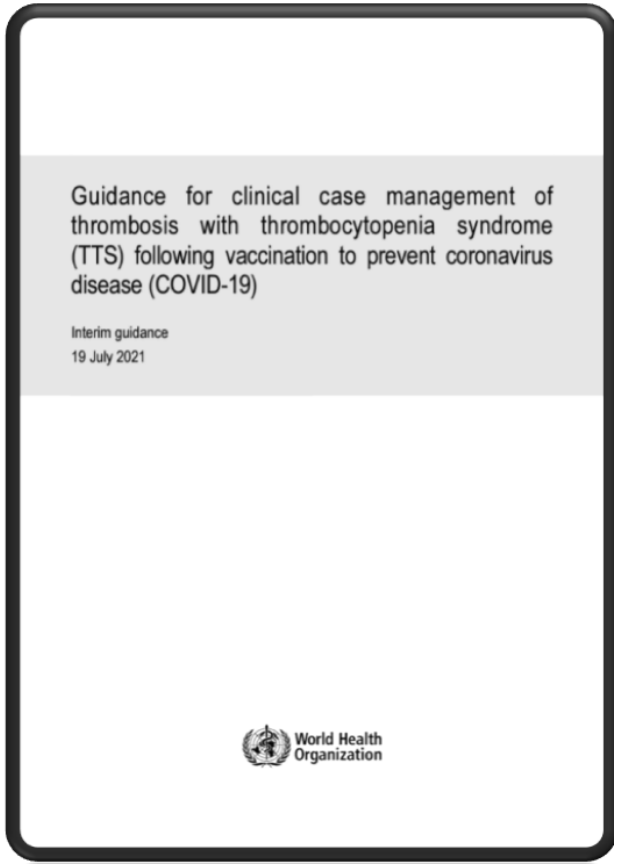
Updating the Interim Guideline



Interim TTS Guidelines Published	Need for Updates expressed by SAGE/ GACVS	Identification of experts, contact and clearance	Subgroups defined including for special populations	Research questions developed and focus areas clearly defined by each subgroup	Updated literature review supported by the WHO secretariat	Zero draft harmonized and posted on SharePoint for feedback from all GDG members	GRADE Tables developed	**Under final clearance process**
Jul 2021	**Oct 2021**	**Nov 2021**	**Nov 2021**	**Dec**	**Jan 2022**	**Feb – Mar 2022**	**April 2022**	**June 2022**

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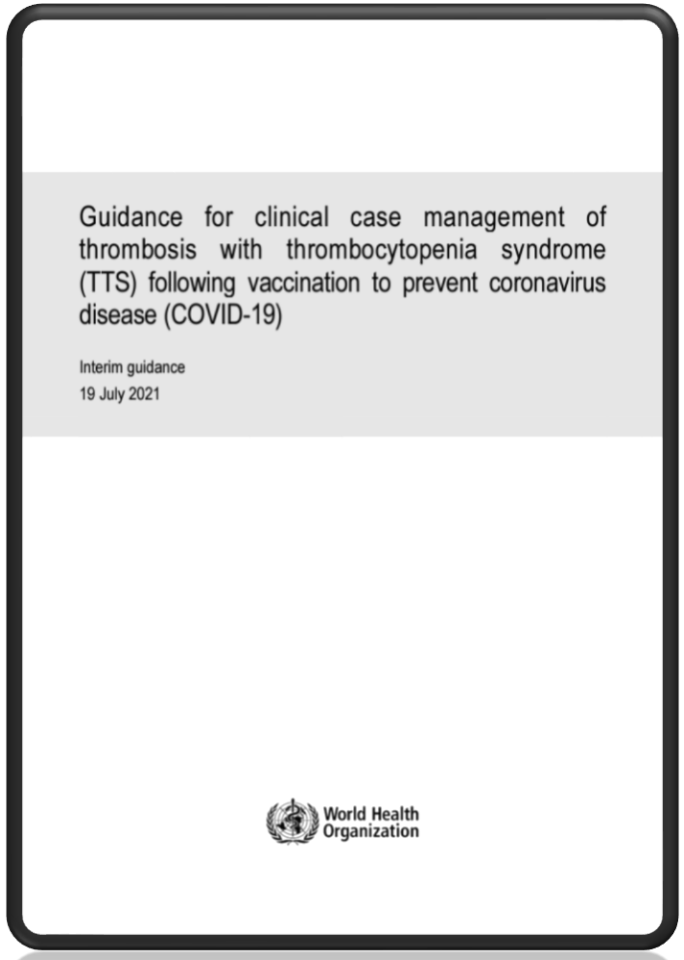
Interim Guidance document for clinical case management of thrombosis with thrombocytopenia syndrome following vaccination to prevent COVID-19



Interim Guidance of July 2021

- Provide the clinical case definition of TTS
- Describe the clinical presentation including the signs and symptoms of TTS, to guide clinicians in the recognition of TTS
- Guide the laboratory diagnosis and imaging for confirmation of TTS
- Provide recommendations for the clinical care, and management of TTS.

Guidance being updated in 2022

- Incorporated the recent scientific updates and developments that have occurred between July 2021 and November 2021
- A section on management in special populations (e.g., Pregnancy/ Lactation) and children added
- Included a communications component to the guidance with foundations to target/ seed a wider audience including vaccine recipients/ guardians, general public, primary care HCP, clinicians, policy makers and journalists

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A Note about Terminology Discussed by GACVS

- **Thrombosis with Thrombocytopenia Syndrome (TTS)**
  - Clinical syndrome (analogous to Acute Flaccid Paralysis or AFP used in polio surveillance)
    - Useful for surveillance and diagnostic/clinical management purposes

  - **Vaccine-induced thrombosis with thrombocytopenia (VITT)**
    - Terminology reflects causality assessment complete
    - Analogous to vaccine-associated paralytic polio (VAPP)
      - AFP cases in which investigation (e.g., stool testing for polio viruses) concludes the a case of AFP that is vaccine-associated will be considered VAPP (i.e., a subset of AFP)

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Need for an updated guideline

- Terminological reasons: VITT / TTS
- A *prodromal?* Phase was described prior to the thrombosis onset: pre-VITT
- Non-heparin-based anticoagulants are not widely available
- Evidence suggested that heparin could be safe and effective

Salih. N Engl J Med. 2021;Kennedy. Blood Adv. 2021. Schönborn. N Engl J Med. 2021

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WHO TTS Classification

Classification	Level 1			Level 2		Level 3
Surveillance term	VITT	pre-VITT	Confirmed clinical case of TTS	Probable clinical TTS case		Possible clinical TTS case
Thrombosis	Any thrombosis	Delayed-onset headache, persistent with red flags without thrombosis	Multiple thromboses or uncommon location thrombosis	Common location thrombosis	Multiple thromboses or uncommon location thrombosis	Common location or non-confirmed (including symptom-based) diagnosis
Thrombocytopenia	<150 x10^9 / L OR >50% decrease from baseline platelet count	<150 x10^9 / L	<50 x10^9 / L	<50 x10^9 / L	<150 x10^9 / L OR >50% decrease from baseline platelet count	<150 x10^9 / L OR >50% decrease from baseline platelet count
D-dimer	Any value	D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)	D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)	D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)	D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)	D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)
Anti-PF4 antibodies	Positive anti-PF4 antibodies (with ELISA) or PF4 enhanced platelet functional assay	Positive anti-PF4 antibodies (with ELISA) or PF4 enhanced platelet functional assay	No anti-PF4 or negative test	No anti-PF4 or negative test	No anti-PF4 or negative test	No anti-PF4 or negative test
Blood smear	Any result	Any result	Any result	Small platelet aggregates	Small platelet aggregates	Small platelet aggregates OR No laboratory

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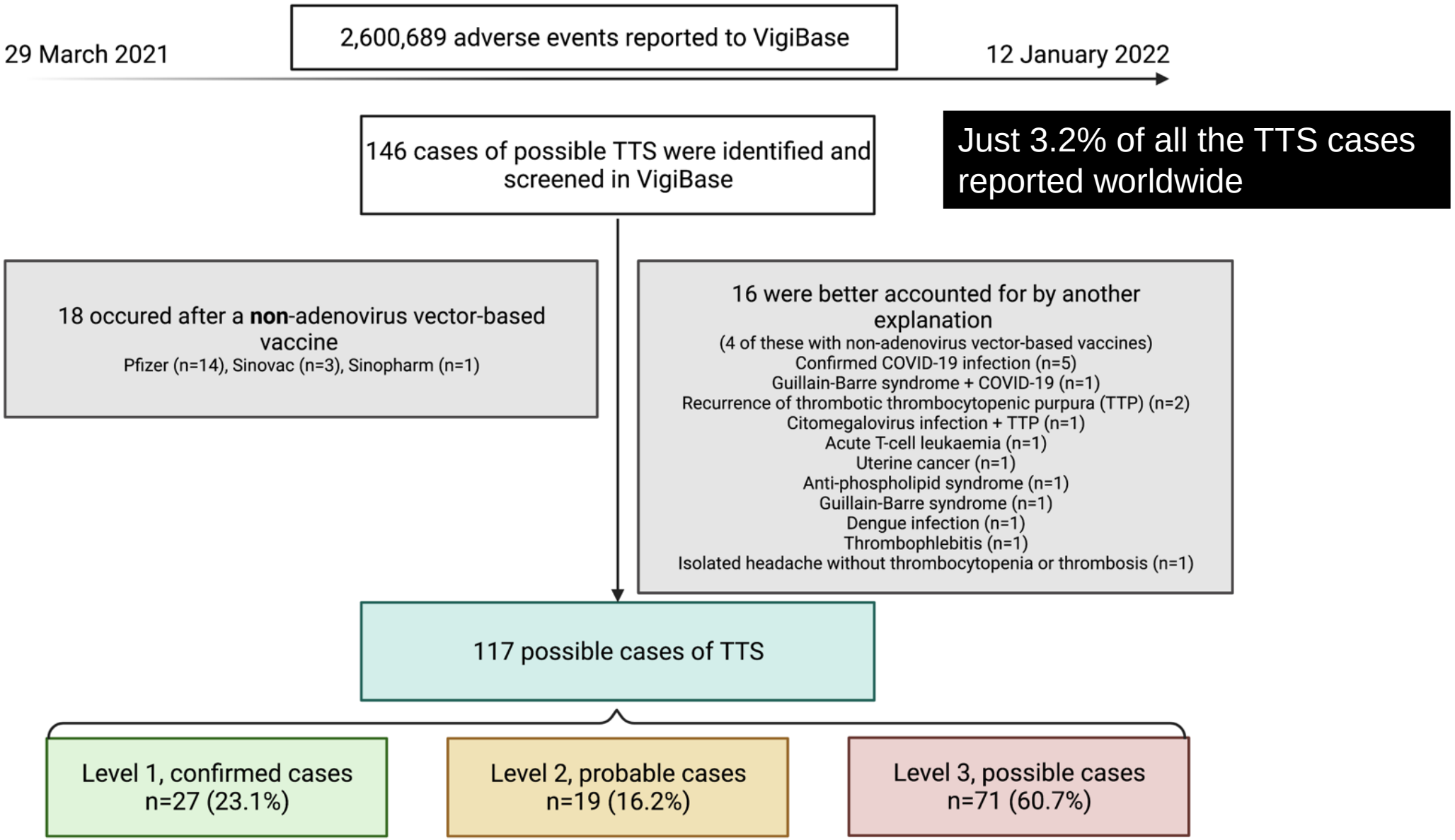
VigiBase analysis



VigiBase analysis

Variable	Results (n=117)
Age (median – IQR)	42 (32-48.5) years, range: 19-84
Female sex (n, %)	69 (59%)
Employed vaccine (name, %)	AstraZeneca 106 (90.6%) Janssen 10 (8.5%) Sputnik V 1 (0.9%)
Presence of thrombosis risk factors (n, %)	36 (29.9%)
Median time between vaccination and onset (median – IQR)	9 (5-12) days
Thrombosis location	Intracranial hemorrhage 28 (23.9%) Cerebral veins 23 (19.7%) Pulmonary arteries 21 (17.9%)
Treatment	Non-heparin based anticoagulants 21 (17.9%) Heparin-based anticoagulants 14 (12%) IVIG 11 (9.4%) Steroids 11 (9.4%)
Mortality (n, %)	**37 (31.6%)**

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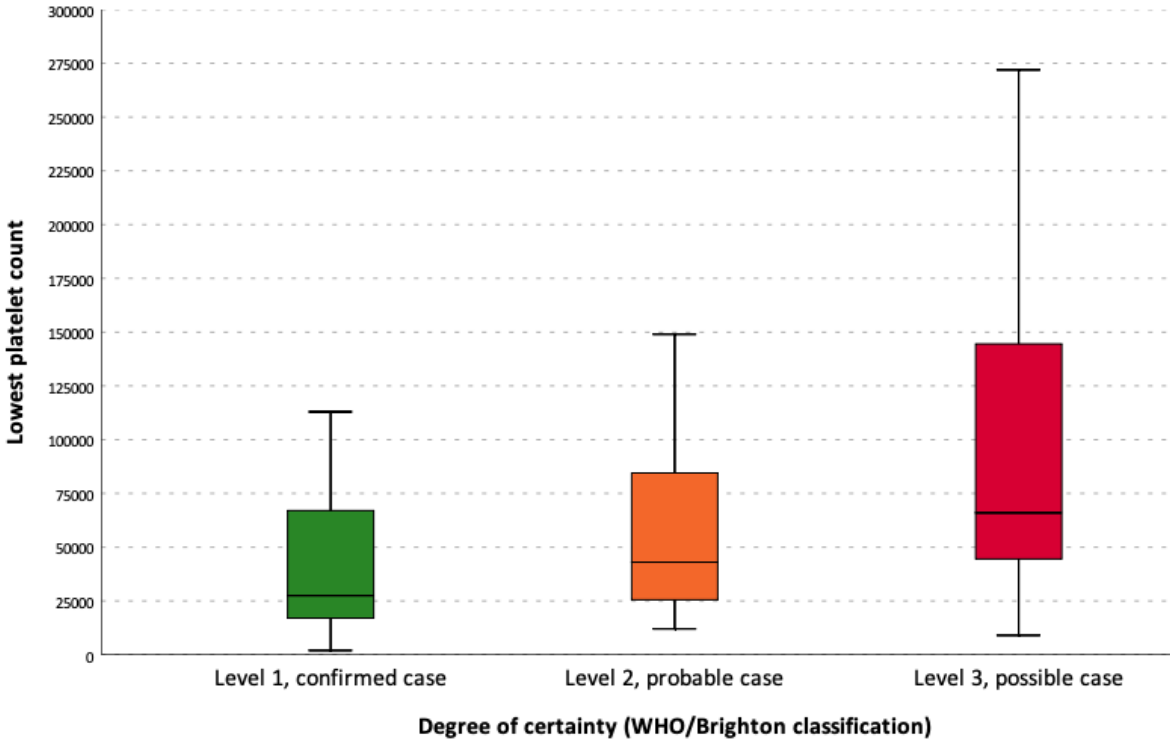
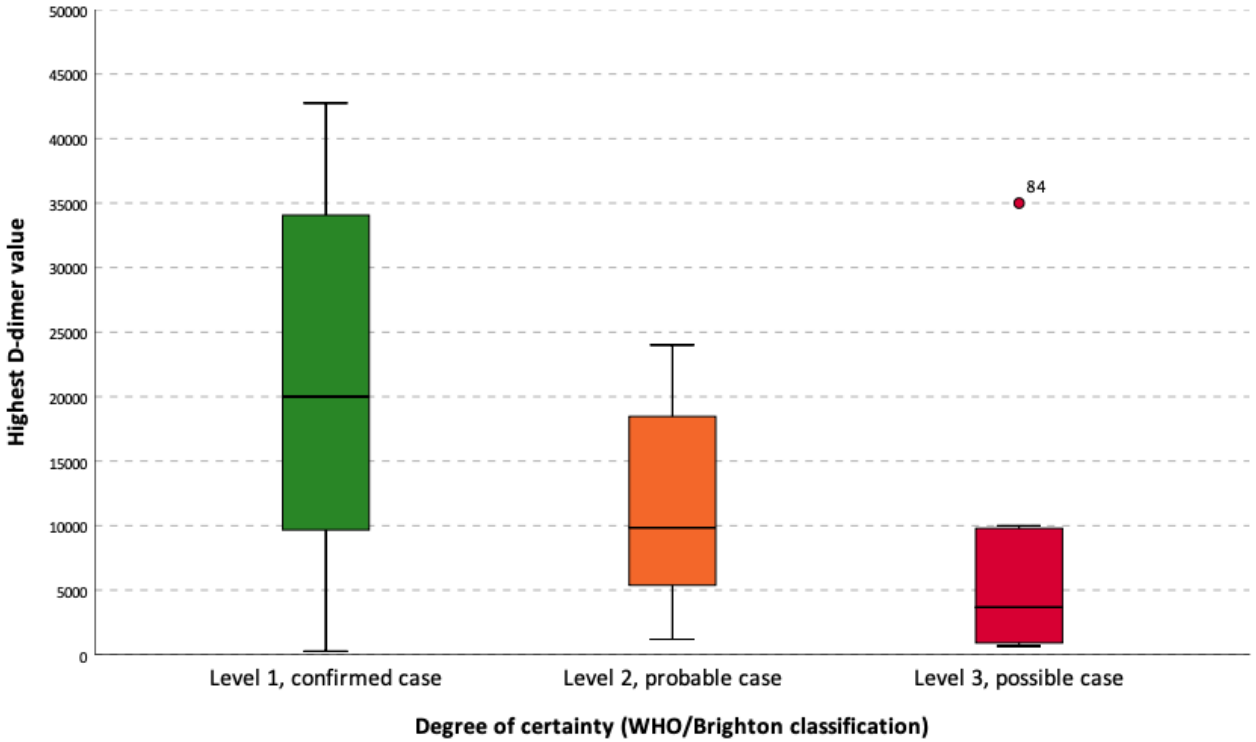
VigiBase analysis – laboratory parameters





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Treatment: Summary of findings

Population: Patients diagnosed with TTS following COVID-19 vaccination

Comparator: Patients **not treated** with the treatment of interest in each question

Intervention: Treatment with

1) Non-heparin-based anticoagulants
2) IVIG
3) Steroids
4) Platelet transfusion
5) Heparin-based anticoagulants

Outcomes:

1) Recovery
2) Death (all-cause)
3) Intracranial hemorrhage

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Evidence-to-decision tables: Heparin

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recovery									
25	observational studies	serious[a]	serious[b]	serious[c]	serious[d]	publication bias strongly suspected	In the case of heparin, 25 studies (9 case reports and 16 case series), including 587 patients with TTS, provided valid data for recovery rate, including 145 patients treated with heparin, and 19 studies (11 case series and 8 case reports), including 450 patients with TTS, provided specific data for recovery, including 107 patients treated with heparin. Recovery rate in the treated arm was: 69.2% (95% CI: 59.4-77.5%), while in patients not treated with heparin was: 58.3% (95% CI: 52.9-63.5%).	⊕◯◯◯ Very low	CRITICAL
Death									
26	observational studies.	serious[a]	serious[b]	serious[c]	serious[d]	publication bias strongly suspected	In the case of heparin, 26 studies (10 case reports and 16 case series), including 588 patients with TTS, provided valid data for death rate, including 146 patients treated with heparin, and 22 studies (13 case series and 9 case reports), including 465 patients with TTS, provided specific data for death, including 115 patients treated with heparin. Death rate in treated patients was 24.3% (95% CI: 17.0-33.4%), and death rate in non-treated patients it was 31.3% (95% CI: 26.7-36.6%).	⊕◯◯◯ Very low	CRITICAL
Hemorrhage									
25	observational studies	serious[a]	serious[b]	serious[c]	serious[d]	publication bias strongly suspected	In the case of heparin, 25 studies provided evidence, including 9 case reports and 16 case series, including 2-220 patients, among which, 19 studies provided specific information about patients treated with heparin. Hemorrhage rate was 34.1% (95% CI: 20.9-50.0%) in treated patients and 27.5% (95% CI: 19.9-36.5%) in non-treated patients.	⊕◯◯◯ Very low	CRITICAL

Explanations

a. Risk of Bias: Downgraded once for selection bias and reporting bias. The initial reports tended to publish the cases which had a fatal outcome. In the present update, large series could balance these results. In most studies, not all confounding factors (age, setting, time between diagnosis and treatment onset) were adjusted for in the analyses. Due to the observational nature of the data, it was not possible adjusting the risk of each outcome to other relevant variables, including age, comorbidities or the rest of the received treatment.
b. Inconsistency: Downgraded once. Although statistical heterogeneity could not be assessed as no meta-analysis was conducted, there was clinical heterogeneity (different treatment paradigms, location, and severity of thromboses) and methodological heterogeneity between studies. Duration of follow-up was different, and in the case of recovery, the definition of recovery was not always harmonized, and in some studies, “recovered” patients could present some sequelae.
c. Indirectness: Downgraded once. The final outcome was not available at the moment of publication in many cases in many/several studies. Most cases came from high-income countries, except for the VigiBase analysis.
d. Imprecision: Downgraded once. The confidence interval of the treated group crossed the confidence interval of the non-treated group .
d. Confidence interval was large
Is this theoretical or was it reported?
Both, it is explicitly mentioned in some studies. I think that it is not mandatory to specifically say which ones.
See above. The GRC will specifically look at how imprecision was judged as they know this is not done well, so revise this and note that the CI was greater than 5% or whatever you choose in both directions

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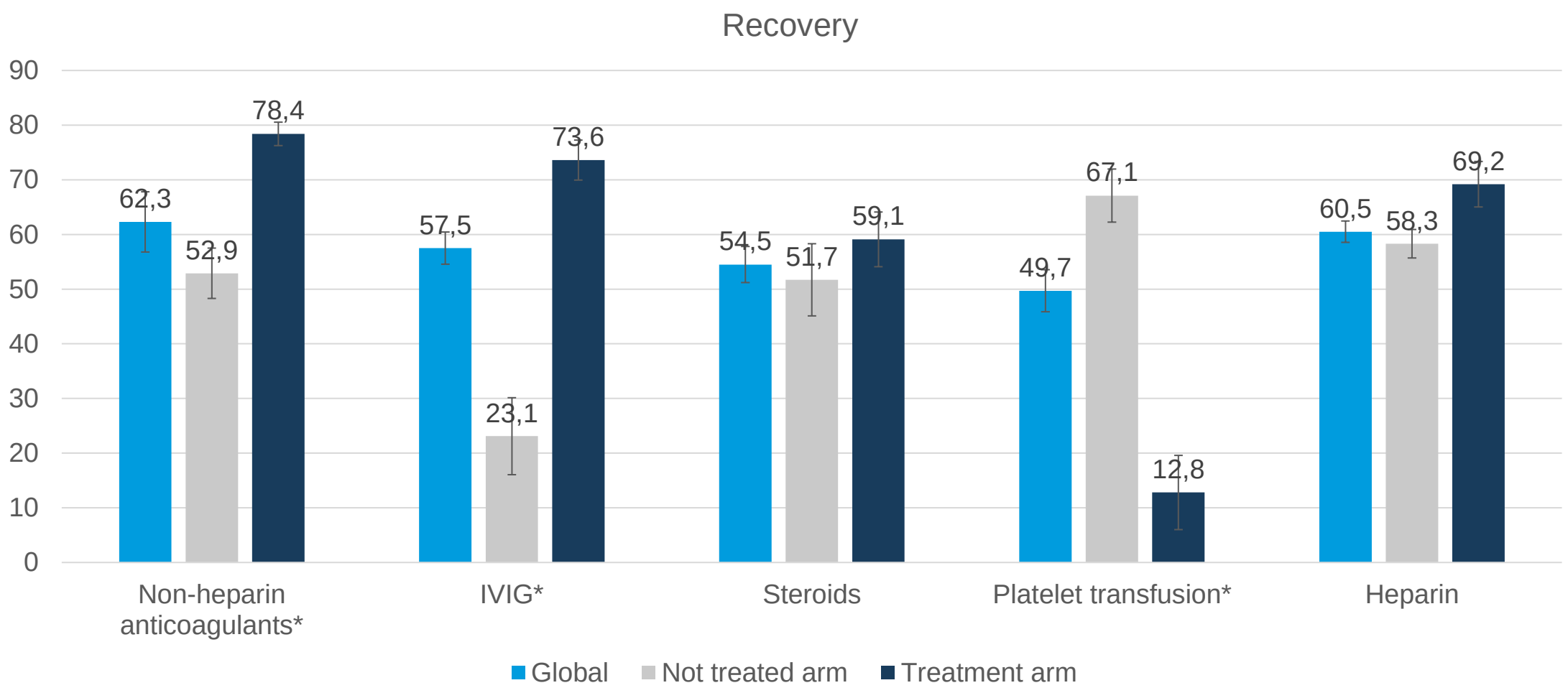
Outcome recovery



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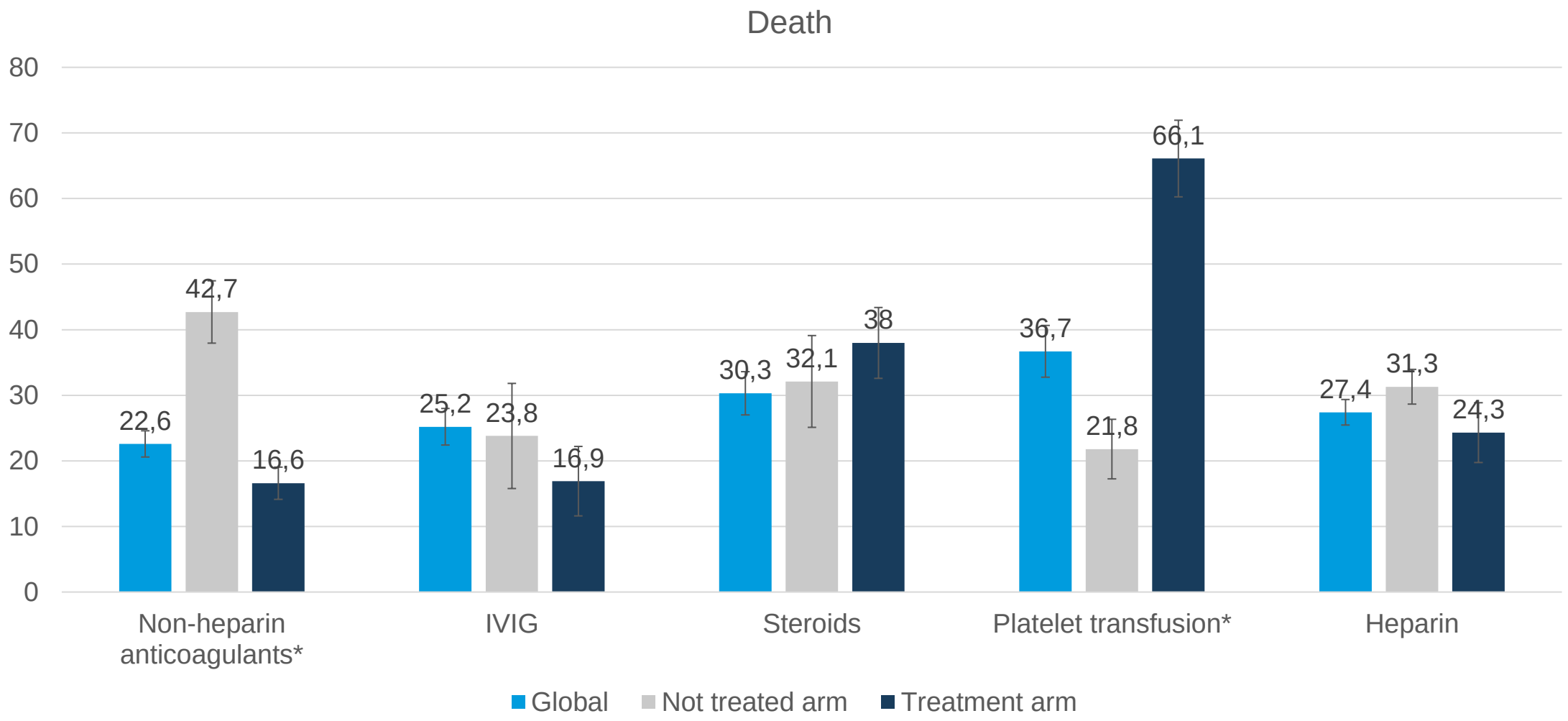
Outcome death



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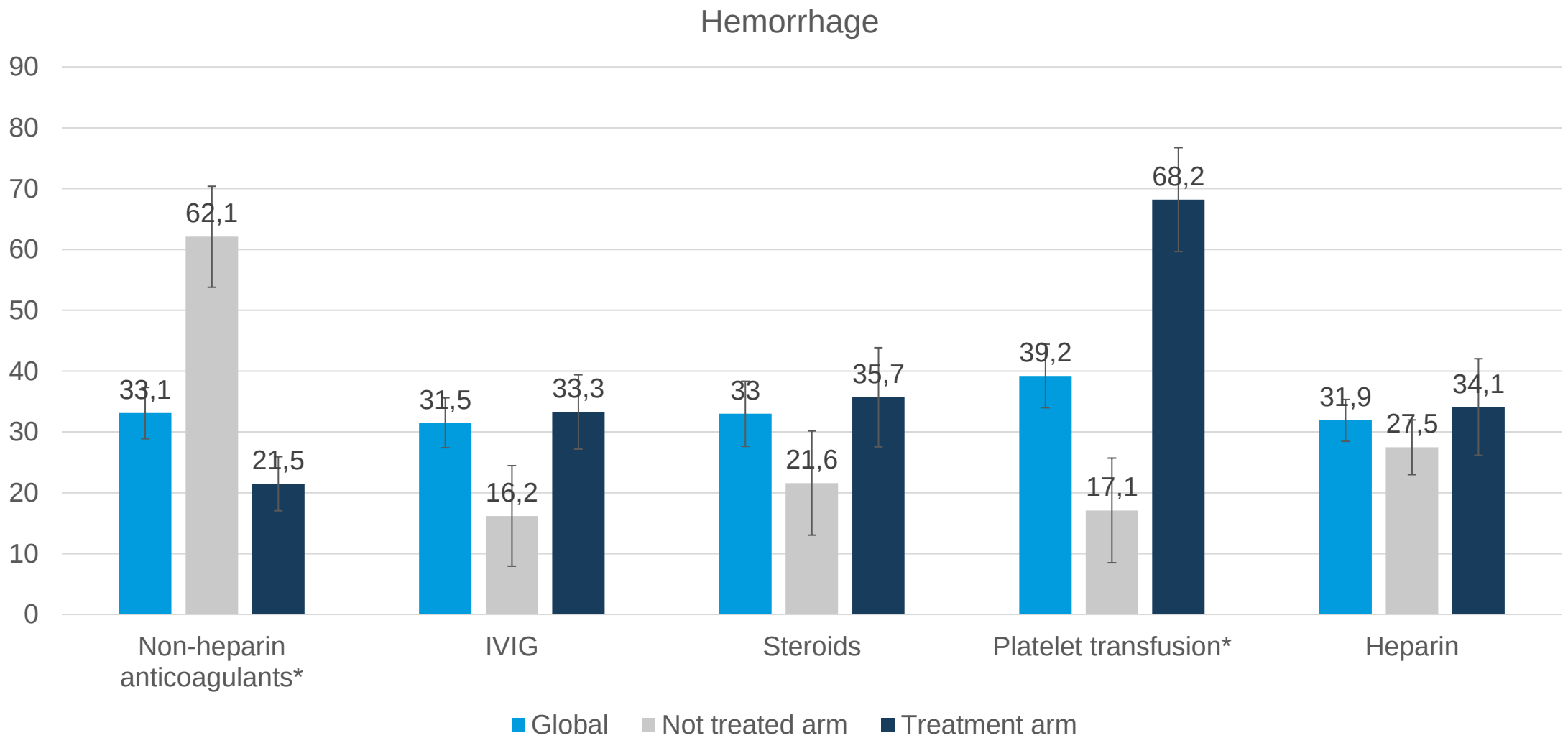
Outcome haemorrhage



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Treatment recommendations

- **IVIG and non-heparin-based anticoagulants (NHAC) should be used for individuals with TTS following vaccination with a COVID-19 vaccine** *(strong, very low certainty)*

- **Heparin may be used for anti-coagulation for individuals with TTS following vaccination with a COVID-19 vaccine** *(conditional, very low certainty)**
  - *REMARKS*
    *****This is applicable to settings were NHAC are not available***
  - **Given the ongoing vaccination roll-out and the risk of TTS,* ***countries should attempt to procure and make NHAC and IVIG available***

- **Platelet infusion should not be used for individuals with TTS following vaccination with a COVID-19 vaccine in all cases other than emergency situations where it is strongly indicated (active bleeding */* requirement for surgery)** *(strong, very low certainty)*

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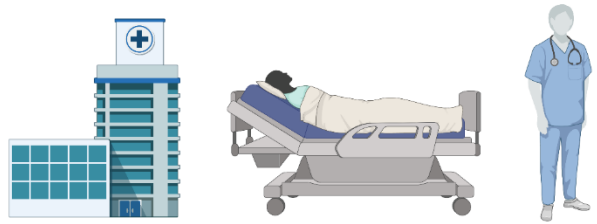
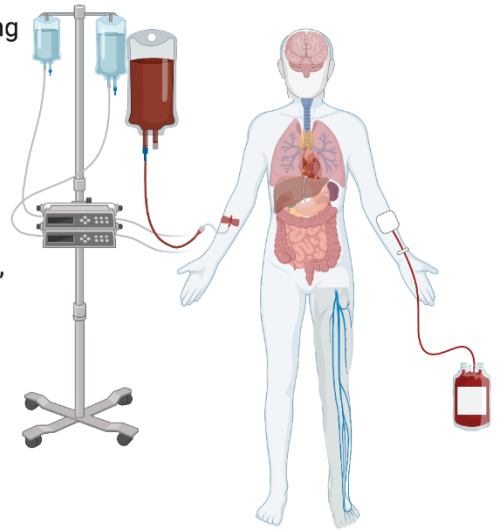
TTS treatment and work-up



Patients should be hospitalized and closely monitored

Avoid vitamin K antagonists
E.g. Warfarin or acenocoumarin

Avoid platelet transfusions
In all cases other than emergency situations where surgery is strongly indicated or there is an active bleeding

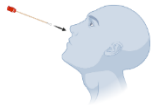


Anticoagulate the patient

Preferably with non-heparin based anticoagulants
Argatroban, bivalirudin, fondaparinux, danaparoid, rivaroxaban, apixaban, dabigatran

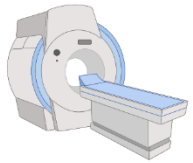
Or with heparin based anticoagulation
In settings where NHBA are not available

Administer IV Immunoglobulins
1 g/kg x 2 days or 0.4g/kg x 5 days



PCR test for COVID-19

Monitor platelet count and D-dimer



Complete examinations per patient

Report the case

Additional content of the guideline

- Public and patient-centered communication on TTS
  - Targeted to health workforce
    - Diagnosis, treatment, communication.
- Management in special populations
  - Pregnancy and lactation
  - Children
    - Limited evidence

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Thank you