



Mayo Clinic Cancer Center  
Jacksonville, FL

# MEDICAL THERAPIES FOR COVID RELATED THROMBOEMBOLIC DISEASE

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## **DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY**

- Nothing to disclose

## **REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS**

- Nothing to disclose

# LEARNING OBJECTIVES

- Review treatment options for COVID19 associated thromboembolism
- Discuss prophylactic anticoagulation treatment for hospitalized patients with COVID19
- Discuss treatment of COVID19 vaccine induced thrombotic syndrome

# COVID related Thromboembolism (TE)

- Hypercoagulable state
- Large vessel thrombosis and *in situ* microthrombi
- Aug 2020 meta analysis of hospitalized pts prevalence 9.5% (18.7% in ICU) without screening ultrasound and 40% (45.6% in ICU) with screening
- Lower risk reported in later studies
- Risk of TE increases with age, malignancy, obesity, increasing d dimer

# Treatment of COVID- related venous thromboembolism (VTE)

- Same as non- COVID related VTE



**2 wks**

**3-6 months**

**beyond 6 months**

Consider LMWH or heparin for Initial treatment of hospitalized patient

Consider tPA for Initial treatment with massive PE, proximal lower extr. DVT

Primary treatment 3-6 months preferably DOAC over VKA

Consider secondary prevention in high risk patients

# Anticoagulation caveats

- VKA preferred in renal failure, antiphospholipid syndrome, mechanical valves
- Rivaroxaban and Apixaban can interact with Ritonavir (Paxlovid) – consider alternative antiviral or alternative anticoagulant

# Thromboembolism prophylaxis

- All hospitalized patients
- LMWH preferred over UFH
- Intensity dependent on severity of illness: prophylactic, intermediate or therapeutic
- Consider AC escalation in certain clinical scenarios (i.e. clotting of vascular access)

# MPT of Therapeutic Anticoagulation (AC) with Heparin in Critically Ill and Noncritically Ill Patients with Covid-19

N Engl J Med 2021; 385:777-789 DOI: 10.1056/NEJMoa2103417

N Engl J Med 2021; 385:790-802 DOI: 10.1056/NEJMoa2105911

Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (**REMAP-CAP**)

A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (**ACTIV-4a**)

Antithrombotic Therapy to Ameliorate Complications of Covid-19 (**ATTACC**) trial.



# MPT of Therapeutic Anticoagulation (AC) with Heparin in Patients with Covid-19

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## CRITICALLY ILL

- 1098 patients (534 therapeutic AC vs 564 usual thromboprophylaxis)
- Median organ support–free days 1 on therapeutic AC vs 4 on usual thromboprophylaxis (OR 0.83; 95% CI, 0.67 to 1.03)
- Similar survival to hospital discharge 62.7% vs 64.5% (OR 0.84; 95% CI, 0.64 to 1.11).
- Major bleeding 3.8% vs 2.3%

## NONCRITICALLY ILL

- 2219 (1048 therapeutic vs 1171 prophylactic)
- 79.3% therapeutic AC vs 75.4% thromboprophylaxis survived until hospital discharge without receipt of organ support during the first 28 days (99.1% probability effect)
- Survival till discharge 92.7% vs 91.% (87.1% probability effect of therapeutic AC)
- Major thrombotic event or in-hospital death 8.0% vs 9.9%

# Critically ill patients with COVID INSPIRATION trial

JAMA. 2021;325(16):1620-1630. doi:10.1001/jama.2021.4152

- 562 patients in ICU with COVID-19 randomized to intermediate vs prophylactic dose AC
- **45.7%** in the intermediate-dose AC vs **44.1%** prophylactic anticoagulation group had occurrence of primary outcome (composite of adjudicated venous or arterial thrombosis, treatment with ECMO, or mortality within 30 days), **OR 1.06**

# Non Critically Ill Patients with COVID

## RAPID trial

BMJ 2021;375:n2400

- 465 hospitalized non-ICU patients with elevated D-dimer randomized to therapeutic or prophylactic dose heparin
- **primary outcome** (composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or ICU admission) **16.2% vs 21.9%** (OR, 0.69; 95% CI, 0.43-1.10; **p=0.12**)
- Deaths: 1.8% therapeutic heparin vs 7.6% prophylactic heparin (0.22, 0.07 to 0.65; P=0.006)
- Venous thromboembolism: 0.9% vs 2.5% (0.34, 0.07 to 1.71; P=0.19)
- Major bleeding: 0.9% vs 1.7% (0.52, 0.09 to 2.85; P=0.69)

# HIGH Risk Patients with COVID

## HEP-COVID trial

JAMA Intern Med. 2021;181(12):1612-1620

- 257 pts with COVID randomized to therapeutic vs prophylactic and intermediate AC
- Primary outcome (venous and arterial thromboembolism or death) met in 28.7% vs 41.9% patients
- Death: 19.4% vs 25 %
- Thromboembolism: 10.9% vs 29% ( RR 0.37; 95% CI, 0.21-0.66;  $P < .001$ )
- Major bleeding: 4.7% vs 1.6% (RR 2.88; 95% CI, 0.59-14.02;  $P = .17$ )
- The primary efficacy outcome was **not reduced in ICU** patients (55.3% vs 51.1%; RR, 0.92; 95% CI, 0.62-1.39;  $P = .71$ ).

# What about non hospitalized patients?

JAMA 2021 Nov 2;326(17):1703-1712

*Lancet* 2022; 399: 50–59

- **ACTIV-4B** trial did not show reduction of events between ASA, Apixaban and placebo
- **MICHELLE** trial compared prophylactic Rivaroxaban 10 mg daily vs no AC in pts with high IMPROVE VTE score

primary efficacy outcome (venous and arterial TE and CV death at day 35) occurred in 3% of Rivaroxaban pts vs 9% of pts w/out AC (RR 0.33, 95% CI 0.12–0.90; p=0.0293)

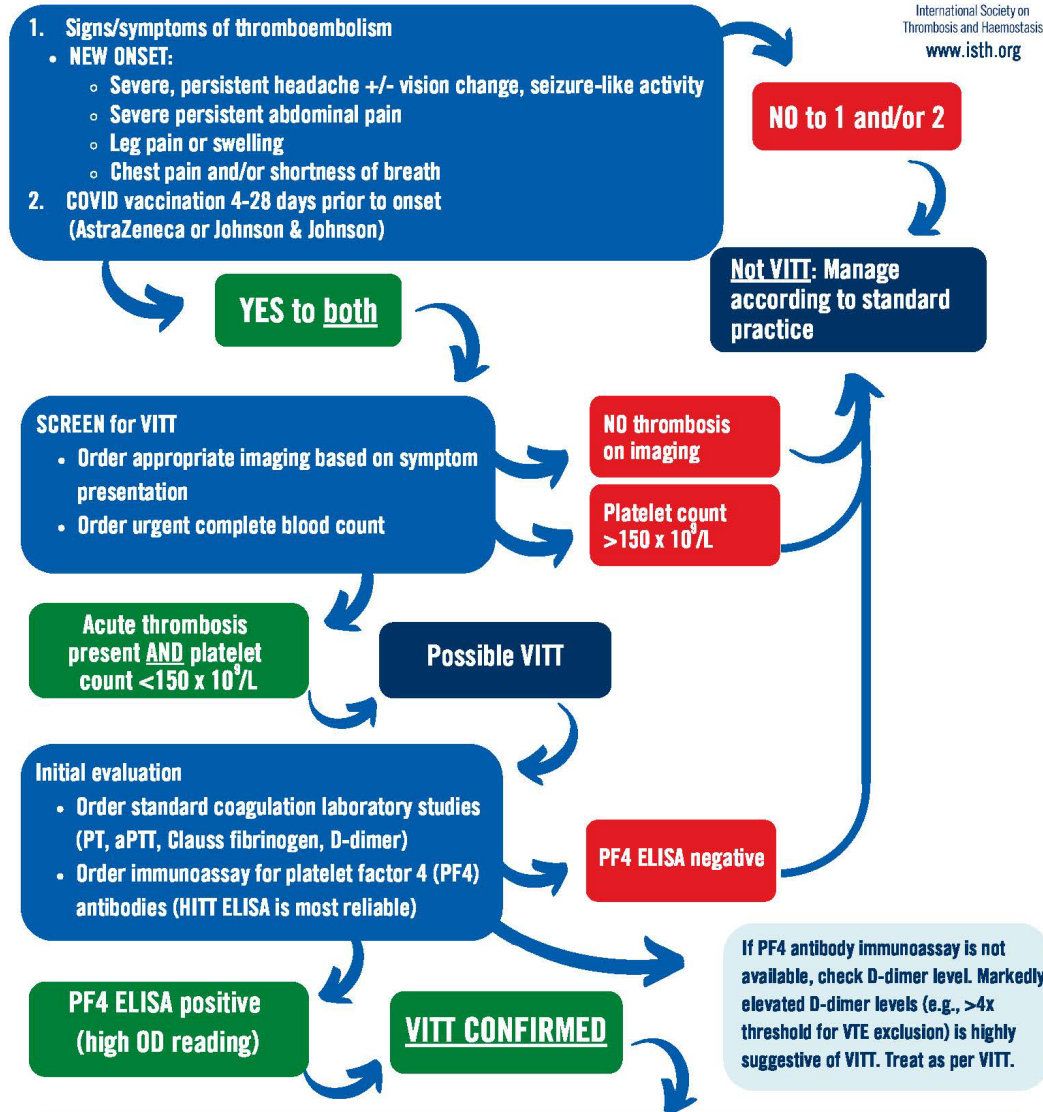
# Current ASH recommendations

<https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>

- advise that **critically ill patients in ICU receive standard prophylactic doses of anticoagulants**, since increased doses of heparin do not confer a benefit for preventing progression of COVID-19 or death (conditional recommendation based on very low certainty in the evidence of effects)
- For **hospitalized patients not requiring ICU care (...)** ASH draft guideline panel **suggests using therapeutic-intensity anticoagulation** (conditional recommendation based on very low certainty in the evidence about effects)

**What about vaccine associated thrombosis?**

## Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Diagnostic Flow Chart (Updated 20 April, 2021)



# VITT Diagnostic criteria

COVID vaccine 4 to 42 days prior to symptom onset<sup>#</sup>

Any venous or arterial thrombosis (often cerebral or abdominal)

Thrombocytopenia (platelet count < 150 x 10<sup>9</sup>/L)\*

Positive PF4 “HIT” (heparin-induced thrombocytopenia) ELISA

ELISA

Markedly elevated D-dimer (> 4 times upper limit of normal)

<https://www.isth.org/news/561406/The-ISTH-Releases-Interim-Guidance-on-Vaccine-Induced-Immune-Thrombotic-Thrombocytopenia-VITT-.htm>

<https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia>

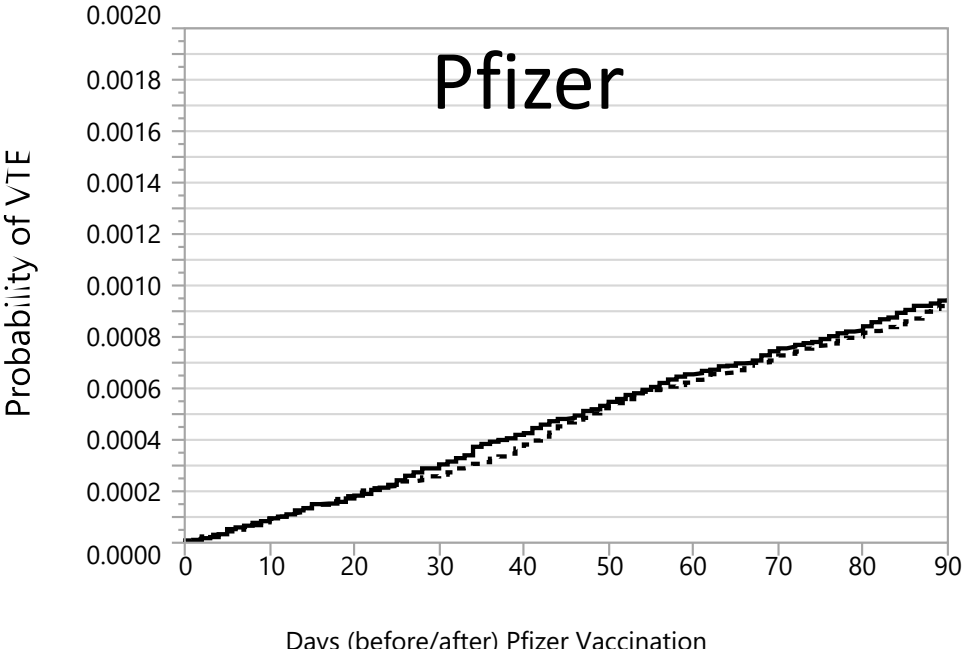


# VITT Treatment

- Avoid heparin or LMWH; use direct thrombin inhibitors or direct oral anticoagulants
- Avoid platelet transfusions
- IVIG mg/kg daily for 2 days
- Consider Dexamethasone 40 mg x 4 d
- Consider plasma exchange if no response to IVIG

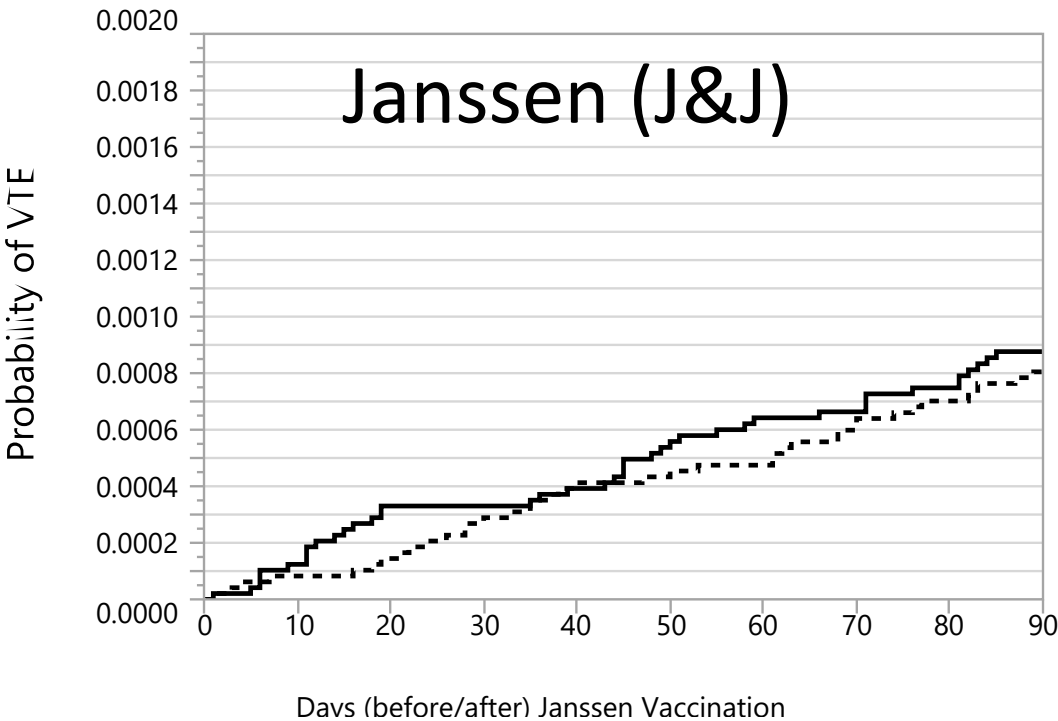
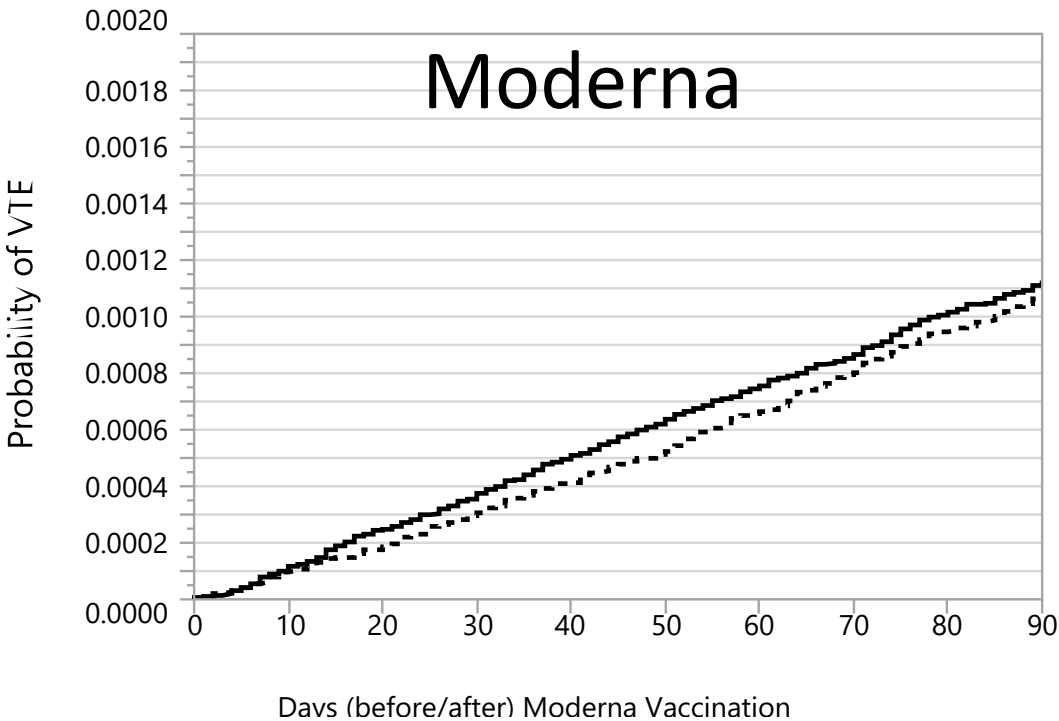
# No Increased Risk for Venous Thromboembolism

Janssen (J&J)	Moderna	Pfizer
N=48,453	N=290,607	N=452,950



— After

- - - Before



# In summary

- Thrombosis is a significant complication of COVID19, especially in hospitalized patients
- Prophylaxis is recommended in all patients; consider therapeutic dosing in select groups
- Anticoagulation treatment is similar to TE caused by other medical reasons
- Beware of rare Vaccine induced thrombotic complications, though overall vaccines do not appear to be related to higher VTE risk

# QUESTIONS & DISCUSSION

