Trombosi post vaccino Vs trombosi da Covid

CONGRESSO GIOVANI MEDICI SNAMI-4S
29-30 settembre
1 ottobre 2021

Dott. Vincenzo Bonasia
MEDICINA INTERNA 2
Azienda Sanitaria Universitaria Friuli Centrale

Trombosi da Covid

Febbre, tosse, polmonite

15% forma severa

5% ricovero in terapia intensiva per ARDS o MOF[1]

Fattori di rischio per evoluzione sfavorevole: età, sesso maschile, diabete mellito, ipertensione, malattie cardiovascolari[2]

Manifestazioni trombotiche: 5-30%[3]

[1]JAMA 2020;323
[2]BMJ 2020;369
[3]J Thomb Haemost. 2020

Trombosi da Covid-19

Malattia che comporta anomalie della coagulazione

D-dimero, piastrinopenia, aumento del PT

Casistica cinese di oltre 1000 pazienti[1]

D-dimero elevato nel 46%

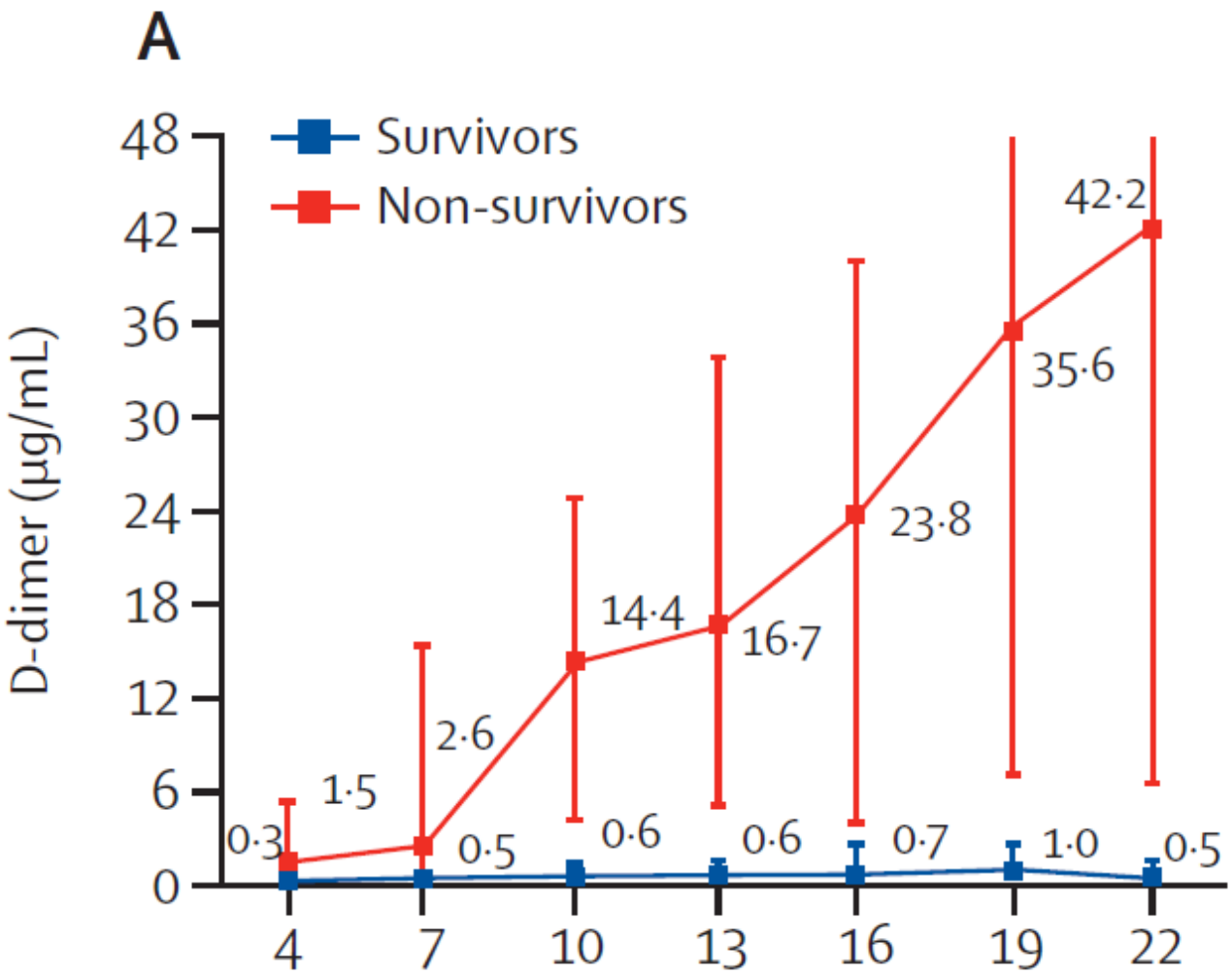
60% se ricoverati in terapia intensiva

Altre anomalie: aumento di fibrinogeno, f. VIII, NETs, iperviscosità

[1]NEJM 2020; 382

Trombosi da Covid-19

aumento del D-dimero e prognosi[1]



[1]Lancet 2020; 395

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 3058–3068
doi:10.1093/eurheartj/ehaa500

Pulmonary embolism in COVID-19 patients: a French multicentre cohort study

Table 3 **Multivariable analysis for prediction of PE occurrence**

	Odds ratio	95% CI	*P*-value
Male	1.03	1.003–1.069	**0.04**
Age	1.00	1.00–1.00	0.52
Smoking	0.96	0.91–1.00	0.08
Malignancy	0.98	0.93–1.03	0.46
Venous thrombo-embolic disease	1.00	1.00–1.01	0.52
Time from illness onset to hospitalization*, days	1.02	1.006–1.038	**0.002**
C-reactive protein†	1.03	1.01–1.04	**0.001**
Anticoagulation prophylactic dose introduced during the hospitalization	0.83	0.79–0.85	**<0.001**
Anticoagulation therapeutic dose before the hospitalization	0.87	0.82–0.92	**<0.001**

Trombosi da Covid-19

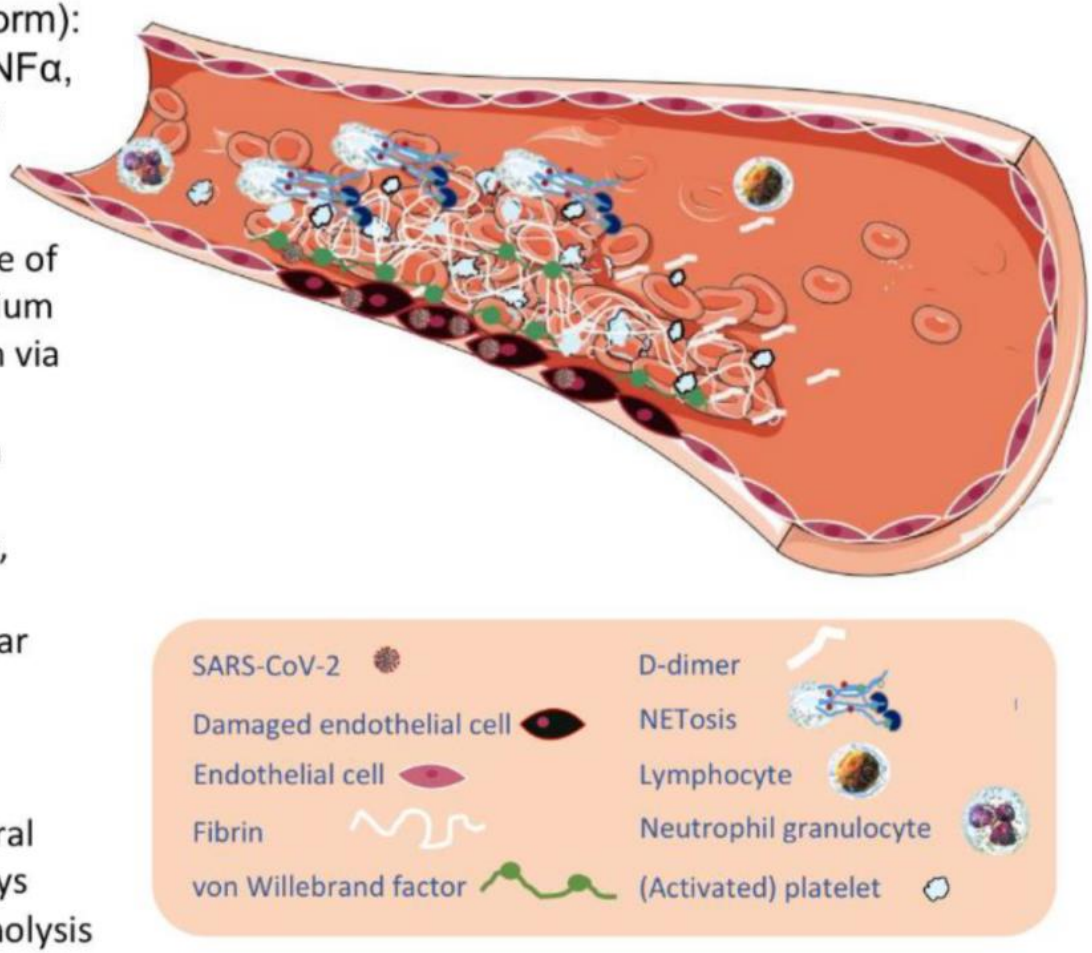
Coagulopatia associata al Covid

Pathomechanism

Excessive immune response (cytokine storm): elevated IL-1, IL-6, TNFα, chemokine levels

↓

- Activation and damage of the vascular endothelium
- Coagulation activation via multiple pathways ➔increased thrombin generation
- Activation of platelets, white blood cells
- Neutrophil extracellular trap formation
- Complement system activation
- Dysregulation of natural anticoagulant pathways
- Dysregulation of fibrinolysis



Laboratory findings

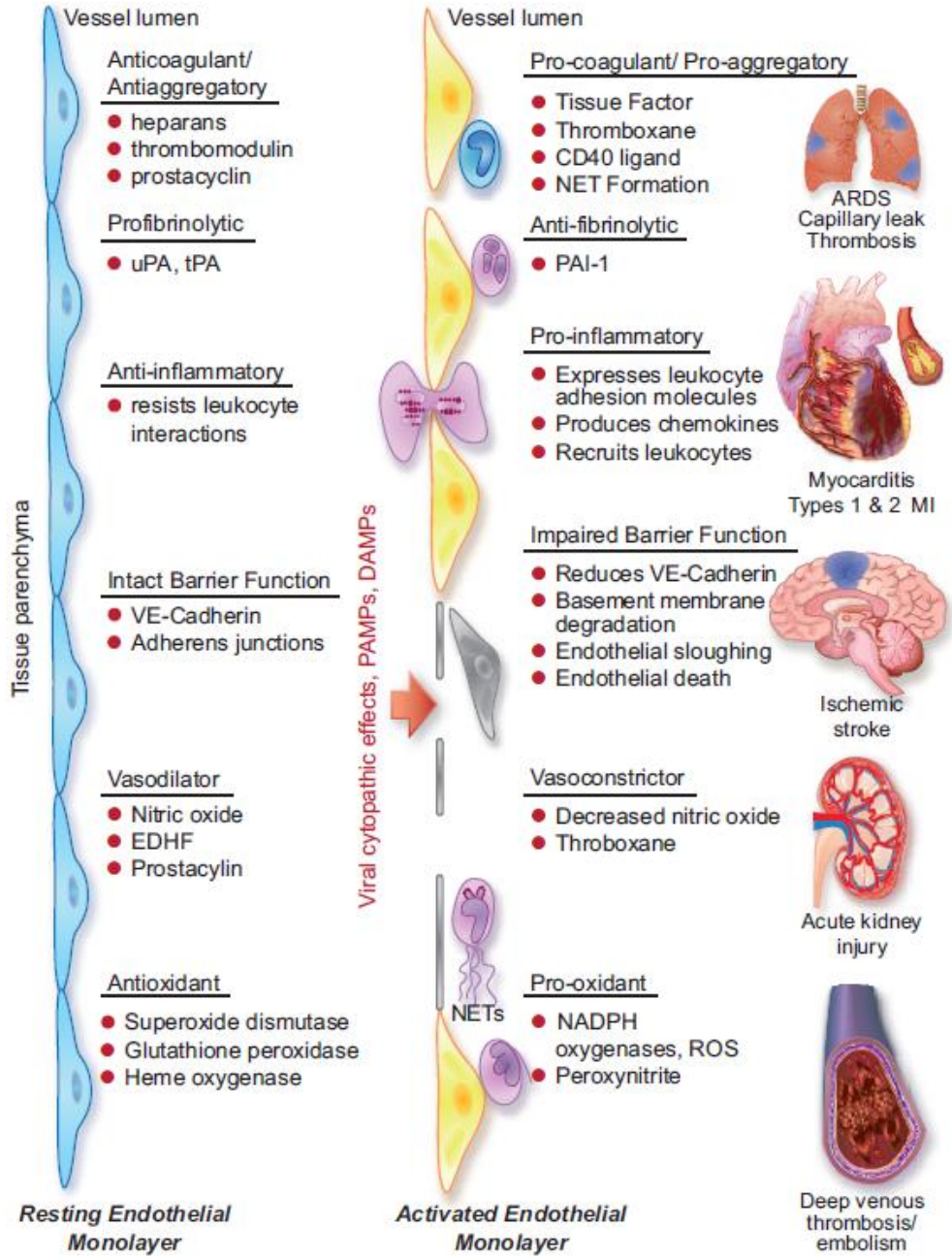
- Elevated D-dimer levels
- Increased FDP levels
- Slightly prolonged prothrombin time
- Thrombocytopenia, if present, is usually mild
- Elevated ferritin levels

J. Clin. Med. 2020, *9*

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 3038–3044
doi:10.1093/eurheartj/ehaa623

VIEWPOINT
Disease management

COVID-19 is, in the end, an endothelial disease



Trombosi da Covid-19

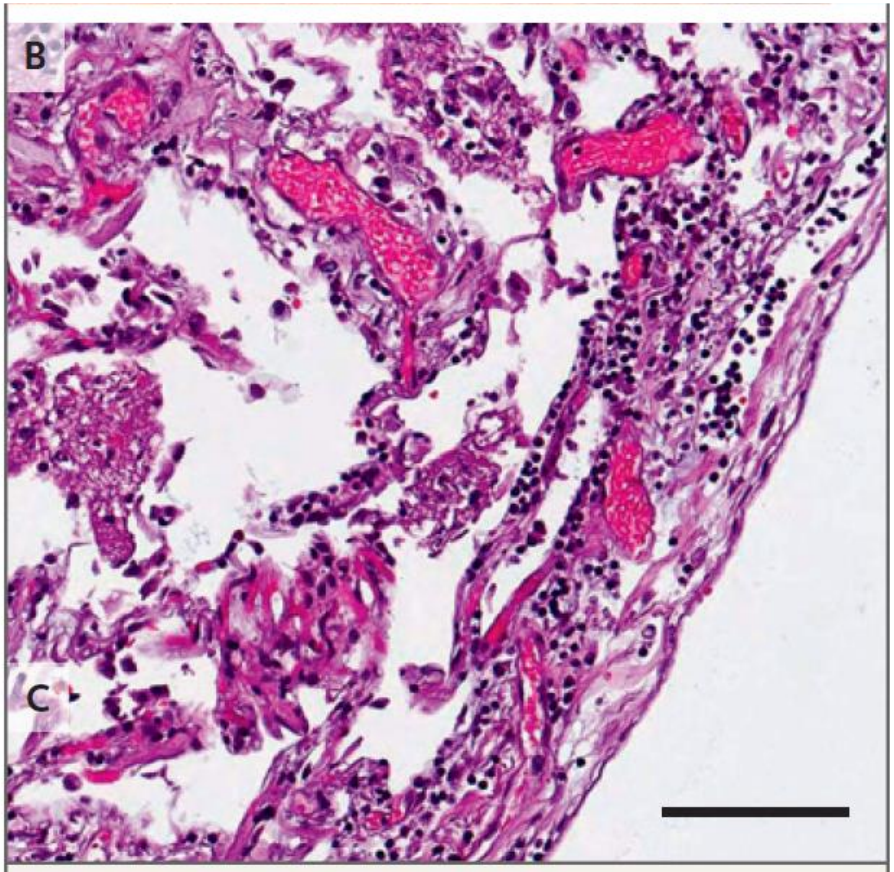


Figure 1. Lymphocytic Inflammation in a Lung from a Patient Who Died from Covid-19.

positive cells per field of view, in uninfected control lungs showed scarce expression of ACE2 in alveolar epithelial cells (0.053±0.03) and capillary endothelial cells (0.066±0.03). In lungs from

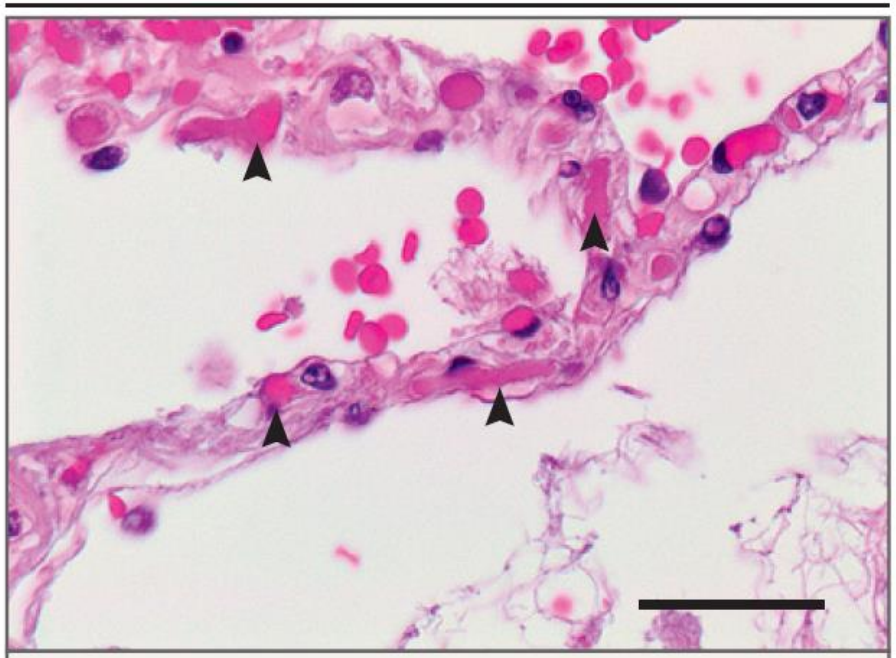


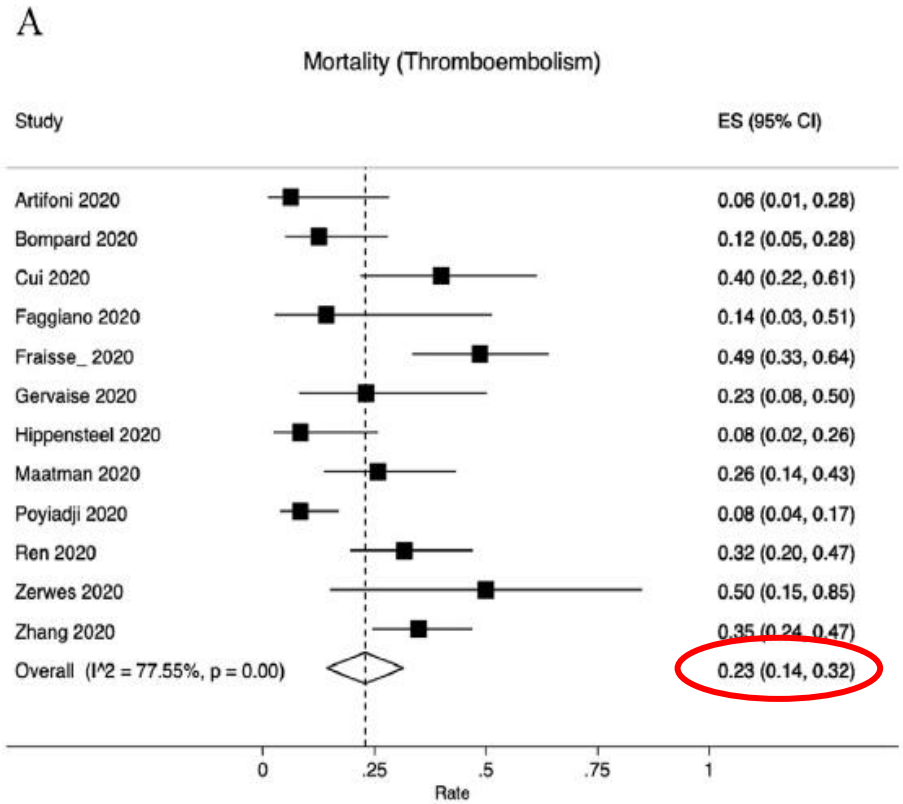
Figure 2. Microthrombi in the Interalveolar Septa

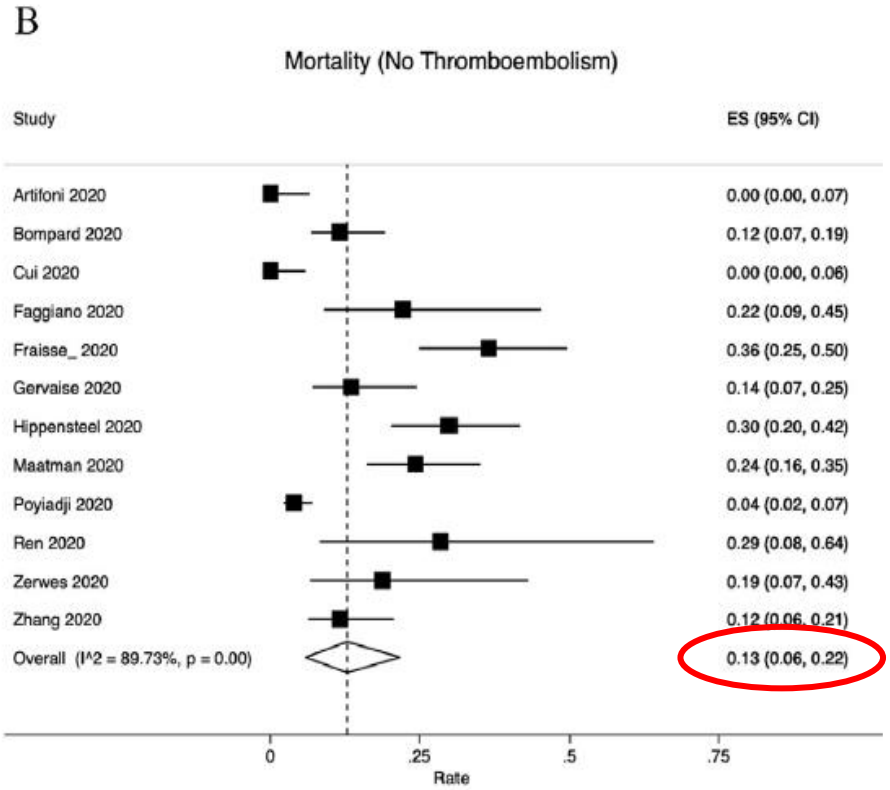
N Engl J Med 2020;383.

Research Paper

Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis

42 studi, oltre 8mila pazienti
TVE: 21%; 31% in Terapia Intensiva
Trombosi arteriose: 2%; 5% in Terapia Intensiva





EClinicalMedicine 2020; 2930

Trombosi da Covid-19

… non solo venosa

Trombosi arteriose

I primi dati provenienti da Wuhan: ictus, 5%

Il più grande studio ha incluso 3300 pz (800 ICU)

- ictus: 1.6%
- IMA: 9%;

Tali eventi si associano ad aumento della mortalità HR 1.99[1]

Review

Stroke as a Potential Complication of COVID-19-Associated Coagulopathy: A Narrative and Systematic Review of the Literature

Journal of *Clinical Medicine*

[1]JAMA. 2020;324

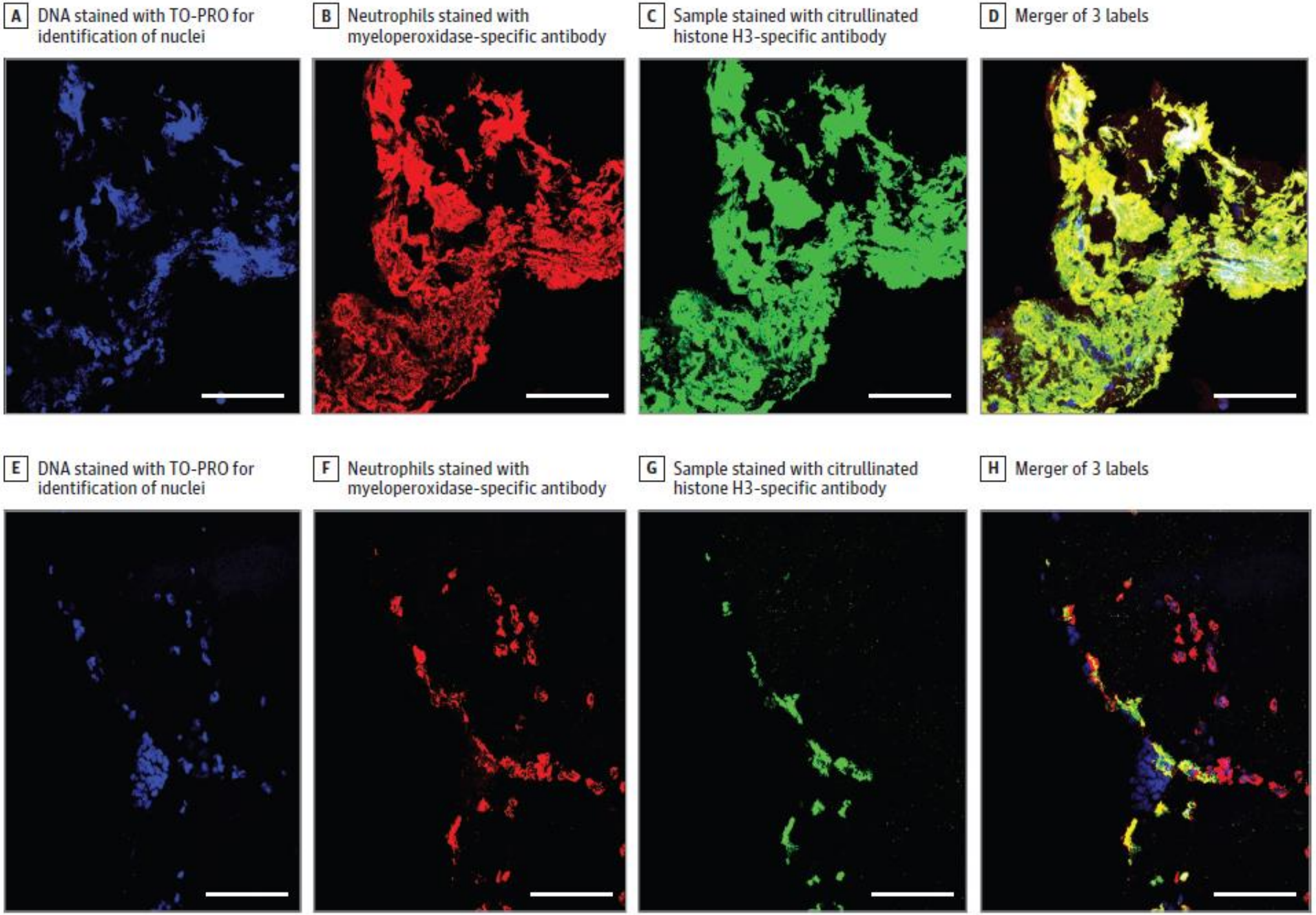
Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

Table 1. Clinical Characteristics of Five Young Patients Presenting with Large-Vessel Stroke.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age — yr	33	37	39	44	49
Sex	Female	Male	Male	Male	Male
Medical history and risk factors for stroke†	None	None	Hyperlipidemia, hypertension	Undiagnosed diabetes	Mild stroke, diabetes
Medications	None	None	None	None	Aspirin (81 mg), atorvastatin (80 mg)
NIHSS score‡					
On admission	19	13	16	23	13
At 24 hr	17	11	4	19	11
At last follow-up	13 (on day 14)	5 (on day 10)	NA; intubated and sedated, with multiorgan failure	19 (on day 12)	7 (on day 4)
Outcome status	Discharged to rehabilitation facility	Discharged home	Intensive care unit	Stroke unit	Discharged to rehabilitation facility
Time to presentation — hr	28	16	8	2	8
Signs and symptoms of stroke	Hemiplegia on left side, facial droop, gaze preference, homonymous hemianopia, dysarthria, sensory deficit	Reduced level of consciousness, dysphasia, hemiplegia on right side, dysarthria, sensory deficit	Reduced level of consciousness, gaze preference to the right, left homonymous hemianopia, hemiplegia on left side, ataxia	Reduced level of consciousness, global dysphasia, hemiplegia on right side, gaze preference	Reduced level of consciousness, hemiplegia on left side, dysarthria, facial weakness
Vascular territory	Right internal carotid artery	Left middle cerebral artery	Right posterior cerebral artery	Left middle cerebral artery	Right middle cerebral artery

NEJM 2020; 382

Figure. Immunofluorescence of Neutrophil Extracellular Traps in Thrombi Aspirated During Primary Coronary Intervention in Patients With ST-Elevated Myocardial Infarction



Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

CONCLUSIONS

In noncritically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis. (ATTACC, ACTIV-4a, and REMAP-CAP ClinicalTrials.gov numbers, NCT04372589, NCT04505774, NCT04359277, and NCT02735707.)

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

CONCLUSIONS

In critically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual-care pharmacologic thromboprophylaxis. (REMAP-CAP, ACTIV-4a, and ATTACC ClinicalTrials.gov numbers, NCT02735707, NCT04505774, NCT04359277, and NCT04372589.)

Anticoagulazione nei non ricoverati?

PADUA score (rischio TVP in pazienti ricoverati)

PADUA PREDICTION SCORE (PPS)	
Cancro attivo	+3
TEV precedente (no TVS)	+3
Ipomobilità > 3 giorni	+3
Trombofilia nota	+3
Trauma e/o chirurgia recente (< 1 mese)	+2
Età> 70 anni	+1
Insuff. cardiaca e/o respiratoria	+1
IMA o Stroke	+1
Infezione acuta e/o patologia reumatica	+1
Obesità (BMI> 30)	+1
Trattamento ormonale in atto	+1
PUNTEGGIO TOTALE	❑ ≥ 4 ALTO RISCHIO TEV ❑ < 4 BASSO RISCHIO TEV

Trombosi da vaccino

In linea generale, gli eventi tromboembolici venosi occorsi in soggetti vaccinati con Vaxzevria (Astra Zeneca) e con il vaccino Janssen non sono risultati più frequenti rispetto a quelli attesi nella popolazione non vaccinata. **Tuttavia sono stati accertati casi del tutto peculiari…**

***Trombocitopenia Trombotica Indotta dal Vaccino* (VITT) *o Sindrome Trombotica con Trombocitopenia* (TTS)**

- Sindrome caratterizzata da trombosi venose e arteriose, in particolare in sedi inusuali, come le vene cerebrali e splancniche.
- Caratteristiche peculiari che ricordano la HIT
- Descritta per la prima volta in seguito a vaccinazione con Vaxzevria

Trombocitopenia Trombotica Indotta da Vaccino

In base ai dati EMA e UK l'incidenza stimata è di 1 ogni 100mila-250mila vaccini, anche se è un dato incerto

L'incidenza della trombosi del seno venoso cerebrale

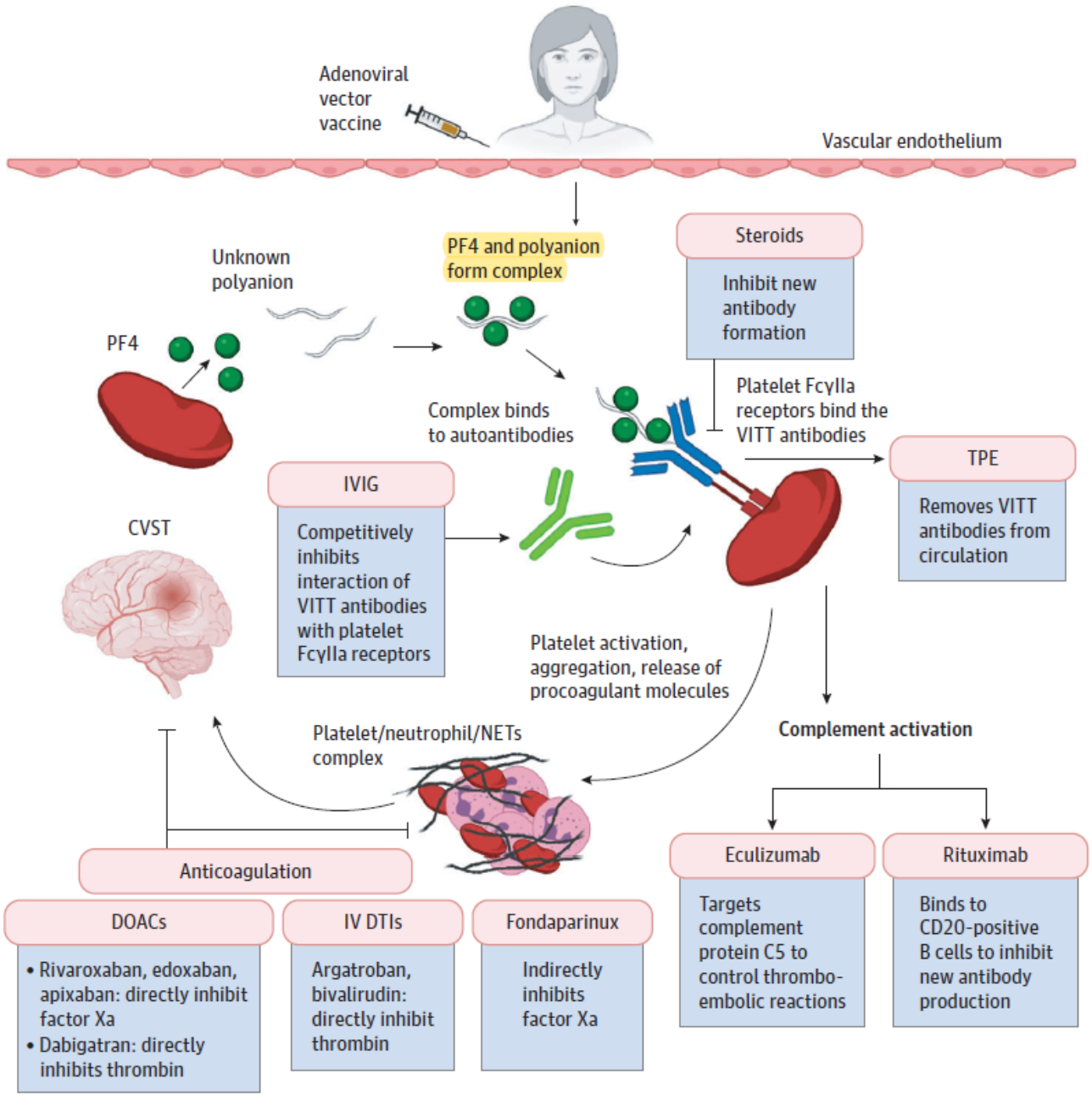
1 / 100mila per A.Z.

1 / milione per Johnson & J

Maggior parte donne, sotto i 60 anni di età

JAMA *Cardiol* August 10, 2021

Trombocitopenia Trombotica Immune indotta dal Vaccino



JAMA *Cardiol* August 10, 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis

Definizione dei casi:

- **accertato: esordio a 5-30gg dal vaccino AZ, trombosi, piastrinopenia, anti-PF4, D-dimero > 4000FEU**
- **probabile** D-dimero > 4000 ma uno degli altri non soddisfatti o D-dimero 2000-4000
- **possibile** D-dimero 2000-4000 e uno o due altro criteri non soddisfatti
- **improbabile** piastrinopenia senza trombosi o trombosi senza piastrinopenia e D-dimero < 2000, altra diagnosi più probabile (PF-4 non considerati)

The NEW ENGLAND JOURNAL of MEDICINE

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Prime dosi somministrate: 16milioni > 50aa, 8 milioni < 50aa

Risultati

- Dati raccolti da marzo al 6 giugno
- **220 casi definiti**; incidenza stimata **1/100.000 > 50aa**, **1/50.000 < 50aa**
- Esordio: 97% entro 30gg
- 85% sotto i 60aa; non prevalenza di sesso; in buona salute
- Sito più frequente: trombosi venosa cerebrale (110/220)
- Il 36% di queste complicato da emorragia cerebrale
- 49/220 decessi (22%)
- Mortalità associata a piastrine < 30mila ed emorragia cerebrale

ORIGINAL ARTICLE

Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis

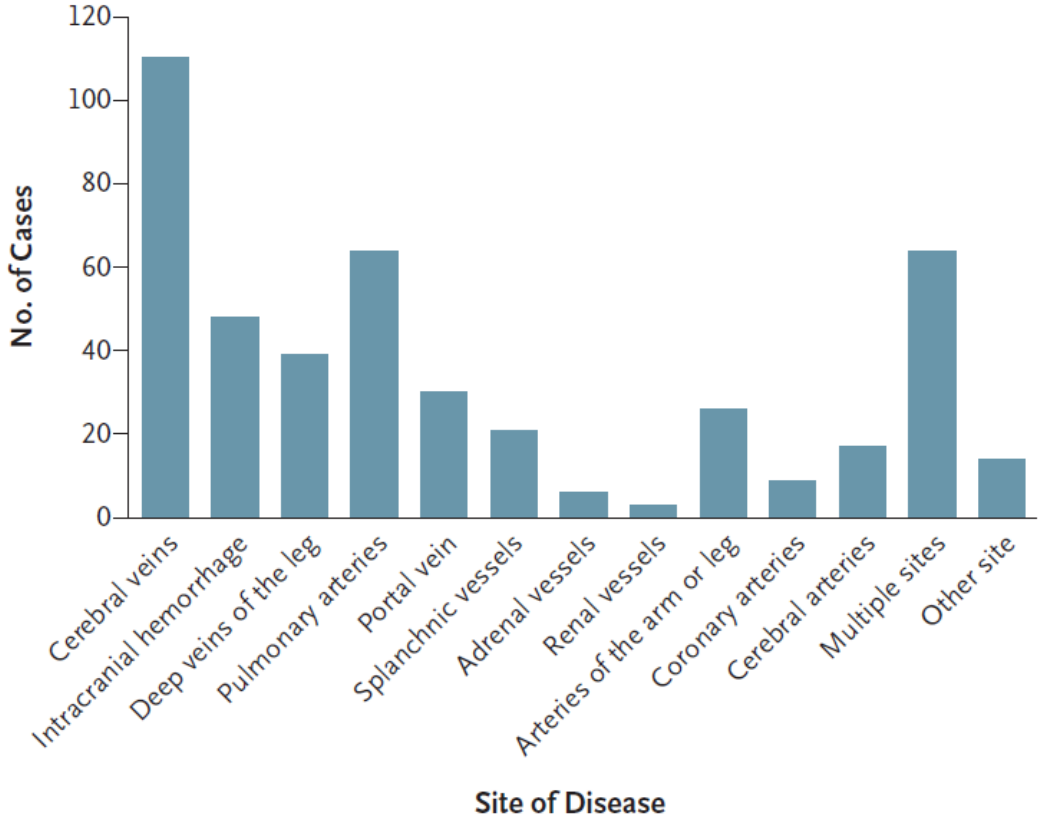


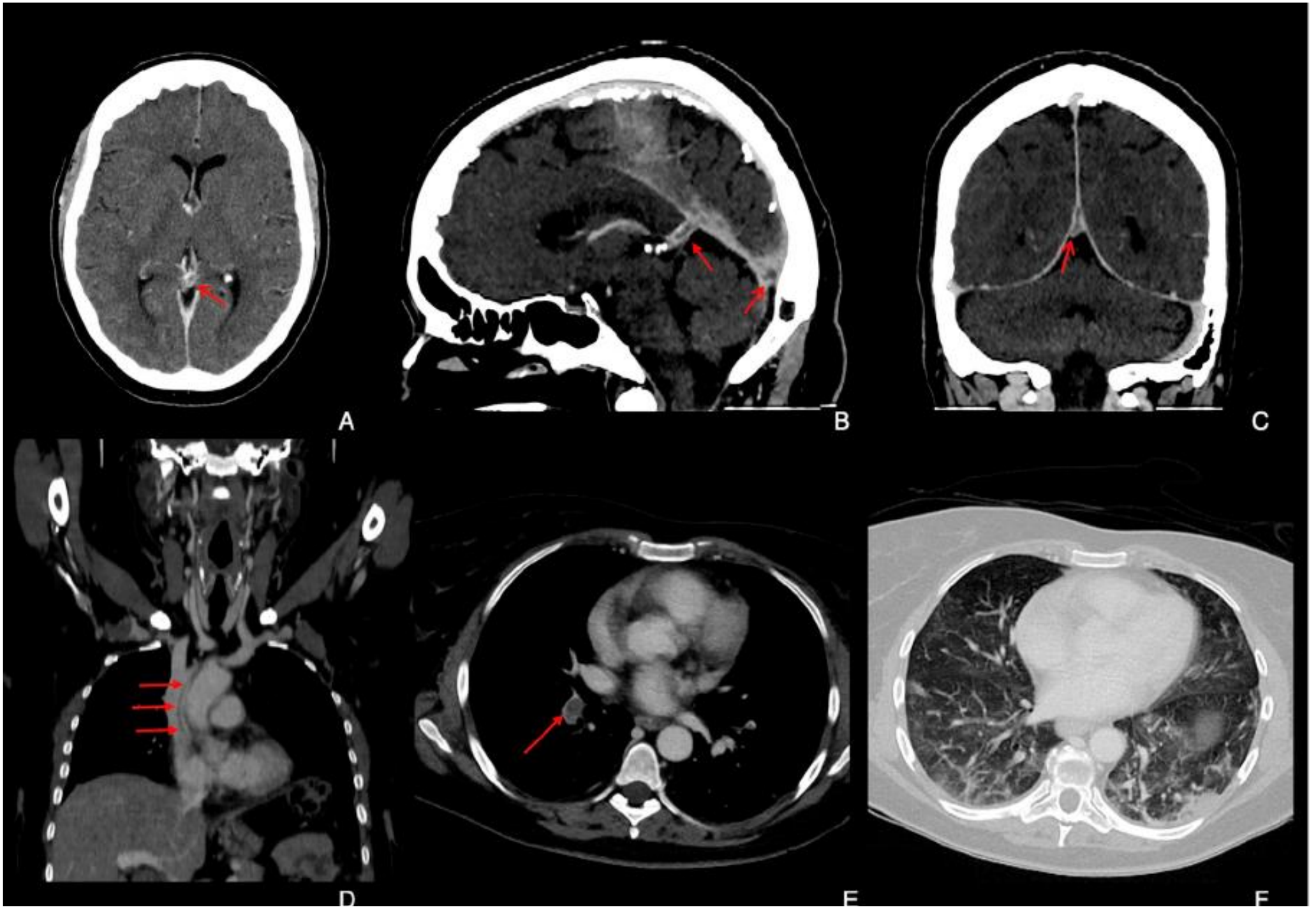
Figure 2. Sites of Disease in 220 Patients with Definite or Probable VITT.

American Society of Hematology

Aggiornamento 12 agosto 2021

- **DEFINIZIONE DI CASO, 5 CRITERI**
  1. ESORDIO 4-42 GIORNI
  2. QUALSIASI TROMBOSI VENOSA O CEREBRALE (+ frequenti cerebrale o addominale)
  3. PIASTRINOPENIA (< 150.000/ul)*
  4. D-dimero marcatamente aumentato (x 4)
  5. anti PF4 (ELISA)
- **INCIDENZA ESTREMAMENTE BASSA***
- **VALUTAZIONE URGENTE IN CASO DI:** cefalea severa, alterazioni visive, dolore addominale, dispnea, dolore/edema arto …
- SE sospetto → esami urgenti: emocromo; imaging in base al sintomo

  → Se piastrinopenia: D-dimero, fibrinogeno, anti PF4; esperto in emostasi
- Terapia: **Immunoglobuline e anticoagulanti (non eparina)** se trombosi e piastrinopenia* / D-dimero aumentato


A
B
C
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E
F

Trombosi venosa cerebrale e COVID

- Baldini T. et al. **Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: a systematic review and meta-analysis.** *Eur J Neurol*. Published online January 11, 2021.

- Mowla A. et al. **Cerebral venous sinus thrombosis associated with SARS-CoV-2: a multinational case series**. *J Neurol Sci*. 2020;419:117183.

- Al-Mufti F. et al. **Cerebral venous thrombosis in COVID-19: a New York Metropolitan cohort study.** *AJNR Am J Neuroradiol*. 2021;42(7):1196-1200.

- Bikdeli B. et al. **Cerebral venous sinus thrombosis in the U.S. population, after adenovirus-based SARS-CoV-2 vaccination, and after COVID-19**. *J Am Coll Cardiol*. 2021;78(4):408-411.

Research Paper

Cerebral venous thrombosis and portal vein thrombosis: A retrospective cohort study of 537,913 COVID-19 cases

Maxime Taquet[a,b,*], Masud Husain[c,d], John R Geddes[a,b], Sierra Luciano[e], Paul J Harrison[a,b]

Incidenza di trombosi cerebrale in corso di COVID19: 42/milione

Cerebrovascular events and outcomes in hospitalized patients with COVID-19: The SVIN COVID-19 Multinational Registry

International Journal of Stroke
2021, Vol. 16(4) 437–447

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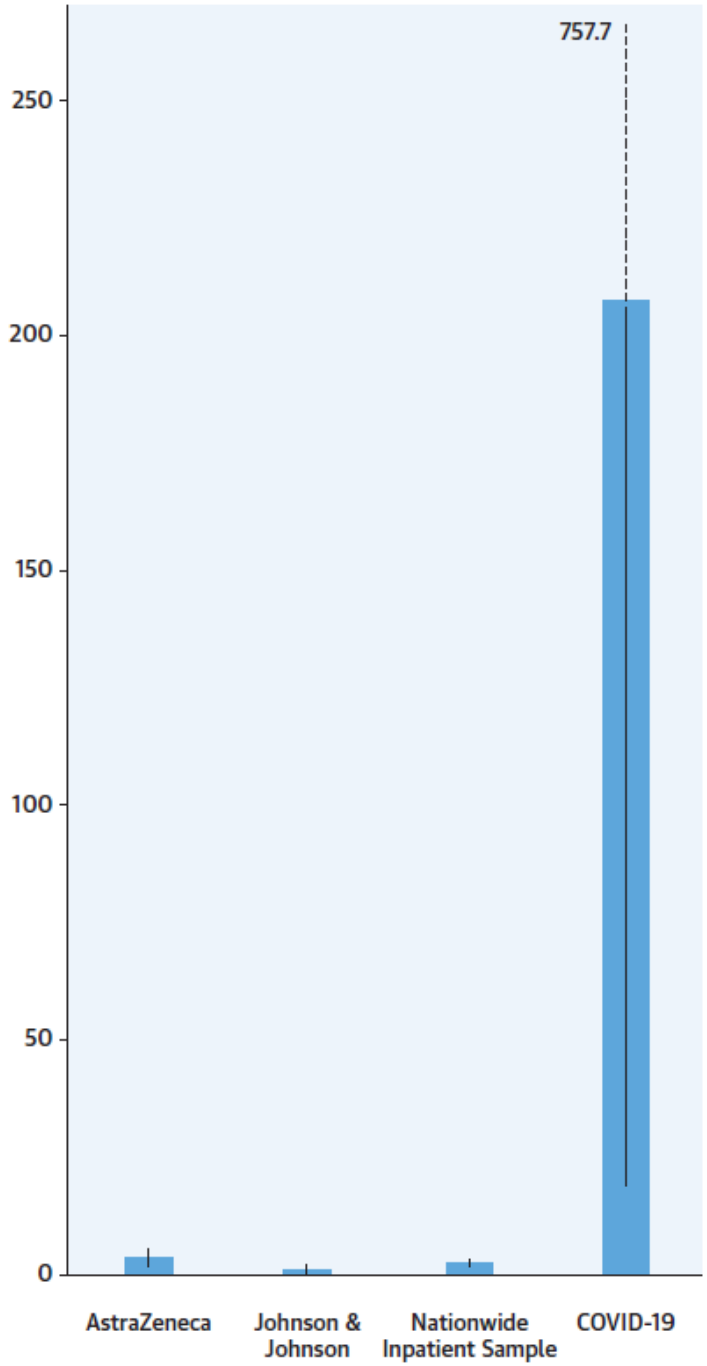
Incidenza di trombosi cerebrale in corso di COVID19: 200/milione

vs incidenza nella popolazione generale: 0.53-0.77/milione
vs incidenza dopo prima dose Astra Zeneca: 5/milione (dati EMA)

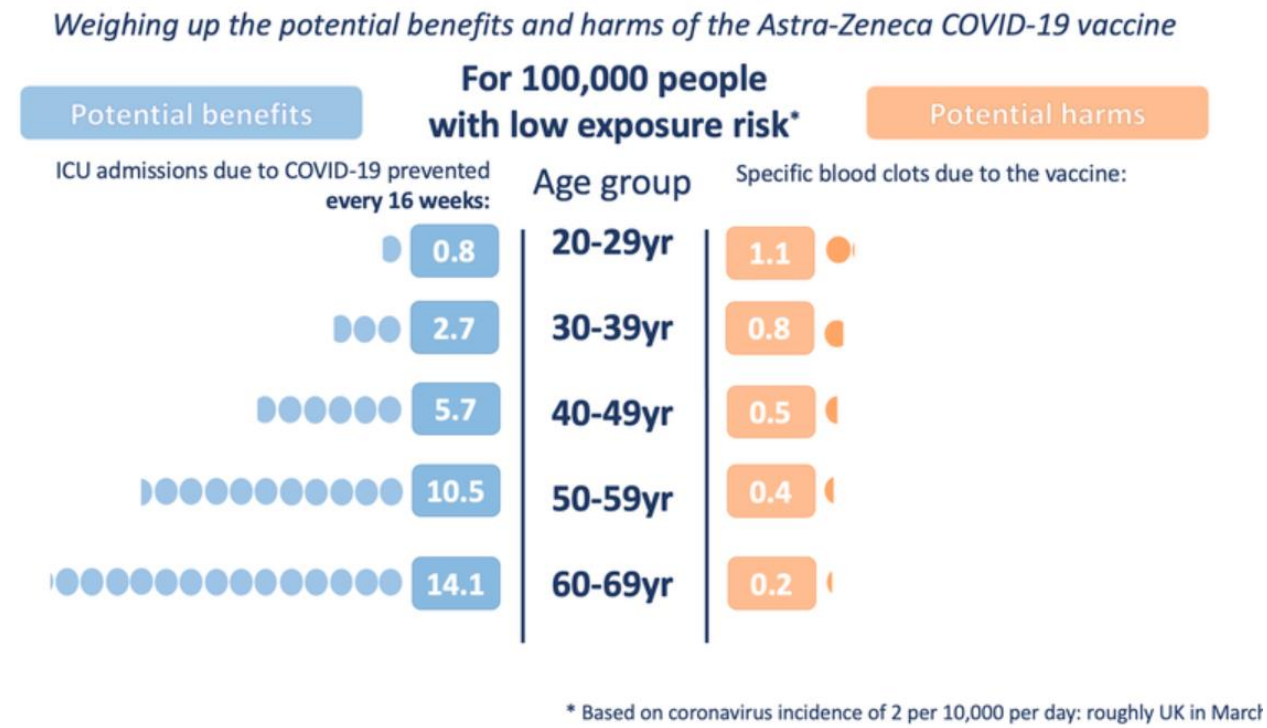
FIGURE 1 Estimated Rate of CVST Per 1,000,000 People



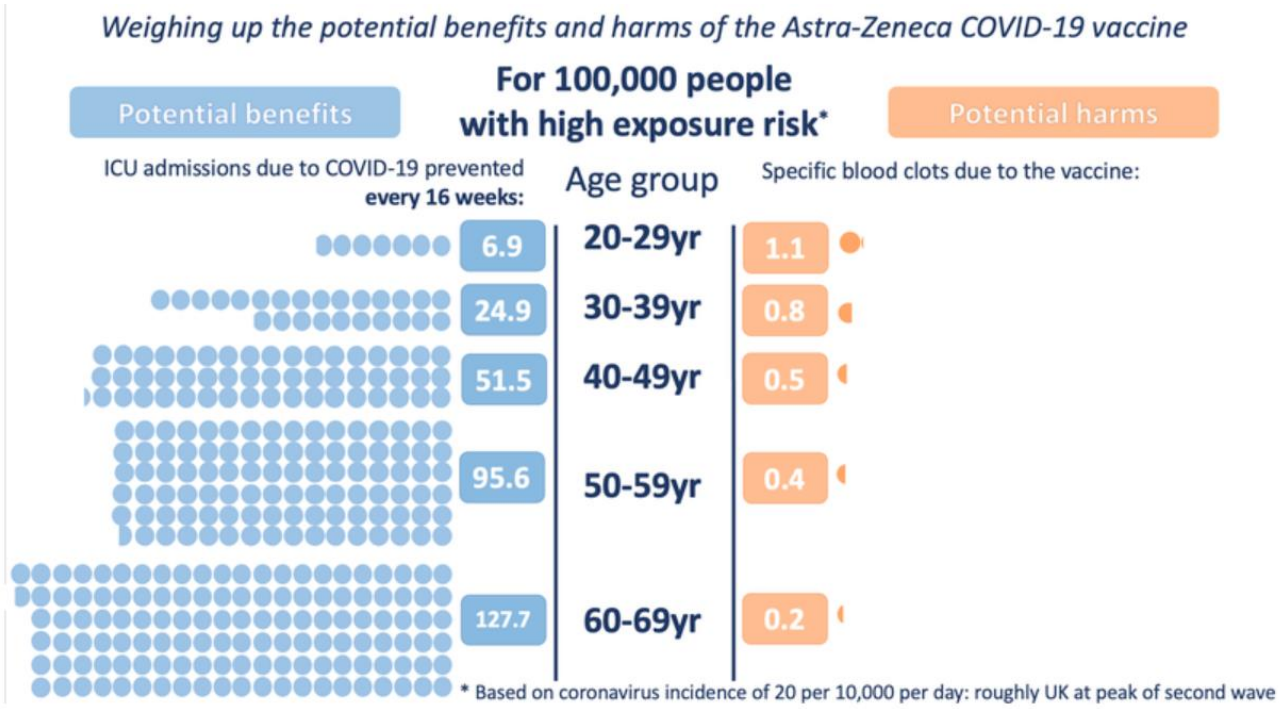
Cerebral Venous Sinus Thrombosis in the U.S. Population, After Adenovirus-Based SARS-CoV-2 Vaccination, and After COVID-19

JACC 2021; 78

Winton Centre for Risk and Evidence Communication University of Cambridge



BASSA esposizione



ALTA esposizione

Trombosi post vaccino Vs trombosi da Covid

Elementi chiave

- Le complicanze trombotiche in corso di malattia sono frequenti e si associano a decorso sfavorevole e mortalità aumentata
- La disfunzione endoteliale e l'infiammazione hanno un ruolo centrale nella patogenesi
- La trombosi trombocitopenica immune da vaccino è una evenienza rarissima, non prevedibile
- Non vi è dubbio che il rapporto rischio / beneficio sia a favore della vaccinazione

GRAZIE PER
L'ATTENZIONE