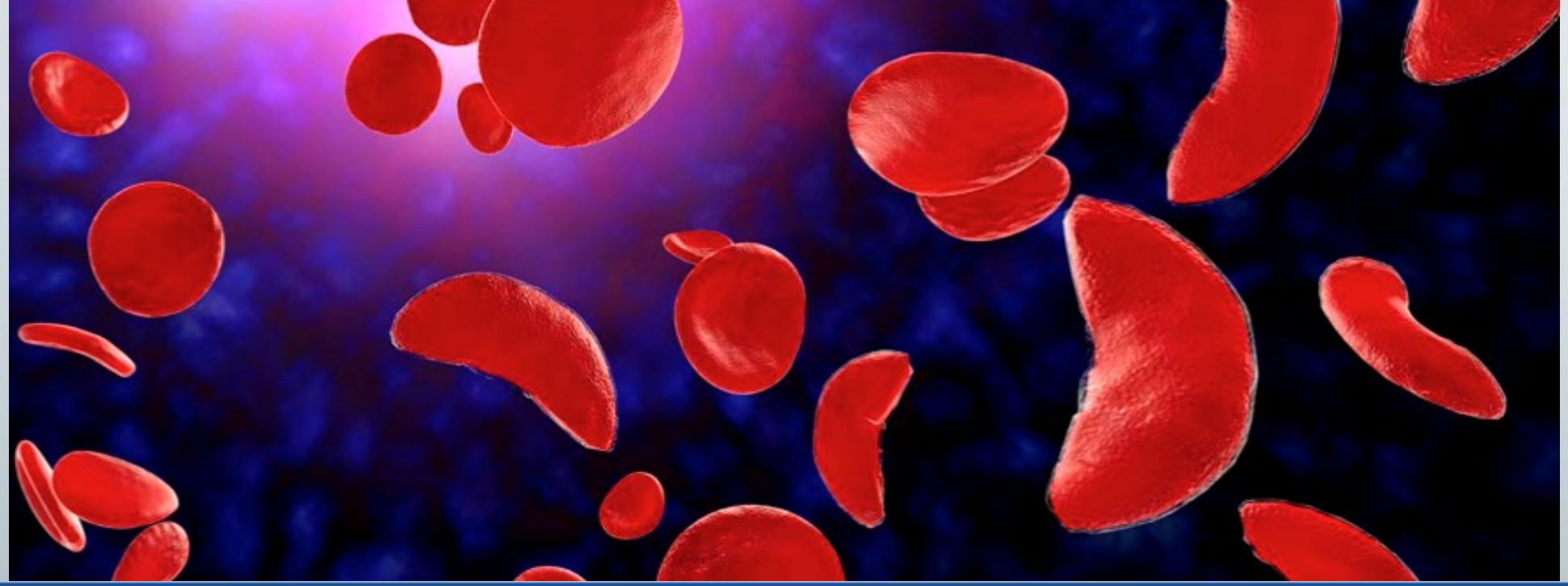

Updates & Impacts: Treating Hematologic Malignancies in 2022

New Developments in Non-Malignant Hematology

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Abstracts

Paper 0291: Deep Vein Thrombosis After COVID-19 Vaccinations

- Damon E. Houghton, MD, MS

Paper 0292: Vaccine-Induced Thrombocytopenia and Thrombosis (VITT) Antibodies Recognize Neutrophil-Activating Peptide 2 (NAP2) as Well as Platelet Factor 4 (PF4): Mechanistic and Clinical Implications

- Lubica Rauova, MD, PhD

Deep Vein Thrombosis After COVID-19 Vaccinations

Background

- Concern for thrombotic risk due to thrombotic events in close proximity to vaccination
- VITT has been observed with some COVID-19 vaccines

Methods

- Adult patients with COVID-19 vaccination with Pfizer, Moderna, Janssen across Mayo clinic enterprise 11/1/2020 – 6/1/2021
- Primary outcomes: acute upper extremity DVT, lower extremity DVT, pulmonary embolism
- Documented radiology reports

Deep Vein Thrombosis After COVID-19 Vaccinations

Analysis

- Day 0 = First recorded COVID-19 vaccination
- Confirmed VTE occurring within 90 days before or after and in close proximity to the day of vaccination was used
- Compared DVT and PE outcomes by vaccine, within the pre- and post-vaccination timeframe using time to event curves, Cox proportional hazard models, and with death as a competing risk

Baseline Characteristics

	Janssen (J&J)	Moderna	Pfizer	
	N=16,271	N=120,682	N=245,570	
Age, mean (SD)	54.7 (16.3)	61.0 (17.7)	56.5 (19.1)	
Female, n (%)	8,050 (49.5)	65,306 (54.1)	138,223 (56.3)	<.001
Race, White, n (%)	14,693 (91.0)	108,619 (90.5)	218,970 (89.7)	<.001
2 Doses Administered, n (%)	NA	99,436 (82.4)	222,926 (90.8)	
Median Interval Between Doses (days), mean (SD)	NA	29.0 (4.4)	22.5 (4.1)	
Cancer, n (%)	2,279 (14.0)	24,763 (20.5)	40,847 (16.6)	<.001
Diabetes, n (%)	2,384 (14.7)	21,365 (17.7)	33,986 (13.8)	<.001
Pulmonary Disease, n (%)	2,953 (18.2)	23,998 (19.9)	44,681 (18.2)	<.001
Myocardial Infarction/ Stroke, n (%)	991 (6.1)	9,747 (8.1)	15,956 (6.5)	<.001
Renal Disease, n (%)	1,040 (6.4)	11,466 (9.5)	18,717 (7.6)	<.001

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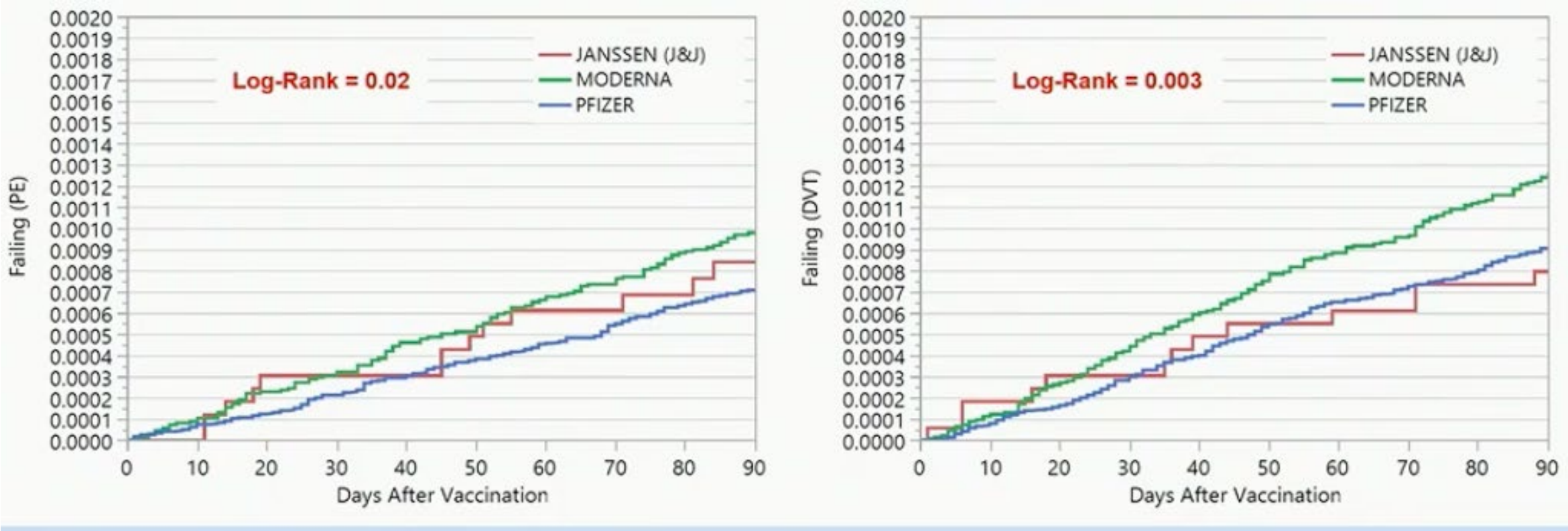
Rates of VTE After COVID-19 Vaccination



No significant difference in VTE risk was observed between different vaccines after adjusting for age, sex, race, surgery, COVID-19 infection, and other comorbidities

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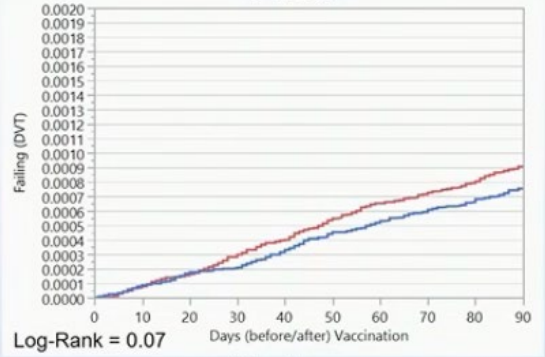
No Increased Risk for Deep Vein Thrombosis

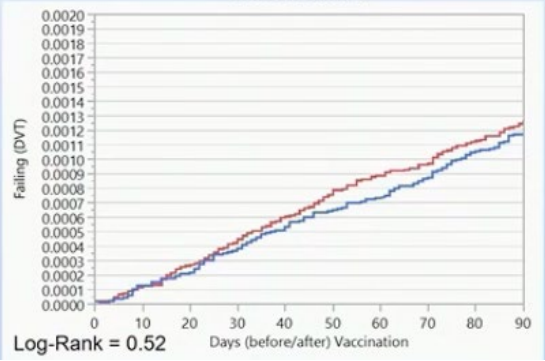
Unadjusted HR 1.12 (0.97-1.29)

Post-vaccination
Pre-vaccination

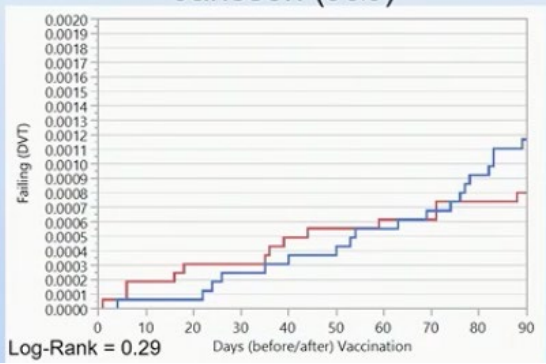
Pfizer



Moderna



Janssen (J&J)

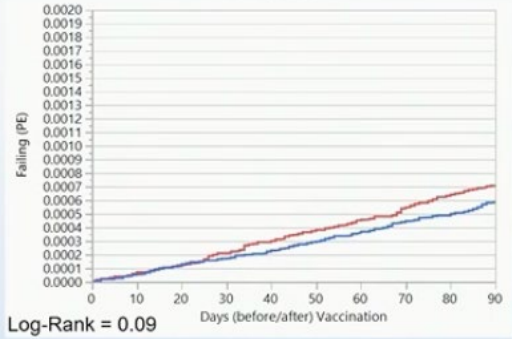


Higher Risk for Pulmonary Embolism Post-Vaccination

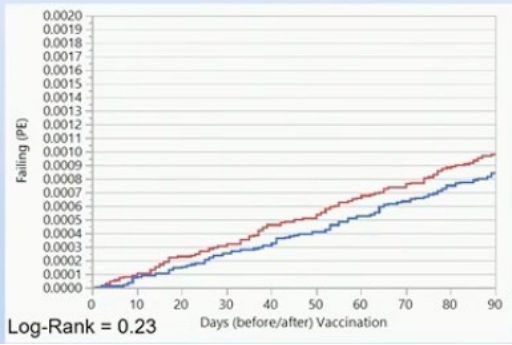
Unadjusted HR 1.21 (1.02-1.43)

Post-vaccination
Pre-vaccination

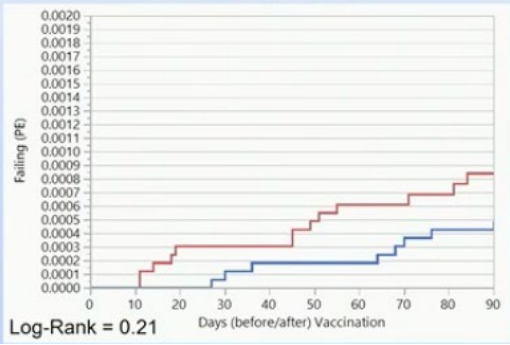
Pfizer



Moderna

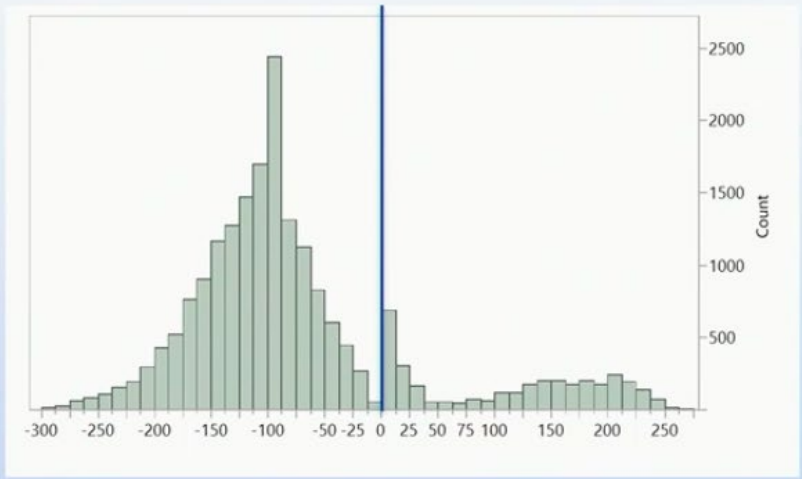


Janssen (J&J)



Timing of COVID-19 infections in vaccinated patients

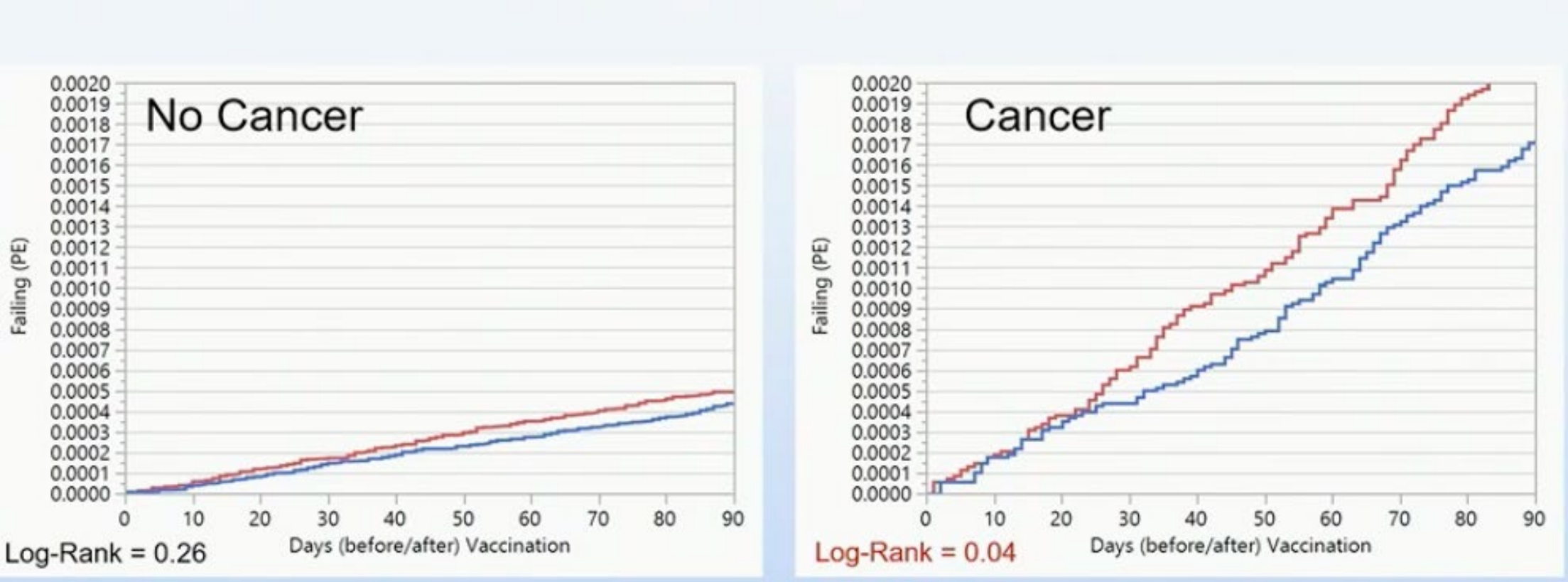
	Janssen (J&J) n (%)	Pfizer n (%)	Moderna n (%)
Never	15,212 (93.5)	232,665 (94.74)	115,281 (95.52)
Before Vaccination	922 (5.7)	10,620 (4.32)	4,518 (3.74)
First 30 days	30 (0.18)	709 (0.29)	312 (0.26)
After 30 days	108 (0.66)	1,576 (0.64)	571 (0.47)



Pre/Post-vaccination covariates and outcomes

Covariates (within 90 days)	Pre n, (%)	Post n, (%)	P value
Surgery	11,541 (3.0)	12,775 (3.3)	<.001
Hospital/Emergency	11,235 (2.9)	12,722 (3.3)	<.001
COVID-19 Infection	5,014 (1.3)	1,339 (0.35)	<.001
Non-CT angiogram	4,698 (1.2)	5,287 (1.4)	<.001
Outcomes (within 90 days)			
Pulmonary Embolism	255 (0.07)	303 (0.08)	0.04
Deep Vein Thrombosis	347 (0.09)	389 (0.10)	0.12
Death	NA	713 (0.19)	

Cancer patients have higher post-vaccination PE rates



No increased rate of post-vaccination DVT

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Death as a competing risk factor for PE

- Post-vaccination PE risk with death as a competing risk adjusting for pre- and post-surgeries, hospitalizations, COVID-19 infections, and non angiogram CT scans
  - Non-cancer patients HR 1.16 (0.92-1.47)
  - Cancer patients HR 1.23 (0.96-1.57)

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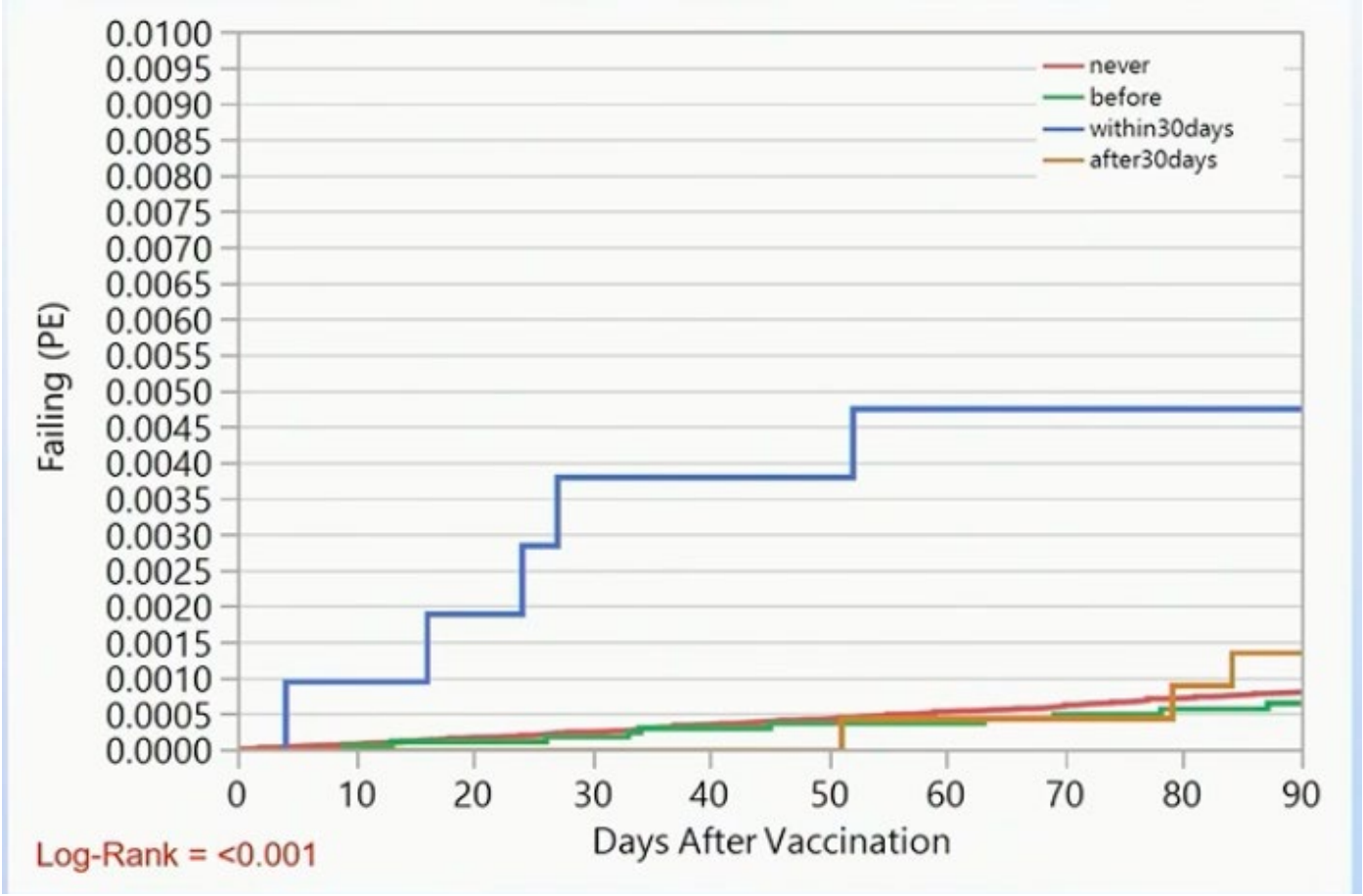
COVID-19 infection timing and post-vaccination PE risk



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Strengths/Limitations

- Large sample size
- Highly accurate thrombotic outcome data (did not include CVST or other atypical sites)
- Smaller sample size of patients receiving Janssen vaccine

Conclusions

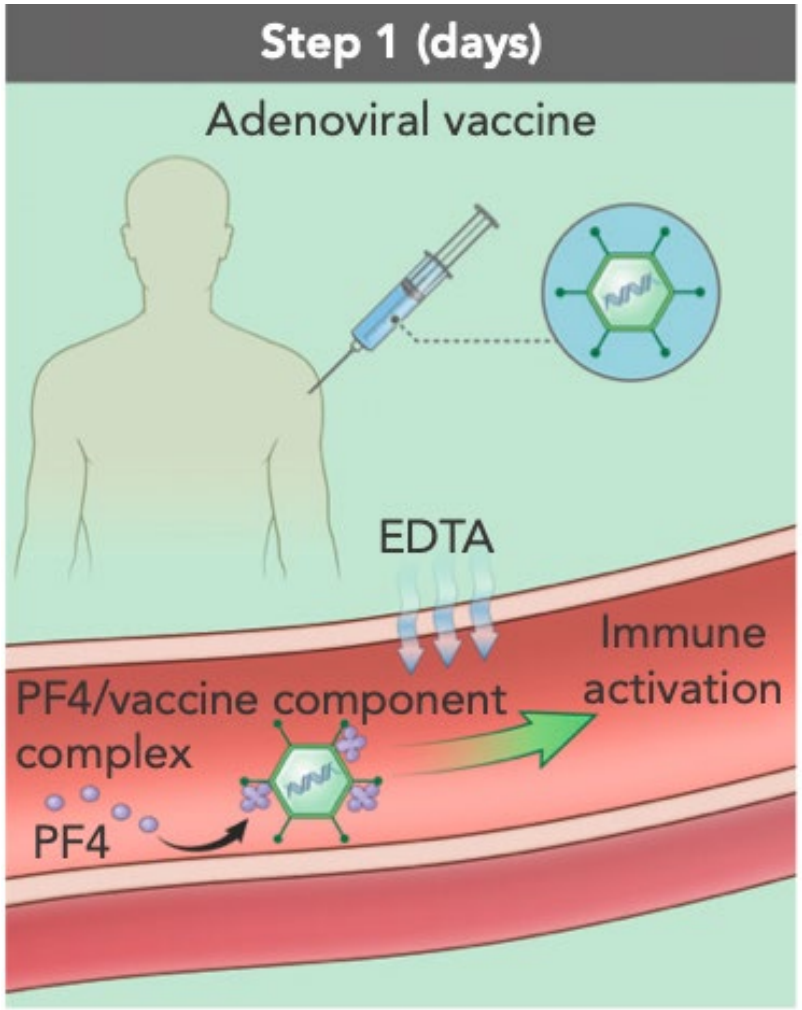
- Rates of VTE after COVID-19 vaccination are low and similar to what might be expected for population rates
- No difference in post-vaccination VTE rates between vaccines after adjustment
- COVID-19 infection prior to vaccination was not a risk factor for post-vaccination VTE

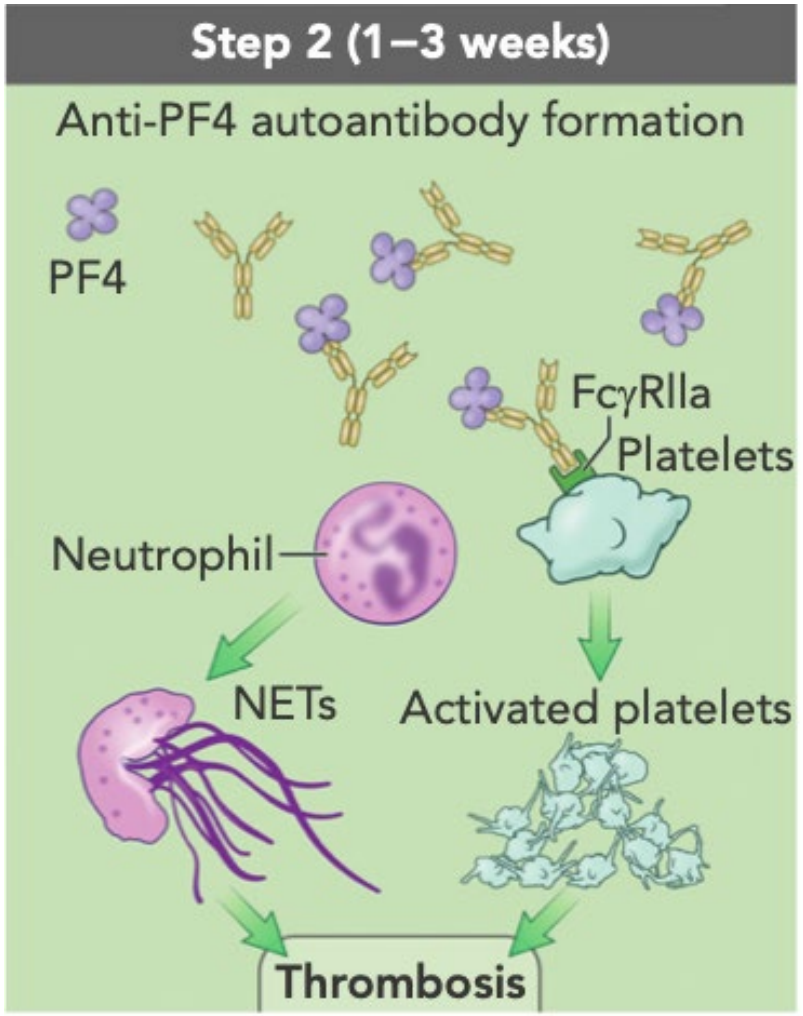
VITT Antibodies Recognize Neutrophil-Activating Peptide 2 (NAP2) as Well as Platelet Factor 4 (PF4)

Background

- VITT occurs 5-40 days post-vaccination after adenovirus-based SARS-Cov-2 vaccines
- Incidence: ~$1/10^5$ after ChAdOx1 vaccine (AZ) and ~$3/10^6$ after Ad26.COV2.S vaccine (J&J)
- Mortality: 20-40%
- Plasma from patients with VITT contain high levels of platelet activating IgG Ab to PF4
- VITT Ab recognizes a PF4 epitope that is distinct from HIT Ab

VITT Proposed Mechanism

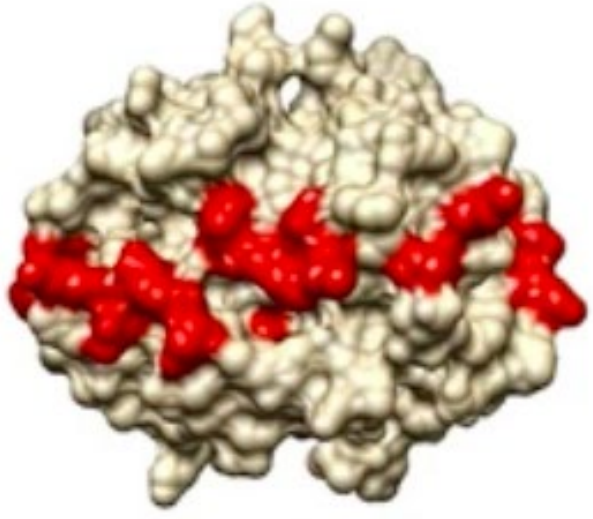




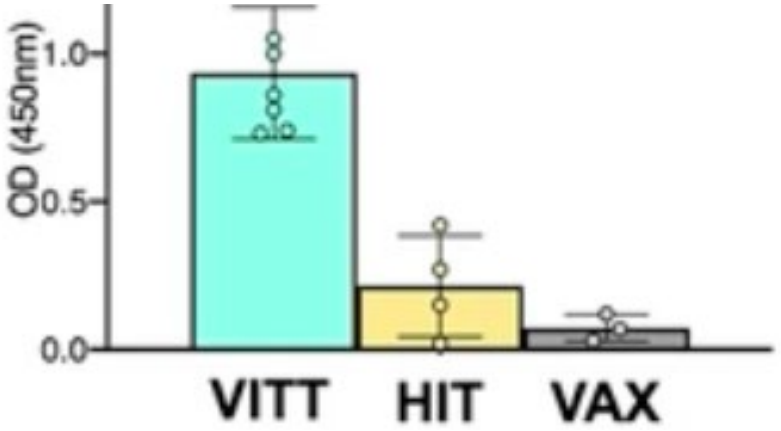
Alan Hoofring, National Institutes of Health. *Blood*. 138; 22. Dec 2021

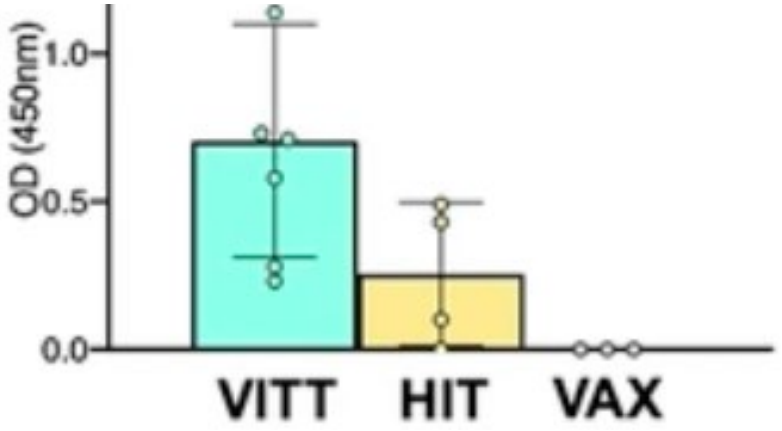
VITT binding site is conserved on NAP2

PF4



NAP2





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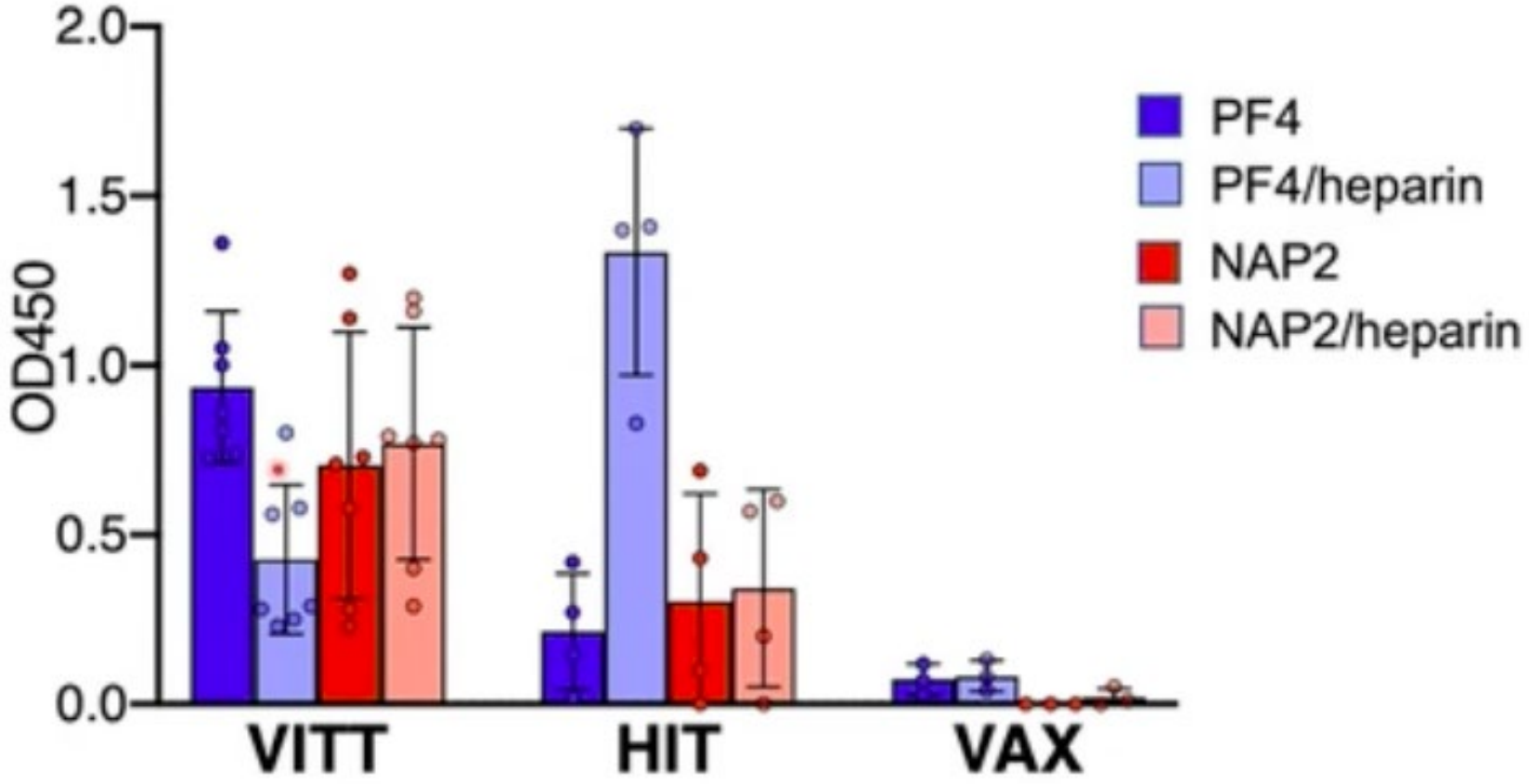
Effect of heparin on Ab binding to PF4 and NAP2



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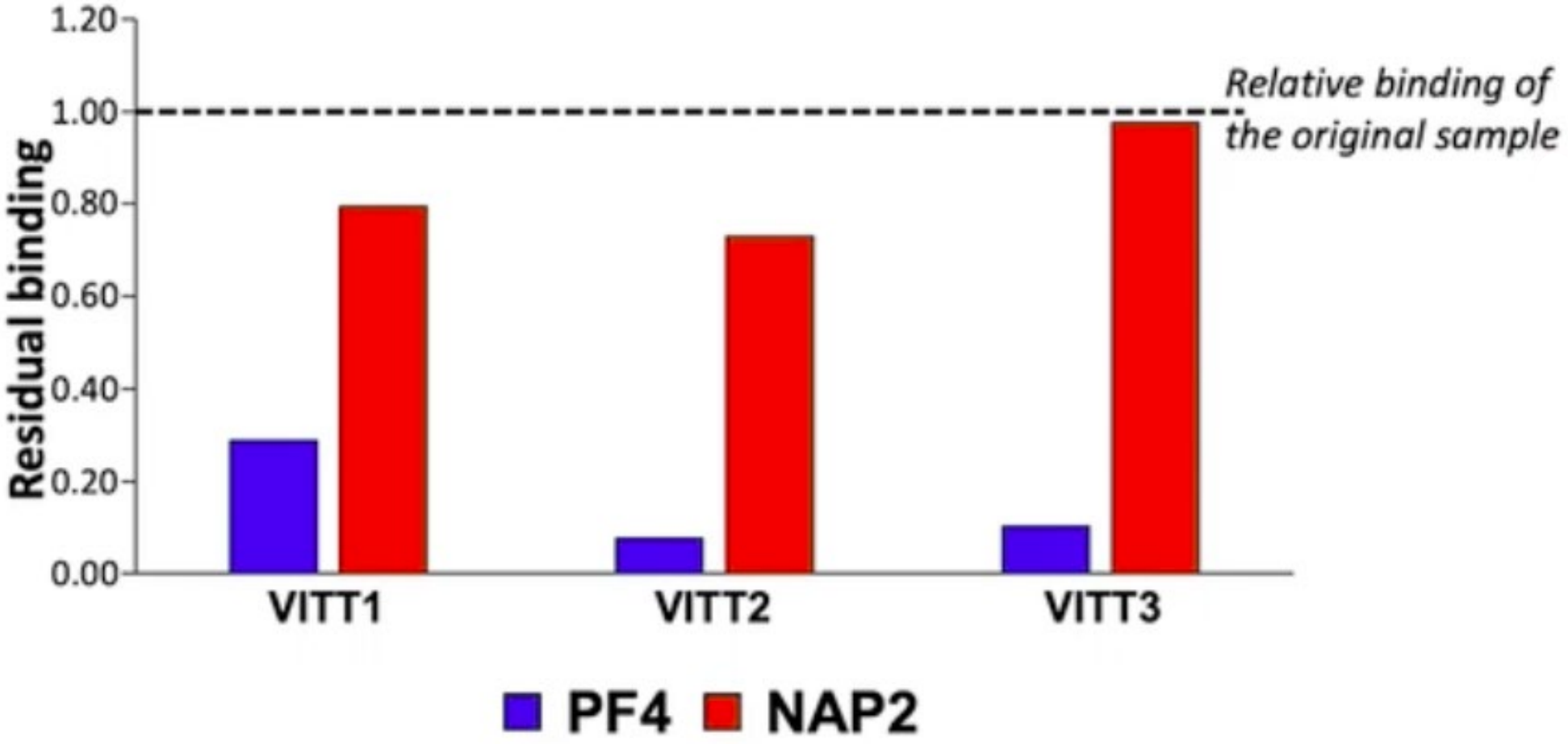
Removal of specific anti-PF4 Ab does not significantly reduce binding to NAP2



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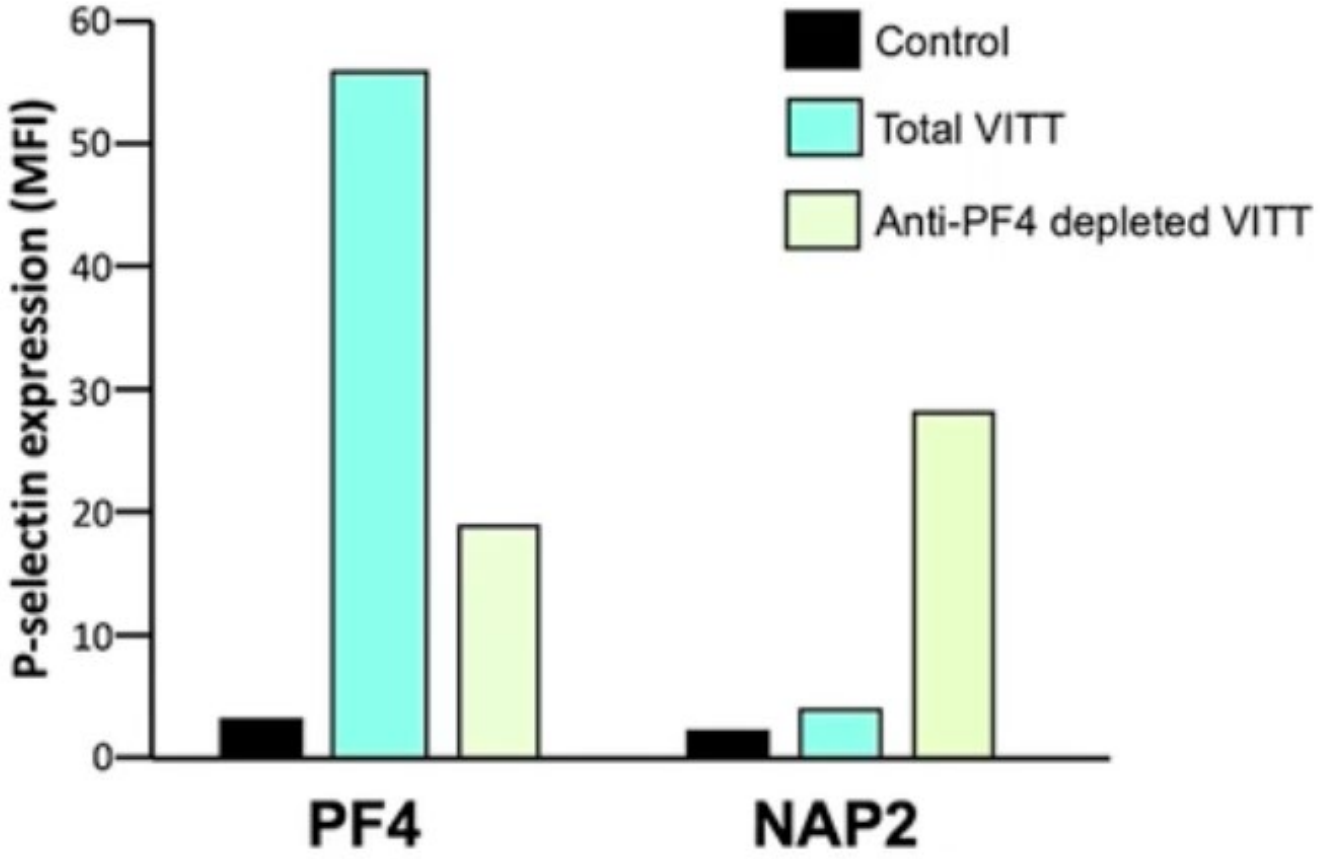
Anti-PF4 depleted VITT IgG activates platelets in the presence of NAP2



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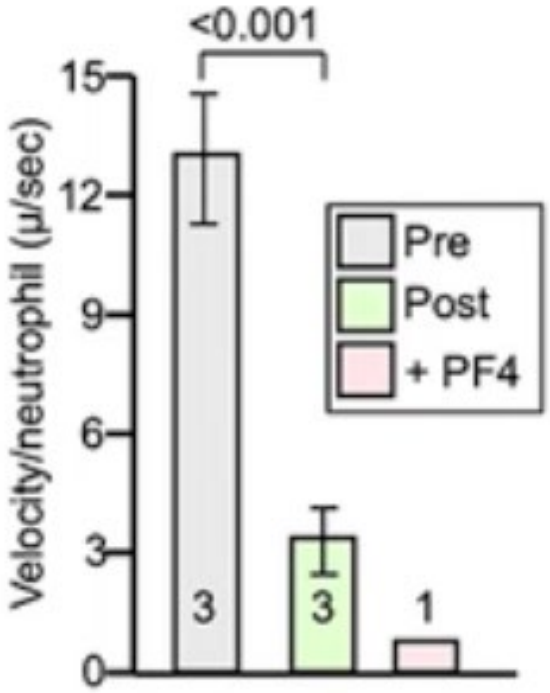
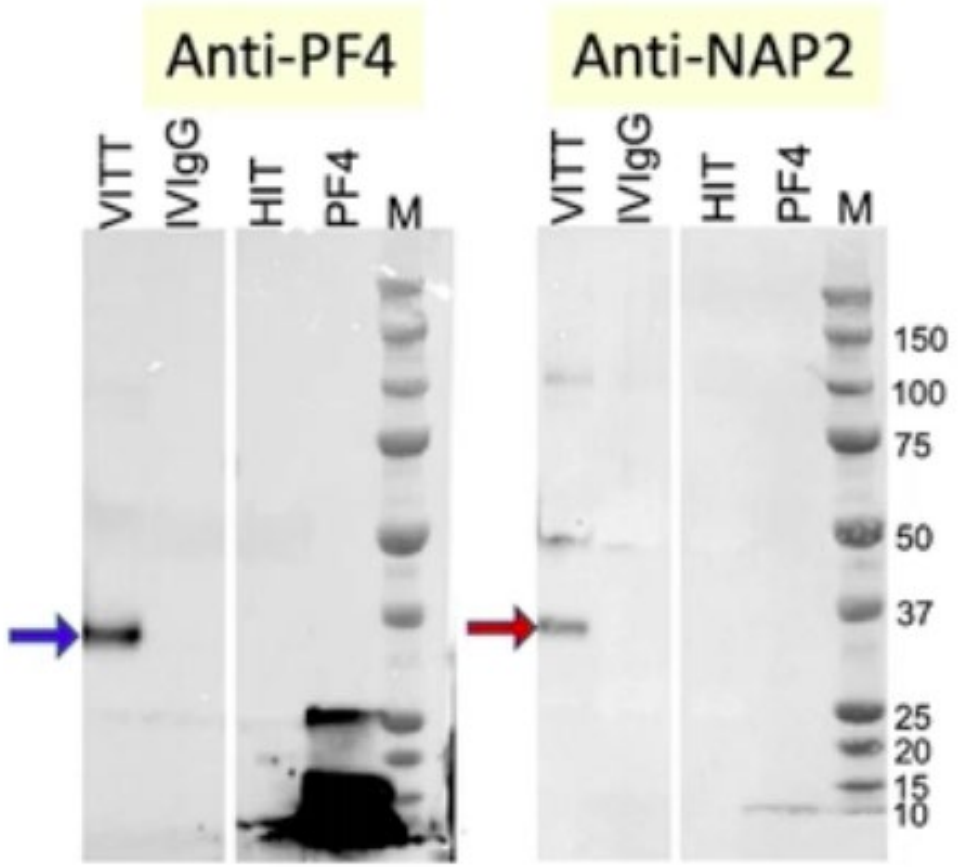
VITT IgG activates mouse neutrophils in the absence of PF4 in vivo

- FcyRIIIA^{+}/PF4^{KO} mice that have mNAP2
- Assessed neutrophil velocity pre-VITT IgG, with VITT IgG, VITT IgG + PF4
- Slowing of neutrophil velocity



VITT IgG contains PF4 and NAP2 immune complexes



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Conclusions

- VITT IgG, in contrast to HIT IgG, binds to a shared antigenic site on closely related platelet chemokines, PF4 and NAP2
- VITT plasma has distinct anti-PF4 and anti-NAP2 Abs that might have distinct functional properties
- NAP2 may contribute to the pro-thrombotic nature of VITT
- NAP2 might be involved in the initiation and propagation of the immuno-thrombotic response in VITT