

## ILLUSTRATED REVIEW

# Illustrated State-of-the-Art Capsules of the ISTH 2022 Congress

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 Lara N. Roberts MBBS, MD Res<sup>36</sup> | Bianca Rocca MD, PhD<sup>37</sup> |  
 Susan Shapiro MD, PhD<sup>38,39</sup> | Deborah M. Siegal MD, MSc, FRCPC<sup>40</sup> |  
 Lirlândia P. Sousa PhD<sup>41</sup> | Katsue Suzuki-Inoue MD, PhD<sup>42</sup> |  
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**Handling Editor:** Dr Michelle Sholzberg

## Abstract

The ISTH London 2022 Congress is the first held (mostly) face-to-face again since the COVID-19 pandemic took the world by surprise in 2020. For 2 years we met virtually, but this year's in-person format will allow the ever-so-important and quintessential creativity and networking to flow again. What a pleasure and joy to be able to see everyone! Importantly, all conference proceedings are also streamed (and available recorded) online for those unable to travel on this occasion. This ensures no one misses out. The 2022 scientific program highlights new developments in hemophilia and its treatment, acquired and other inherited bleeding disorders, thromboinflammation, platelets and coagulation, clot structure and composition, fibrinolysis, vascular biology, venous thromboembolism, women's health, arterial thrombosis, pediatrics, COVID-related thrombosis, vaccine-induced thrombocytopenia with thrombosis, and omics and diagnostics. These areas are elegantly reviewed in this Illustrated Review article. The Illustrated Review is a highlight of the ISTH Congress. The format lends itself very well to explaining the science, and the collection of beautiful graphical summaries of recent developments in the field are stunning and self-explanatory. This clever and effective way to communicate research is revolutionary and different from traditional formats. We hope you enjoy this article and will be inspired by its content to generate new research ideas.

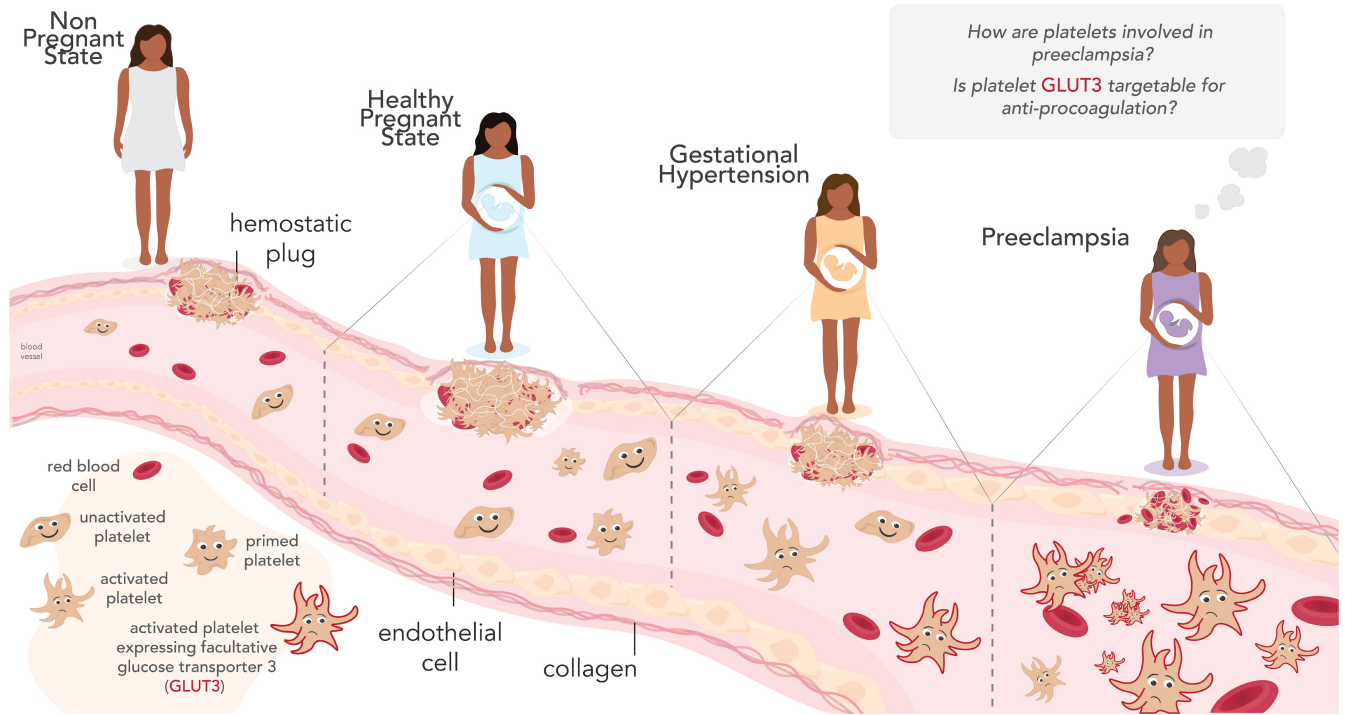


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Katsue Suzuki-Inoue	Crosstalk between hemostasis and lymphangiogenesis
Tahira Zafar	Raising awareness of women's bleeding/health issues in culturally challenging settings
Jiaxi Zhou	Megakaryocyte single-cell transcriptomics

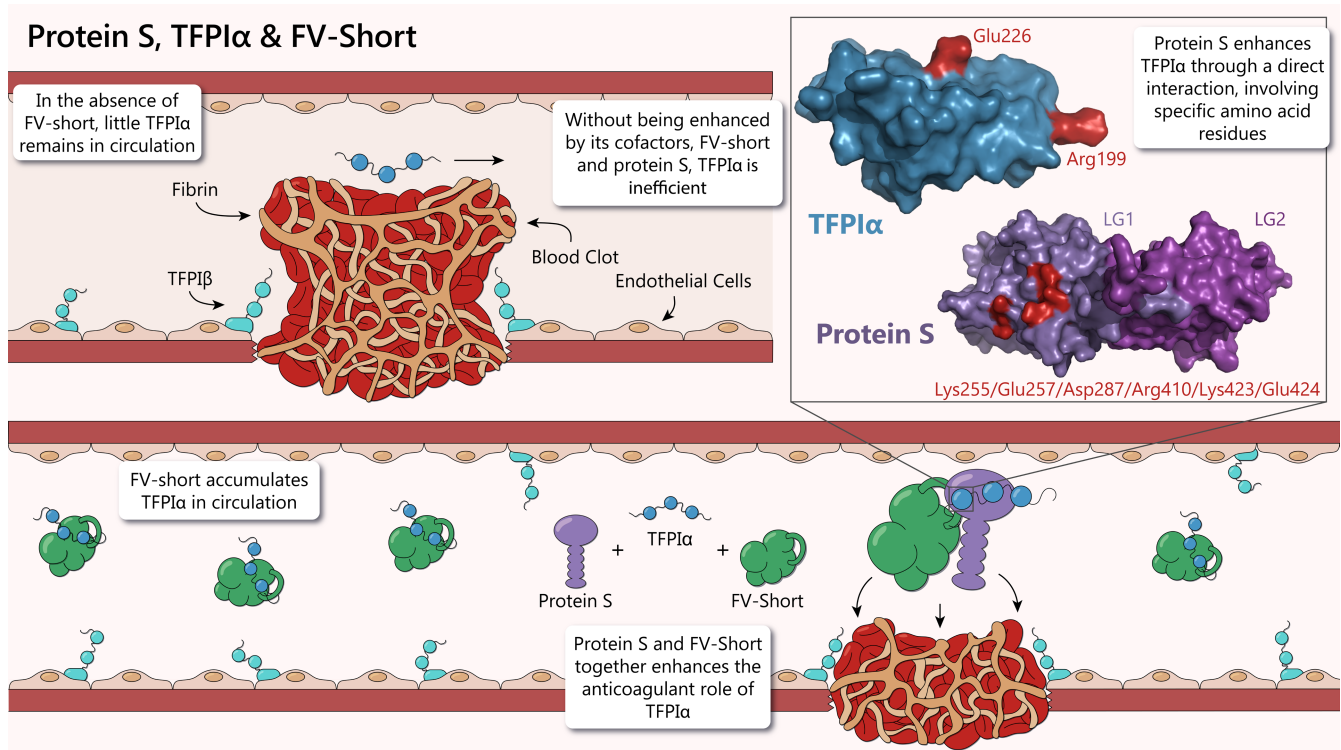
# Preeclampsia and platelet procoagulant membrane dynamics

Ejaife O. Agbani BPharm, MSc, PhD



## Protein S, tissue factor pathway inhibitor, & factor V

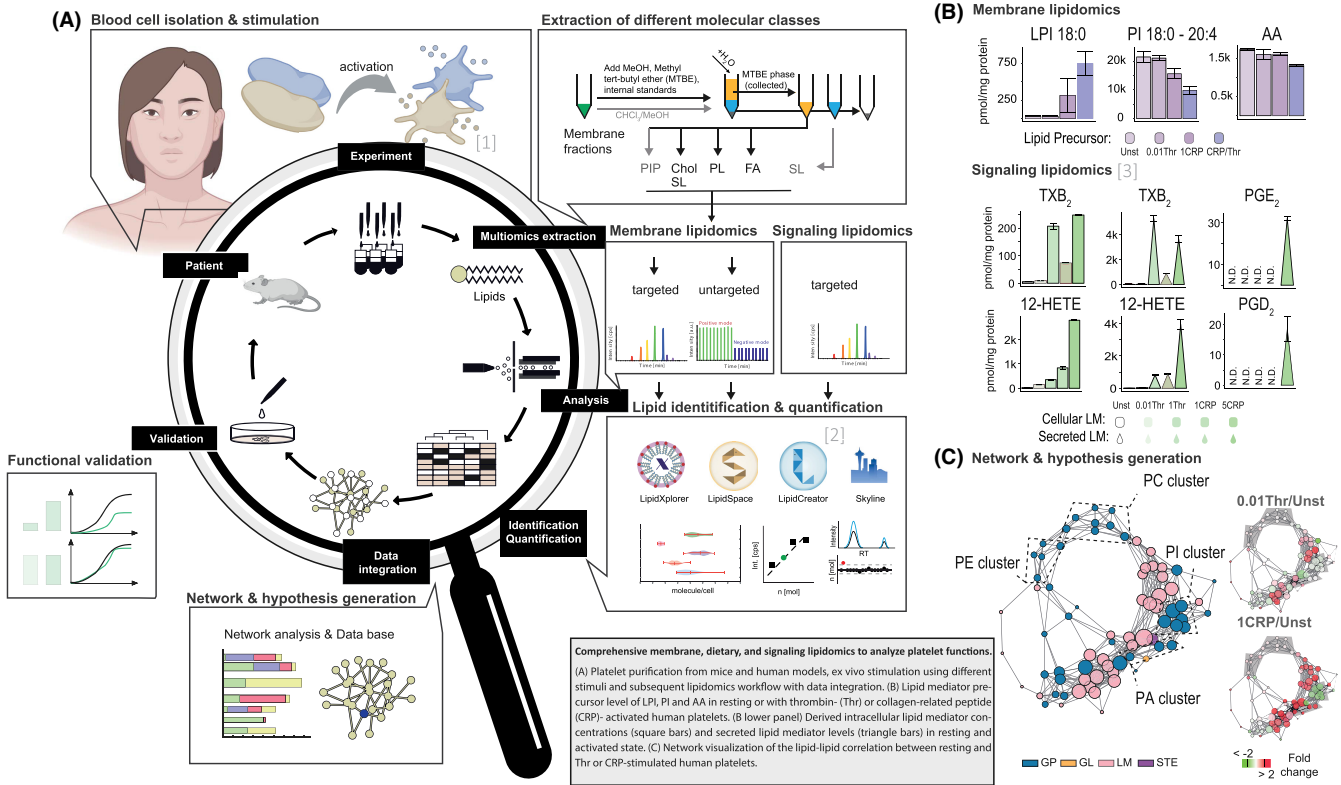
Josefin Ahnström PhD



The initiation phase of coagulation is regulated by tissue factor pathway inhibitor (TFPI), which efficiently reduces/delays thrombin generation. In contrast to the endothelium-bound TFPI $\beta$ , which in itself is an effective regulator of coagulation, the soluble form, TFPI $\alpha$ , is completely dependent on cofactors (compare the top and bottom figures for the absence and presence of cofactors, respectively).<sup>1</sup> Protein S enhances the anticoagulant properties of TFPI $\alpha$  through a direct protein-protein interaction, involving specific amino acid residues in TFPI $\alpha$  Kunitz 3 and protein S laminin G-type 1.<sup>1,2</sup> This interaction enables TFPI $\alpha$  to interact with and inhibit membrane-bound factor Xa more efficiently. A splice variant of factor V (FV), FV-short, regulates TFPI $\alpha$  levels through a high-affinity interaction, likely resulting in an increased half-life, as well as functioning as a synergistic TFPI $\alpha$  cofactor, together with protein S.<sup>1,3</sup>

# Probing the membrane landscape and identifying key lipids critical for platelet activation by lipidomics

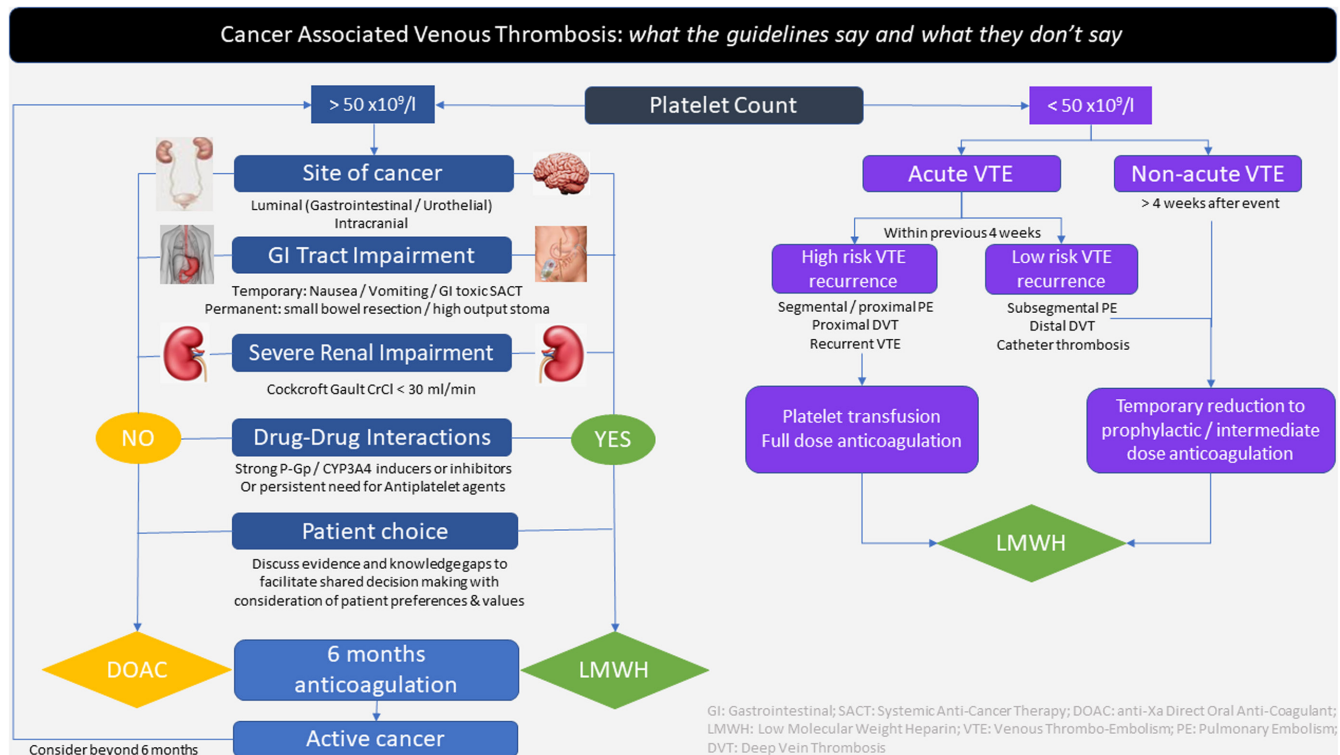
Robert Ahrends PhD



For references, see Peng et al.<sup>4,5</sup>; Holinstat<sup>6</sup>

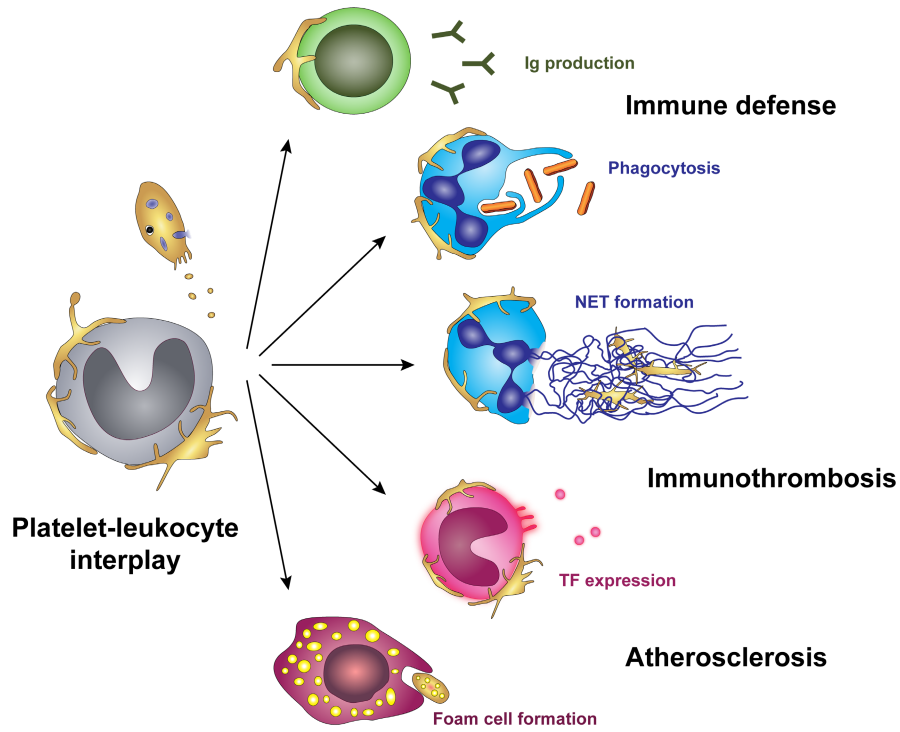
# Cancer associated thrombosis: What the guidelines say and what they do not say

Raza Alikhan MD, FRCP, FRCPath



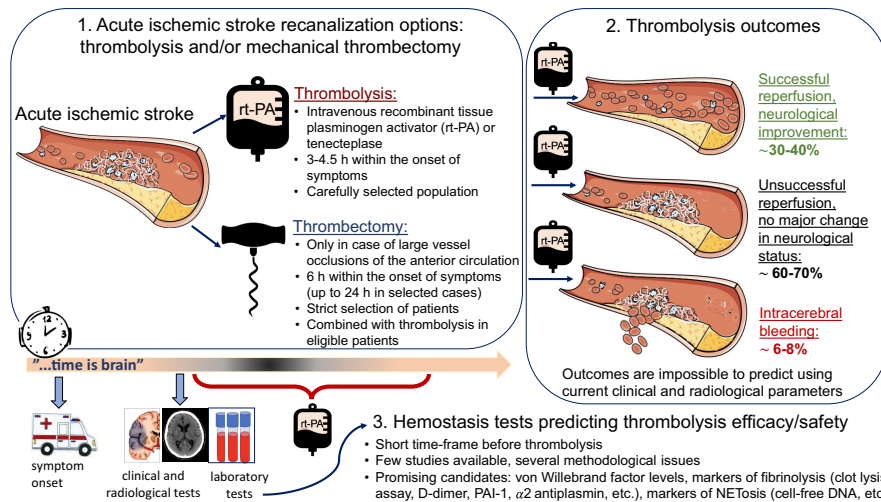
# Platelet-leukocyte interaction: Detection and functional relevance in infection and sterile inflammation

Alice Assinger PhD



## Monitoring efficacy of fibrinolysis in stroke

Zsuzsa Bagoly MD, PhD

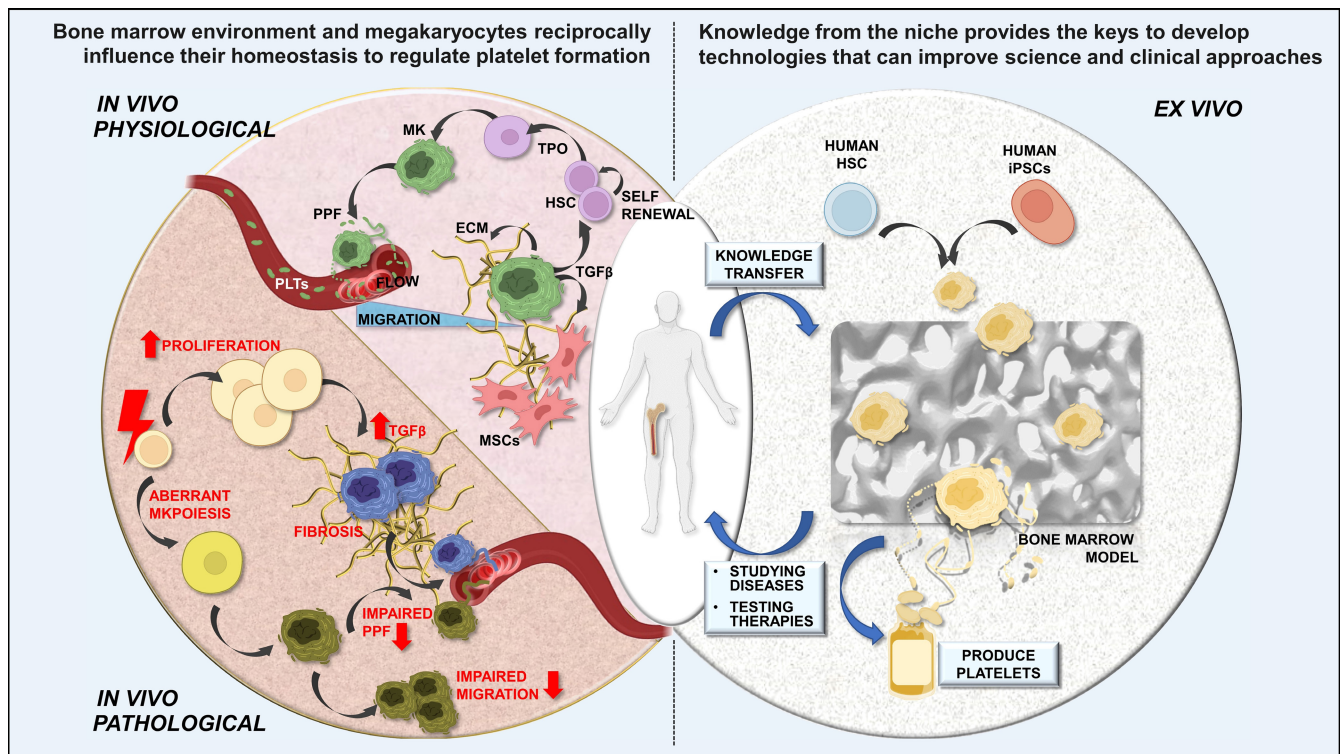


Currently, there are two proven reperfusion strategies for the opening of the occluded vessel in patients with acute ischemic stroke (AIS): intravenous thrombolysis using recombinant tissue-type plasminogen activator (rt-PA; alteplase) or tenecteplase, and mechanical thrombectomy.<sup>7</sup> Both therapies must be delivered within a rapid time frame in selected patients; moreover, mechanical thrombectomy is eligible in only a fraction of patients with large-artery occlusion. Despite the unquestionable effectiveness of rt-PA as first-line treatment of AIS, successful reperfusion is achieved in only  $\approx$ 30% to 40% of patients, while  $\approx$ 6% to 8% of patients develop intracranial hemorrhage as a side effect. As of today, outcomes cannot be foreseen at the initiation of therapy, and this remains one of the greatest challenges of AIS treatment.<sup>8</sup> Due to the short time frame before treatment, few studies are available on hemostasis tests, and several methodological issues are raised.<sup>8,9</sup> Nevertheless, some assays show promising results and need to be further investigated and validated in large populations.



## Megakaryocytes and different thrombopoietic environments

Alessandra Balduini MD

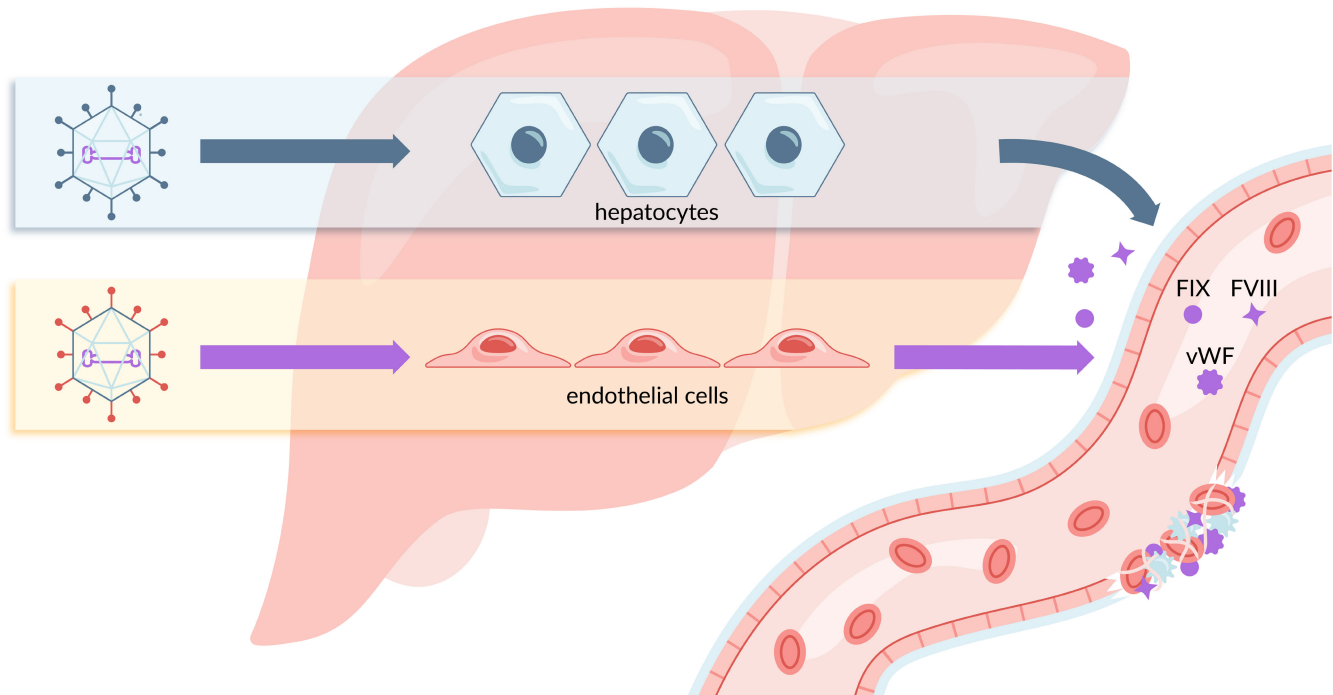


Circulating platelets are specialized cells produced by megakaryocytes through the formation of proplatelets. Leading studies point to the bone marrow niche as the core of hematopoietic stem cell (HSC) differentiation, revealing interesting and complex environmental factors for consideration. Megakaryocytes take cues from the physicochemical bone marrow microenvironment, which includes contact with extracellular matrix components, interaction with endothelium, and contact with the turbulent flow generated by the blood circulation into the sinusoid lumen.<sup>10</sup> Germinal and acquired mutation in HSCs may manifest in altered megakaryocyte maturation, proliferation, and platelet production. Alterations of the whole hematopoietic niche may also occur, highlighting the central role of megakaryocytes in the control of the physiological bone marrow homeostasis. Tissue-engineering approaches have been developed to create a functional mimic of the native tissue.<sup>11,12</sup> Reproducing the thrombopoietic environment is instrumental to gaining new insight into its activity and answering the growing demand for human platelets for fundamental studies and clinical applications in transfusion medicine. (ECM, extracellular matrix; MK, megakaryocyte; iPSC, induced pluripotent stem cell; MSC, mesenchymal stem cell; PPF, proplatelet formation; PLT, platelet; TPO, thrombopoietin; TGFβ, transforming growth factor-β).

The figure was created with [BioRender.com](https://www.biorender.com)

## Engineering of adeno-associated viruses to enhance cell-specific transduction

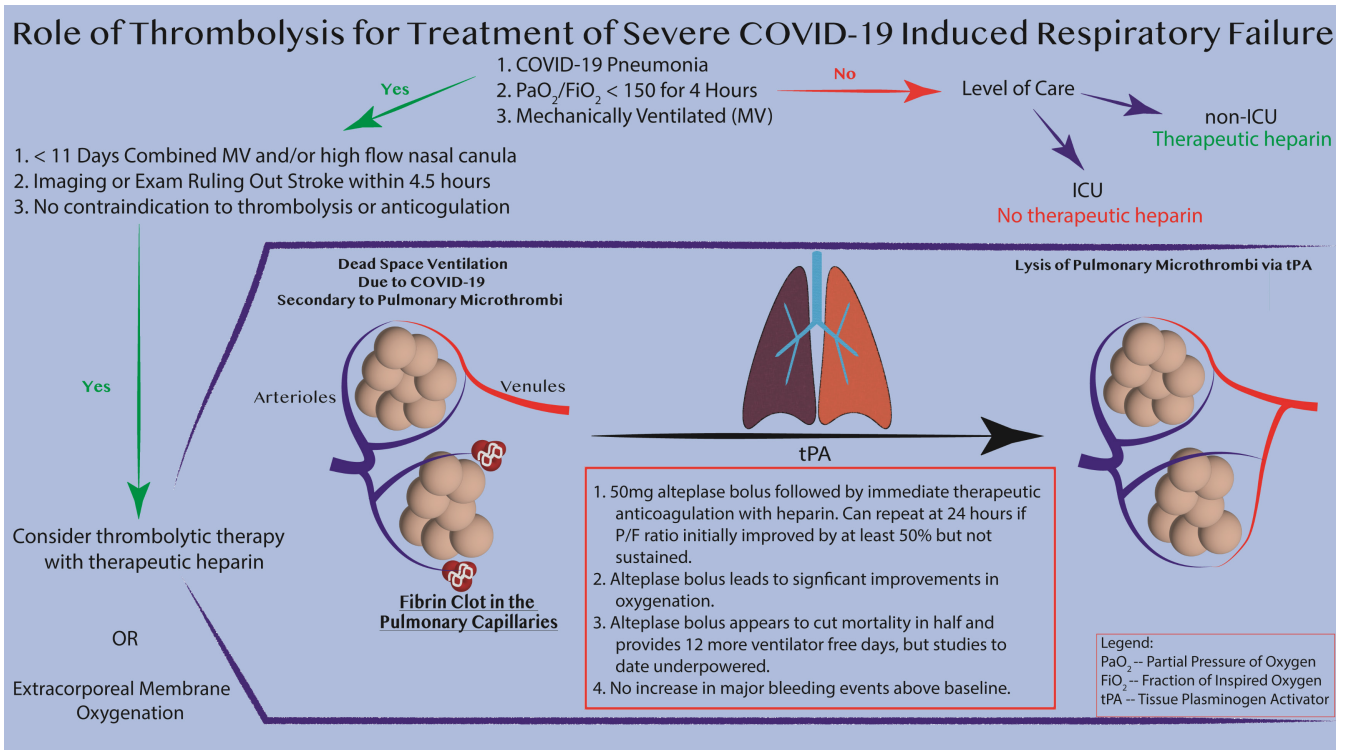
Elena Barbon PhD



Adeno-associated viral vectors have emerged as one of the most promising gene delivery platforms for in vivo liver-directed gene therapy for the treatment of blood coagulation disorders, particularly hemophilia A (HA) and B (HB). The ongoing clinical trials are based on adeno-associated virus (AAV)-mediated hepatocyte-targeted expression of coagulation factor VIII or IX for HA and HB, respectively.<sup>13</sup> Nevertheless, there is increasing interest in the possibility of improving the targeting of different cell types. To this aim, AAV capsid engineering represents an attractive strategy to enhance cell-specific transduction.<sup>14,15</sup> This may represent a promising approach in coagulation diseases such as HA or von Willebrand disease, where expressing the therapeutic protein from its natural biosynthetic site, that is, endothelial cells, could be beneficial to guarantee an optimized protein biosynthesis, secretion, and activity.

# Fibrinolysis and thrombolytic therapy in COVID-19 respiratory failure

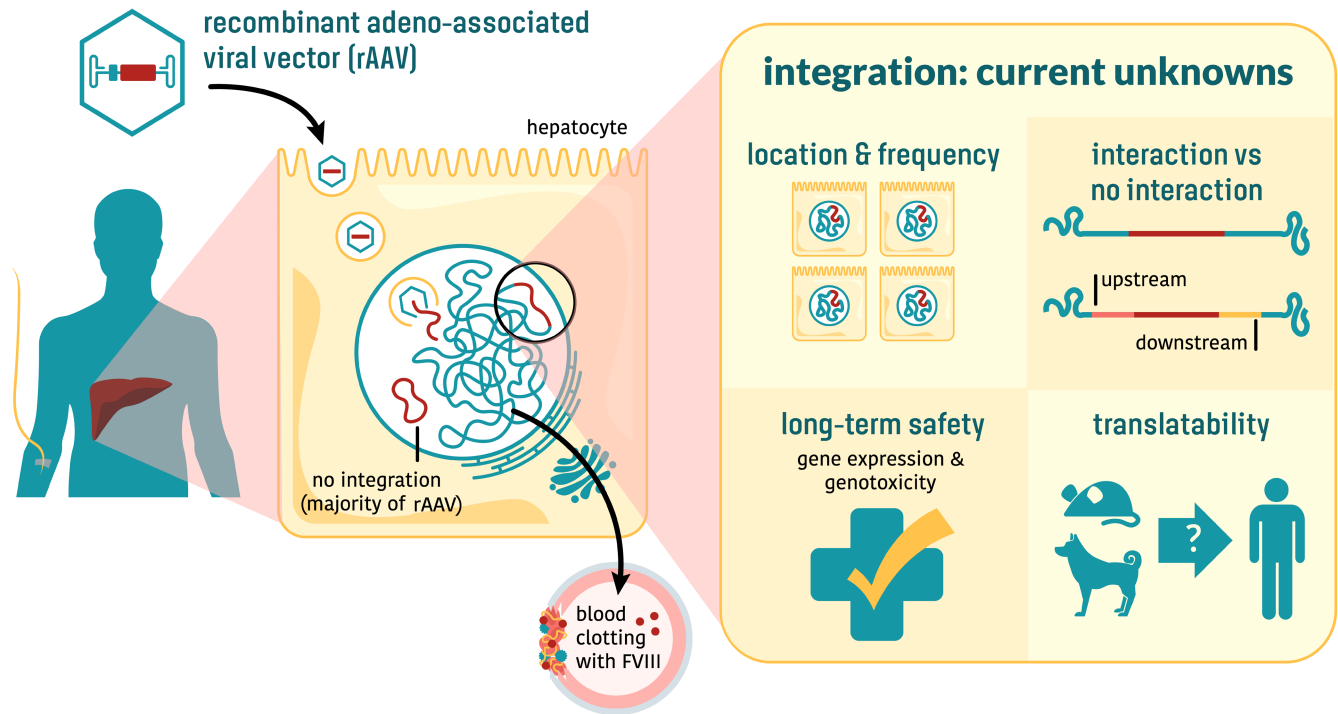
Christopher D. Barrett MD



For references, see Barrett et al.<sup>16,17</sup>; ATTACC Investigators et al.<sup>18</sup>

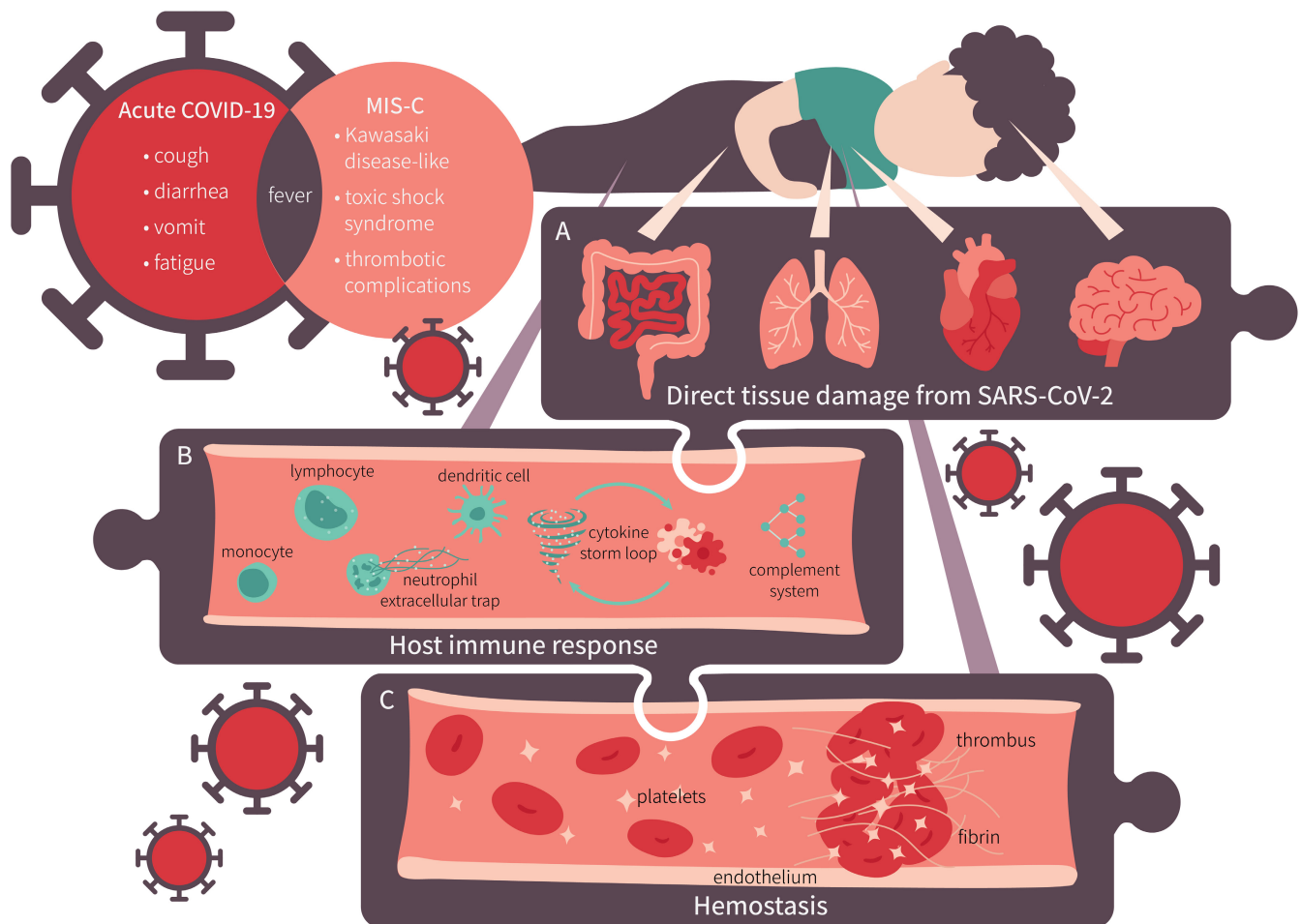
## Adeno-associated virus integration

Paul Batty MBBS, PhD



## Update on the pathogenesis of COVID-19 and multisystem inflammatory syndrome in children

Jorge David Aivazoglou Carneiro MD, PhD



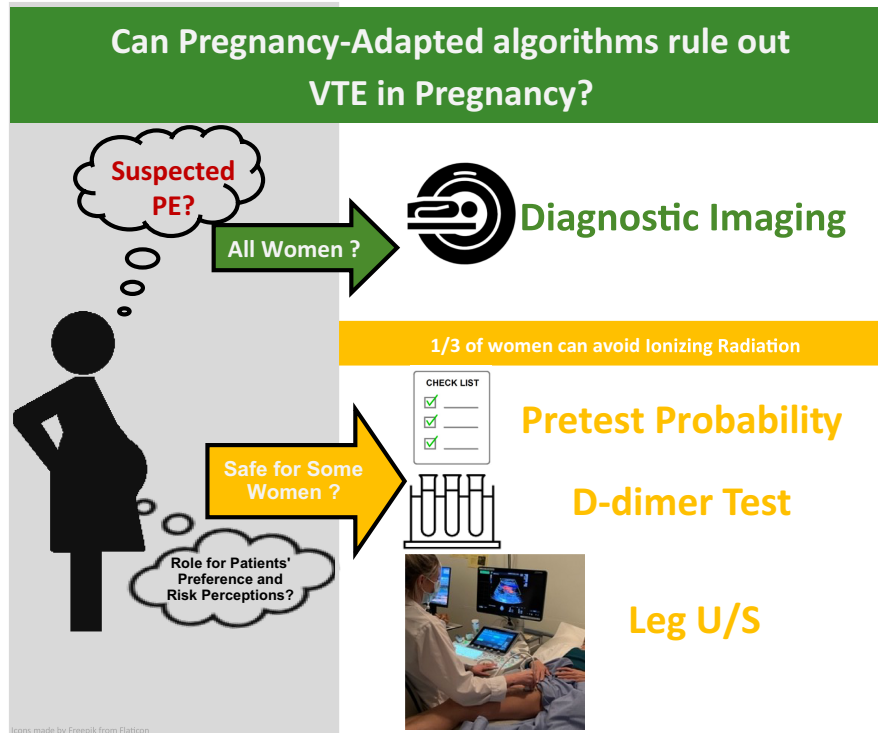
Pathogenesis of COVID-19 and multisystem inflammatory syndrome in children (MIS-C)

1. Severe acute respiratory syndrome coronavirus 2 infection affects several body organs in special respiratory, cardiovascular, gastrointestinal, and nervous systems, causing direct tissue damage.
2. Innate immune system activation is the first step of host immune response initiating inflammatory pathways that provide viral clearance. However, an innate immune response out of control may result in severe COVID-19 or MIS-C.
3. The endothelium plays an important role in the balance of hemostasis. Therefore, endothelial damage and inflammation promote a hypercoagulable state and thrombosis.

For references, see Yuki et al.<sup>19</sup>; Gustine and Jones<sup>20</sup>; Diamond and Kanneganti<sup>21</sup>

## Can pregnancy-adapted algorithms rule out venous thromboembolism in pregnancy?

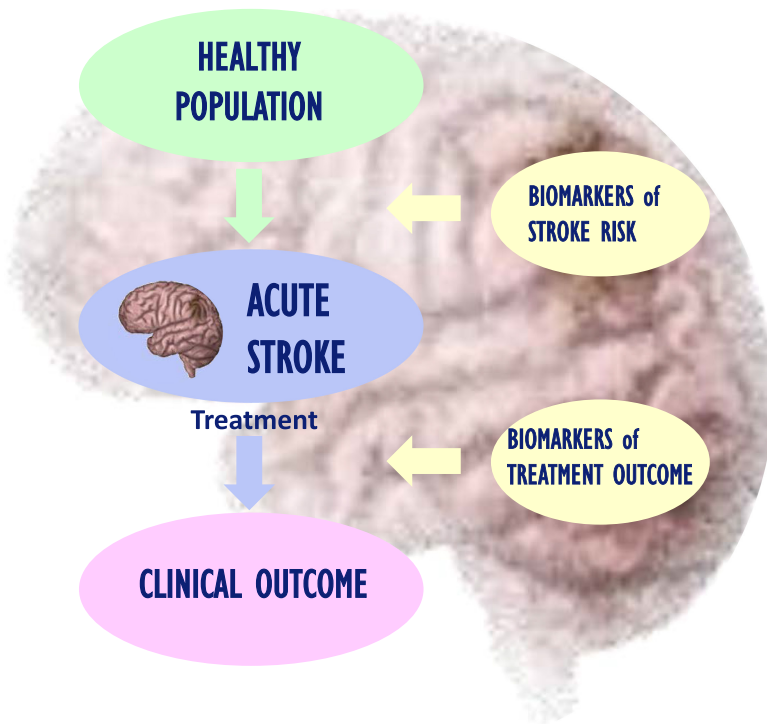
Wee Shian Chan MD, MSc, FRCP



For references, see Konstantinides et al.<sup>22</sup>; van der Pol et al.<sup>23</sup>; Righini et al.<sup>24</sup>

# Biomarkers for stroke prediction

Moniek de Maat PhD

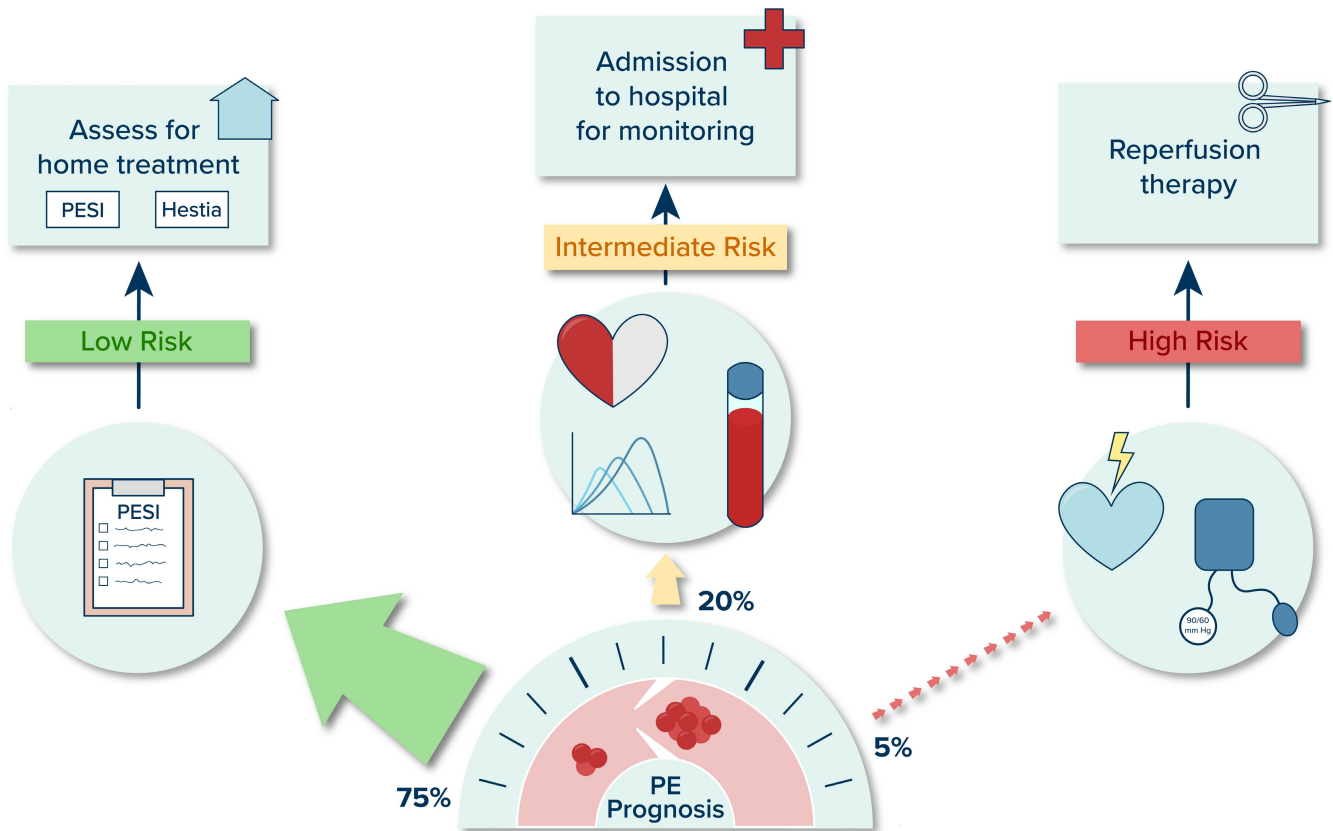


	ischemic stroke risk in healthy population	outcome after stroke	outcome after tPA treatment
<b>Primary hemostasis</b> von Willebrand factor ADAMTS13 platelet activation markers	↑ ↓ -/↑	-/↑ -/↓ -/↑	- ↓ no data
<b>Secondary hemostasis</b> fibrinogen FVIII thrombin generation	↑ ↑ ↓↑	-/↑ -/↑ no data	- - no data
<b>Fibrinolysis</b> PAI-1 clot lysis time D-dimer	- no data ↑	-/↑ no data ↑	-/↑ ↓ no data
<b>Thrombus characteristics</b> mechanical, fibrin network	no data	no data	no data
<b>Inflammation</b> C-reactive protein, cytokines	↑	no data	no data
<b>Immunothrombosis</b> NETs, eDNA	no data	no data	↓



## Risk stratification for acute venous thromboembolism

Kerstin de Wit MBChB, MD, MSc

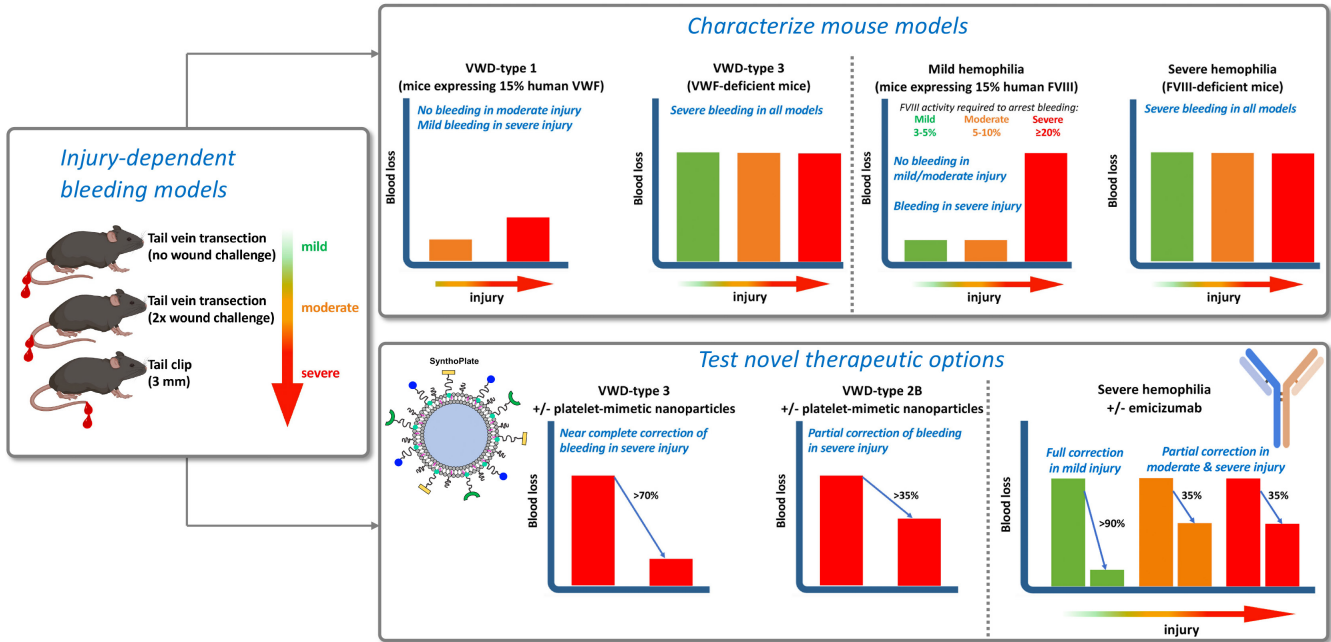


Patients with acute pulmonary embolism (PE) can be classified as having low-risk PE (75% of cases), intermediate-risk PE (20% of cases), or high-risk PE (5% of cases). Low-risk patients can be assessed for outpatient treatment with rapid follow-up. Intermediate-risk patients are admitted for monitoring, and high-risk patients require immediate reperfusion therapy.<sup>22</sup>

PESI, pulmonary embolism severity index; VTE, venous thromboembolism.

# New animal models for bleeding disorders and treatments

Cécile Denis PhD



FVIII, factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor.

## Myeloproliferative neoplasms in pregnancy: Implications for mother and child

Martin H. Ellis MD

### MPN in pregnancy: Incidence



**3.2 per 100 00 pregnancies per year**

### Pregnancy-related complications are common in MPN

**Pregnancy loss=28.7%**

**Adverse outcomes\* =9.8%**

\*VTE, ATE, preeclampsia, abruption, IUGR



### MPN in pregnancy: Treatment recommendations

#### First pregnancy

##### **Maternal VTE /ATE prophylaxis**

- LMWH (VTE)  
(Only for co-existent VTE risk factors: previous VTE, C/S, advanced age, obesity)
- Aspirin (ATE)

##### **Placenta-related prophylaxis**

- Observation or aspirin

#### Subsequent pregnancies

(in case of previous placenta-related complications)

##### **Maternal VTE/ATE prophylaxis**

- As for first pregnancy

##### **Placenta-related prophylaxis**

- Interferon
- Aspirin-low dose

MPN=myeloproliferative neoplasm IUGR=Intrauterine growth restriction

VTE=venous thromboembolism ATE=arterial thromboembolism C/S=Cesarean section LMWH=low molecular weight heparin

Polycythemia vera, essential thrombocythemia, and primary myelofibrosis (termed *myeloproliferative neoplasms* [MPNs]) are clonal diseases that may result in fatal end-stage bone marrow fibrosis or acute leukemia. During the long natural history of these diseases, thrombosis is an important complication.

The median age at diagnosis of the MPNs is >60years; however, 20% of patients are <40years old when diagnosed, making MPNs in pregnancy a relevant clinical issue. Indeed, the estimated incidence of MPNs among pregnant women in the United Kingdom is 3.2 in 100 000 pregnancies per year.<sup>25</sup>

The risk of maternal (venous or arterial thrombosis or hemorrhage), or placenta-related (fetal loss or preeclampsia/eclampsia) complications is higher in pregnancies in patients with MPNs than in the general population. Meta-analysis data demonstrate that 28.7% pregnancies are lost among these patients and that an additional 9.6% of women experience an adverse outcome such as thrombosis, preeclampsia, eclampsia, placental abruption, or intrauterine growth retardation.<sup>26</sup>

Treatment is based on observational data and expert opinion and includes aspirin, low-molecular-weight heparin, and interferon- $\alpha$ . Prospective studies are needed to better define appropriate treatment for these patients.

## Management of thrombocytopenia in pregnancy

Renee Eslick BMed, FRACP, FRCPA

# Management of Thrombocytopenia in Pregnancy

Eslick R



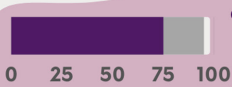
### Frequency

1 in 10 women develop thrombocytopenia in pregnancy.



### Treatment

- Optimise antenatal iron and haemoglobin
- Delivery for PET
- Corticosteroids and/or IVIg for ITP



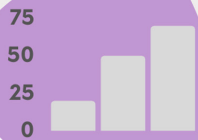
### Aetiology

- 75% gestational
- 20% preeclampsia (PET)
- 3% immune (ITP)



### Mode of Delivery

- Per obstetrical indications
- Active management of third stage of labour - prophylactic uterotonics and assisted delivery of the placenta



### Platelet Thresholds

- Limited evidence and individualised decision making recommended
- In the absence of bleeding, consider aiming for the following thresholds:
- $>20 \times 10^9/L$  during pregnancy
- $>50 \times 10^9/L$  for Caesarean or vaginal birth
- $>70 \times 10^9/L$  for neuraxial anaesthesia



### Neonatal Issues

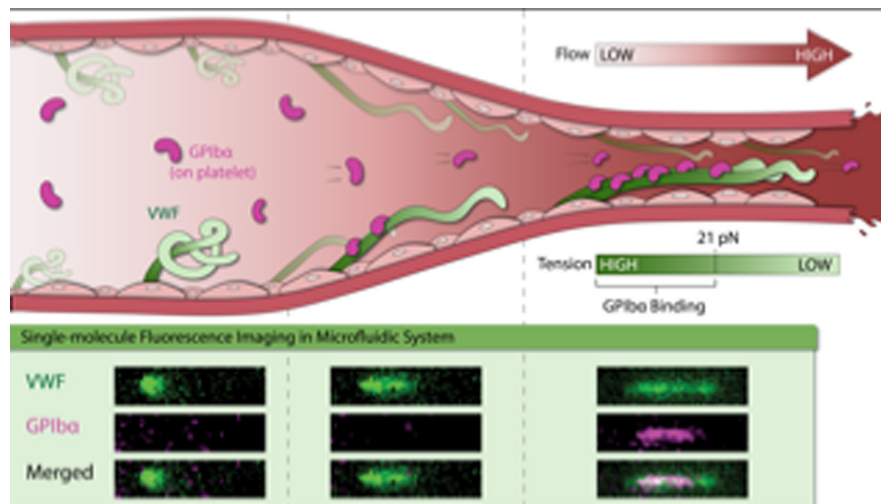
- Avoid instrumental delivery if possible
- For maternal ITP / hereditary thrombocytopenia:
  - Check cord platelet count
  - Evaluate infant for signs/symptoms of bleeding

IVIg, intravenous immunoglobulin; ITP, immune thrombocytopenia; PET, preeclampsia.

For reference, see Eslick et al.<sup>27</sup>

## Binding of flow-activated von Willebrand factor to glycoprotein Ib

Hongxia Fu PhD



Blood protein von Willebrand factor (VWF; green) is essential in thrombosis and hemostasis. Force induced by blood flow is an important regulator to mediate VWF hemostatic function. Dynamic single-molecule imaging in a microfluidic system reveals that a two-step conformational transition induces VWF activation mechanism.<sup>28,29</sup> First, VWF elongates from compact to linear form. Second, a tension above 21 pN (dark green shading) induces VWF transition to a state with high affinity for platelet glycoprotein Ib $\alpha$  (GPIb $\alpha$ ; magenta). For clarity, platelets are not shown. GPIb $\alpha$  dissociates rapidly when tension is under 21 pN. This mechanism allows VWF to be activated by hydrodynamic force at sites of hemorrhage but avoid thrombus formation downstream. (Single-molecule fluorescence images were reproduced from Fu et al.,<sup>28</sup> *Nature Communications*, 2017 with modifications and shared via a Creative Commons 4.0 license.)

# Hemostatic defects in fibrinolytic disorders

Catherine P. M. Hayward MD, PhD

### Inherited Fibrinolytic Diseases Phenotype

<p><b>SHARED</b></p> <ul style="list-style-type: none"> <li>• Increased bleeding, delayed onset</li> <li>• Responsive to fibrinolytic inhibitors</li> <li>• Frequently: delayed diagnosis</li> </ul>	<p><b>PAI-1 DEFICIENCY ONLY</b></p> <ul style="list-style-type: none"> <li>• Antenatal bleeds</li> <li>• Cardiac fibrosis</li> <li>• Longevity</li> </ul> <p><b>QPD ONLY</b></p> <ul style="list-style-type: none"> <li>• Reduced platelet counts</li> </ul>
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**PLASMINOGEN**

PAI-1 → tPA (1)  
PAI-1 → uPA (2)

(F11a, F12a, kallikrein)

**PLASMIN**

α<sub>2</sub> antiplasmin (α<sub>2</sub>macroglobulin) (3)

Inherited fibrinolytic disorder	Pathophysiology	Diagnosis
1. PAI-1 deficiency	<ul style="list-style-type: none"> <li>• ↑↑↑ fibrinolysis (loss-of-inhibitor defect)</li> <li>• Cause: ↓↓↓ uPA &amp; tPA inhibition resulting in ↑↑↑ plasmin generation</li> </ul>	<ul style="list-style-type: none"> <li>• ↓↓↓ ELT</li> <li>• ↓↓↓ PAI-1 antigen</li> <li>• Can ↓α2 antiplasmin</li> <li>• Genetic investigations</li> </ul>
2. Quebec platelet disorder	<ul style="list-style-type: none"> <li>• ↑↑↑ fibrinolysis (gain-of-function defect)</li> <li>• Cause: PLAU "rewired" in megakaryocytes → ↑↑↑ platelet uPA</li> <li>• ↑↑↑ plasmin generation in wounds (&amp; in α-granules)</li> </ul>	<ul style="list-style-type: none"> <li>• Genetic test for QPD duplication mutation</li> </ul>
3. α2 antiplasmin deficiency	<ul style="list-style-type: none"> <li>• ↑↑↑ fibrinolysis (loss-of-inhibitor defect)</li> <li>• Cause: ↓↓↓ plasmin inhibition</li> </ul>	<ul style="list-style-type: none"> <li>• ↓↓↓ α2-antiplasmin</li> <li>• Genetic investigations</li> </ul>

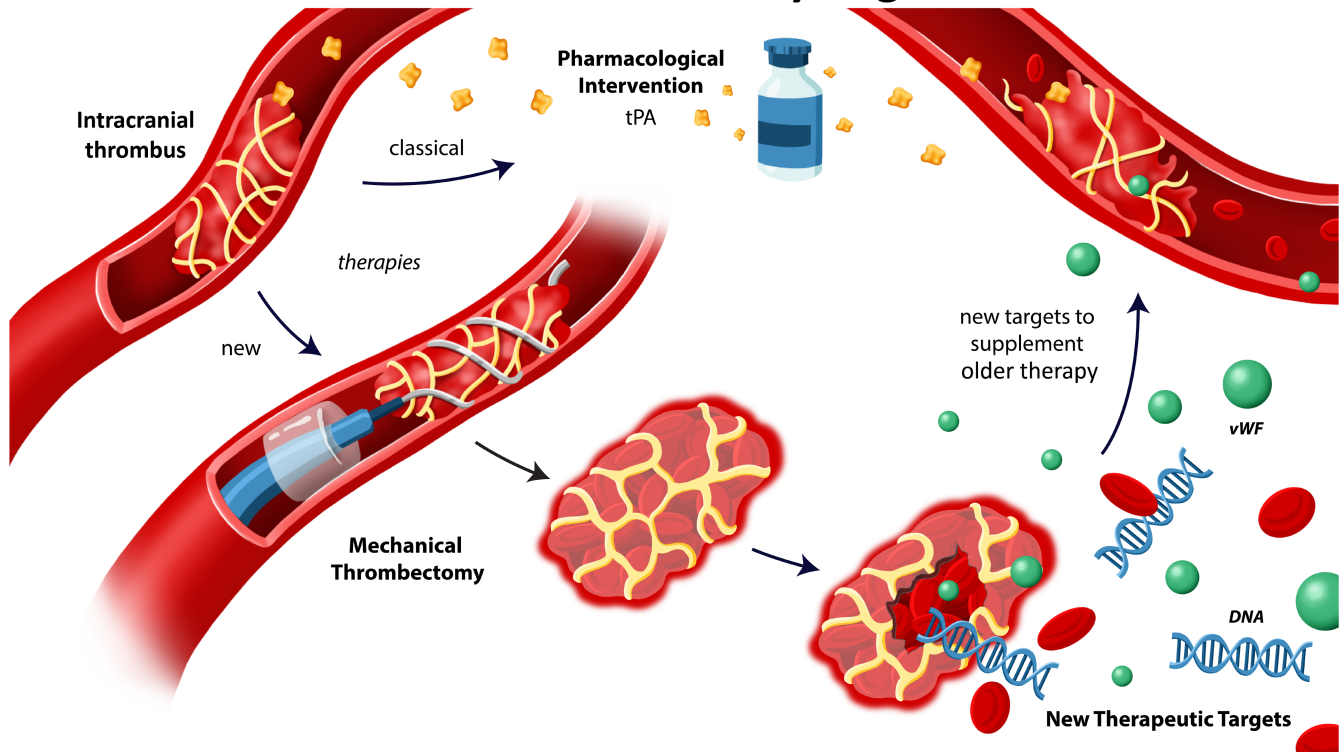
  

**Accelerated Lysis of Platelet Fibrin Clot**

## Thrombus composition and thrombolysis resistance in stroke

Benoit Ho-Tin-Noé PhD

### Past, present and future recanalization therapies for acute ischemic stroke caused by large vessel occlusion

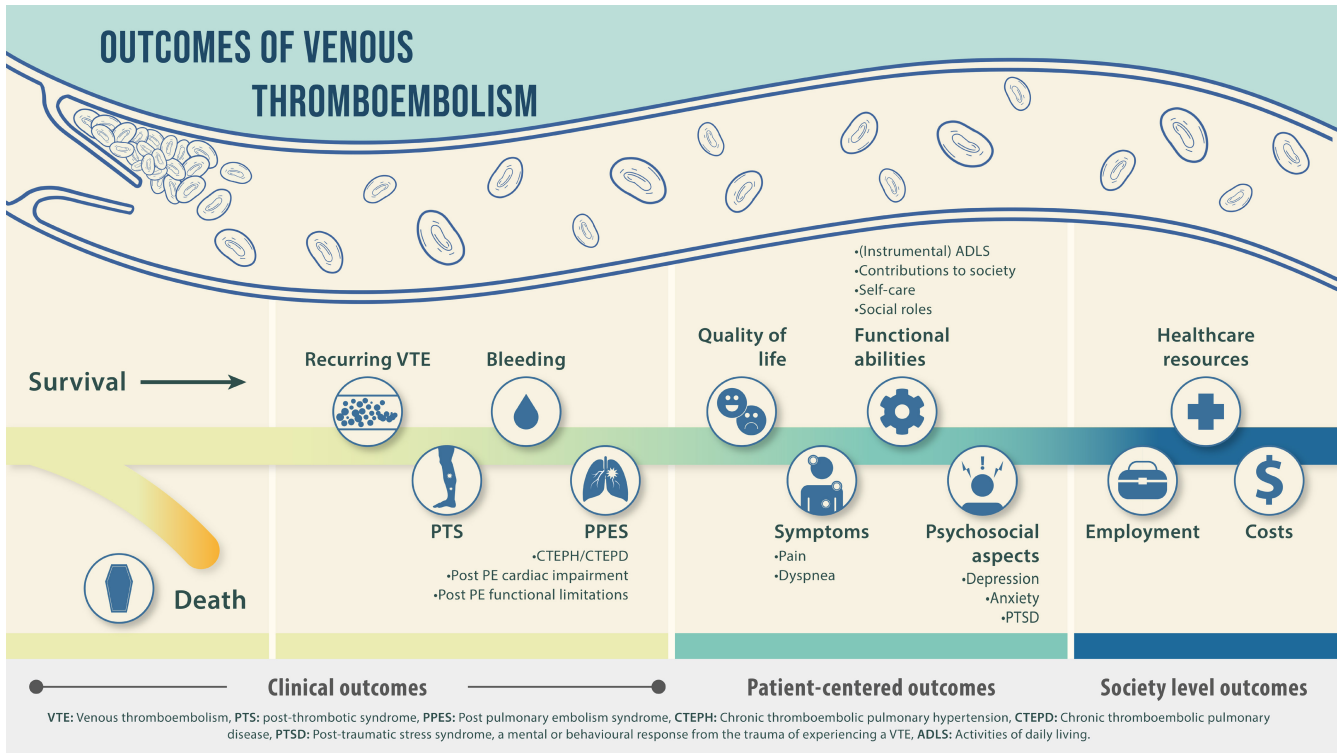


The introduction of mechanical thrombectomy has considerably increased the rate of successful recanalization in large-vessel occlusion stroke. From a basic research standpoint, it has enabled the analysis of stroke thrombi and a better understanding of the mechanisms underlying resistance to intravenous thrombolysis. Therefore, although the efficacy of mechanical thrombectomy could have caused the end of thrombolysis, it has instead opened the way for its rethinking and improvement, through the development of innovative thrombolytic strategies.



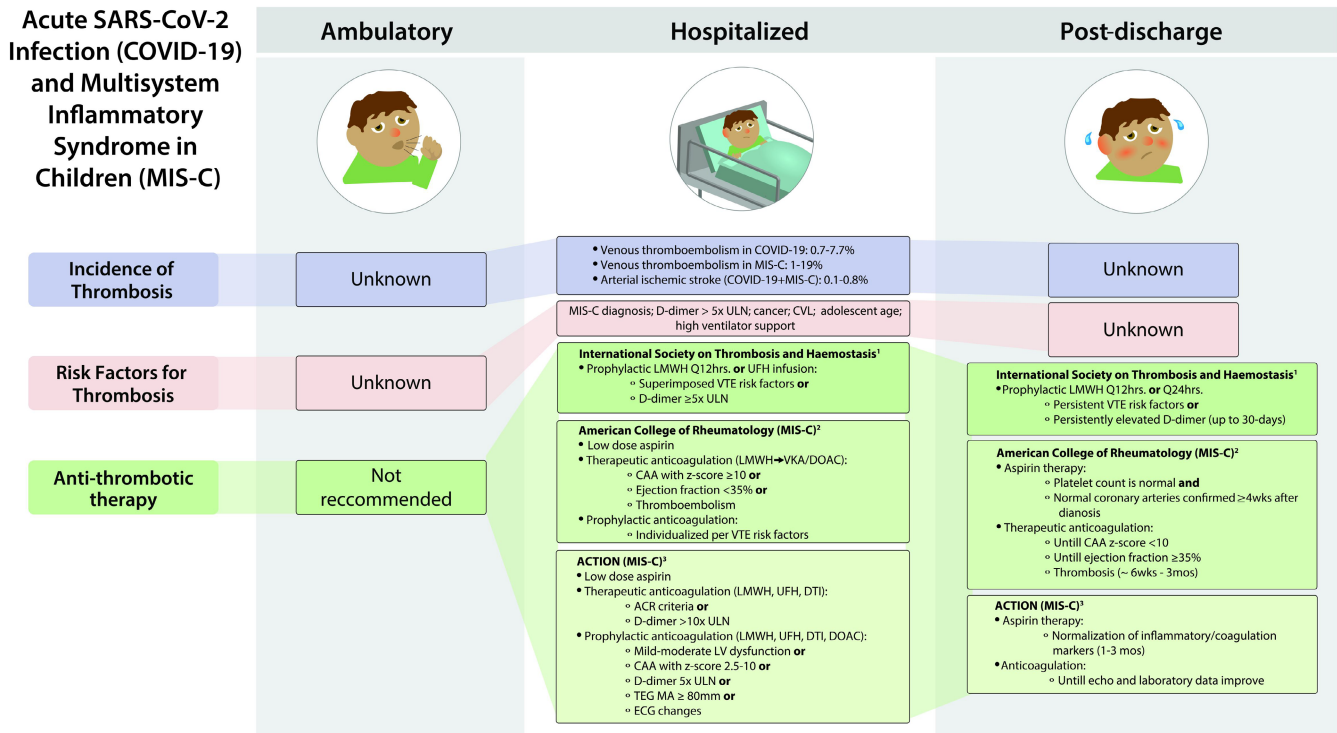
# Outcomes of venous thromboembolism

Frederikus A. Klok MD, PhD



# Multisystem inflammatory syndrome in children and thrombotic complications of COVID-19 in children

Riten Kumar MD, MSc



ACR, American College of Rheumatology; ACTION, Advanced Cardiac Therapies Improving Outcomes Network; anti-FXa, anti-factor Xa; CAA, coronary artery aneurysm; CVL, central venous line; DOAC, direct oral anticoagulant; DTI, direct thrombin inhibitor; ECG, electrocardiogram; LMWH, low-molecular-weight heparin; LV, left ventricular; MA, maximum amplitude; TEG, thromboelastogram; UFH, unfractionated heparin; ULN, upper limit of normal; VKA, vitamin K antagonist; VTE, venous thromboembolism

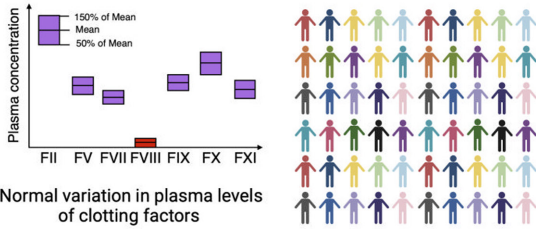
For references, see Goldenberg et al.<sup>30</sup>; Henderson et al.<sup>31</sup>; Bansal et al.<sup>32</sup>

# Mathematical modeling to study variability in bleeding

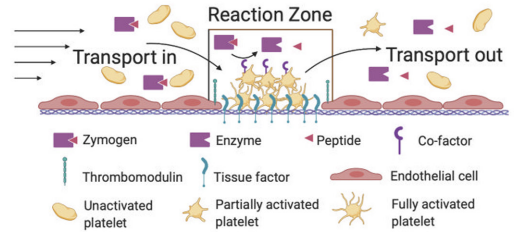
Karin Leiderman PhD

## Mathematical Modeling to Study Variability in Bleeding

Create synthetic data set representing the plasma levels of thousands of hemophilia patients

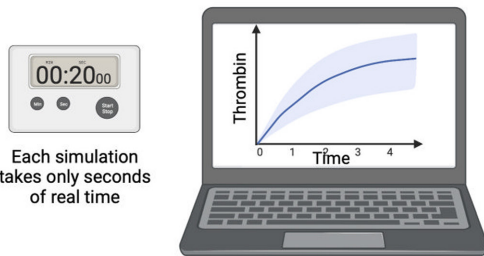


Mathematical Model of Flow-Mediated Coagulation

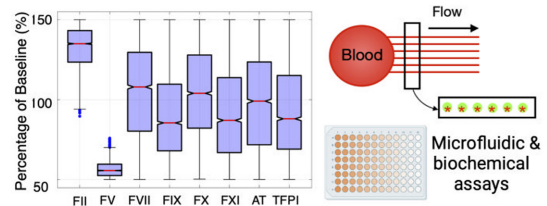


$$\left( \text{Rate of change of concentrations in reaction zone} \right) = \left( \text{Rate of supply} \right) + \left( \text{Rate of removal} \right) + / - \left( \text{Rate of generation, inhibition, etc.} \right)$$

Perform thousands of simulations using synthetic data set as input to the mathematical model



Statistically analyze the model output, identify modifiers of bleeding, experimentally validate

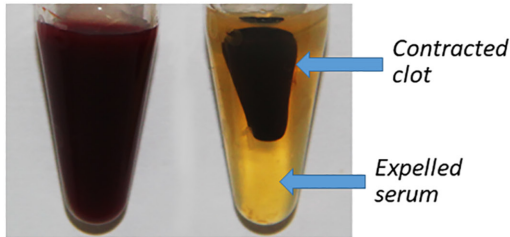


## Blood clot contraction: Mechanisms, pathophysiology, and disease

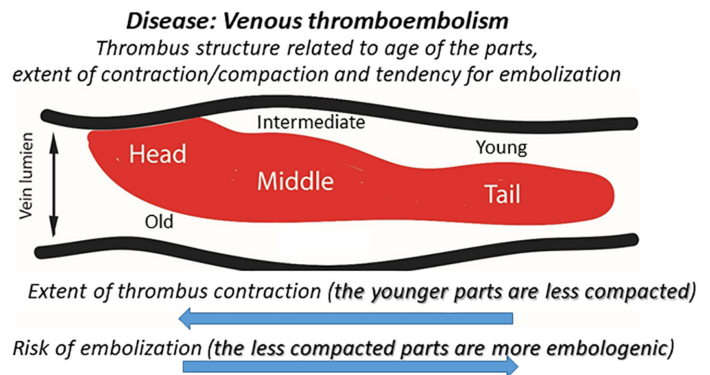
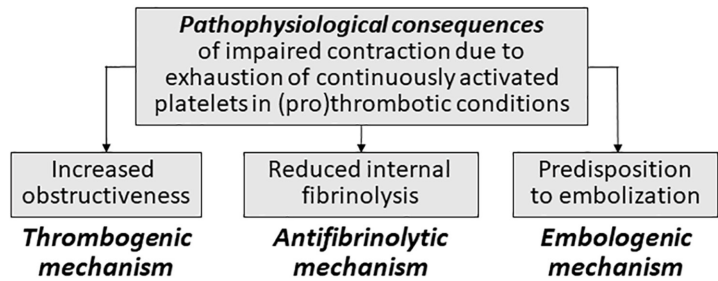
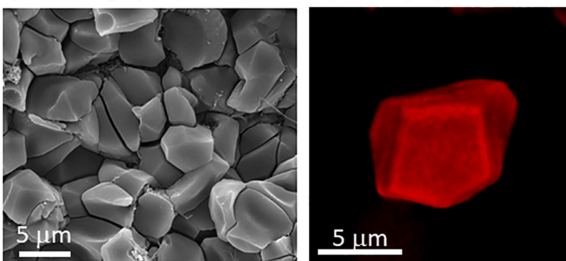
Rustem I. Litvinov MD, PhD

### Blood Clot Contraction: Mechanisms, Pathophysiology, and Disease

*Contraction (retraction, shrinkage) of in vitro clots and in vivo thrombi is driven by activated platelets*



*A new pathogenic mechanism: Contraction of clots and thrombi results in formation of polyhedrocytes - tightly packed, highly impermeable, compressed polyhedral RBCs*

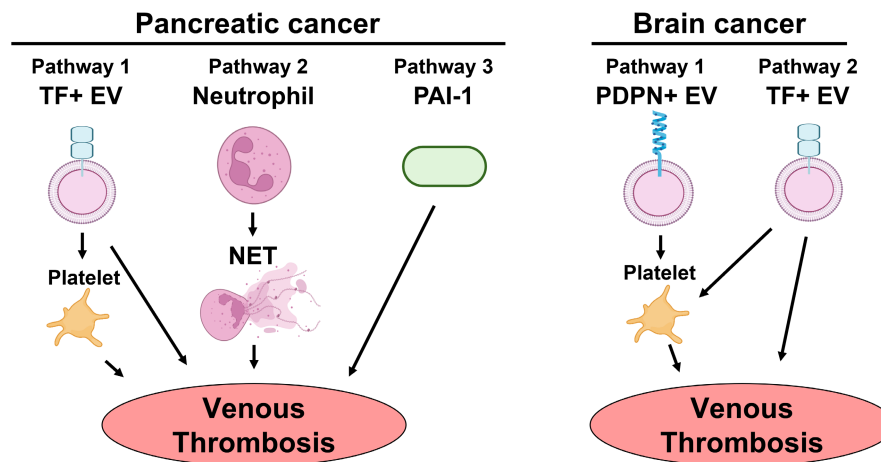


Contraction (retraction) of blood clots and thrombi is clinically important since it can affect their obstructiveness, permeability, susceptibility to fibrinolysis, and the propensity to rupture (embologenicity). The rate and extent of clot contraction in vitro and in vivo can be enhanced or inhibited by altered platelet functionality as well as pathological cellular and molecular composition of the blood.<sup>33</sup> Clot contraction is reduced in the blood of patients with various (pro)thrombotic conditions, due to continuous platelet activation followed by their exhaustion and reduced contractility.<sup>34</sup> Impaired clot contraction is a significant but understudied and underappreciated pathogenic factor that can influence the course and outcomes of thrombotic disorders.<sup>35</sup>

## Mechanisms of cancer-associated thrombosis

Nigel Mackman PhD

### Pathways of Cancer-Associated Thrombosis








The majority of studies on the mechanisms of cancer-associated thrombosis (CAT) have focused on pancreatic cancer and brain cancer because they have the highest rates of venous thromboembolism (VTE). There are several pathways that contribute to venous thrombosis in pancreatic and brain cancer. Human studies have identified circulating biomarkers that are associated with VTE. Mouse cancer models are used to directly examine the role of a pathway in venous thrombosis. Taken together, these studies suggest that tissue factor-positive extracellular vesicles (EVs) directly and indirectly (via activation of platelets) enhance venous thrombosis in both pancreatic and brain cancer.<sup>36,37</sup> Neutrophils form neutrophil extracellular traps that can enhance venous thrombosis in pancreatic cancer.<sup>36</sup> Plasminogen activator inhibitor-1 contributes to venous thrombosis in pancreatic cancer by inhibiting fibrinolysis.<sup>38</sup> In brain cancer, podoplanin-positive EVs activate platelets and enhance venous thrombosis.<sup>37</sup> Targeting these pathways may reduce CAT.

Image created with [BioRender.com](https://www.biorender.com)

## When to use tranexamic acid in bleeding

Zoe McQuilten MBBS, PhD

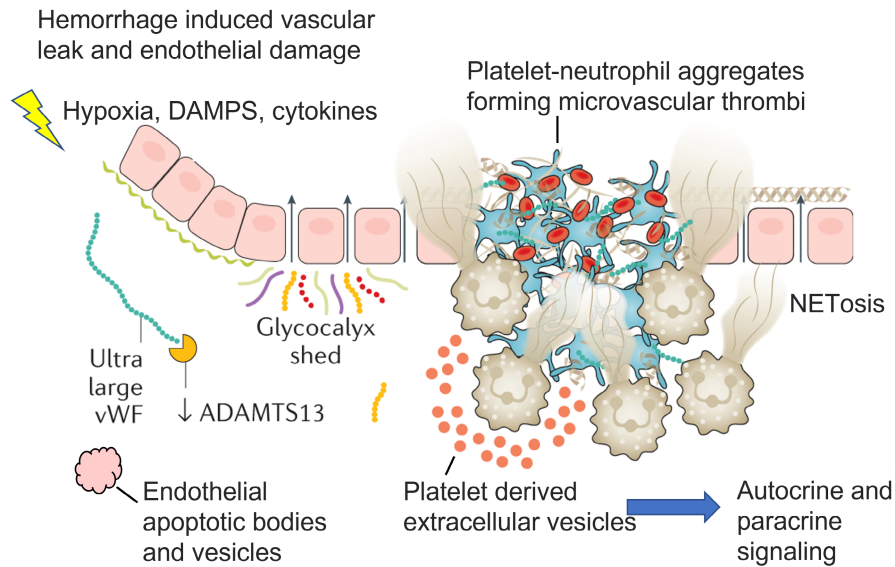
### SUMMARY OF RANDOMIZED CONTROLLED TRIALS OF TRANEXAMIC ACID FOR BLEEDING

CLINICAL SITUATION		TRANEXAMIC ACID			EVIDENCE TO SUPPORT USE?		
	RCT#	DOSE (IV)*	MORTALITY	OTHER	THROMBO-EMBOLISM	SEIZURES	
TRAUMATIC HEMORRHAGE	 5	Loading: 1g/10 min Infusion: 1g/8 hr  vs. placebo	EVIDENCE OF BENEFIT		NO DIFFERENCE	NO DIFFERENCE	✓ YES, best if given within 3 hrs
TRAUMATIC BRAIN INJURY	 9	Loading: 1g/10 min Infusion: 1g/8 hr  vs. placebo	EVIDENCE OF BENEFIT if given <3hrs of mild-moderate injury	Possibly reduced hematoma expansion	NO DIFFERENCE	NO DIFFERENCE	✓ MAYBE, if given to mild-moderate TBI within 3 hrs
SPONTANEOUS INTRACEREBRAL HEMORRHAGE	 4	Loading : 1g Infusion: 1g/8 hr  vs. placebo	NO EVIDENCE OF BENEFIT	Reduced hematoma expansion	NO DIFFERENCE	NO DIFFERENCE	● NO, further research needed
POSTPARTUM HEMORRHAGE	 2	1g + 1g if bleeding after 30 min or stopped and restarted within 24hrs, vs. placebo	EVIDENCE OF REDUCTION IN DEATH due to bleeding	No change in hysterectomy or transfusion rates	NO DIFFERENCE	NO DIFFERENCE	✓ YES, best if given within 3 hrs of birth
GASTRO-INTESTINAL HEMORRHAGE	 5	Loading Dose: 1g Infusion: 3g/24 hrs  vs. placebo	NO EVIDENCE OF BENEFIT		HIGHER RISK OF VENOUS THROMBO-EMBOLISM	HIGHER RISK	● NO

\*STUDIED IN LARGEST TRIAL

## Platelet and endothelial biology in bleeding

Matthew D. Neal MD

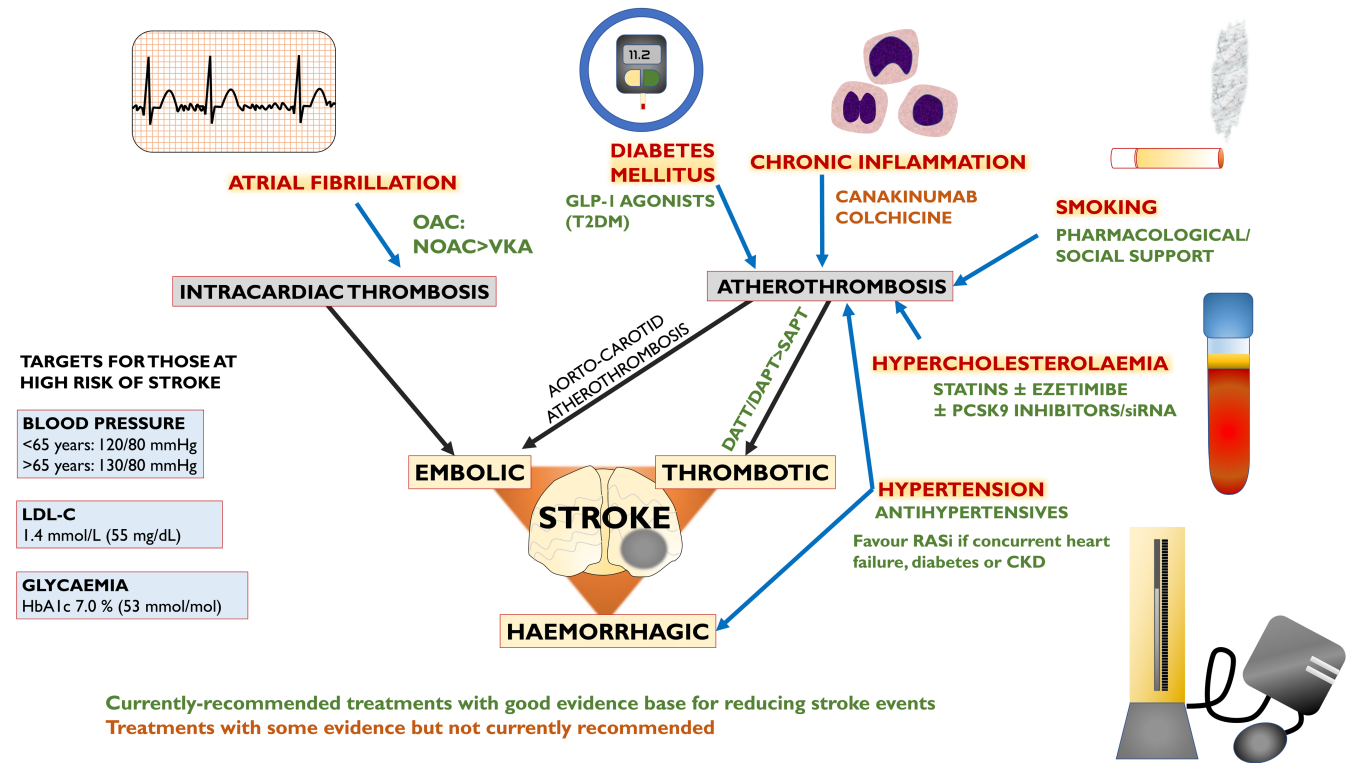


Following trauma and hemorrhage, the systemic signals of hypoxia, danger-associated molecular patterns and cytokines produce endothelial injury in addition to direct endothelial disruption.<sup>39</sup> The platelet is the sentinel responder to injury, orchestrating the complex processes of hemostasis and coagulation through interaction with damaged endothelium.<sup>40</sup> This State of the Art will review the adaptive and maladaptive responses of platelets and endothelium to bleeding with a focus on key mediators including von Willebrand factor, the metalloprotease ADAMTS-13,<sup>41</sup> neutrophil extracellular trap release, and the role of endothelial and platelet extracellular vesicles in cell signaling.



## Drug therapy for stroke prevention

William A. E. Parker MB, PhD, MRCP

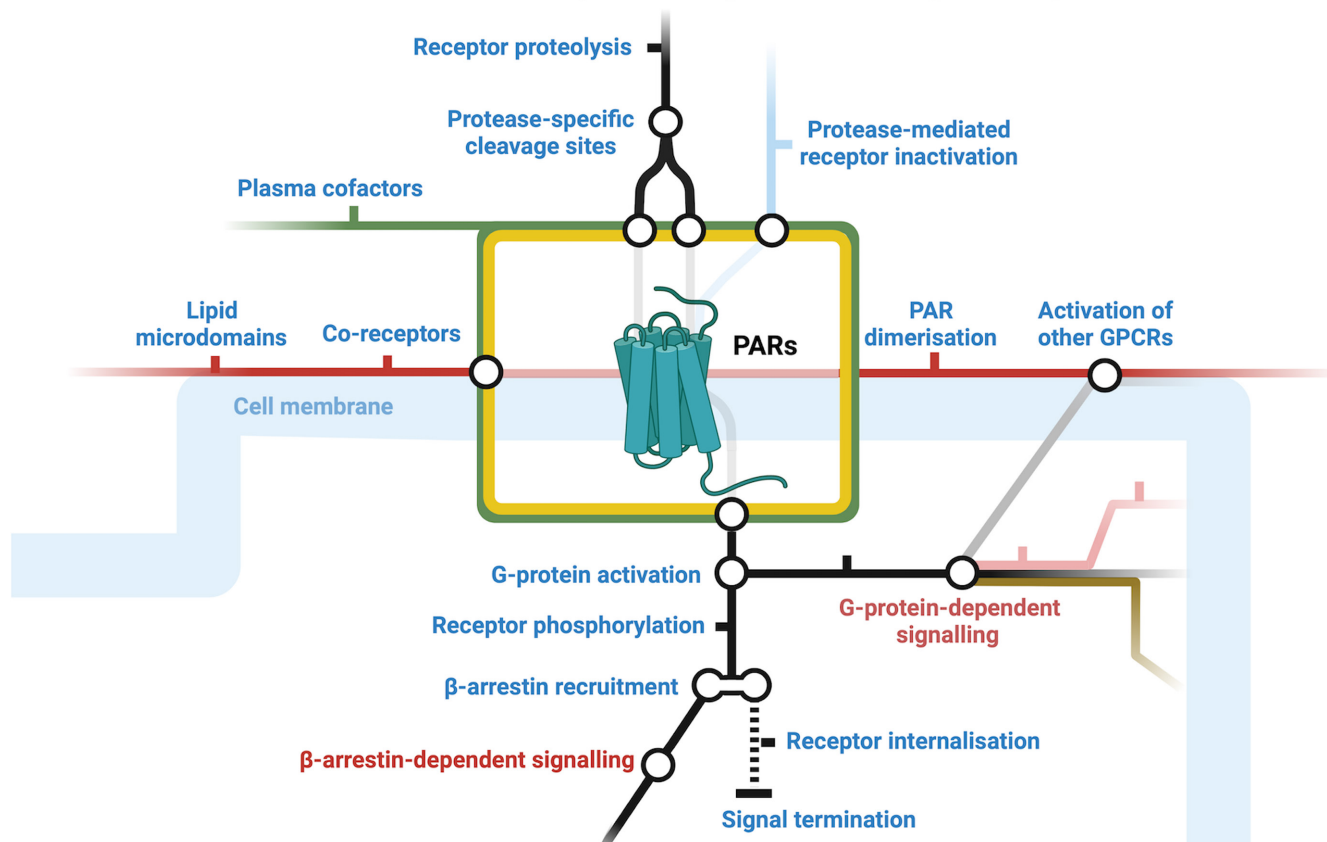


Drugs for control of modifiable risk factors in the prevention of stroke. Modified with permission from Parker et al. 2020 under Creative Commons CC-BY-NC license.<sup>42</sup> CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DATT, dual antithrombotic therapy; GLP-1, glucagonlike peptide 1; HbA<sub>1c</sub>, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; LEAD, lower-extremity arterial disease; NOAC, non-vitamin-K antagonist oral anticoagulant; OAC, oral anticoagulant; PCSK9, proprotein convertase subtilisin/kexin type 9; RASi, renin-angiotensin system inhibitor; SAPT, single antiplatelet therapy; T2DM, type 2 diabetes mellitus; VKA, vitamin K antagonist.

## Coagulation factor signaling

Roger J. S. Preston PhD

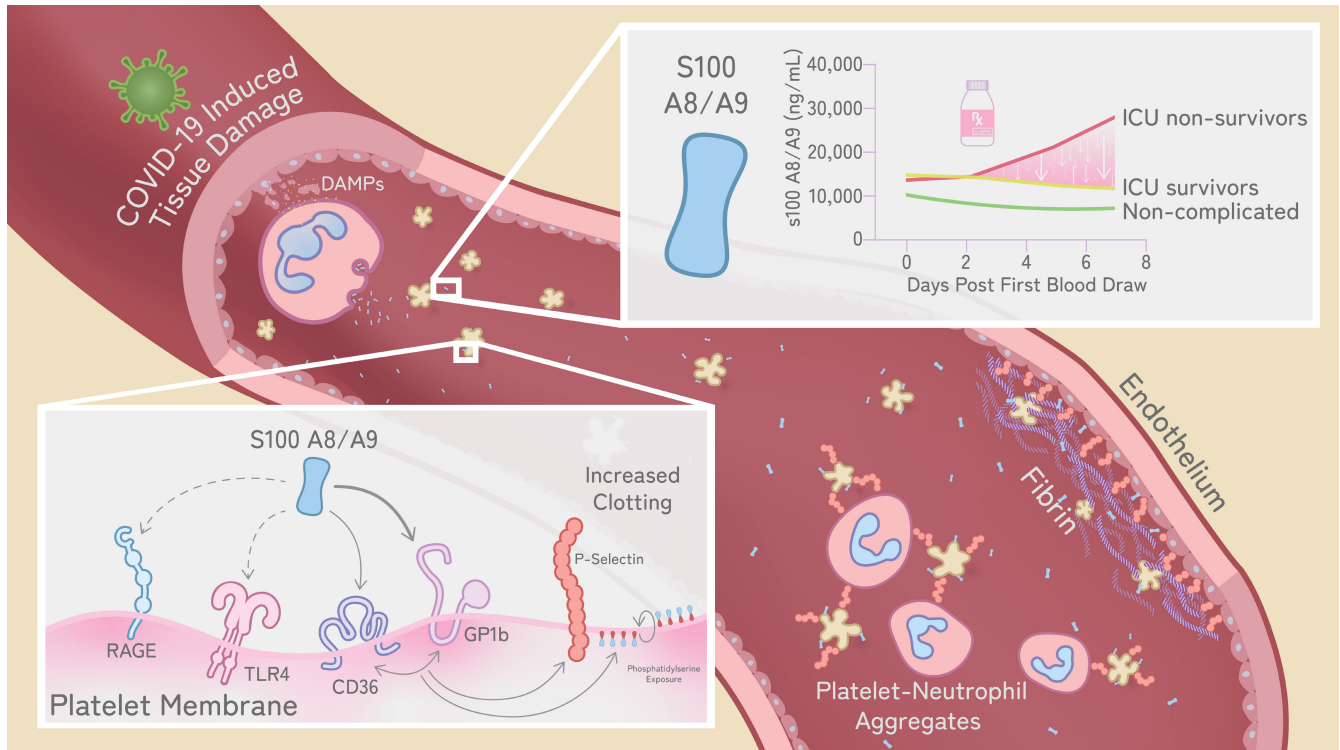
### Determinants of coagulation protease signalling



Most coagulation factor cell signaling is mediated by protease-activated receptors (PARs), a unique family of G-protein-coupled receptors whose activation is triggered by receptor proteolysis. Cell signaling output arising from PAR activation is shaped by both the activating protease and the specific cellular contexts in which receptor activation has occurred. Although not yet fully understood, intra- and extracellular regulatory determinants of PAR signaling diversity include protease-specific cleavage sites, association with protease coreceptors, receptor oligomerization, and recruitment of distinct signaling intermediates. These mechanisms combine to enable coagulation proteases to initiate a spectrum of downstream signaling pathways in multiple cell types.

## Novel mechanisms of thromboinflammation during infection and hemolysis

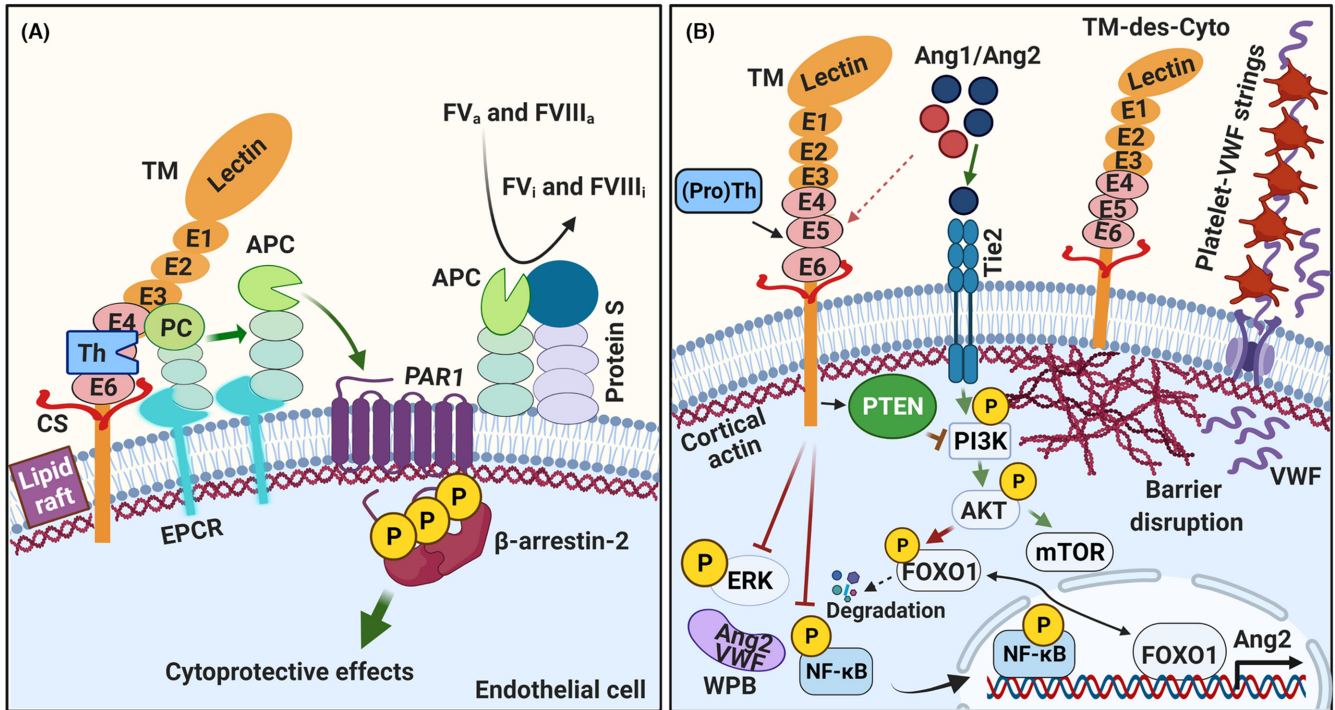
Julie Rayes PhD



- S100A8/A9 is a damage-associated molecular pattern with prothrombotic and proinflammatory properties.
- S100A8/A9 levels are increased in the plasma of patients with COVID-19.
- Deposition of S100A8/A9 on the vessel wall in patients with COVID-19 correlates with thrombotic complications.
- S100A8/A9 induces the formation of procoagulant platelets and amplifies fibrin generation.
- Glycoprotein Iba is the main receptor for S100A8/A9 on platelets, with a supporting role for CD36.

## Thrombomodulin regulates endothelial quiescence

Alireza R. Rezaie PhD



(A)

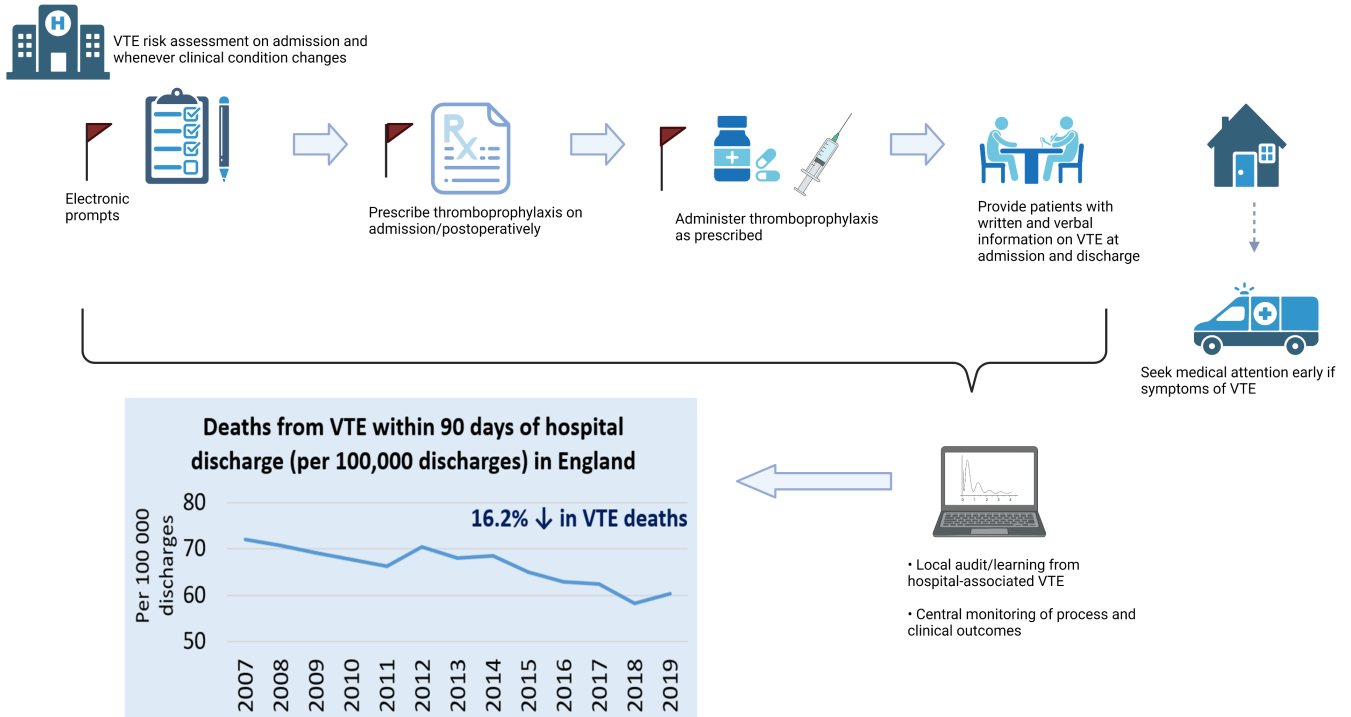
1. Thrombomodulin (TM), endothelial protein C receptor (EPCR), and protease-activated receptor-1 (PAR1), are colocalized in lipid rafts of endothelial cells.
2. Thrombin binds TM and activates EPCR-bound protein C.
3. Activated protein C (APC) in association with EPCR functions in the anti-inflammatory pathway by activating PAR1 and inducing cytoprotective  $\beta$ -arrestin-2 biased signaling.
4. APC functions in the anticoagulant pathway by binding protein S and inactivating factors Va and VIIIa ( $FV_i/FVIII_i$ ).

(B)

1. TM has anti-inflammatory and barrier-stabilizing functions and extracellular signal-regulated and nuclear factor kappa-light-chain-enhancer of activated B cells signaling.
2. (Pro)exosite-1 of (pro)thrombin binds epidermal growth factor (EGF)-like domains of TM and induces cytoprotective signaling.
3. Cytoplasmic domain of TM is involved in recruiting phosphatase and tensin homolog to plasma membrane, thereby regulating endothelial cell proliferation, angiogenesis, and metabolism through PI3K/AKT/FOXO1/mTOR signaling.
4. TM knockdown or deletion of its cytoplasmic-domain leads to barrier destabilization, constitutive expression/secretion of von Willebrand factor (VWF), cell surface platelet-VWF strings formation, reduced angiopoietin 2 expression and deregulated endothelial cell proliferation, angiogenesis and Tie2 receptor signaling. (Pro)Th, (pro)thrombin; WPCB, Weibel Palade body.

# Systematic approach to venous thromboembolism prevention

Lara N. Roberts MBBS, MD Res



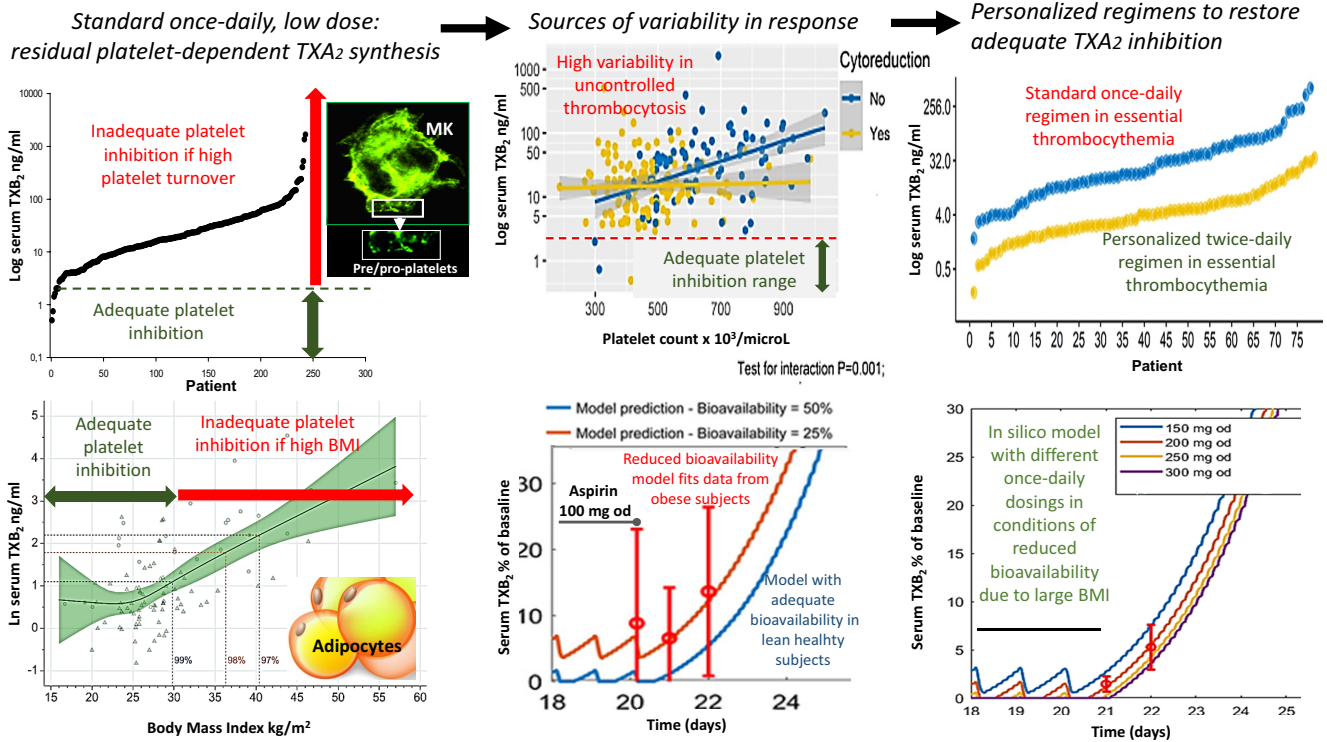
Created with [BioRender.com](https://BioRender.com)

VTE, venous thromboembolism.

For references, see Roberts et al.<sup>43</sup>; NHS Digital<sup>44</sup>

## Personalizing antiplatelet therapy based on platelet turnover and metabolic phenotype

Bianca Rocca MD, PhD



Variability in the response to fixed-dose antiplatelet drugs can be increased by primary (essential thrombocythemia) or secondary (reactive inflammatory states) pathological conditions associated with increased platelet turnover and count, that is, pharmacodynamic (PD) variability, as well as by high-degree obesity, that is, pharmacokinetic (PK) variability.

Understanding PK- and/or PD-related mechanisms of variability is central to design personalized regimens and to optimize the risk/benefit balance of common antiplatelet drugs by increasing the daily frequency or the once-daily dosing.

Moreover, in silico PK/PD modeling and in silico trials can be instrumental in designing clinical trials, developing antithrombotic therapy, and generating new personalized drug regimens.

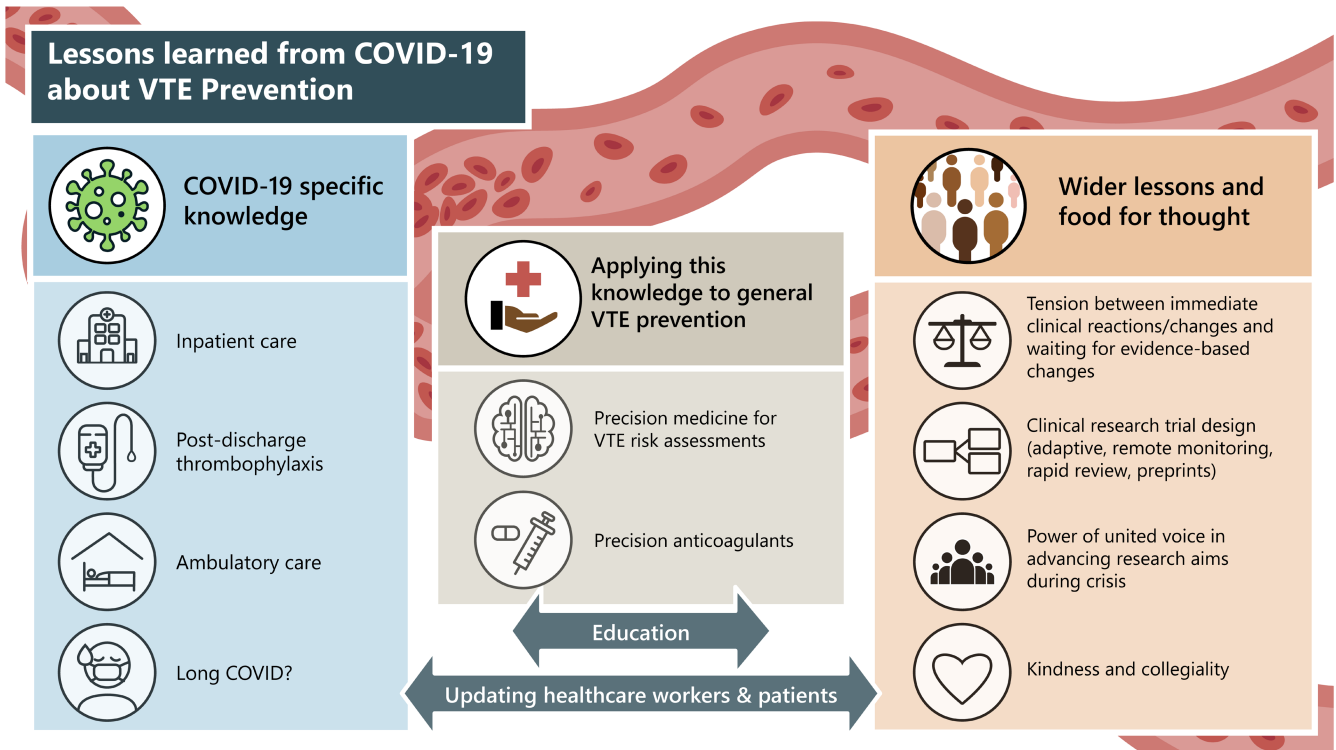
Finally, in silico PK/PD modelling can be essential in rare diseases and “special” populations such as extreme ages (elderly and children), extreme body sizes (underweight and high-degree obesity), severe comorbidities (severe kidney and liver dysfunction), which are either underrepresented or excluded from cardiovascular randomized trials.

A, acetylsalicylic acid; MK, megakaryocyte; od, once daily; P, placebo; TXB<sub>2</sub>, thromboxane B<sub>2</sub>.

For references, see Tosetto et al.<sup>45</sup>; Rocca et al.<sup>46</sup>; Petrucci et al.<sup>47</sup>

# VTE prevention—What have we learned from COVID-19?

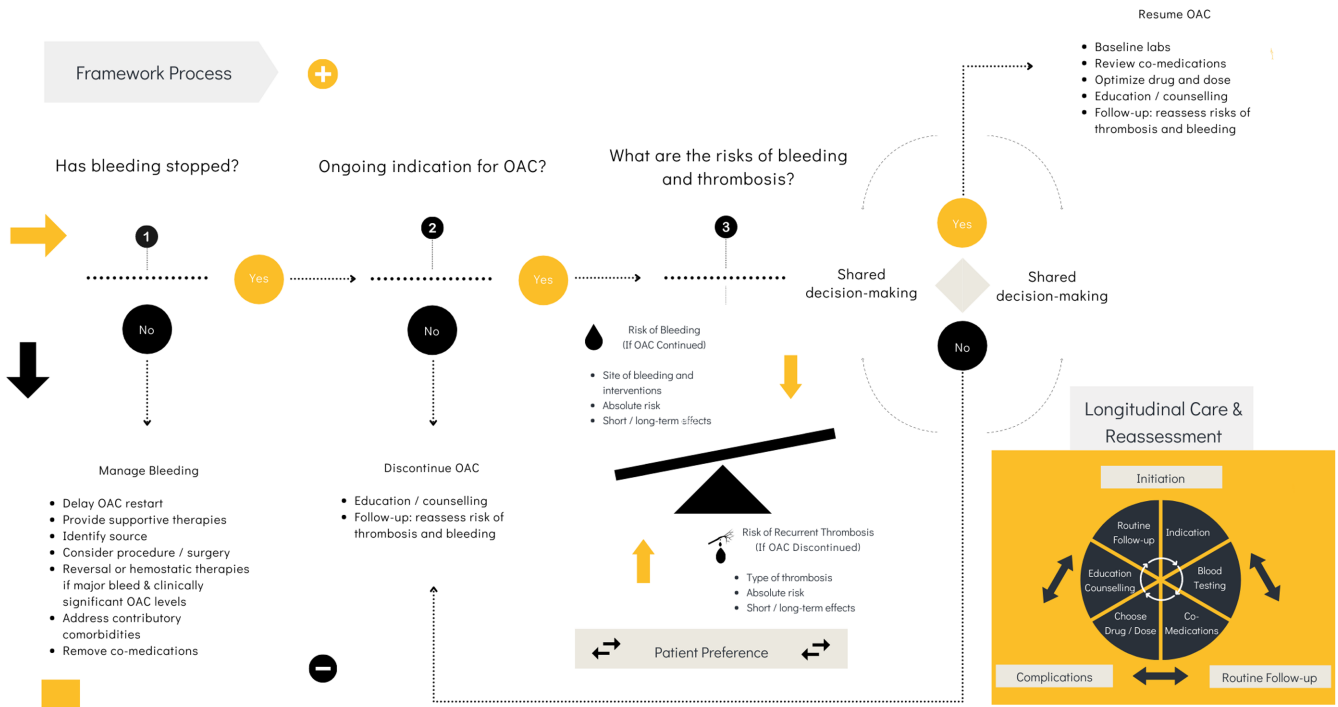
Susan Shapiro MD, PhD



# Restarting anticoagulants after major bleeding

Deborah M. Siegal MD, MSc, FRCPC

## Restarting Antithrombotics after Major Bleeding



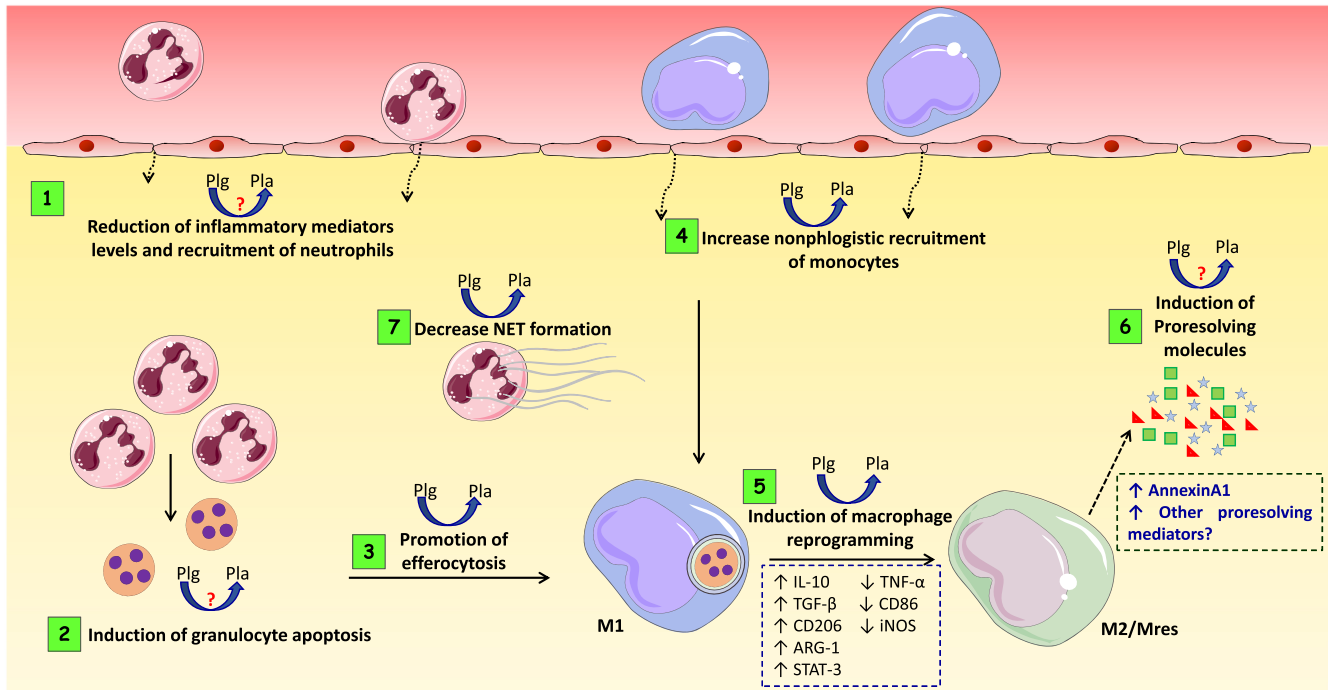
For reference, see Xu and Siegal<sup>48</sup>



## The plasminogen/plasmin system beyond fibrinolysis: Emerging players in resolution of inflammation

Lirlândia P. Sousa PhD

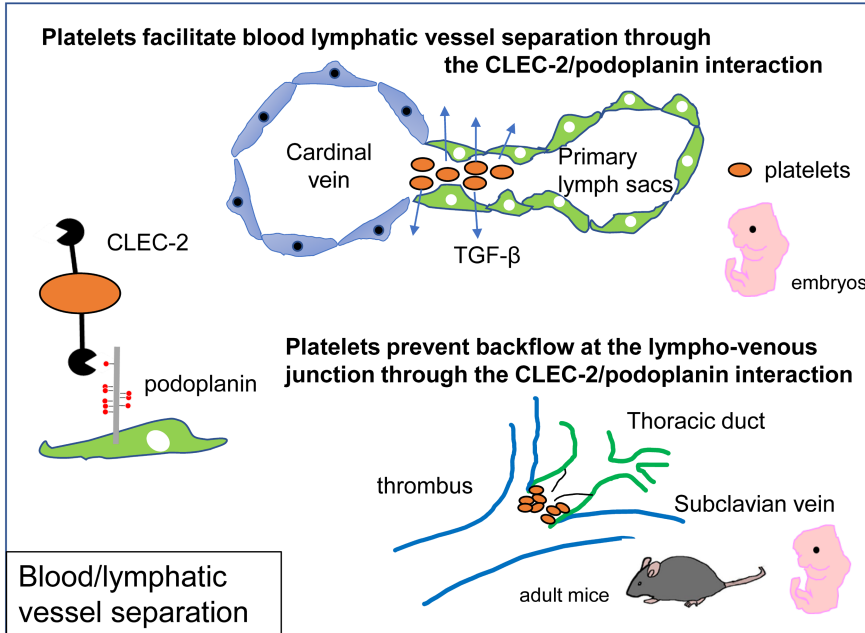
### The Plasminogen/Plasmin system beyond fibrinolysis: Emerging players in resolution of inflammation



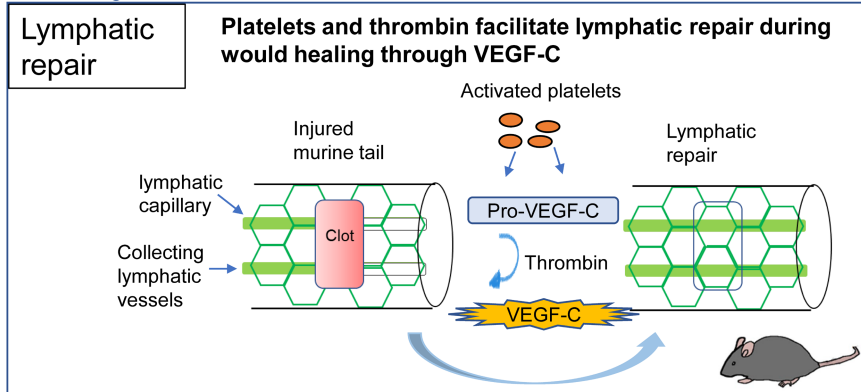
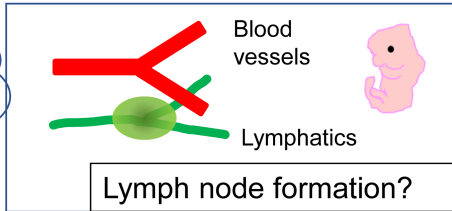
The plasminogen/plasmin (Plg/Pla) system is associated with a variety of biological activities beyond the classical dissolution of fibrin clots, including cell migration, tissue repair, and inflammation. Inflammation is an evolutionarily conserved response that guarantees the maintenance of tissue homeostasis through resolution—an active process mediated by molecules named proresolving mediators.<sup>49</sup> Despite the classical view of the Plg/Pla system on inflammation, emerging studies from our group<sup>50,51</sup> and others have revealed its anti-inflammatory and proresolving actions that includes reduction of proinflammatory mediators (1) enhanced neutrophil apoptosis (2), and efferocytosis (3); promotion of nonphlogistic recruitment of mononuclear cells (4); induction of macrophage reprogramming toward resolving phenotypes (5); and induction of expression of the proresolving mediator annexin A1 (6). We have now identified a novel proresolving feature of Plg/Pla during sepsis that is the regulation of neutrophil extracellular trap release (7). Red question marks indicate specific processes that Pla-protease activity need to be covered.

# Crosstalk between hemostasis and lymphangiogenesis

Katsue Suzuki-Inoue MD, PhD

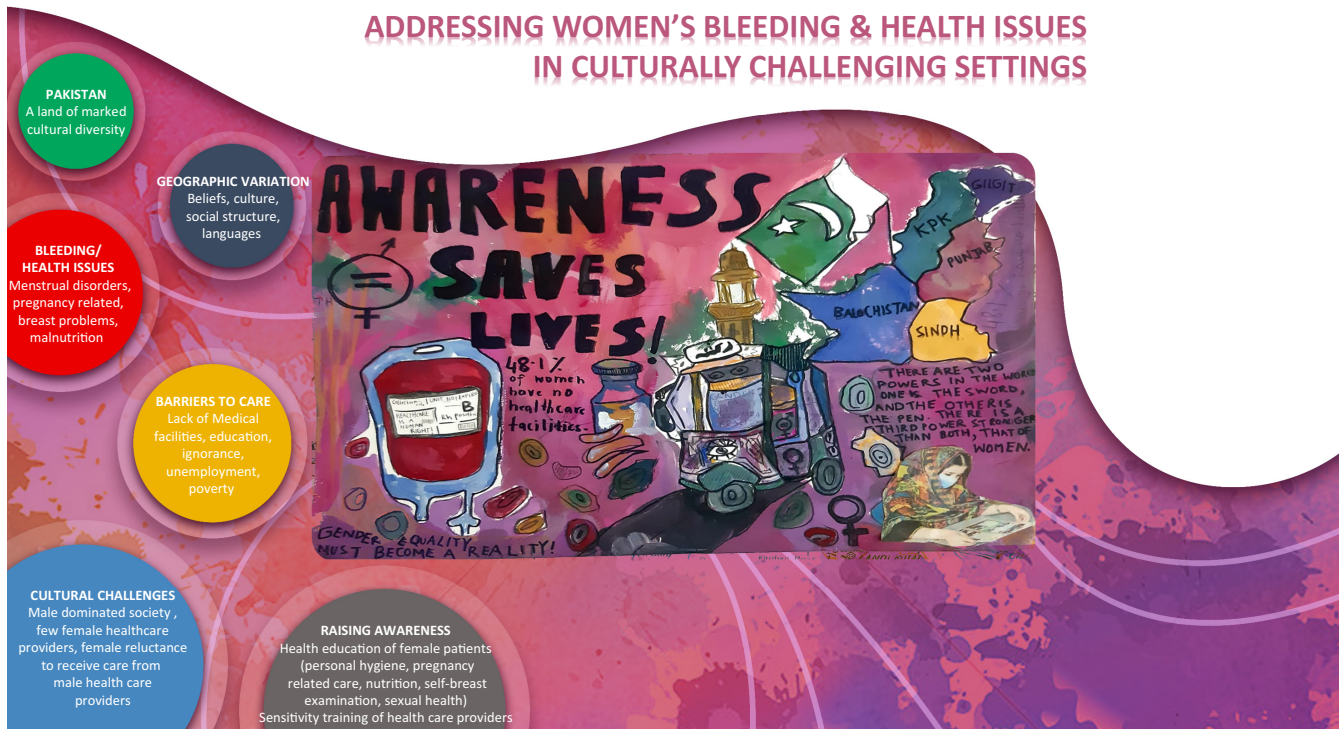


**Crosstalk between hemostasis and lymphangiogenesis**



## Raising awareness of women's bleeding/health issues in culturally challenging settings

Tahira Zafar MB, DCP, FRCPath

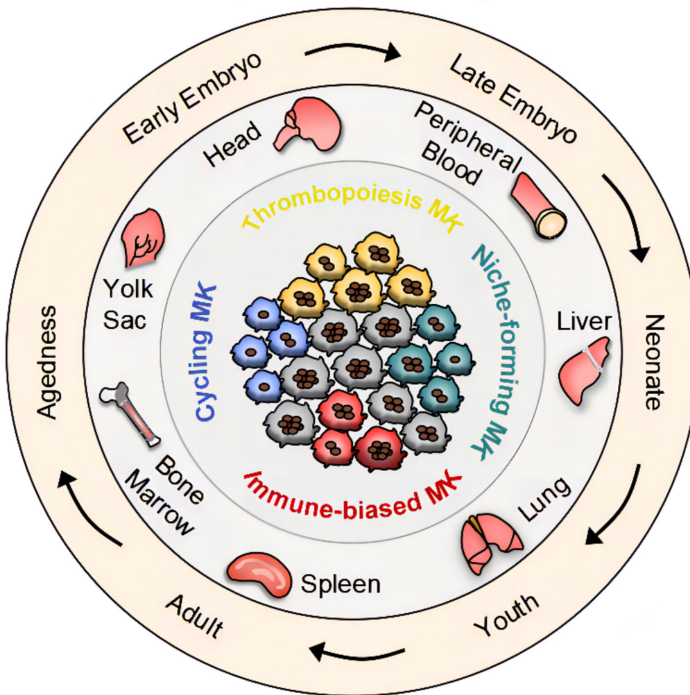


For references, see Ali<sup>52</sup>; Butt<sup>53</sup>; UN.<sup>54</sup>

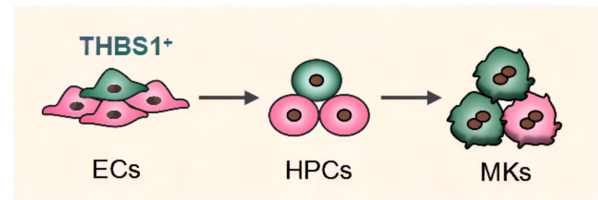
## Megakaryocyte single-cell transcriptomics

Jiaxi Zhou PhD

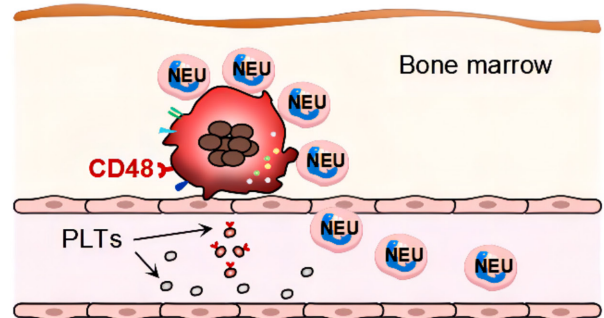
MKs are spatio-temporal heterogeneous.



THBS1<sup>+</sup> ECs are biased toward megakaryopoiesis<sup>[1]</sup>, probably generating niche-forming MKs that prompt malignant HSC expansion.



CD48<sup>+</sup> MKs function as immune-surveillance cells by neutrophil recruitment and platelet release<sup>[2-3]</sup>.



EC, endothelial cell; HPC, hematopoietic progenitor cell; HSC, hematopoietic stem cell; MK, megakaryocyte; NEU, neutrophil; PLT, platelet. For references, see Wang et al.<sup>55</sup>; Liu et al.<sup>56,57</sup>

## RELATIONSHIP DISCLOSURE

JA has received grant funding from the British Heart Foundation and is a consultant for Silence Therapeutics; RAA is a consultant for Bristol Myers Squibb, Bayer, and Pfizer; AB has received support from Horizon 2020 FETOpen SilkFusion, NIH, and Novartis; CDB has received grant funding from NHLBI and NIH and is a consultant for Camurus AB; PB has received funding from BioMarin and is a consultant for BioMarin, Pfizer, and the Institute for Medical & Nursing Education; KdW has received grant funding from Pfizer; CD has received grant funding from Haima Therapeutics; MHE is a consultant for Novartis and Gad Medical; CPMH has received grant funding from the Canadian Institutes for Health Research and is a consultant for Werfen and Diagnostica Stago Inc; FAK has received research support from Bayer, Actelion, the Dutch Thrombosis Association, Actelion, BSCI, The Netherlands Organisation for Health Research and Development, and the Dutch Heart foundation; ZM has received grant funding from CSL Behring; MDN has received grant funding from Haemonetics, Instrumentation Laboratories, and Janssen Pharmaceuticals, is consultant for Haemonetics and Janssen Pharmaceuticals, and serves on the advisory board for Haima Therapeutics; BR has received grant funding from Bayer AG and is a consultant for SOBI and Bayer AG; SS is a consultant for Pfizer, Takeda, and Roche and received support for attending meetings from CSL Behring; DMS is a consultant for BMS-Pfizer, Leo Pharma, Portola Pharmaceuticals, and Servier; KS is a consultant for Novo Nordisk, Chugai Pharmaceutical Co, and Mitsubishi Tanabe Pharma Co; all other authors declare no conflicts of interest.

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