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ILLUSTRATED REVIEW

rpth research & practice in thrombosis & haemostasis

# Illustrated State-of-the-Art Capsules of the ISTH 2020 Congress

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## Abstract

The 2020 Congress of the International Society of Thrombosis and Haemostasis (ISTH) was held virtually July 12-15, 2019, due to the coronavirus disease 2019 pandemic. The congress convenes annually to discuss clinical and basic topics in hemostasis and thrombosis. Each year, the program includes State of Art (SOA) lectures given by prominent scientists. Presenters are asked to create Illustrated Capsules of their talks, which are concise illustrations with minimal explanatory text. Capsules cover major themes of the presentation, and these undergo formal peer review for inclusion in this article. Owing to the shift to a virtual congress this year, organizers reduced the program size. There were 39 SOA lectures virtually presented, and 29 capsules (9 from talks omitted from the virtual congress) were both submitted and successful in peer review, and are included in this article. Topics include the roles of the hemostatic system in inflammation, infection, immunity, and cancer, platelet function and signaling, platelet function disorders, megakaryocyte biology, hemophilia including gene therapy, phenotype tests in hemostasis, von Willebrand factor, anticoagulant factor V, computational driven discovery, endothelium, clinical and basic aspects of thrombotic microangiopathies, fibrinolysis and thrombolysis, antithrombotics in pediatrics, direct oral anticoagulant management, and thrombosis and hemostasis in pregnancy. Capsule authors invite virtual congress attendees to refer to these capsules during the live presentations and participate on Twitter in discussion. *Research and Practice in Haemostasis and Thrombosis* will release 2 tweets from @RPTHJournal during each presentation, using #IllustratedReview, #CoagCapsule and #ISTH2020. Readers are also welcome to utilize capsules for teaching and ongoing education.

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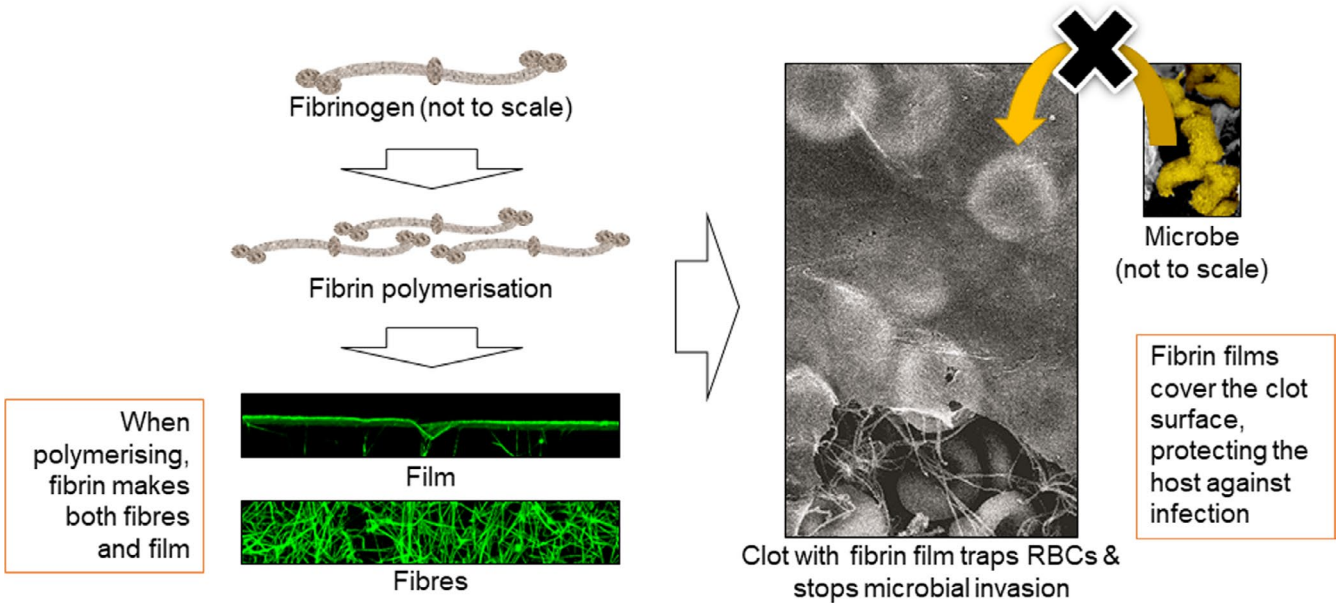
# Fibrin microfilms protect clots from microbes

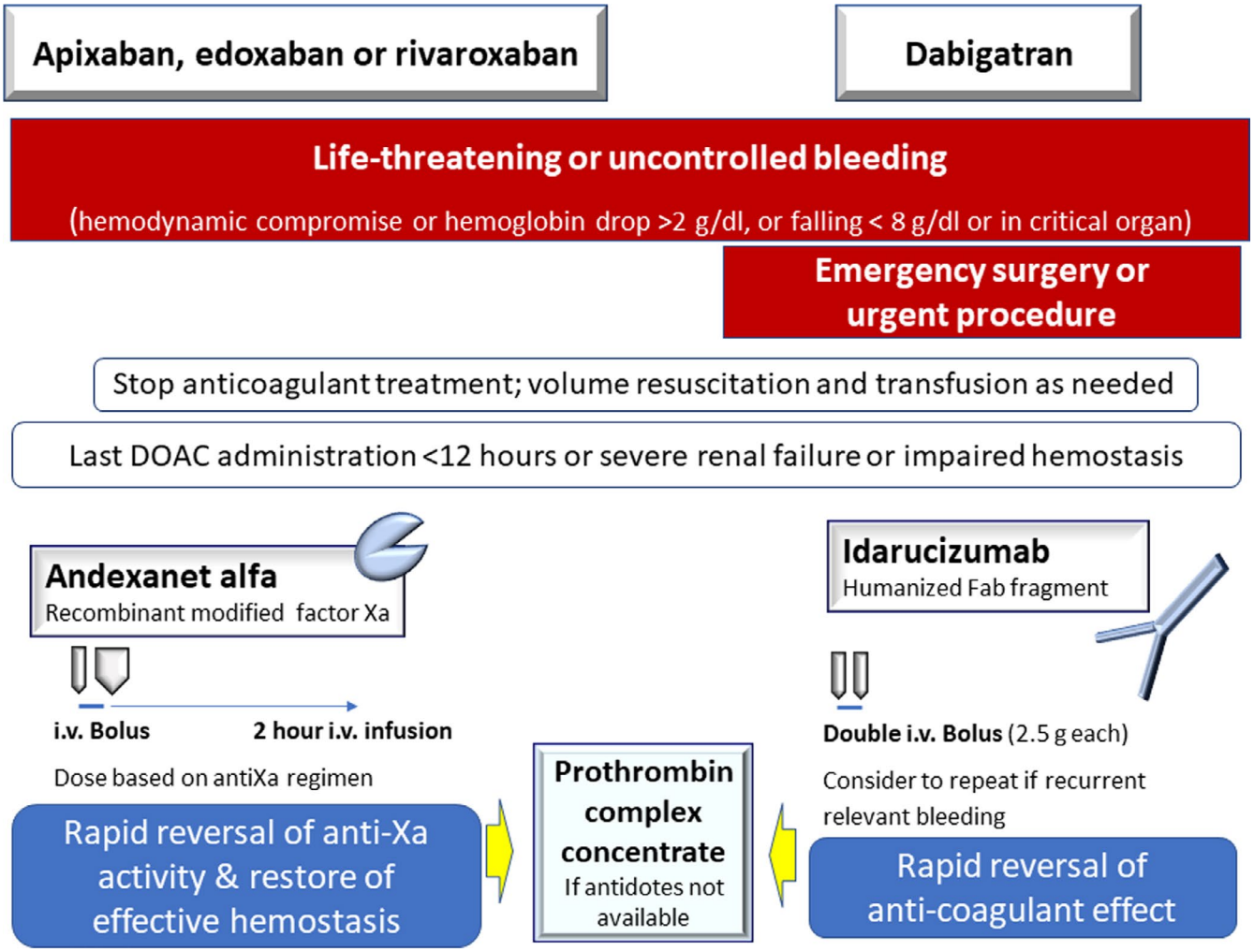
Robert Ariëns PhD




When thrombin cleaves fibrinogen, the resulting fibrin was known to spontaneously polymerize into protofibrils that aggregate and branch to form fibrin fibers. The fibrin fibers provide the structural and elastic backbone to the blood clot. Our recent study has shown that fibrin can also produce Langmuir-Blodgett films at phase boundaries (eg the liquid/air interface).[1] These fibrin films help to trap host cells into the clot, and prevent microbial infection from entering the clot to infect the host. Films have also been observed on intracoronary thrombi obtained by thrombectomy from patients with myocardial infarction,[2] and from clots obtained by stent retriever from patients with ischemic stroke.[3] Films or shell-like structures in intravascular thrombi have been reported to slow down thrombolysis,[3] but their origin and full functional role(s) require further investigation.

# Managing DOACs in emergencies

Cecilia Becattini MD, PhD




Clinicians should tailor treatment of patients with emergencies occurring while on treatment with direct oral anticoagulants (DOACs) based on the severity of major bleeding and the need for emergency access to the operative room.[4,5] Interruption of DOACs and general supportive measures should be considered while trying to confirm that anticoagulant treatment has a role in bleeding and/or in deciding the timing of surgery. Time and dose of last intake, renal function, and the measurement of plasma levels of DOAC, if available, should be considered.[6] If measurement of plasma levels of DOAC is not feasible, standard coagulation tests can be useful to assess DOAC-related anticoagulation.

No evidence on the effect of idarucizumab and andexanet in survival has been reported so far. Effective hemostasis is assessed by methods developed for assessment of prothrombin complex concentrates in warfarin reversal for andexanet and by diluted thrombin time or ecarin clotting time for idarucizumab.[4,5]

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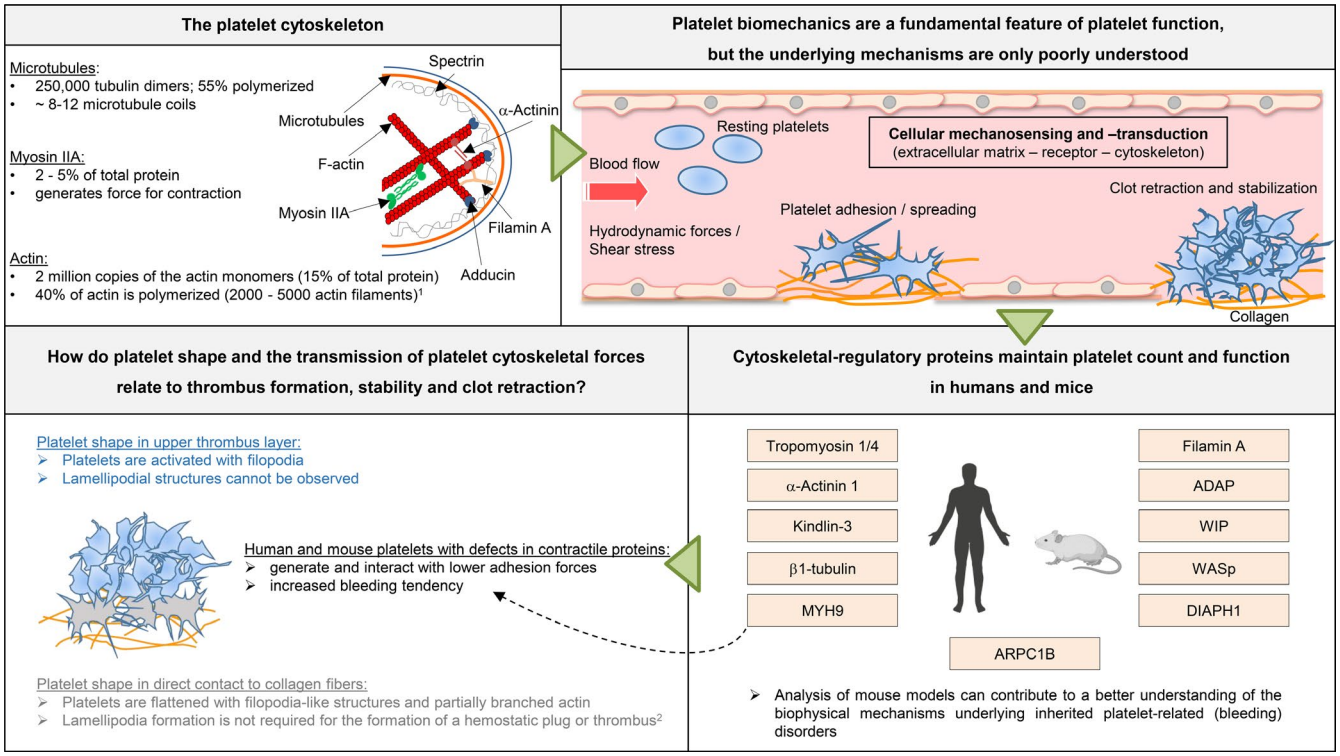
# Platelet cytoskeleton and its disorders

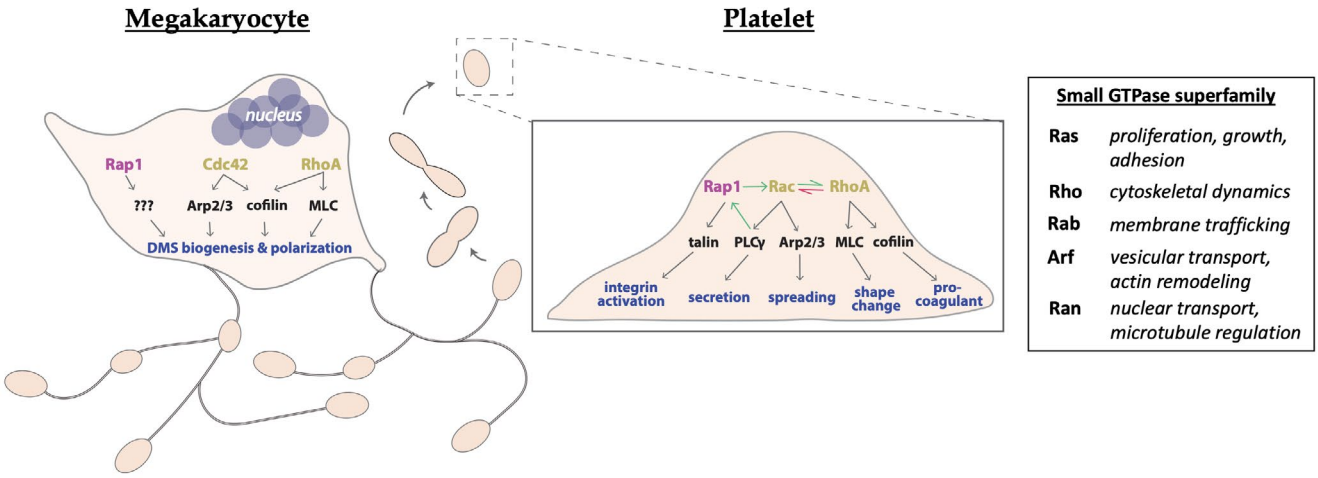
Markus Bender PhD




For references, see Hartwig[7] and Schurr et al.[8]

# Small GTPases in megakaryocyte and platelet biology

Wolfgang Bergmeier PhD




Small GTPases are a large superfamily of monomeric G proteins, which can be divided into five branches based on similarities in sequence and function. Rho and Ras GTPase biology has been extensively studied in megakaryocytes (MKs) and platelets. Rho GTPases are important regulators of the actin cytoskeleton and as such play a crucial role during proplatelet formation in MKs and activation/adhesion-induced morphological changes in platelets. In MKs, Cdc42 is critical for the biogenesis and polarization of the demarcation membrane system (DMS). In platelets, Rac1 is critical for phospholipase C (PLC) activation and spreading. RhoA is critical in MKs and platelets, where it controls various cellular responses via its effect on myosin light chain (MLC) and cofilin activity. Rap1, a member of the Ras family of small GTPases, is best known for its critical role in platelet integrin signaling. Studies in knockout mice also identified an important role for Rap1 in MK proplatelet formation. Cooperativity and antagonism between individual small GTPases are important for proper MK and platelet function.

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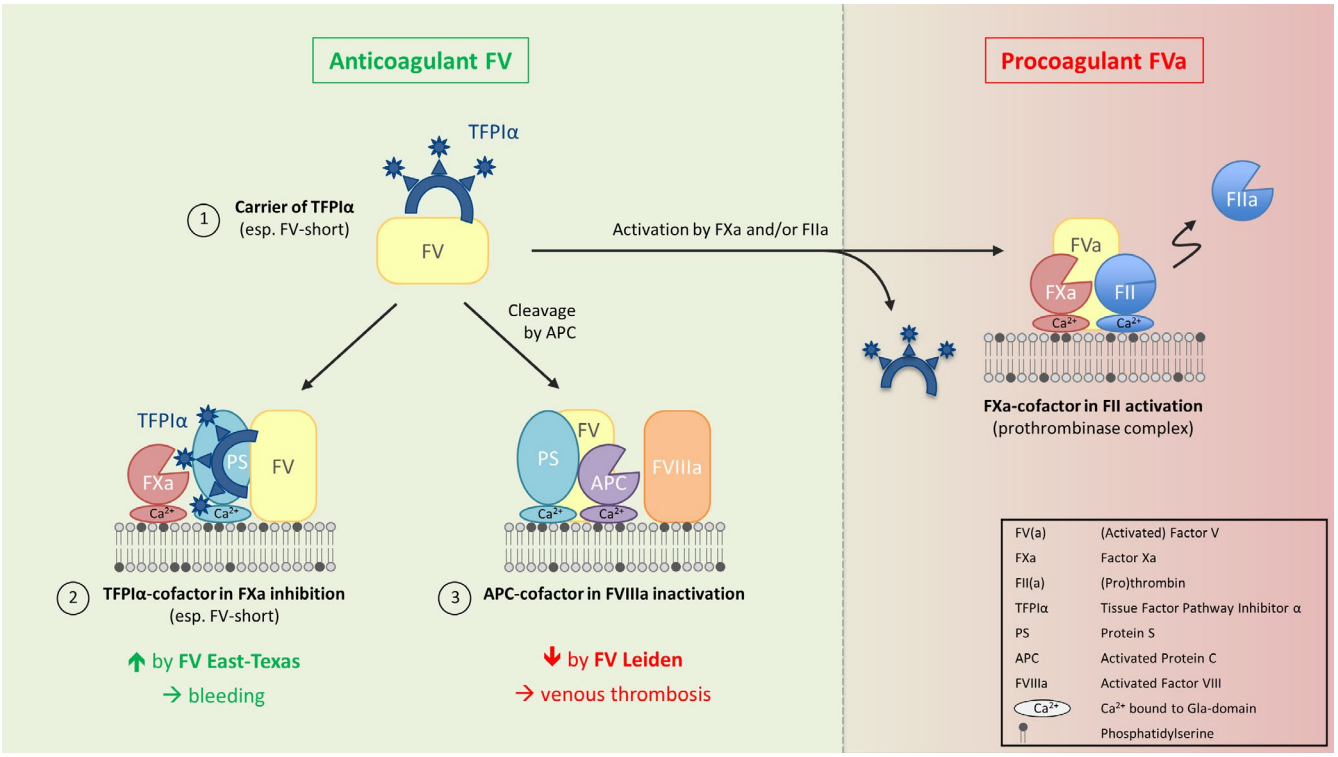
# Anticoagulant factor V

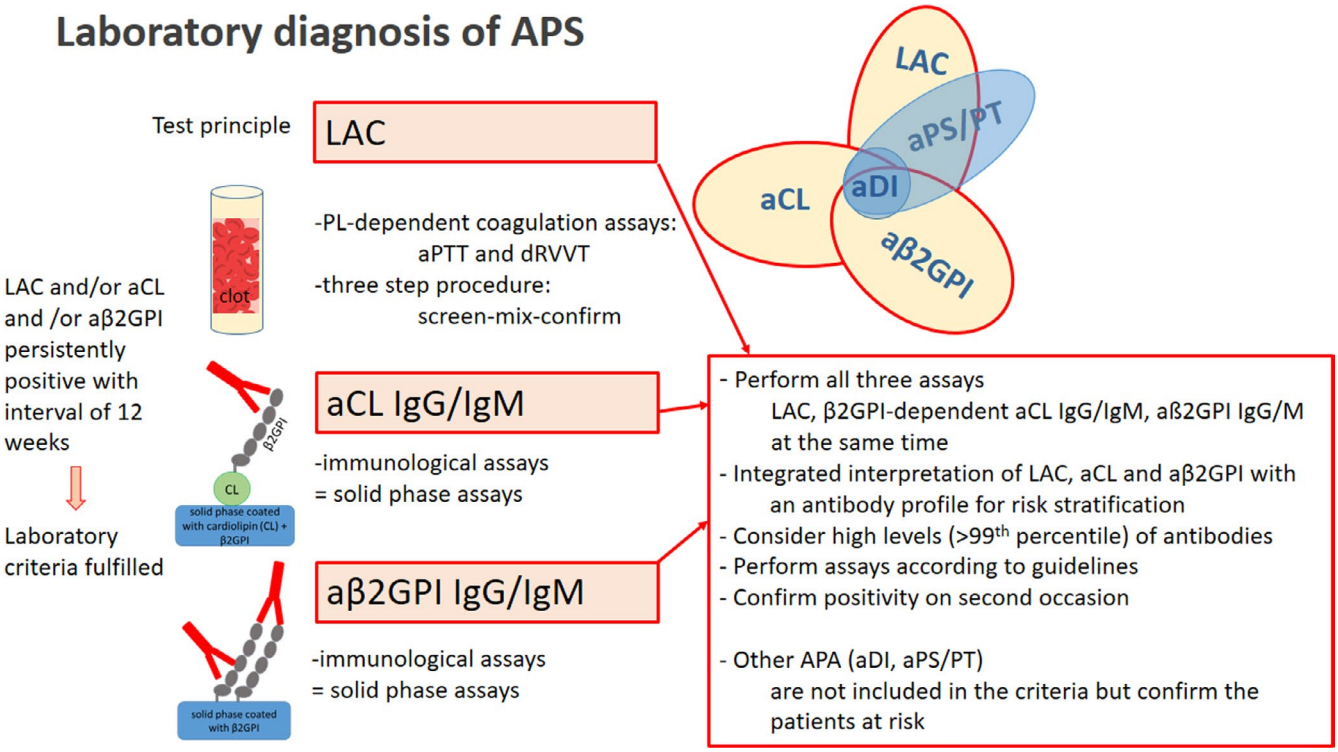
Elisabetta Castoldi PhD




It is common knowledge that activated factor V (FVa) expresses procoagulant activity as an essential cofactor of factor Xa (FXa) in prothrombin (PT) activation. What is less appreciated is that as long as it is not (fully) activated, FV contributes to the anticoagulant cause by (i) maintaining tissue factor pathway inhibitor-α (TFPIα) in the circulation; (ii) enhancing the inhibition of FXa by TFPIα and protein S (PS); and (iii) stimulating the inactivation of factor VIIIa (FVIIIa) by activated protein C (APC) and PS. The first 2 anticoagulant functions are most pronounced in FV-short, a FV splicing variant present in plasma at sub-nM concentrations. The third anticoagulant function requires cleavage of single-chain FV by APC. The physiopathological relevance of these anticoagulant mechanisms is underscored by genetic defects that enhance (FV East-Texas) or impair (FV Leiden) the anticoagulant properties of FV, thereby increasing the risk of bleeding or venous thrombosis.[9]

# Laboratory diagnosis of antiphospholipid syndrome

Katrien M. J. Devreese MD, PhD




The diagnosis of antiphospholipid syndrome (APS) relies on detection of antiphospholipid antibodies (APAs). APAs are a heterogeneous group of antibodies, but only lupus anticoagulant (LAC), anticardiolipin (aCL) and anti-β2-glycoprotein I antibodies (aβ2GPI) IgG or IgM are included in the laboratory criteria. At least 1 criterion has to be persistently positive.10 LAC measurement remains a complex procedure with a 3-step procedure, including screening, mixing, and confirmatory tests in 2 test systems. Solid-phase assays for aCL and aβ2GPI show inter-assay differences. These methodological issues make the laboratory diagnosis of APS challenging, although progress has been made on the standardization and interpretation as reflected in published guidelines on LAC testing and solid-phase assays for aCL and aβ2GPI.10-12 Other APAs, not included in the current criteria, such as antibodies against the domain I of β2GPI and antiphosphatidylserine-prothrombin antibodies may be useful in risk stratification but have no added value for diagnosis of APS.

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# Myeloproliferative neoplasms in pregnancy: Implications for mother and child

**Martin H. Ellis MD**

Myeloproliferative neoplasms in pregnancy: Implications for mother and child

Martin H. Ellis MD Hematology Institute and Blood Bank, Meir Medical Center, Kfar Saba ISRAEL
email: martinel@clalit.org.il

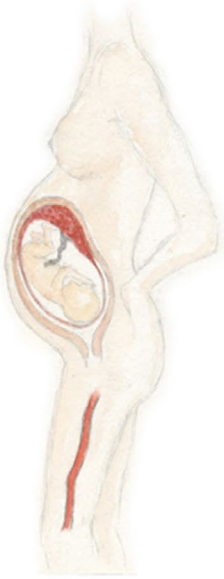
## Pregnancy-related complications

**Maternal**

Venous thromboembolism
Arterial thromboembolism

**Placental-related**

Preeclampsia/eclampsia
IUGR
Early fetal loss
Late fetal loss



## 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)

***Placental-related prophylaxis***

- Observation or aspirin

**Subsequent pregnancies**

(in case of previous placental-related complications)

***Maternal VTE/ATE prophylaxis***

- As for first pregnancy

***Placental-related prophylaxis***

- Interferon
- Aspirin-low dose

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

Polycythemia vera (PV), essential thrombocythemia (ET), 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, particularly PV and ET, thrombosis is an important complication.

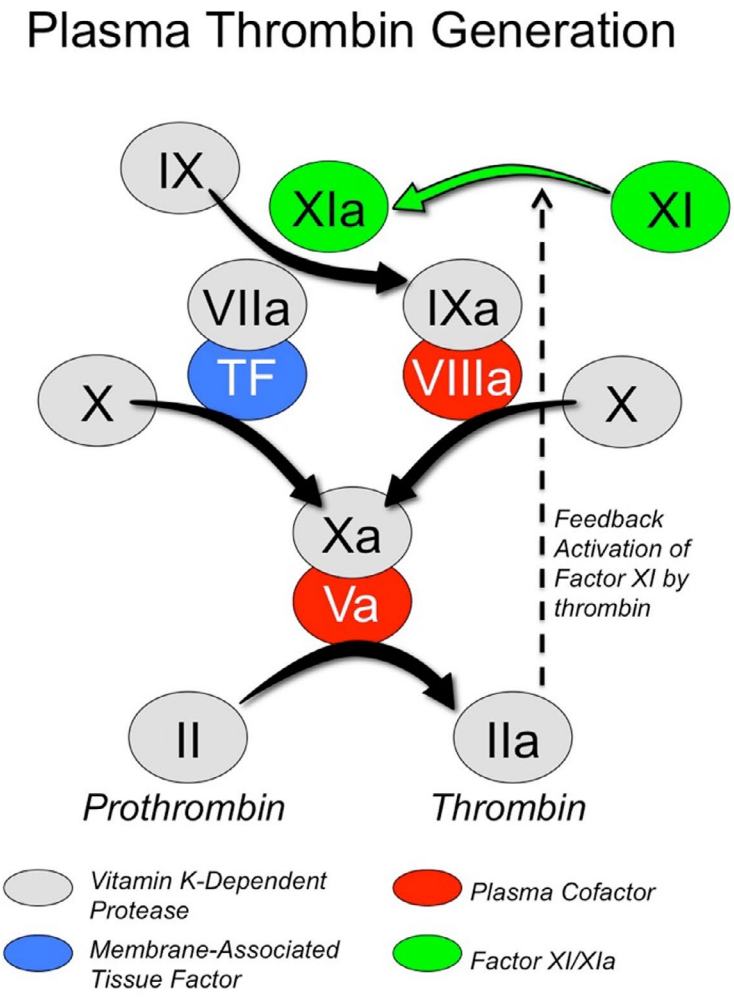
The median age at diagnosis of the MPNs is >60 years; however, 20% are <40 years old when diagnosed. Thus, there is a need to provide appropriate treatment to pregnant patients with MPNs.

Maternal (venous or arterial thrombosis or hemorrhage), or placenta-related (fetal loss or preeclampsia/eclampsia) complications may occur during pregnancy. The incidence and risk factors for complications are poorly defined.

Treatment has been observational data and expert opinion based. Recently a meta-analysis of randomized clinical trials has provided a basis for decision making; however, more data from prospective or registry studies is required to inform appropriate treatment for these patients.[13]

# Clinical heterogeneity in factor XI deficiency

David Gailani MD




## Factor XI Deficiency

Potential Modifiers of Bleeding

***Tissue Factor (TF) Activity***

- TF concentration varies by tissue
- Factor VIIa level
- TFPI level/activity

***Coagulation Protease Regulation***

- Antithrombin activity
- ZPI or protein Z activity
- C1-Inhibitor activity (inhibits Factor XIa)

***Factor Va & VIIIa Regulation***

- Protein C or Protein S activity
- Factor V Leiden

***Fibrinolytic activity***

- PAI-1 activity
- α2-antiplasmin activity

***Platelet Activity***

- Platelet count
- Platelet activity
- von Willebrand Factor level

Factor XI (FXI) is the precursor of FXIa, a protease that contributes to thrombin generation by activating factor IX.[14] While critical to clotting in the activated partial thromboplastin time assay, FXI makes modest contributions to hemostasis.[15] Furthermore, bleeding in FXI-deficient patients correlates poorly with plasma FXI levels.[15] Indeed, completely deficient patients may not experience abnormal bleeding. Thrombin generation is controlled by a group of vitamin K–dependent proteases and their cofactors.[16] The process is initiated at an injury site by a complex of factor VIIa and tissue factor (TF). In this scheme, FXI serves an ancillary role, supplementing factor IXa generated by VIIa/TF.[16] Given this, it seems likely that a number of processes that alter thrombin generation, platelet activity, or fibrinolysis would affect the requirement for FXIa activity in different individuals, and in different tissues. Contributors to variable bleeding in FXI-deficiency may well be similar to those that influence bleeding in people with hemophilia.

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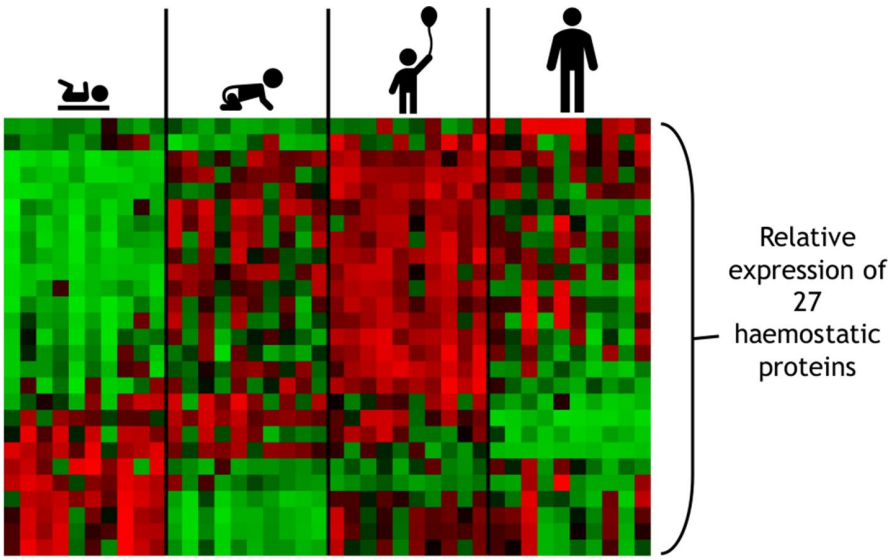
# Proteomics of the hemostatic system

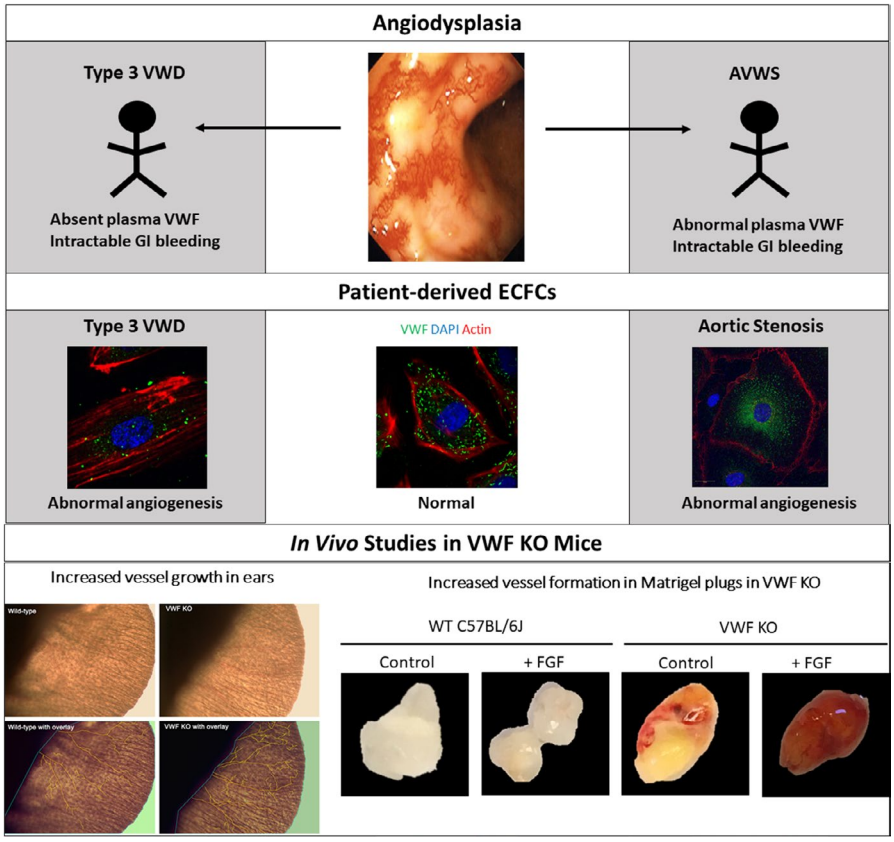
Vera Ignjatovic PhD




Proteomics, as the study of proteins as the functional elements and main drivers of phenotype, is extremely important when it comes to understanding developmental biology. In addition, proteomics, via biomarker discovery, allows for early detection of disease. However, proteomics has, at least until very recently, been underutilized in the setting of thrombosis and hemostasis. We have recently used a proteomics approach to characterise age-specific changes in the hemostatic plasma proteins. This figure outlines age-specific changes in expression of 27 proteins that are associated with coagulation and/or serve as markers of platelet activation or endothelial involvement. Holistic proteomic analysis in the background of dynamic, age-specific nature of hemostasis yields new insights and sets a new standard for using proteomics in thrombosis and hemostasis.[17]

# von Willebrand factor in angiogenesis and angiodysplasia in patients

Paula D. James MD




Angiodysplasia is increased in patients with congenital von Willebrand disease (VWD) and acquired von Willebrand syndrome (AVWS). Both groups of patients experience intractable gastrointestinal bleeding that is often very difficult to treat. Previous studies have shown that endothelial von Willebrand factor (VWF) is a negative regulator of angiogenesis.[18] Patient derived endothelial colony-forming cells from both patients with type 3 VWD and patients with aortic stenosis (AVWS) display abnormal angiogenesis in vitro.[19,20] In vivo studies in VWF knockout mice show increased vessel growth in the ears and increased tubule formation in Matrigel plugs at 7 days when compared with wild type.

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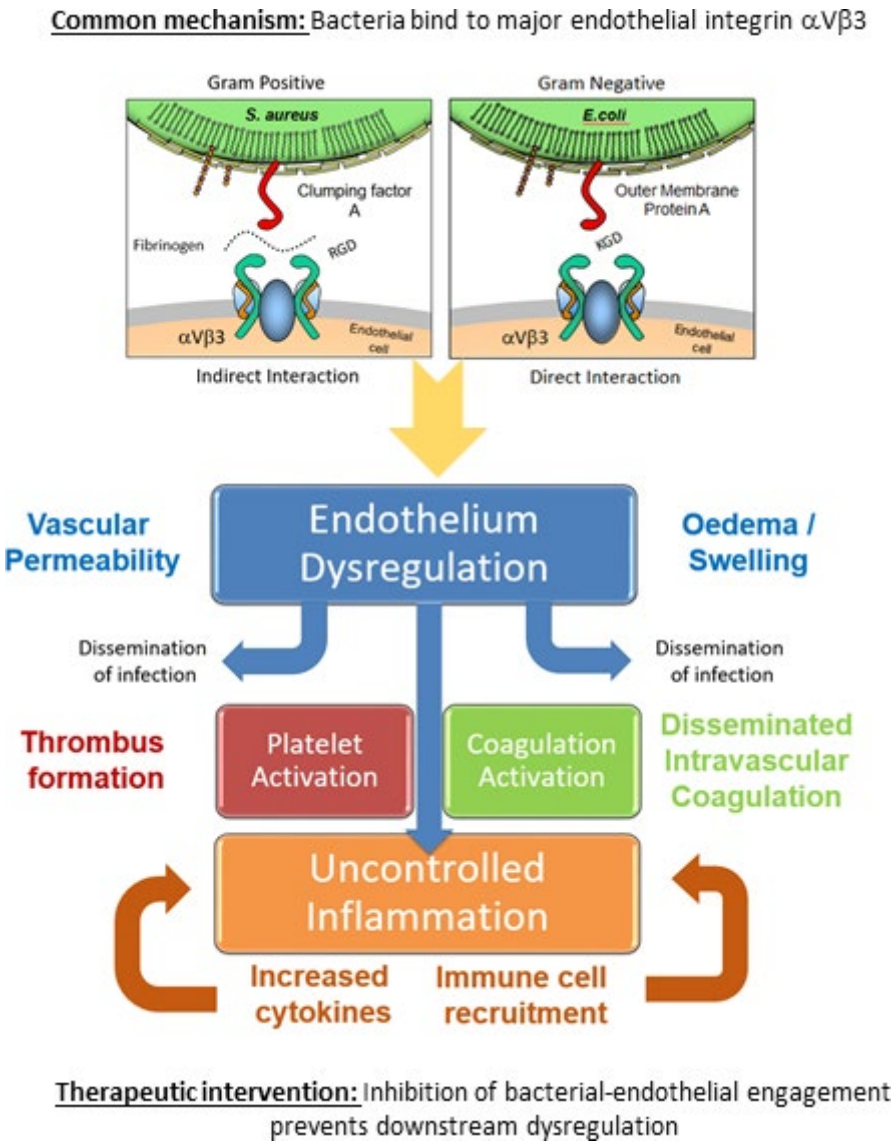
# Vascular endothelial cell dysregulation during sepsis

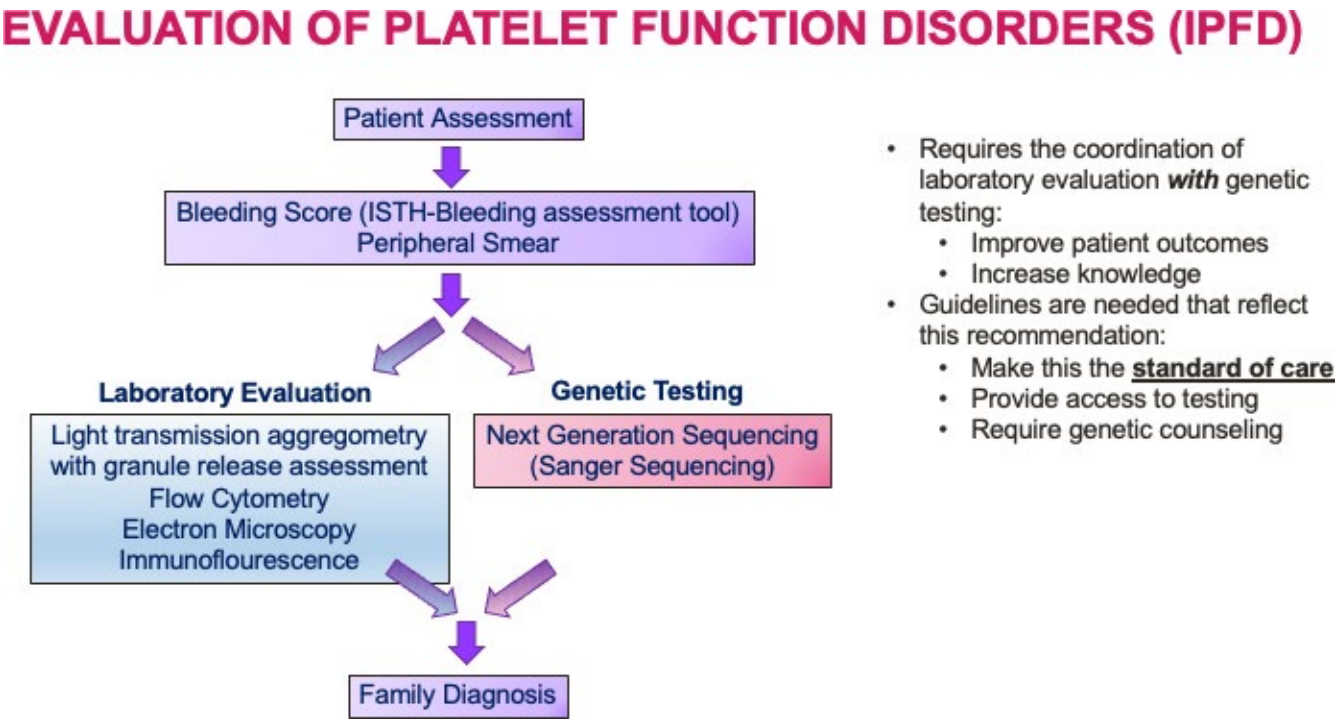
Steve Kerrigan PhD




Sepsis is of significant global concern with 49 million new cases of sepsis worldwide per year and 11 million deaths.[21] Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The vascular endothelium is a major target of sepsis-induced events.[22] Pathogen binding to the vascular endothelium is seen as a pivotal step in driving the dysregulated response to the infection. For example, endothelial dysregulation results in dysfunction of anticoagulation and places the system into a hypercoagulant state. A breakdown of the endothelial barrier results in dissemination of bacteria to distant sites and fluid leakage into the extravascular space leading to life-threatening edema in the lungs, kidney, and brain that can progress to multiorgan failure.[22] The vascular endothelium is therefore a major target of novel therapies to disrupt pathogen attachment in an attempt to slow or stop progression of sepsis to a life-threatening situation.[23]

# Clinical versus genetic approaches to the diagnosis of platelet function disorders

**Michele P. Lambert MD, MSTR**




- Requires the coordination of laboratory evaluation *with* genetic testing:
  - Improve patient outcomes
  - Increase knowledge
- Guidelines are needed that reflect this recommendation:
  - Make this the *standard of care*
  - Provide access to testing
  - Require genetic counseling

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# Obstetric antiphospholipid syndrome

Lai Heng Lee MBBS, M Med, FAMS (Int Med), FRCP (UK)

**Diagnostic Criteria for Antiphospholipid Syndrome (APS) (1)**

**At least one clinical and one laboratory criteria are present**

| Clinical Criteria | Laboratory Criteria |
|---|---|
| Thrombotic event - Venous or arterial | • Present on 2 or more occasions at least 12 weeks apart |
| Pregnancy morbidity –<br>• Recurrent early miscarriages defined as at least three consecutive miscarriages before 10 weeks of gestation<br>• One or more otherwise unexplained fetal deaths at or after 10 weeks of gestation<br>• Delivery before 34 weeks for preeclampsia or placental insufficiency. | • Lupus anticoagulant, detected according to ISTH guidelines<br>• Anticardiolipin antibody of IgG and /or IgM isotype present in medium or high titre, measured by standardised elisa assays (above 40 GPL or MPL, or greater than 99th percentile)<br>• Antibeta2-glycoprotein 1 antibody of IgG and /or IgM isotype present in titre greater than 99th percentile |

**Concerns in Obstetric APS**

- Clinical criteria are relatively non specific as such pregnancy morbidities may be related to many other causes besides the pathogenic effects of the phospholipid auto-antibodies.
- Accuracy of laboratory testing
- Not all patients meet the strict criteria of clinical features and/or laboratory tests but they need treatment (2)
- Current diagnostic criteria last revised in 2006
- New international diagnostic criteria needed for better definition of probability in diagnosis of APS in the context of each of the obstetric clinical features.

**Treatment Strategies**

- Aim to minimise the risks of adverse maternal and foetal outcomes.
- Paucity of good quality prospective randomized controlled trials.
- Stratification of patients' risk profile based on clinical and laboratory features necessary
- Current standard of care include low molecular weight heparin and low dose aspirin
- For high risks and refractory cases, low-dose prednisolone, hydroxychloroquine, intravenous immunoglobulin infusions and/or aphaeresis in addition to a heparin agent have been reported to improve outcomes. (3)

**Pathogenesis**

- Immune mediated activation of inflammatory cascades and complement activation.
- The main histopathologic features of the placenta are thrombosis, infarction and necrosis

**Diagnostic Criteria for Antiphospholipid Syndrome (APS)**

*At least one clinical and one laboratory criteria are present*

| Clinical Criteria | Laboratory Criteria |
|---|---|
| **Thrombotic events**<br>**Obstetric Complications**<br>*Recurrent early miscarriages*<br>*Unexplained fetal death*<br>*Preterm delivery from pre-eclampsia or placenta insufficiency* | **Positive anti-phospholipid antibodies**<br>*Anticardiolipin,*<br>*Anti-beta2-GP1*<br>*Lupus Anticoagulant* |
| **Concerns in Diagnostic Criteria of Obstetric APS**<br>*Clinical features non specific*<br>*Better defined updated diagnostic criteria needed* | **Pathogenesis in Obstetric APS**<br>*Incompletely understood*<br>*Immune mediated activation of inflammatory cascades and complement activation*<br>*Thrombosis, infarction and necrosis of placenta* |

**Treatment Strategies to minimise the risks of adverse maternal and foetal outcomes**

*Stratify Risk profiles*

*High Quality Clinical trial data lacking*

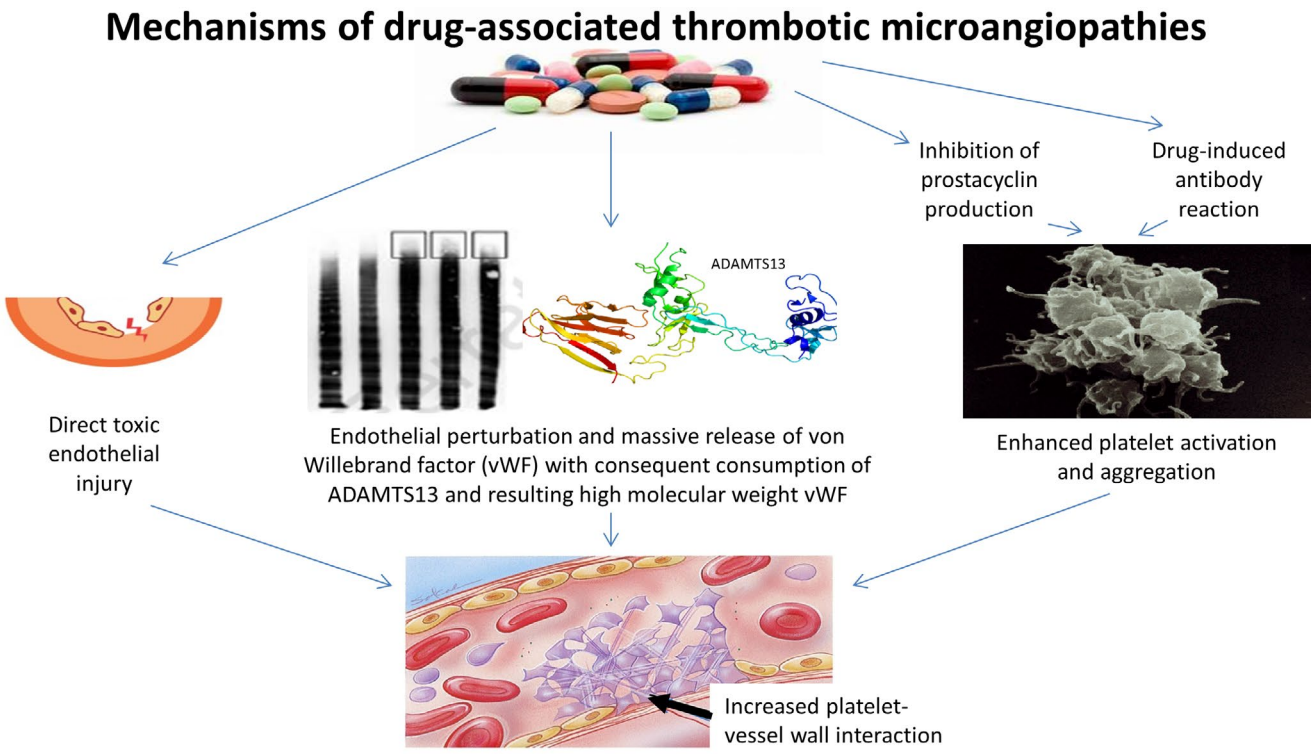
*Standard treatment - Low molecular weight heparin, low dose aspirin*

*High risks and refractory cases – steroids, hydroxychloroquine, pravastatin, IVIG, aphaeresis*

For references see Miyakis et al,[24] Alijotis-Reig et al,[25] and Ruffatti et al.[26]

# Drug-associated thrombotic microangiopathies: Emerging toxicities of novel drugs

Marcel Levi MD, PhD, FRCP




***Conclusion***: *Different pathogenetic pathways may be involved in drug-induced thrombotic microangiopathies*

For references see Pisoni et al,[27] Kreuter and Winters,[28] and Levi and Sivapalaratnam.[29]

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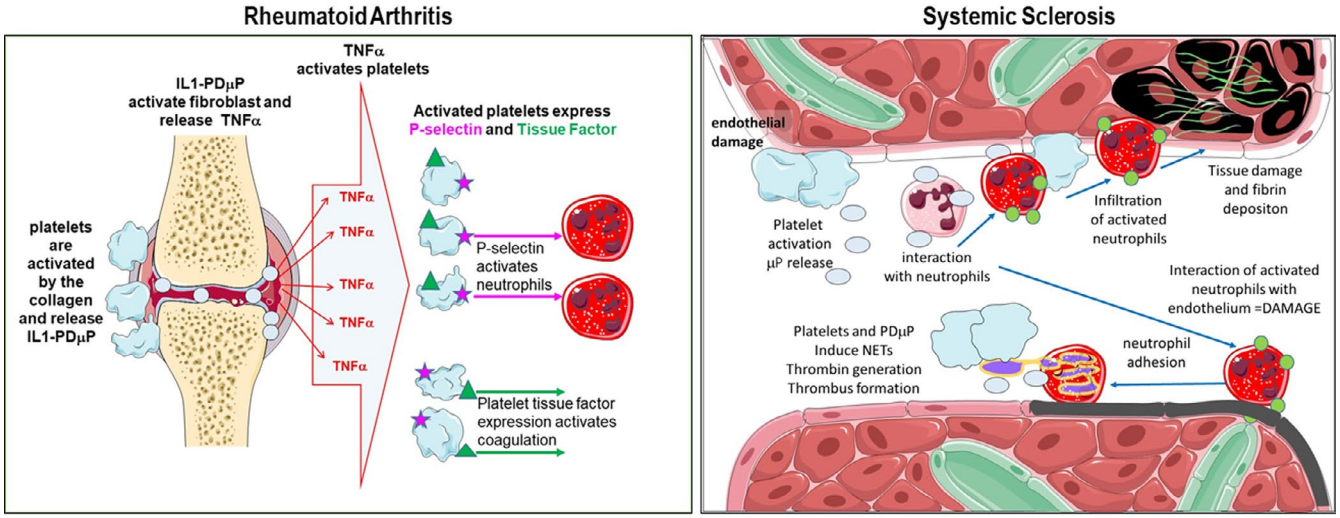
# Platelet-derived microparticles in autoimmune diseases

**Norma Maugeri PhD**

Platelet-Derived Microparticles in Autoimmune Diseases: two modes of involvement

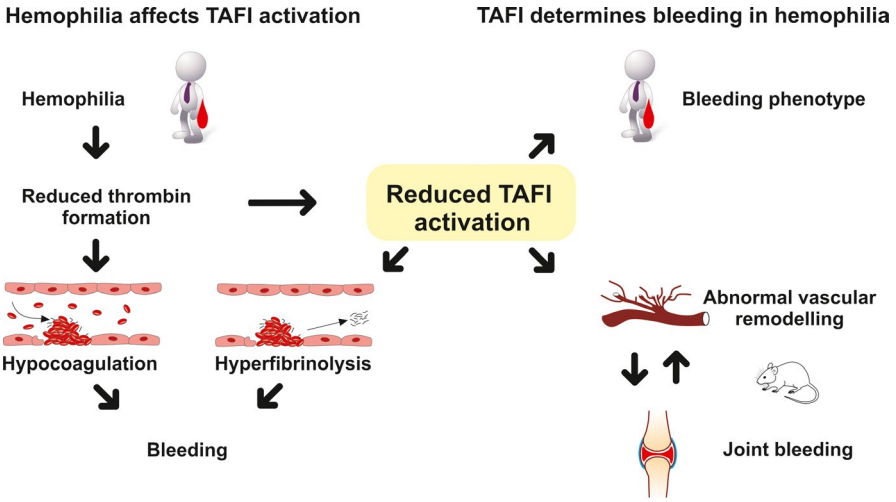



Platelets migration into the joints release of PDμP via collagen-platelet GPVI axis. PDμP bearing IL-1 that induce activation of resident fibroblasts and as a consequence, the release of TNFα. TNFα in turn induces platelet activation and is responsible for the prothrombotic phenotype of platelets and neutrophils

Endothelial injury prompts to the release of PDμP bearing HMGB1. $HMGB1^{+}$PDμP interact with neutrophils and induce NETs generation. Activated neutrophils activate endothelium and migrate within the lung favoring the interstitial fibrosis.

# TAFI pathway in hemophilia

Joost Meijers PhD




For references, see Wyseure et al[30,31] and Semeraro et al.[32]

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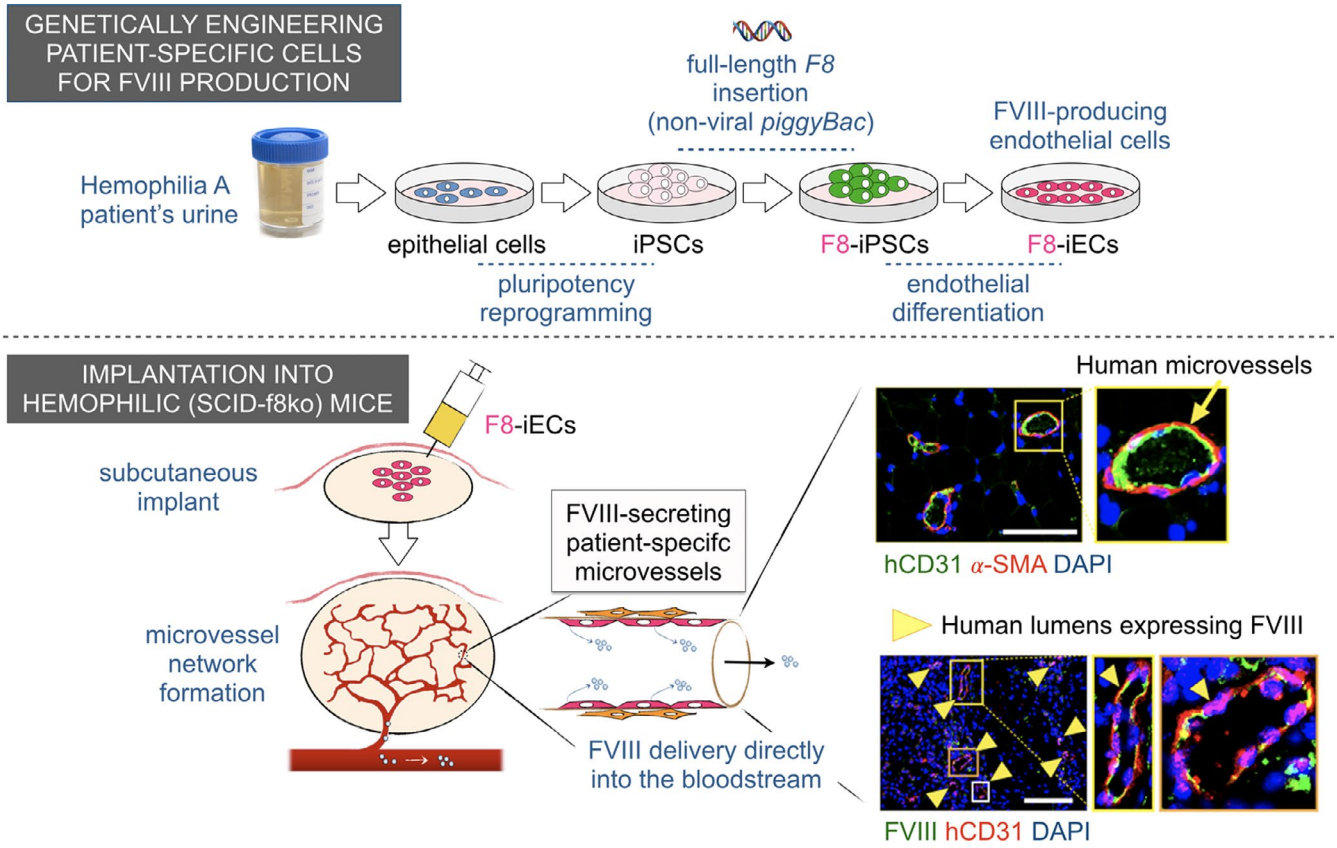
# Cell therapy using endothelial progenitor cells

Juan Melero-Martin PhD

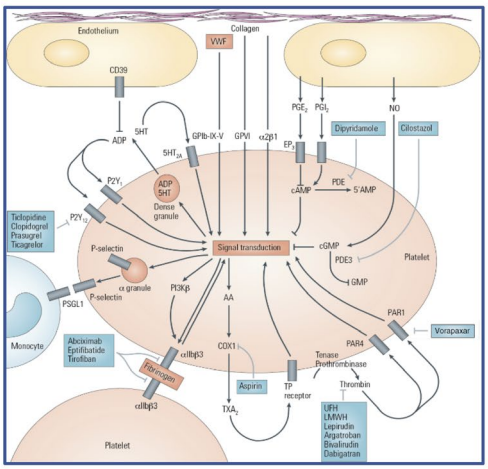



Human induced pluripotent stem cell (iPSC)–derived endothelial cells (iECs) have become a valuable tool in regenerative medicine. Our group has recently developed an application for the treatment of hemophilia A that entails bioengineering patient-specific microvascular grafts for the delivery of full-length factor VIII into the bloodstream.[33] To this end, we first generated patient-specific iPSCs from urine epithelial cells and genetically modified them using a nonviral *piggyBac* DNA transposon system to insert multiple copies of the full-length *F8* gene. We subsequently differentiated the modified F8-iPSCs into competent F8-iECs and demonstrated that the cells were capable of producing high levels of FVIII. Importantly, following subcutaneous implantation into immunodeficient hemophilic (SCID-f8ko) mice, we demonstrated that the F8-iECs were able to self-assemble into vascular networks, and that the newly formed microvessels had the capacity to deliver functional FVIII directly into the bloodstream of the mice, effectively correcting the clotting deficiency.

# When and how to use antiplatelet agents in children

Alan D. Michelson MD

**Mechanism of Action of Antiplatelet Drugs**




**FDA Approval Status of Antiplatelet Drugs in Children**

| Class | Generic Name (Trade Name) | Pediatric Status |
|---|---|---|
| Cyclooxygenase 1 inhibitor | Acetylsalicylic acid (Aspirin) | Routine off-label use |
| $P2Y_{12}$ antagonists | Clopidogrel (Plavix) | Routine off-label use |
| | Ticagrelor (Brilinta) | Investigational |
| | Cangrelor (Kengreal) | Investigational |
| | Prasugrel (Effient) | Not approved (no pediatric use reported) |
| | Ticlopidine (Ticlid) | Not approved (no pediatric use reported) |
| Phosphodiesterase inhibitors | Dipyridamole (Persantine) | Routine off-label use |
| | Cilostazol (Pletal) | Not approved (no pediatric use reported) |
| GPIIb-IIIa antagonists | Abciximab (Reopro) | Not approved (pediatric use reported) |
| | Tirofiban (Aggrastat) | Not approved (pediatric use reported) |
| | Eptifibatide (Integrilin) | Not approved (no pediatric use reported) |
| PAR-1 antagonists | Vorapaxar (Zontivity) | Not approved (no pediatric use reported) |

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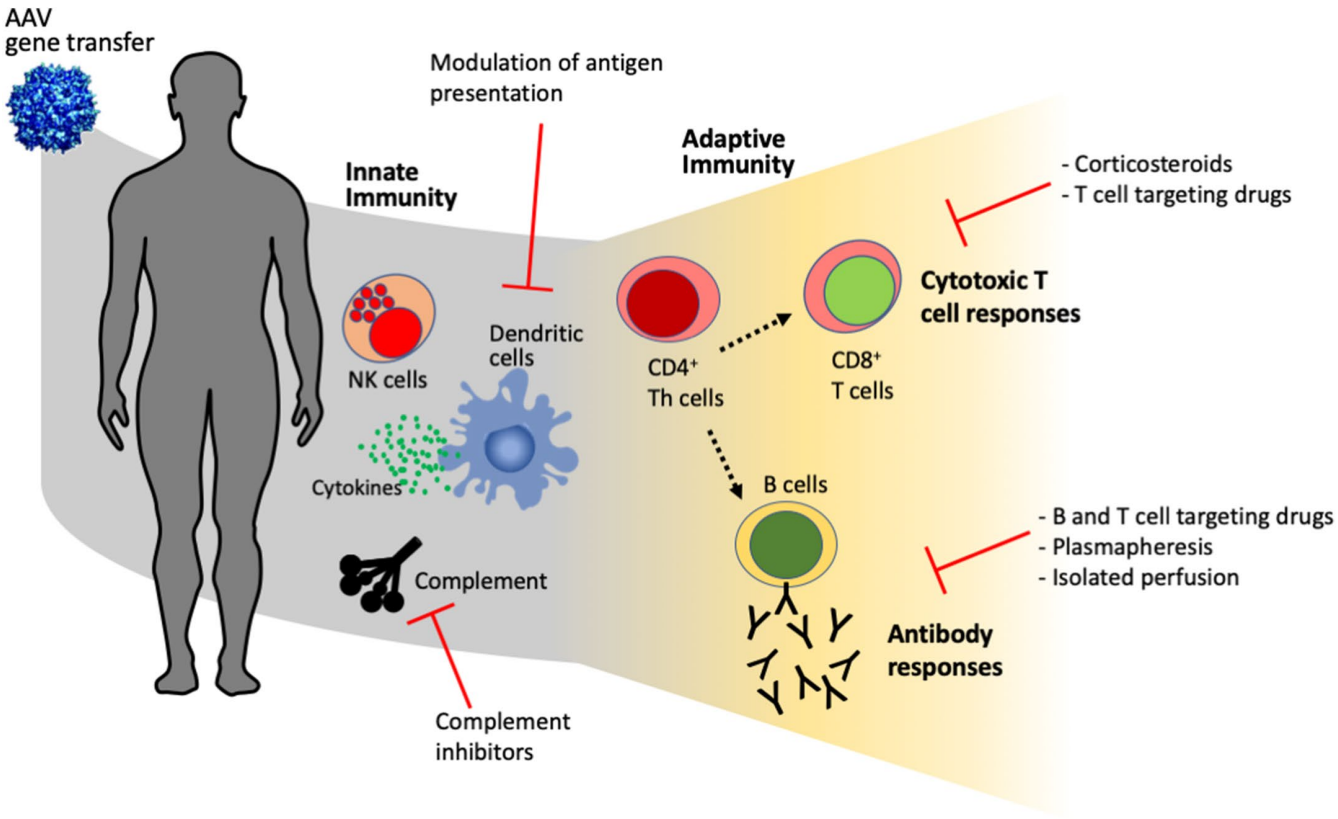
# Immunogenicity of adeno-associated vectors

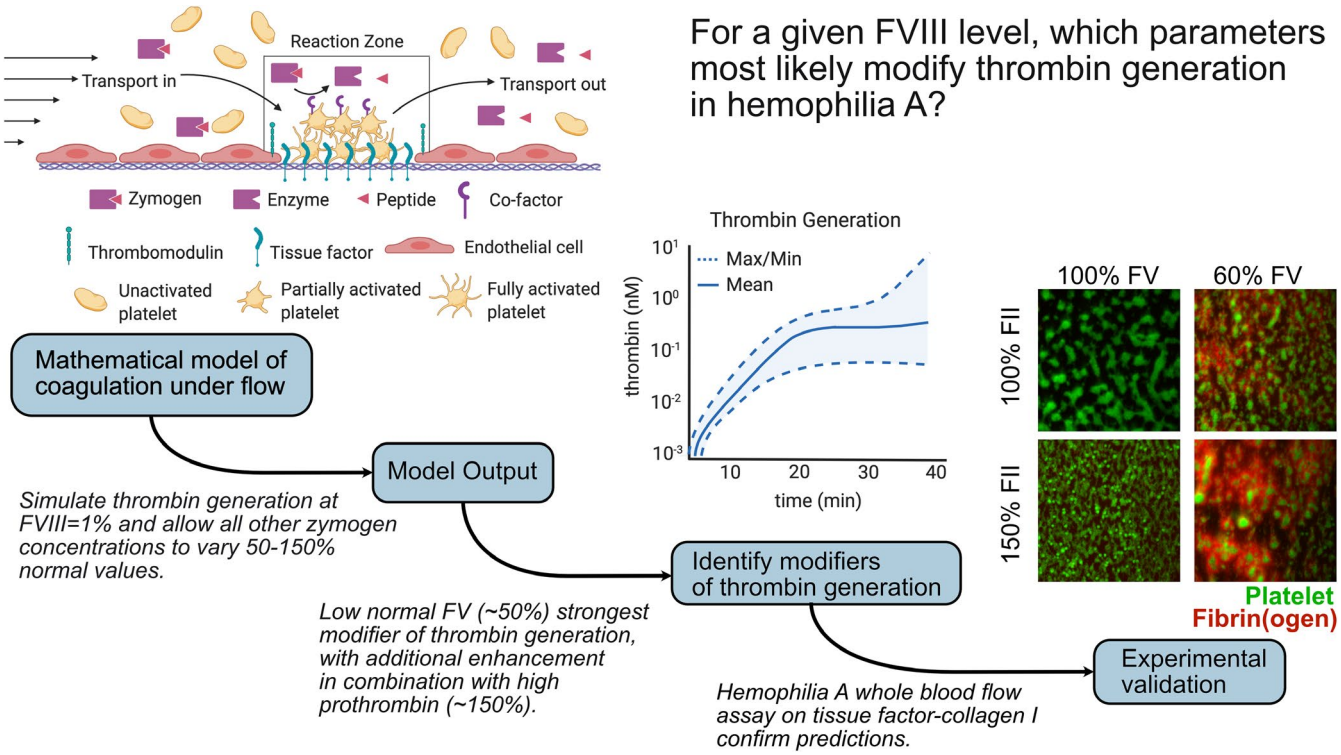
Federico Mingozzi PhD




The adeno-associated virus (AAV) vector gene-transfer platform has an attractive safety and long-term efficacy profile demonstrated in a number of trials for hemophilia A and B. Because humans are naturally exposed to wild-type AAV, they develop both antibody and T-cell immunity to the virus. AAV vectors, like their wild-type counterpart, interact with the host immune system at multiple levels, starting early after vector administration with the induction of innate immune responses. Early activation of immunity is followed by adaptive immune responses, which result in long-term development of neutralizing antibodies and activation of capsid T-cell responses directed against the vector capsid. When not adequately managed, immune responses to AAV vectors can be associated with short-lived or absent expression of the therapeutic transgene.[34]

# Computationally driven discovery in coagulation dynamics

Keith Neeves PhD




For references, see Link et al[35,36] and Biorender.com.[37]

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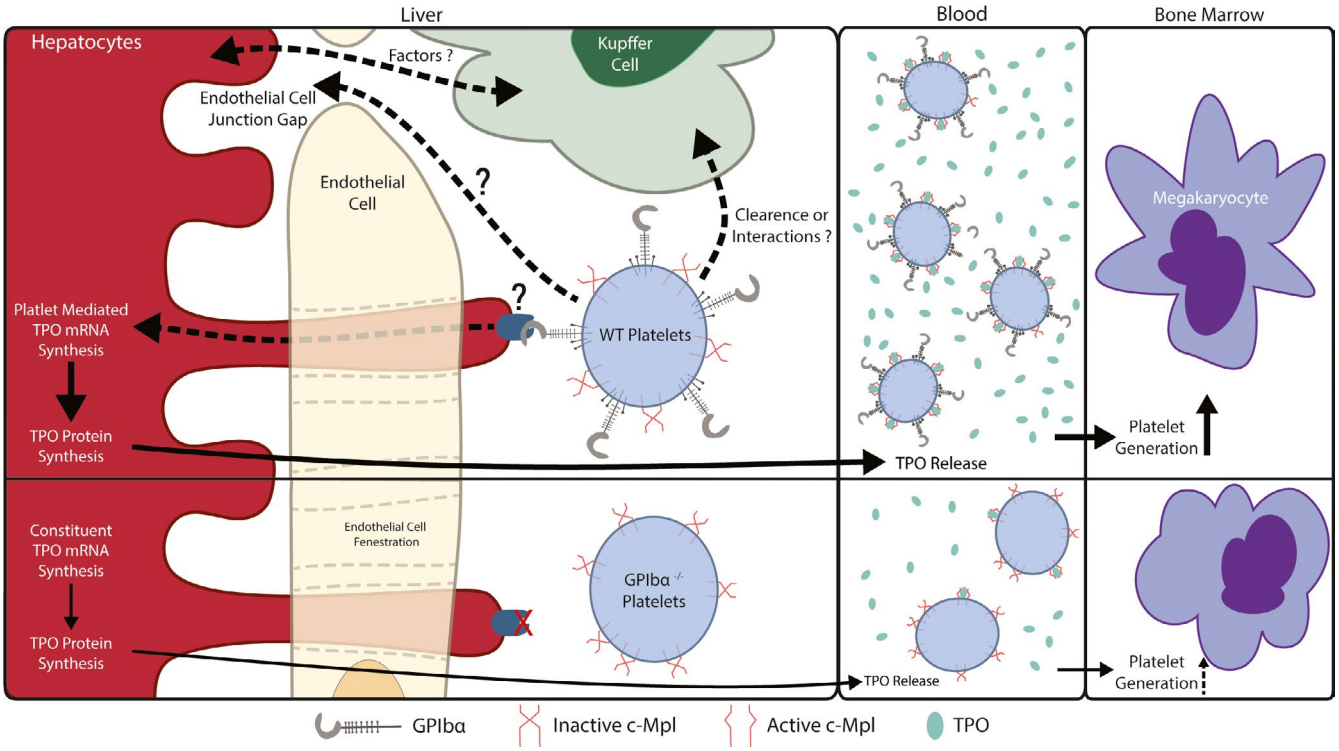
# GPIbα-driving force for liver thrombopoietin generation

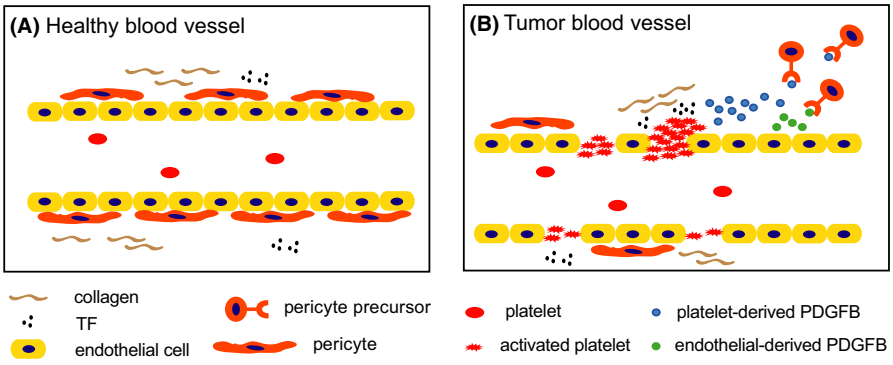
Heyu Ni MD, PhD




Platelet GPIbα plays important roles in thrombosis and hemostasis, but its role in thrombopoietin (TPO) generation was not previously explored. TPO is predominantly produced by the liver, and its circulating levels have been thought to be maintained through its clearance by platelets and megakaryocytes via surface c-Mpl internalization. Unexpectedly, we found TPO levels have a 2- to 3-fold decrease in both GPIbα deficient mice and human patients with Bernard-Soulier syndrome (BSS). Transfusion of platelets from wild-type but not GPIbα-/- or interleukin-4/GPIbα transgenic mice increased the TPO level in GPIbα-/- mice via de novo TPO synthesis in the liver. In vitro cell culture assays further demonstrate GPIbα-hepatocyte interaction is the driving force for TPO generation, which can be inhibited by antibodies blocking the N-terminus of GPIbα. These findings may have important implications in diseases related to GPIbα such as BSS and immune-mediated thrombocytopenia. We are studying the molecular and cellular mechanisms behind this "driving force."[38-40]

# The role of platelets in tumor metastasis

Anna-Karin Olsson MD, PhD




Platelets activated in the tumor microenvironment secrete platelet-derived growth factor subunit B (PDGFB) that contributes to the vascular remodeling process. (A) In healthy tissue, platelets stay in the circulation in a nonactivated state, since they do not come in contact with subendothelial components such as tissue factor (TF) and collagen. (B) In contrast, the discontinuous endothelium in tumors expose platelets to subendothelial spaces, leading to their activation and degranulation in close proximity to the vasculature. Platelet-derived PDGFB will, in the same was as endothelial-derived PDGFB, be retained close to the vasculature due to the heparan sulfate–binding retention-motif and contribute to the pericyte-recruiting gradient of PDGFB.

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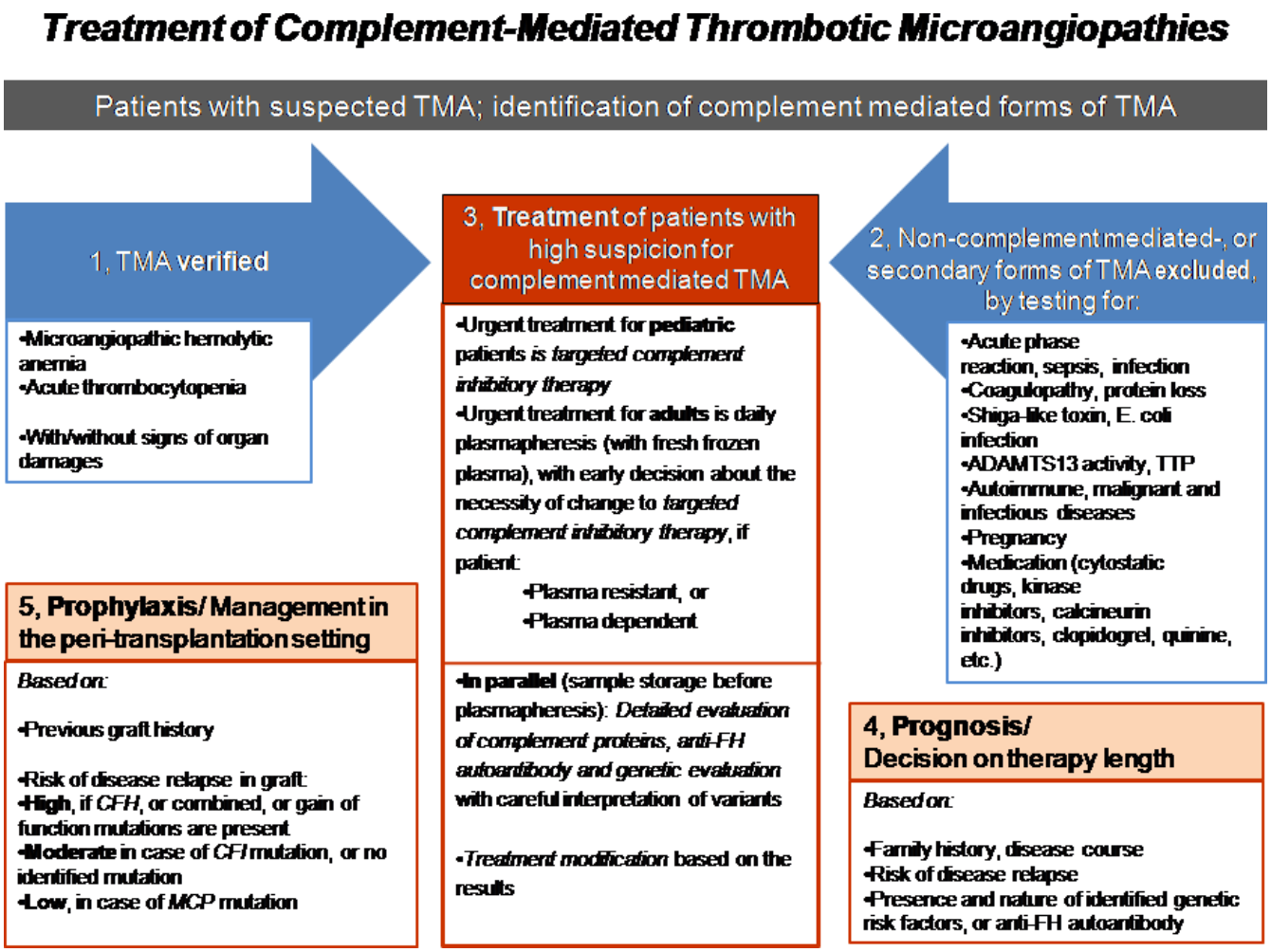
# Treatment of complement-mediated thrombotic microangiopathies

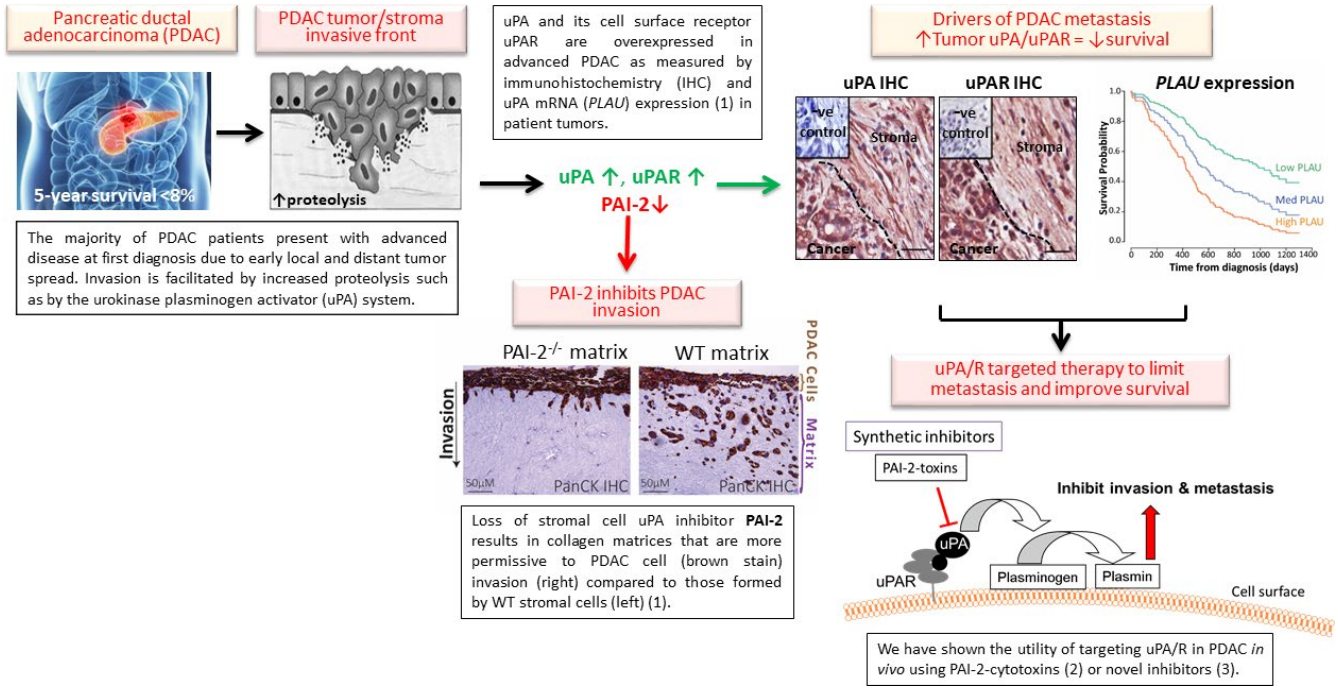
Zoltán Prohászka MD




Thrombotic microangiopathies (TMAs) are heterogeneous diseases with common pathogenic features including endothelial activation and damage, aggregation and consumption of platelets, and hemolysis consequent to mechanical injury to erythrocytes (1). TMAs are rapidly progressing diseases when untreated; therefore, the decision to start the initial, lifesaving treatment should be done quickly, based on clinical and laboratory signs and careful evaluation of the presenting features (2). However, since various targeted therapies are now available to target the molecular etiologic factors or key pathogenic mediators of TMAs, it is of utmost importance to rapidly evaluate the molecular etiology behind TMAs and make discrimination between complement-mediated disease forms including, for example, atypical hemolytic uremic syndrome (aHUS) and other forms of TMAs (2 and 3). First-line therapy of aHUS in pediatric patients is based on complement inhibitory drugs, and for adults, early change from plasmapheresis to complement inhibitory therapy is indicated in case of plasma resistance or plasma dependence (3). There are attempts to identify factors (including rare or common variants of complement genes) that may help facilitate decisions on the length of complement inhibitory therapy (4). For those necessitating kidney transplantation due to complement-mediated TMA, peritransplantation management, including the application of complement inhibitory drugs, should be based on careful genetic evaluation of complement factors and regulators (5).

# Fibrinolytic factors in cancer progression

Marie Ranson PhD




*For references, see Harris et al,[41] Stutchbury et al,[42] and Buckley et al.[43]*

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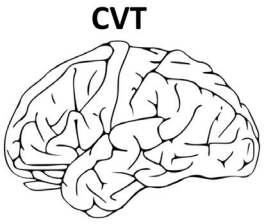
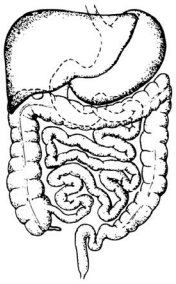
# DOACs for unusual site venous thromboembolism

**Nicoletta Riva MD**

## DOACs in unusual site VTE





| | | | | |
|---|---|---|---|---|
| | Involved veins | • Dural venous sinuses (e.g. cavernous, sagittal, sigmoid, straight, transverse)<br>• Cerebral cortical or deep veins | • Portal vein<br>• Mesenteric veins<br>• Splenic vein<br>• Budd-Chiari syndrome | • Brachial vein<br>• Axillary vein<br>• Subclavian vein<br>• Internal jugular vein |
| Standard anticoagulation | | **LMWH, UFH, VKA** | | |
| Safety and efficacy of the DOACs* | • Recanalization | 55-100% | 65-100% | 100% |
| | • Major bleeding | 0-8% | 0-15% | 0% |
| | • Recurrent VTE | 0% | 0-11% | 0-2% |

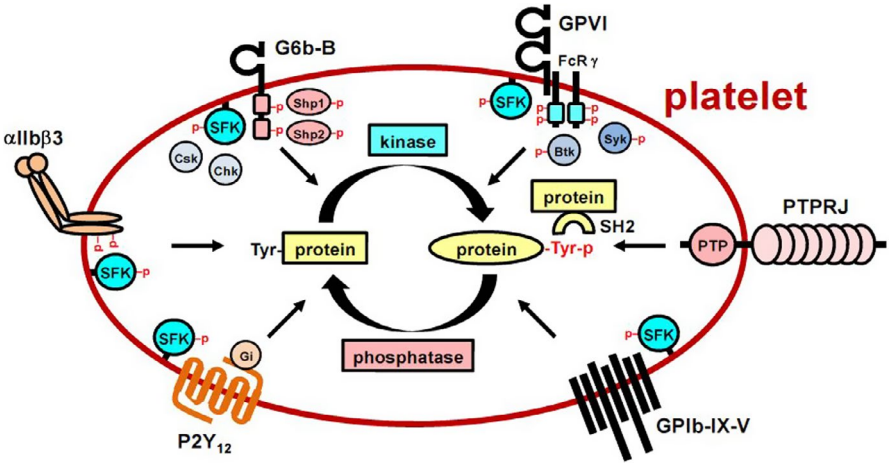
** The evidence is limited by the low number of studies currently published*

Abbreviations: CVT = cerebral vein thrombosis; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; SVT = splanchnic vein thrombosis; UEDVT = upper extremity deep vein thrombosis; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Treatment of unusual site venous thromboembolism (VTE) can be challenging, due to the relative rarity of these thromboses and the paucity of strong evidence in the literature. Patients with unusual VTE were not included in the large phase 3 trials assessing the direct oral anticoagulants (DOACs), but several case series, retrospective and prospective studies, and two small randomized controlled trials[44,45] were recently published. Currently available results suggest that the safety and effectiveness of the DOACs in upper-extremity deep vein thrombosis (UEDVT)[46] is comparable to lower-limb deep vein thrombosis and pulmonary embolism. Studies in splanchnic vein thrombosis (SVT) and cerebral vein thrombosis (CVT) showed promising results, although hampered by low number of patients, variable study design and outcome definitions, and heterogeneity of results, which resulted in a wide range of the major clinical outcomes. A number of ongoing studies will provide further evidence on unusual VTE.

# Tyrosine kinases-phosphatases and platelet activation

Yotis Senis MSc, PhD




Platelet activation is a tightly controlled process, allowing platelets to respond rapidly to vascular injury, while preventing pathological thrombosis. Reversible tyrosine phosphorylation is a primary mode of signal transduction catalyzed by the opposing activities of protein-tyrosine kinases (PTKs) and phosphatases (PTPs), mediating binding of Src homology 2 (SH2) domain-containing proteins to phosphotyrosine residues (p-Tyr), and altering the catalytic activity of enzymes. Src family kinases (SFKs) are essential for initiating and propagating signals from a diverse repertoire of platelet receptors, including GPVI-FcR γ-chain, GPIb-IX-V, $P2Y_{12}$, αIIbβ3 and G6b-B.[47] The structurally distinct PTKs spleen tyrosine kinase (Syk) and Bruton's tyrosine kinase (Btk) play vital roles in amplifying activation signals, whereas C-terminal Src kinase (Csk) and Csk homologous kinase (Chk) inhibit SFK activity.[48] PTPs are equally important regulators of platelet activation, notably, the PTP receptor-type J (PTPRJ, also referred to CD148), which both activates and attenuates SFK activity[48]; and the nontransmembrane SH2 domain-containing PTPs 1 and 2 (Shp1, Shp2), critical for transmitting inhibitory signals from G6b-B.[49] Understanding the molecular interplay between PTKs and PTPs has important scientific and clinical implications, as tyrosine kinase inhibitors are increasingly used clinically, and tyrosine phosphatase inhibitors come into use.

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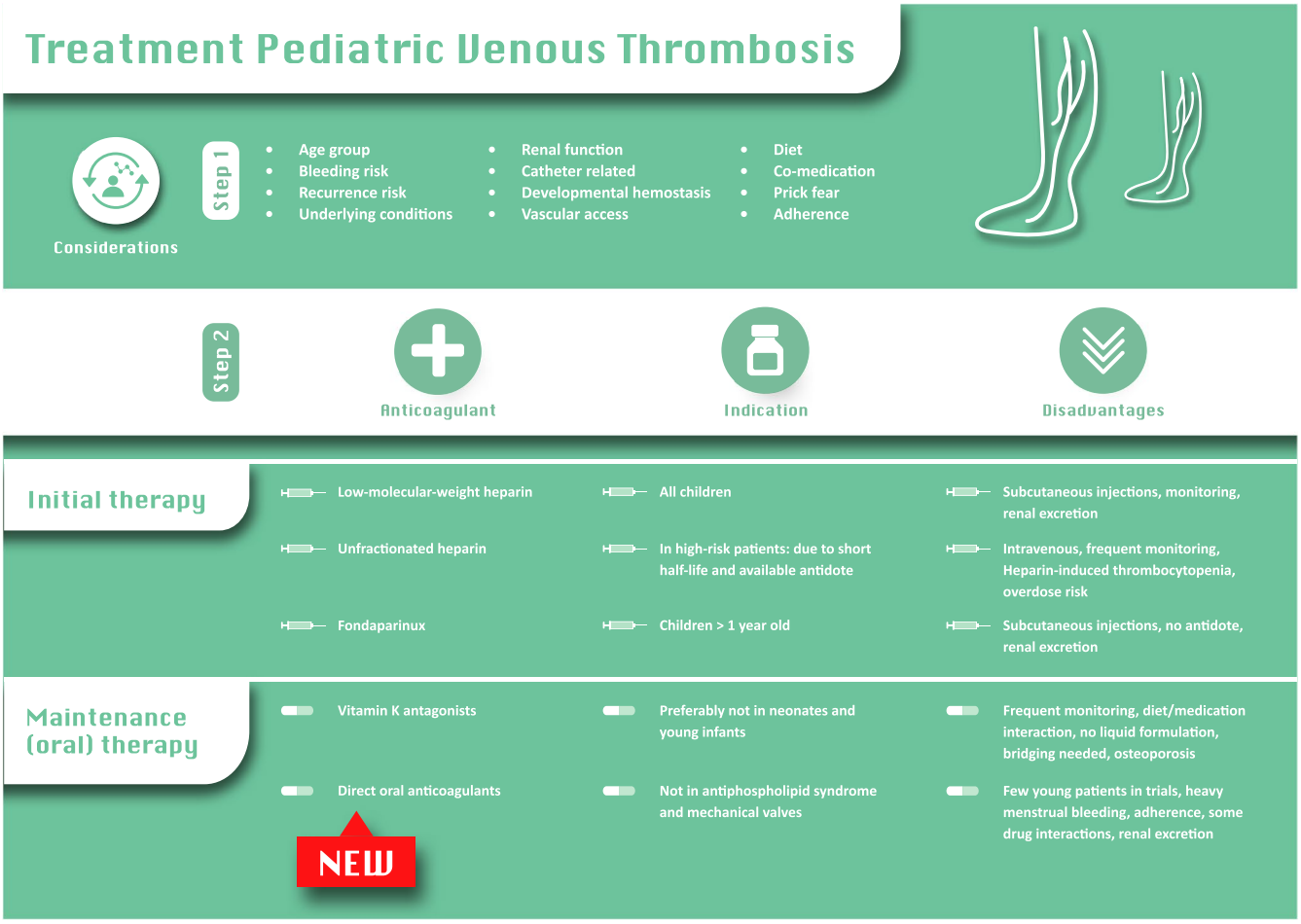
# DOACs in children: Current evidence and future perspectives

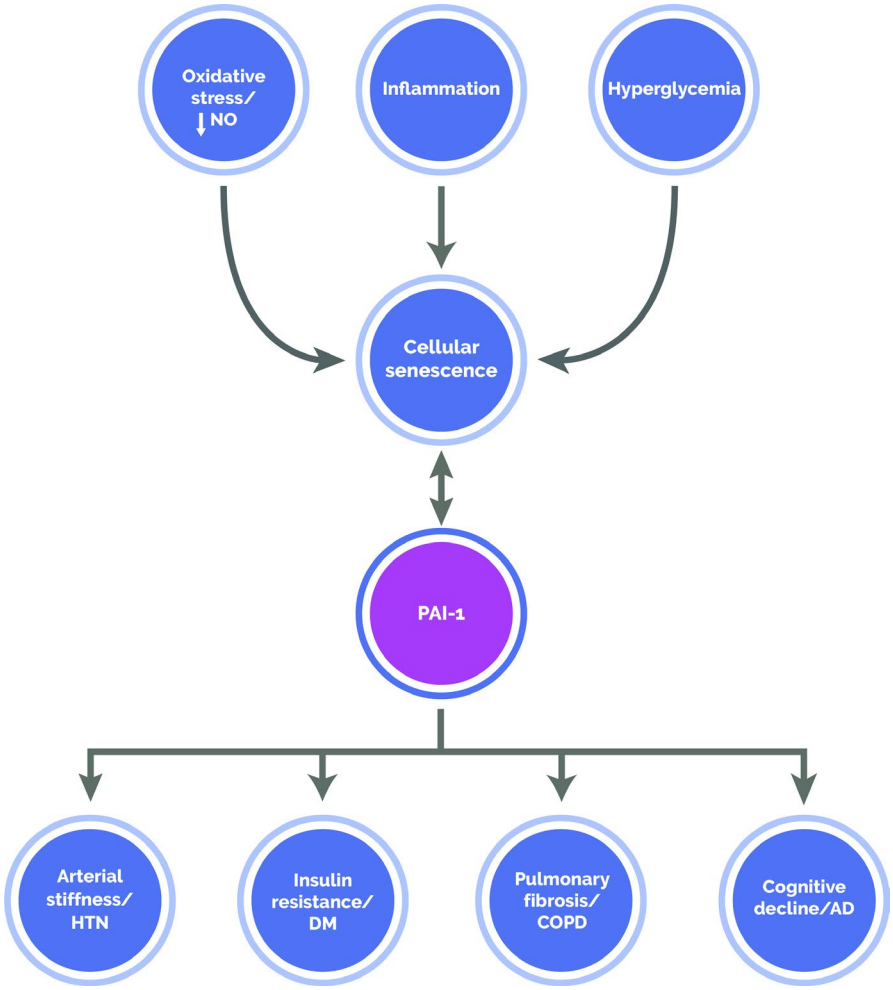
Cornelia H. van Ommen MD, PhD




The first phase 3 direct oral anticoagulant (DOAC) study for the treatment of pediatric venous thromboembolism (VTE) showed similar safety and efficacy in the rivaroxaban and standard of care groups.[50] Consequently, DOACs will probably become the anticoagulants of choice in children. However, certain limitations should be considered. In the rivaroxaban trial, only 37 children <2 years were included. Neonates had to have a gestational age of at least 37 weeks and oral feeding for 10 days; most neonates with VTE will not meet this requirement. Heavy menstrual bleeding, frequently seen in female DOAC users, may be a problem for adolescents with estrogen-associated VTE. Finally, adherence issues with DOACs might be a reason to switch back to "old-fashioned" anticoagulants to increase contact between patients and caregivers. Consequently, postauthorization studies are needed, which require international registries such as the Throm-PED registry.[51] At present, antithrombotic treatment in children requires a personalized approach.

# PAI-1 and the multimorbidity of aging

Douglas E. Vaughan MD




Plasminogen activator inhibitor-1 (PAI-1) is a functional mediator of cellular senescence. Experimental evidence has uncovered direct mechanistic links between PAI-1 and aging-like pathology. Conversely, PAI-1 deficiency provides protection against aging-related pathologies in experimental models. Furthermore, in healthy human populations, plasma PAI-1 predicts the development of vascular stiffness, coronary disease, diabetes, and hepatic steatosis. We have shown that PAI-1 deficiency protects against emphysema and arteriosclerosis and quadruples life span in a mouse model that resembles accelerated human aging. In a remarkable "natural" randomized study in humans, heterozygous carriers of a null variant in the gene that codes for PAI-1 (*SERPINE*1) have longer telomeres, lower fasting insulin levels, protection from diabetes, preserved vascular flexibility, and a longer life span than their unaffected kindred. Based on experimental evidence in cells and mice, epidemiologic studies, and findings in a unique human population, PAI-1 is a validated target for the prevention of numerous aging-related morbidities and perhaps even aging itself.[52-54]

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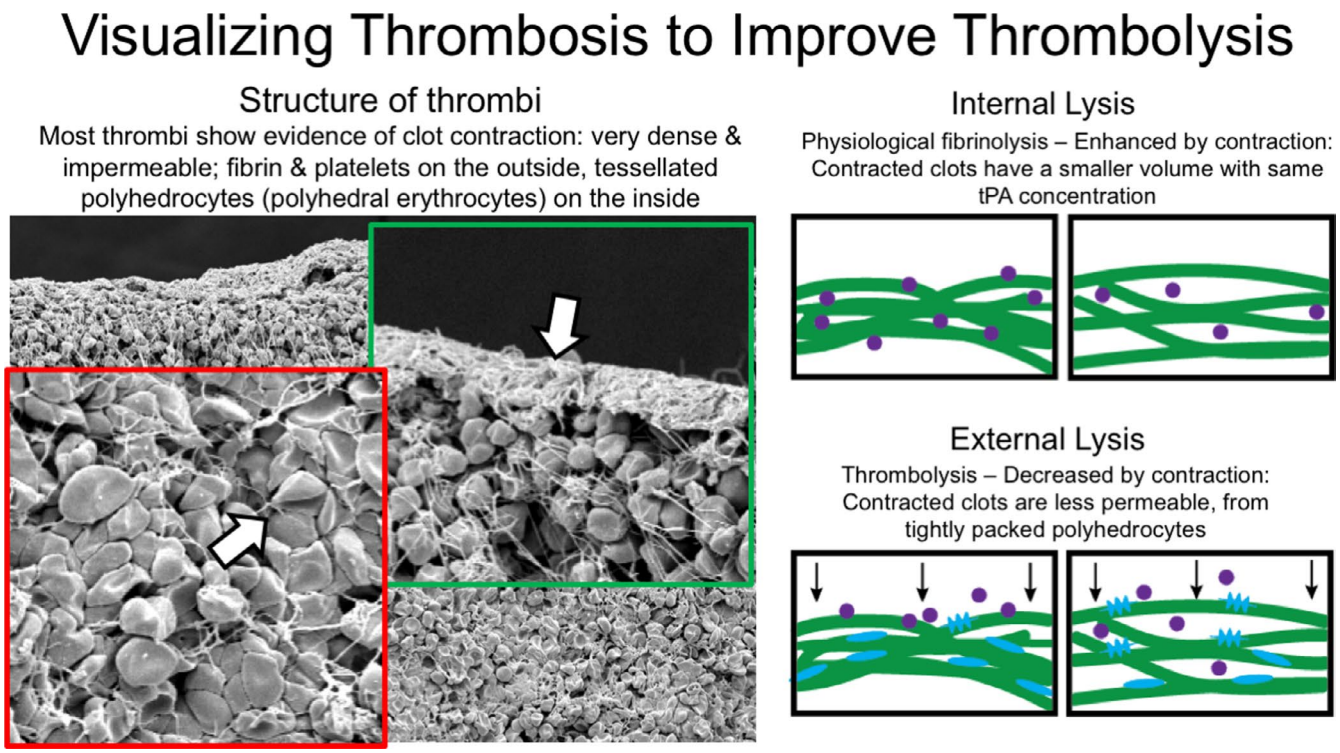
# Visualizing thrombosis to improve thrombolysis

**John Weisel PhD**



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