South-East Europe Initiative for Apheresis

10th Hellenic Haemapheresis Association Conference

Θρομβαγγειοπάθειες από την άποψη του αιματολόγου

Ρουμελιώτη Άννα

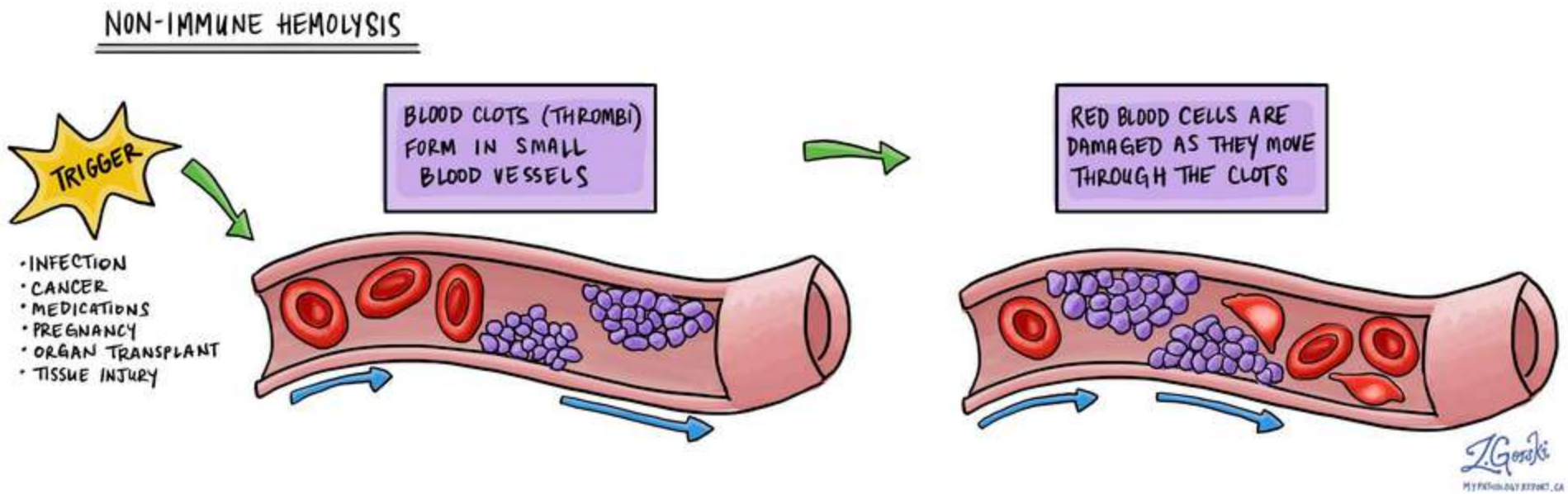
Αιματολόγος, Γ.Ν.Α. Ευαγγελισμός

No disclosures

E. Moschcowitz

Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease

Proc. N Y Pathol. Soc., 24 (1924), pp. 21-24



K. Singer, F.P. Bornstein, S.A. Wile

Thrombotic thrombocytopenic purpura; hemorrhagic diathesis with generalized platelet thromboses

Blood, 2 (6) (1947), pp. 542-554

Regulation of thrombotic phenotype of confluent endothelial cells

Input

Biomechanical
Circumferential stress and strain
Longitudinal stress and strain

Biochemical
Hypoxia, Glucose, Acid stress Balance
Pathogens
Growth factors
Extracellular matrix
Sex hormones
Serine proteases
Chemokines, cytokines
Nucleosides
Sphigolipids
Lipoproteins
Contact system
Nitric oxid, autacoids
Cell-cell interaction
Microvesicles, exosomes

Output

Single cell level
Cellshape
Calcium flux
Gene expression
Protein translation
Post-translational modifications
Proliferation
Migration
Apoptosis

Cell monolayer level
Barrier function
Leukocyte adhesion

Blood vessel/organ/organism
Vasomotor tone
Angiogenesis
Inflammation
Activation of coagulation with fibrin deposition

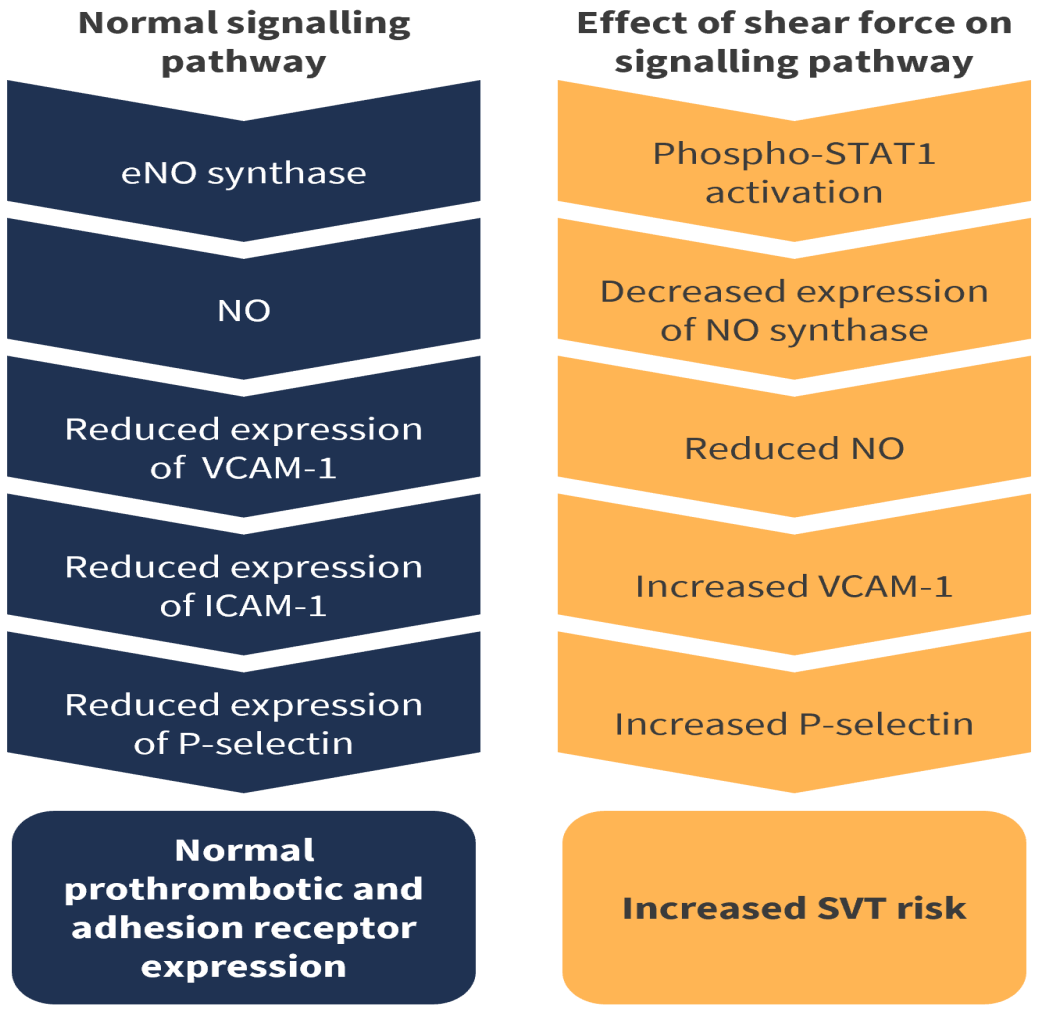
Endothelial cells and primary haemostasis

Activation

Von Willebrandt Factor
Weibel –Palade bodies
-Rod –shaped storage granules
-haemostatic cargo
- Formation entirely driven by the Expression of VW
- Rapidly released(exocytosis)

Inhibition

PGIs and NO



Thrombotic microangiopathies (TMAs)

- a group of

✓ rare

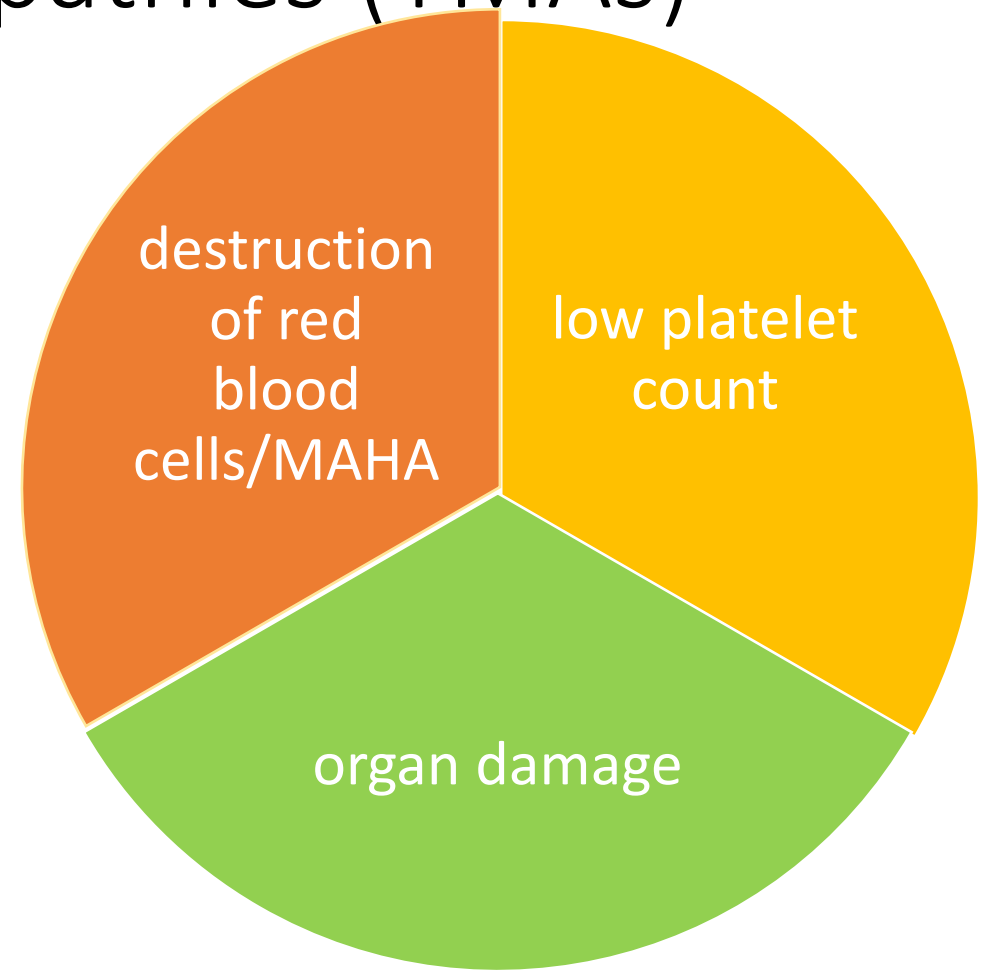
✓serious disorders

=> cause blood clots to form

in small blood vessels

=>leading

leading



Defining features

•**Microangiopathic hemolytic anemia:** Red blood cells are fragmented and destroyed as they pass through tiny blood vessels clogged with clots.

•**Thrombocytopenia:** A low number of platelets in the blood.

•**Organ damage:** Clots can damage organs, most commonly the kidneys and brain, but virtually any organ can be affected. Symptoms can include kidney failure, confusion, seizures, and stroke

Suggested Work Up

CBC with Diff
CMP
Coagulation Panel
LDH
Haptoglobin
Fibrinogen
D dimer
Peripheral Smear (Wright)
Coomb's test
ADAMTS13 (if TTP suspected)
HIV
Urinalysis
Blood cultures
Imaging as needed

What type of work up will help differentiate between these conditions?

While the presentation and history may help differentiate these conditions, the laboratory work up will be important to confirm the diagnosis and differentiate between entities. All of the conditions mentioned above have two major laboratory abnormalities in common: thrombocytopenia and anemia.

TMA : What to know

- **Urgent diagnosis is critical:**
TMAs are life-threatening, and treatment needs to begin as quickly as possible to be effective.

- **Specialty care is needed:**
Once suspected, urgent referral to a specialty service, such as a hematology or nephrology unit, is required.

- **Plasma exchange is a key treatment:**
This procedure helps reduce mortality significantly when administered in a timely manner.

TMA: Classic examples

thrombotic thrombocytopenic purpura (TTP)

hemolytic uremic syndrome (HUS),

which can be caused by underlying conditions like infections, certain drugs, and other diseases.

Secondary forms of TMA

- Infections (e.g., Shiga toxin-producing E. coli)
- Cancer
- pregnancy,
- malignant hypertension
- Drugs Certain medications, such as chemotherapy agents (mitomycin, gemcitabine) and some immunosuppressants (cyclosporine, tacrolimus)
- solid transplantantation
- hematopoietic transplantation
- Autoimmune disease like scleroderma and lupus
- HELLP syndrome (associated with pregnancy)
- metabolic diseases

Despite the varied pathophysiology the presence of endothelial damage leading to microvascular ischemia is the hallmark of TMA

Capillary damage in TMA

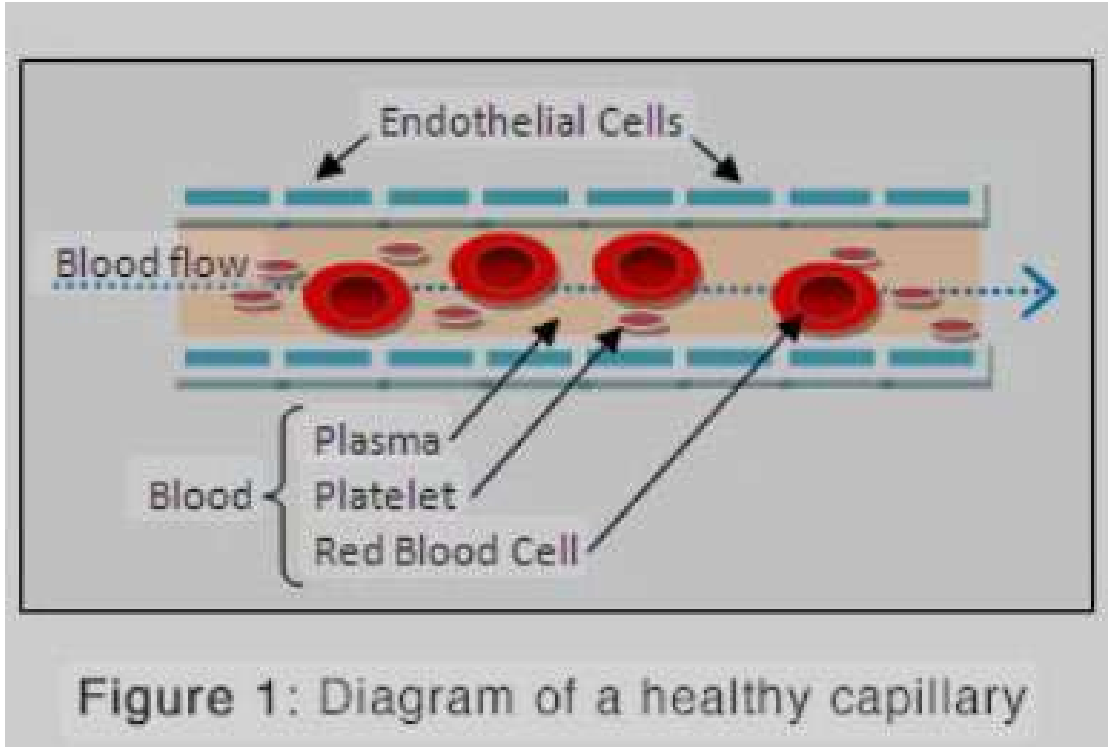


Figure 1: Diagram of a healthy capillary

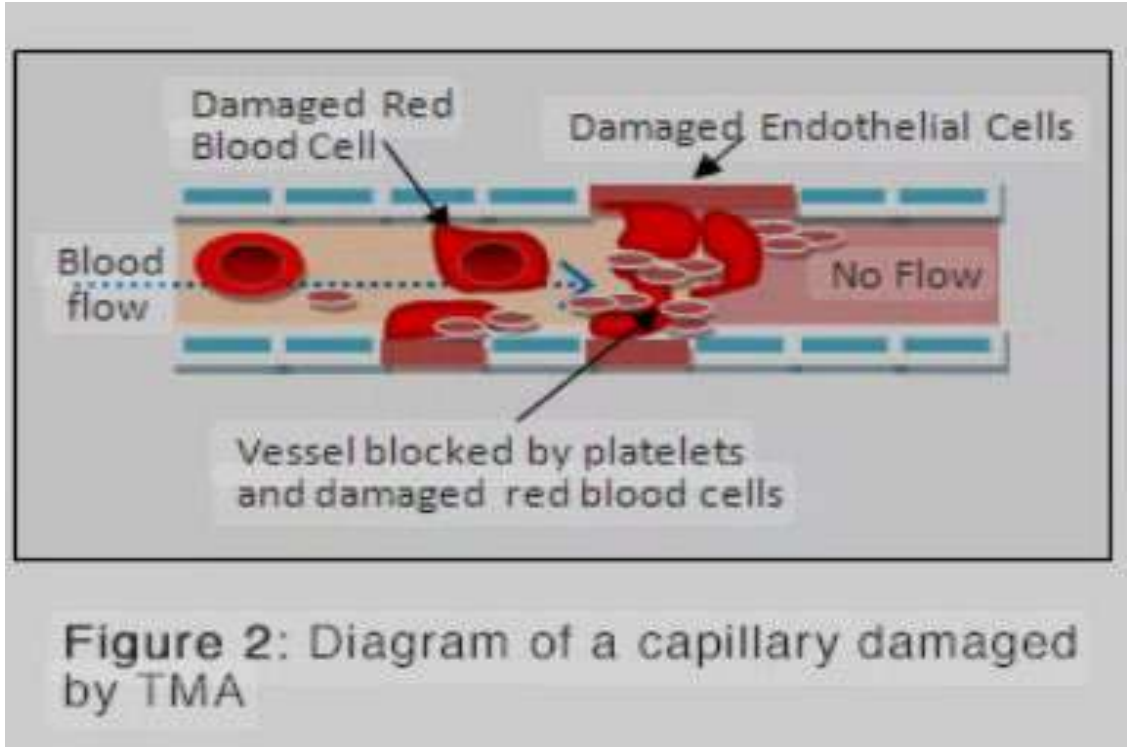
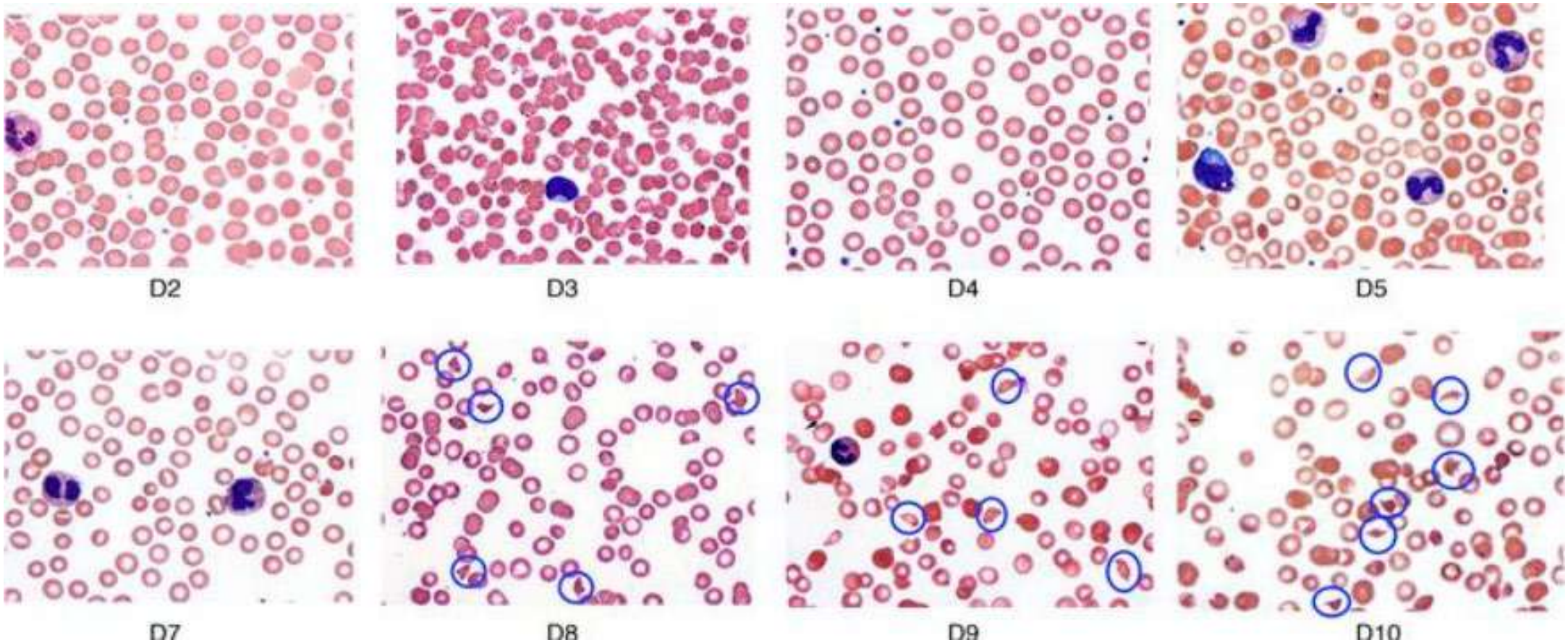


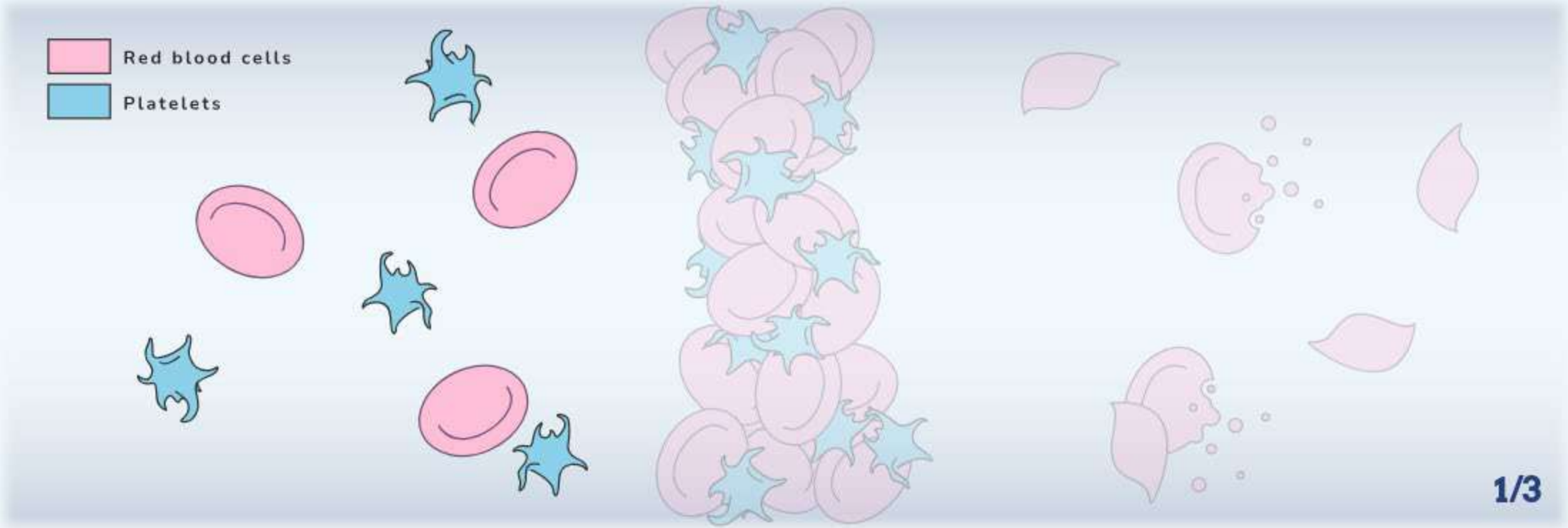
Figure 2: Diagram of a capillary damaged by TMA

Peripheral blood smear in TMA



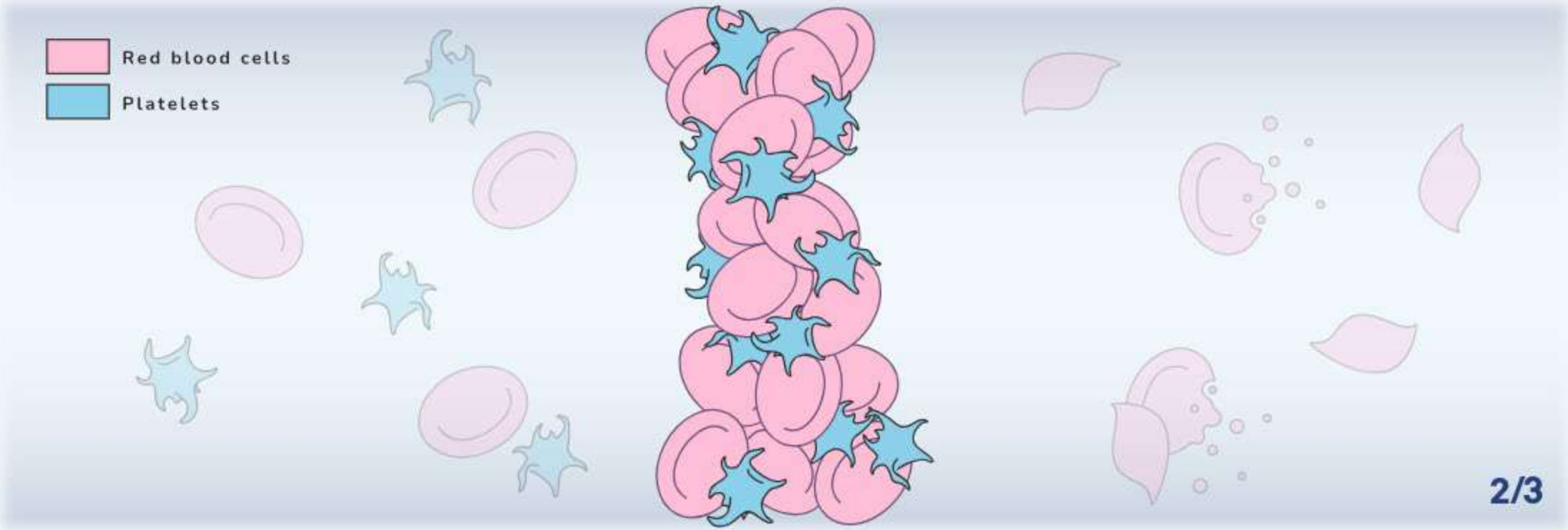
Sequence of peripheral blood smears after a drug therapy administration in patient samples revealing increased schistocytes (blue circles), demonstrating evidence of endothelial damage, burr cells, polychromatic red blood cells, and thrombocytopenia, suggesting thrombotic microangiopathy.

Damage from TMA



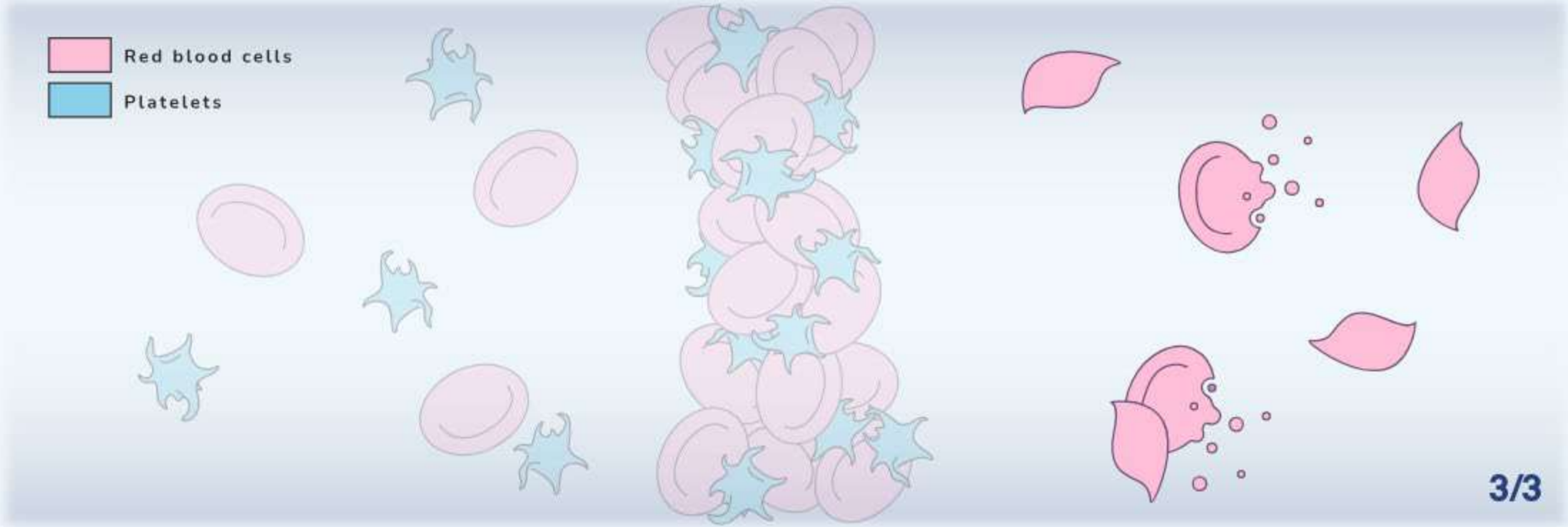
1. In atypical-HUS, uncontrolled complement activity causes blood platelets to become overactive.

Damage from TMA



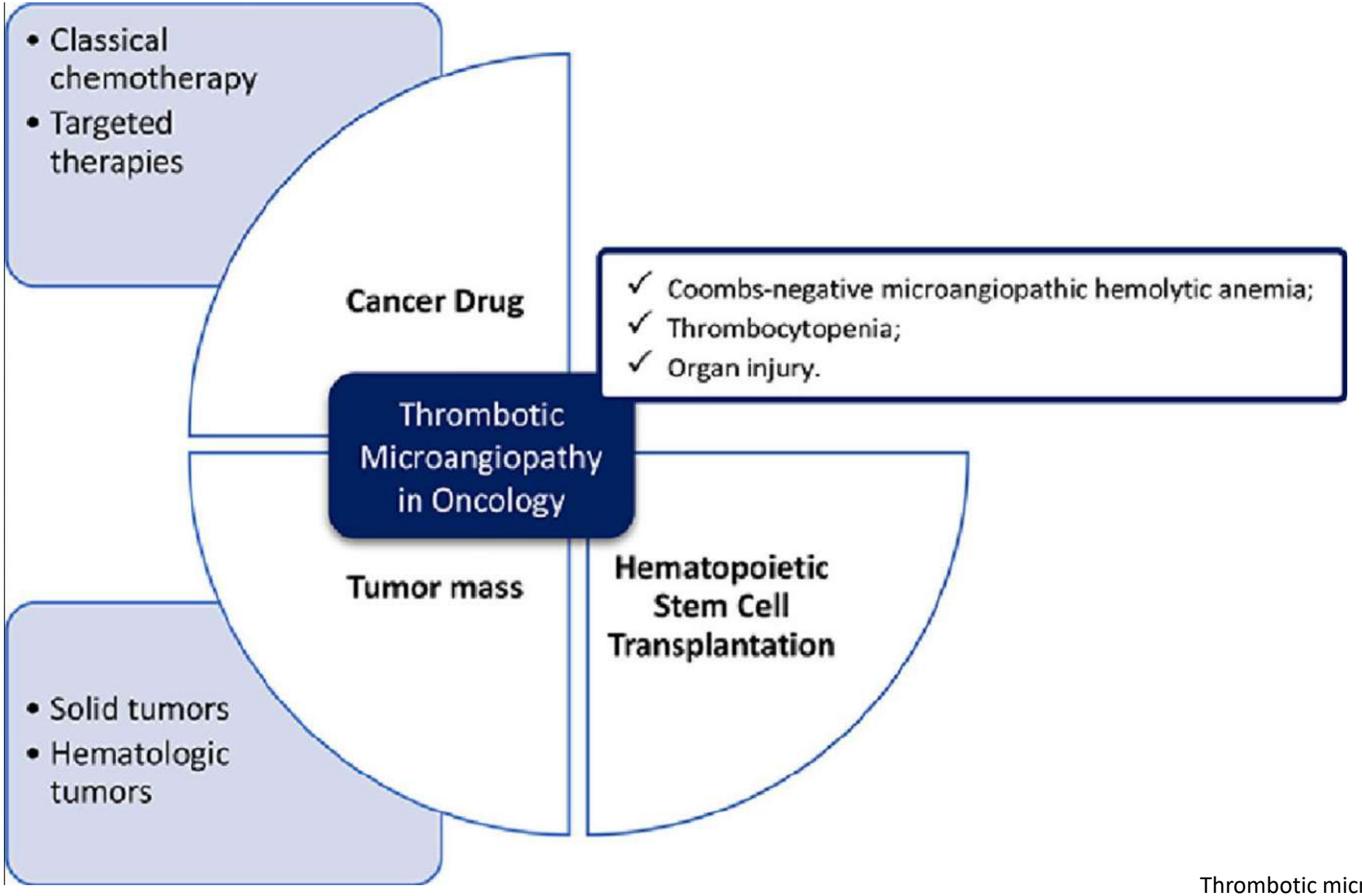
2. Platelets stick together in small blood vessels and cause clots and inflammation in blood vessel walls. Red blood cells become trapped in the clots.

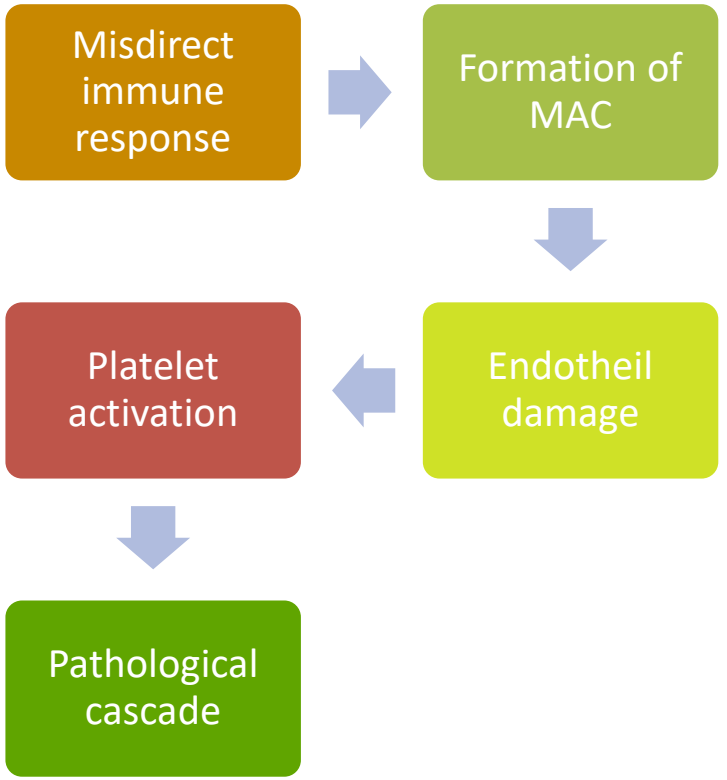
Damage from TMA



3. Any red blood cells that are able to pass through the clots emerge damaged or destroyed. The end result is reduced blood flow to vital organs that is potentially life-threatening.

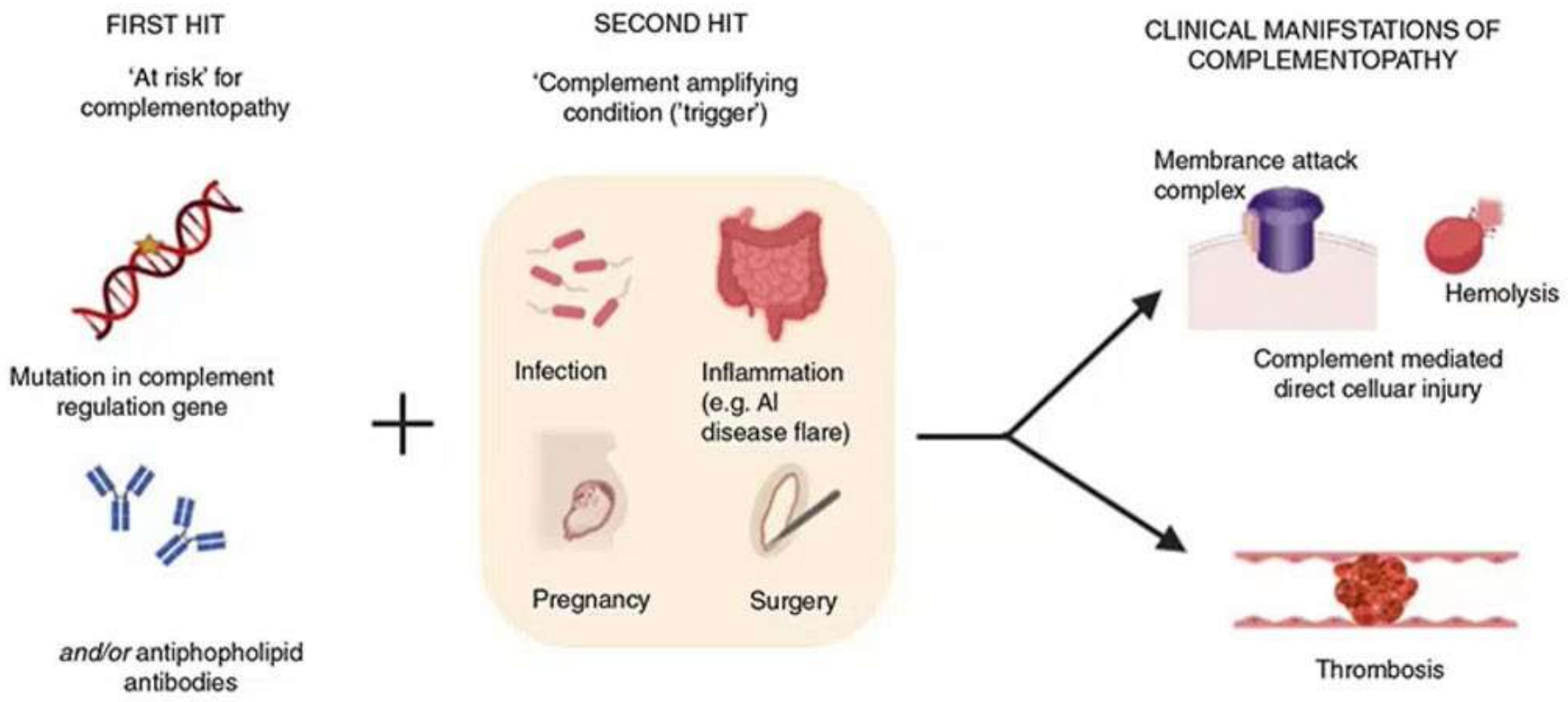
TMA in oncology





Thrombotic microangiopathy in oncology – a review Patricia Valerio et al

Cardinal features of complementopathies

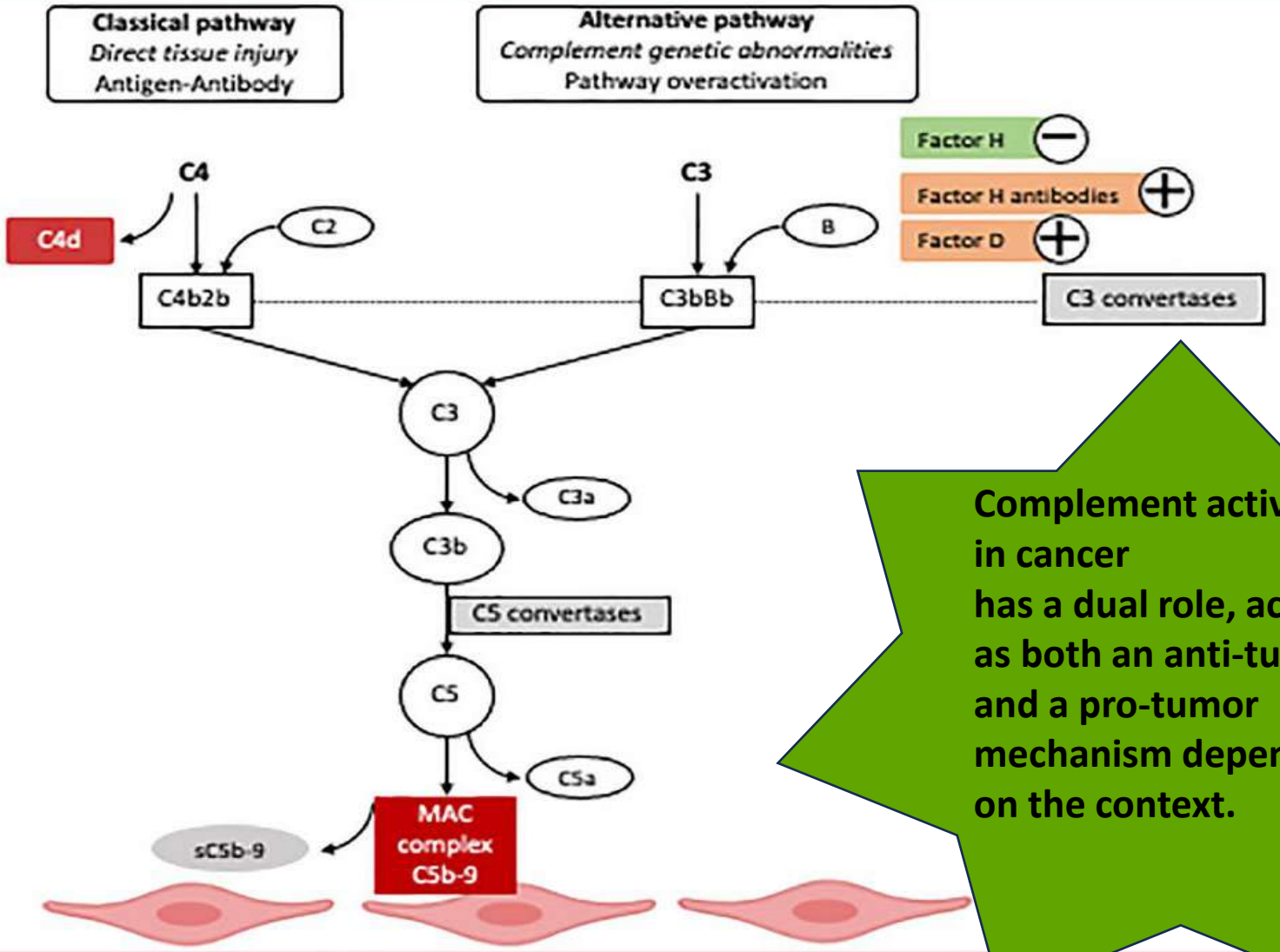


Chatuverdi, McCrae, Brodsky jTH 2021

Potential risk factors:
- CNI/ mTORI;
- GVHD;
- Infections;
- Conditioning regiments/ TBI.

Neutrophil activation ⊕

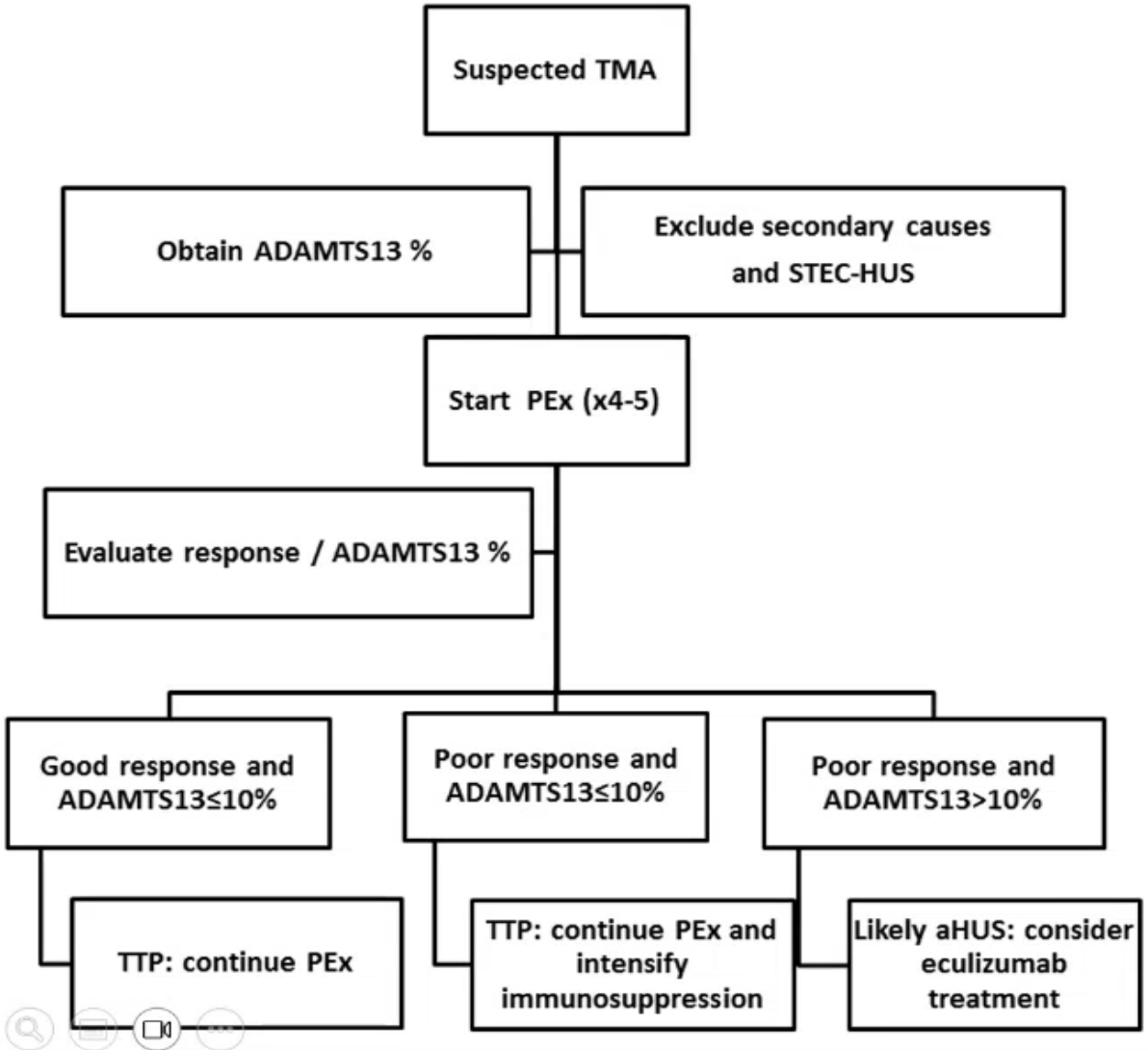
Coagulation cascade activation ⊕



Complement activation in cancer has a dual role, acting as both an anti-tumor and a pro-tumor mechanism depending on the context.

Thrombotic microangiopathy in oncology – a review Patricia Valerio et al

Suspected TMA : algorithm



Gavriilaki E, Brodsky RA. Consultative Hemostasis and Thrombosis. 2017

Characteristics	**DIC**	ITP	TTP	HUS
Fever	No	No	Yes	Yes/No
Splenomegaly	No	No	Yes	Yes
Platelets	Low	Low	Low	Low
Bleeding time	↑	↑	↑	↑
PT	↑	-	-	-
PTT	↑	-	-	-
Shistocytes	Yes	No	Yes	Yes
Trauma	Yes	No	No	No

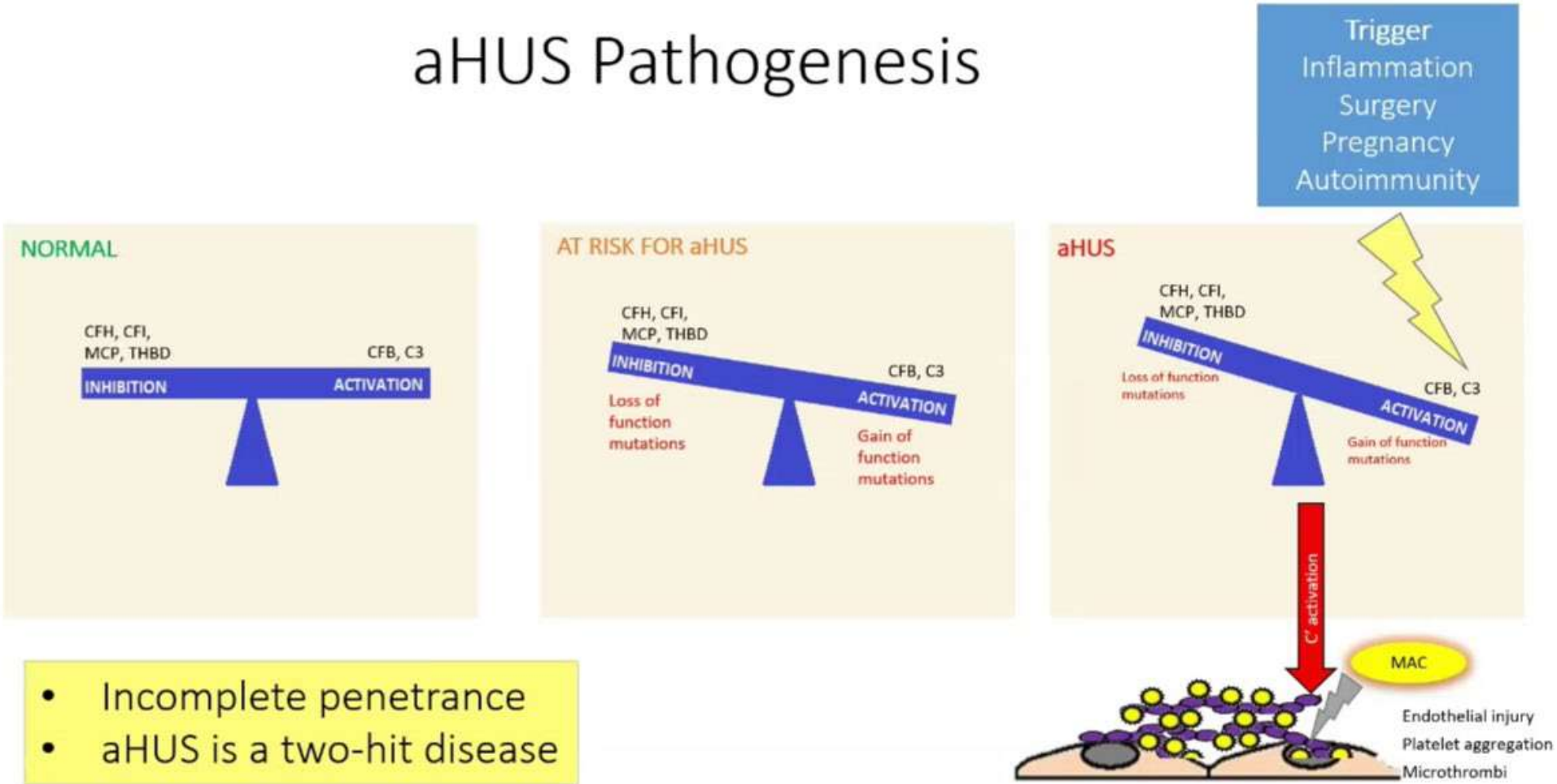
aHUS: a complement-mediated thrombotic microangiopathy

- Associated mutations or autoantibodies that activate complement

- Leads to endothelial damage, platelet activation, and end-organ damage to multiple organs
- Within a year of diagnosis, 50% die or remain at dialysis without a complement inhibitor
- Remains a diagnosis of exclusion

Gavriilaki E, et al. Front Immun 201

aHUS Pathogenesis



- Incomplete penetrance
- aHUS is a two-hit disease

Pathophysiology a HUS

- Dysregulation of the alternative complement pathway in aHUS.
- In physiological conditions,

spontaneous hydrolysis of complement component (C)3 leads to formation of C3b, which binds to CFB to form the C3 convertase (C3bBb).

This complex enzyme amplifies complement activation, generating additional C3b and forming the C5 convertase (C3bBbC3b), which triggers the terminal complement cascade and assembly of MAC. Complement regulatory proteins–CFH, CFI, MCP, and THBD–normally control this process.

In aHUS, loss-of-function mutations in these regulators, gain-of-function mutations in C3 or CFB, or the presence of anti-CFH antibodies lead to uncontrolled complement activation, endothelial injury, and thrombotic microangiopathy. aHUS, atypical uremic syndrome;

CFB, complement factor B; MAC, membrane attack complex; CFH, complement factor H; CFI, complement factor I; MCP, membrane cofactor protein; THBD, thrombomodulin.

aHUS

- Clinical guidelines for managing atypical hemolytic uremic syndrome (aHUS) emphasize *early treatment with a complement inhibitor*, such as a C5 inhibitor, as the primary therapy, ideally within 24 hours of suspicion.

This is supplemented with ***comprehensive supportive care***, including

✓ blood pressure control

✓ fluid management

✓ anemia correction

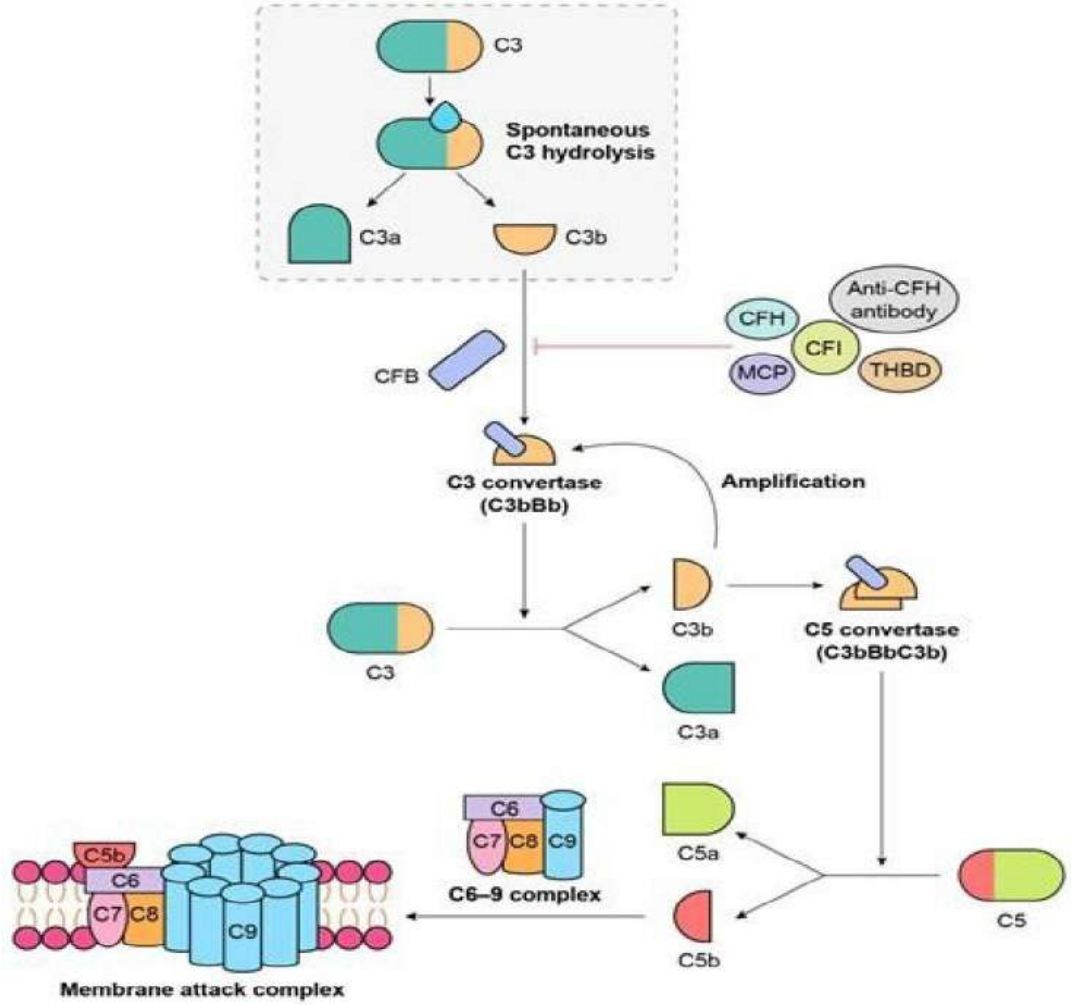
✓ kidney replacement therapy (dialysis) for severe acute kidney injury (AKI)

Plasma therapy is a historical alternative, but C5 inhibitors have largely replaced it due to better outcomes, though it may be used while awaiting complement inhibitor access

aHUS treatment

Primary treatment: Complement inhibitors

- **Initiate C5 inhibitor therapy immediately:** Guidelines strongly recommend starting C5 inhibitors within 24 hours of a clear clinical suspicion of aHUS, particularly in patients with confirmed diagnosis or a family history.
- **Purpose:** This is the first-line treatment to stop the complement-mediated TMA and reduce the need for dialysis and ICU admission.
- **Example:** Eculizumab and ravulizumab are examples of C5 inhibitors used in treatment.
- **Duration:** Treatment duration is individualized but should be maintained for at least 6–12 months, with longer periods potentially necessary for certain patient profiles



aHUS treatment

Terminal complement inhibition with an anti-C5 monoclonal antibody	• Eculizumab – every 2 weeks dosing during maintenance • Ravulizumab – every 2 months dosing during maintenance
Rapid improvement in platelet count, LDH and time dependent improvement in renal function	
Risk of meningococcal infection!	• Vaccination and antibiotics

Rondeau E, et al. ERA EDTA Congress and ASN Kidney Week 2, Legendre et al. NEJM 2013

aHUS treatment

Supportive care

- **Manage kidney function:** Provide prompt initiation of renal replacement therapy (dialysis) for patients with severe AKI, fluid overload, or uremic symptoms.
- **Control blood pressure:** Aggressively manage hypertension with antihypertensive agents.
- **Treat anemia and thrombocytopenia:** Correct anemia with red blood cell transfusions when indicated. Avoid platelet transfusions unless there is bleeding or a necessary procedure.
- **Avoid nephrotoxins:** Minimize or avoid the use of nephrotoxic medications.
- **Prevent infections:** Treat any infections that could trigger a relapse.

Plasma therapy

- **Role:** Before C5 inhibitors became standard, plasma therapy (infusion or exchange) was the primary treatment. It can be used as a bridge to C5 inhibitor therapy if the complement inhibitor is not immediately available.
- **Mechanism:** Plasma exchange removes pathogenic autoantibodies and complement proteins, while plasma infusion provides functional complement regulatory proteins.
- **Transition:** If there is no clinical improvement with plasma therapy, the patient should be transitioned to C5 inhibitor therapy

Guiding principles of this approach are that eculizumab discontinuation is considered if all of the following conditions are met:

(1) no clinical evidence of ongoing thrombotic microangiopathy (platelets <150 × 10^9/L, lactate dehydrogenase > 1.5 times the upper limit of normal, schistocytes on blood smear)

(2) renal function returned to normal or plateaued at a new baseline for at least 3 months

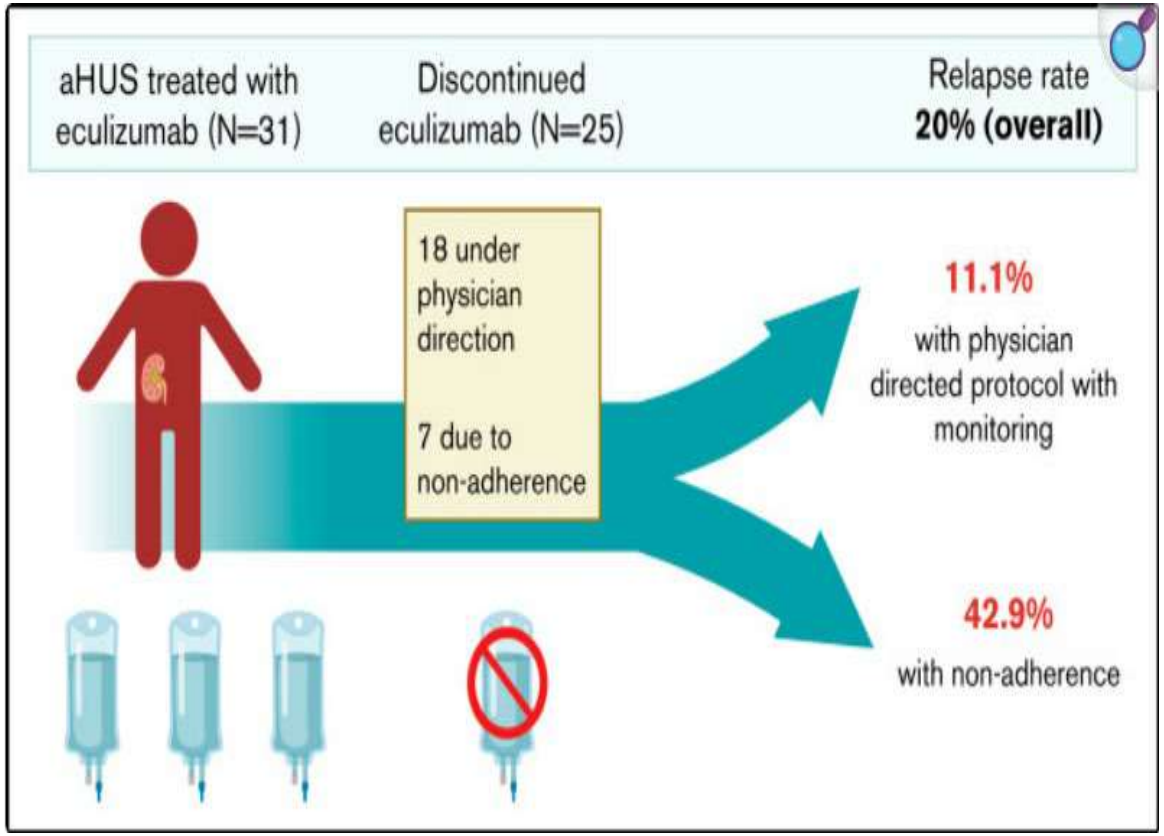
(3) no active trigger (for patients that have an identified trigger) and C reactive protein levels may be obtained when it is unclear whether the trigger has resolved

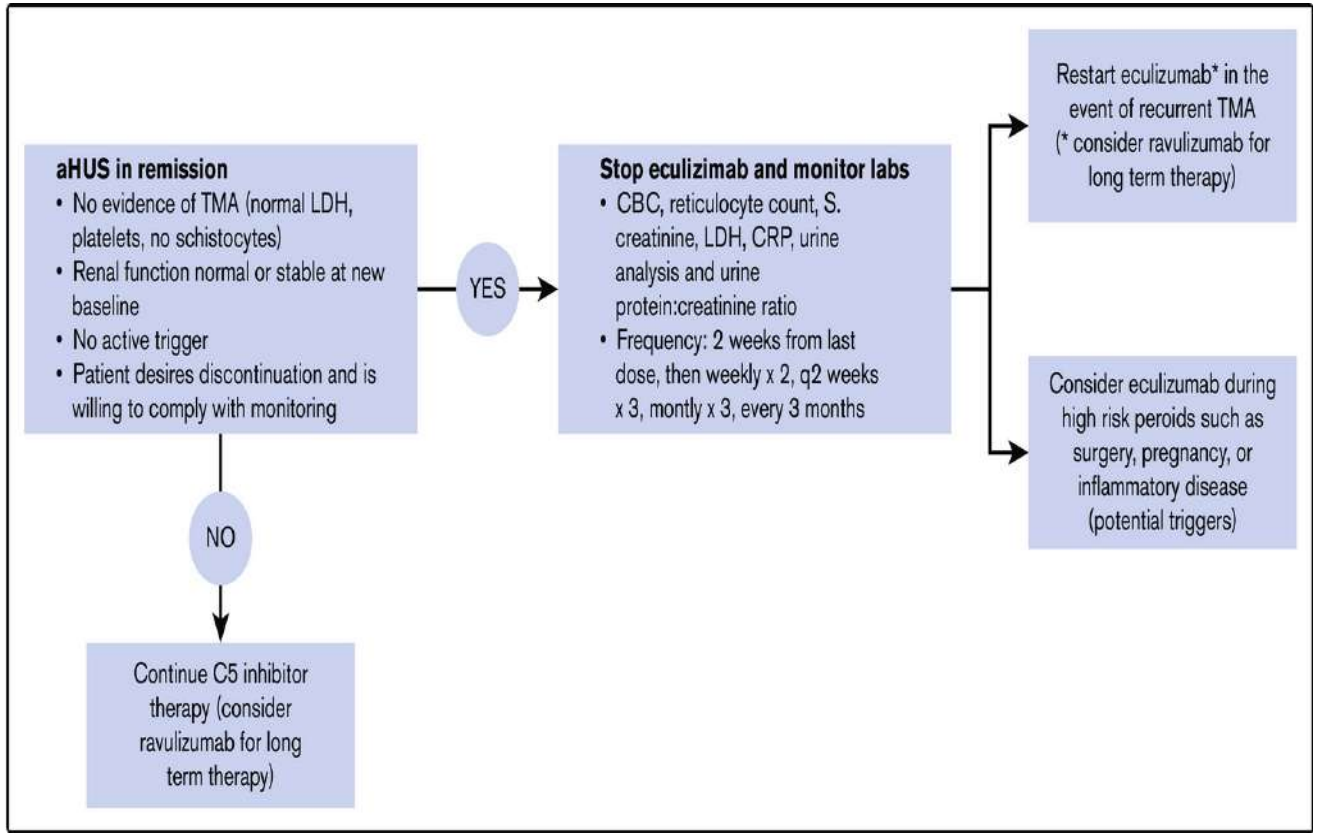
(4) no organ transplantation for aHUS

(5) patient adherent with follow-up and able to make an informed decision regarding the risks vs benefits of discontinuation.

Outcomes of a clinician-directed protocol for discontinuation of complement inhibition therapy in atypical hemolytic uremic syndrome, Chatuverdi et al

Discontinuation of complement inhibition therapy in atypical HUS





Outcomes of a clinician-directed protocol for discontinuation of complement inhibition therapy in atypical hemolytic uremic syndrome, Chatuverdi et al

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice

Therapeutic plasma exchange

A therapeutic procedure in which blood of the patient is passed through a medical device which separates plasma from other components of blood. The plasma is removed and replaced **with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution**.

Plasmapheresis

A procedure in which blood of the patient or the donor is passed through a medical device which separates plasma from other components of blood and the plasma is removed (i.e., less than 15% of

total plasma volume) **without the use of colloid replacement solution**. This procedure is used to collect plasma for blood components or plasma derivatives.

Schwarz J, et al. Journal of Clinical Apheresis 2016

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice

Disease name	TA Modality	Indication	Category
Thrombotic microangiopathy, coagulation mediated	TPE	*THBD* mutation	III
Thrombotic microangiopathy, complement mediated	TPE	Complement factor gene mutations	III
	TPE	Factor H autoantibodies	I
	TPE	MCP mutations	III
Thrombotic microangiopathy, drug associated	TPE	Ticlopidine	I
	TPE	Clopidogrel	III
	TPE	Calcineurin inhibitors	III
	TPE	Gemcitabine	IV
	TPE	Quinine	IV
Thrombotic microangiopathy, hematopoietic stem cell transplantation associated	TPE		III
Thrombotic microangiopathy, Shiga toxin mediated	TPE/IA	Severe neurological symptoms	III
	TPE	Streptococcus pneumoniae	III
	TPE	Absence of severe neurological symptoms	IV
Thrombotic thrombocytopenic purpura	TPE		I

Schwarz J, et al. Journal of Clinical Apheresis 2016

THROMBOTIC THROMBOCYTOPENIC PURPURA:

* RARE BLOOD DISORDER
* INCREASED NUMBER of BLOOD CLOTS in the SMALLEST ARTERIES THROUGHOUT the BODY

SYMPTOMS

- DECREASED PLATELETS
- INCREASED DESTRUCTION of RBCs
- NEUROLOGICAL PROBLEMS

PATHOLOGY

- CAUSE of iTTP UNKNOWN
- OFTEN OCCURS with DEFICIENCY in ADAMTS13 ENZYME
  - breaks down clotting protein von Willebrand factor

CONGENITAL TTP:

- RARER TYPE
- INHERITED in AUTOSOMAL RECESSIVE PATTERN

	T	t
T	TT	Tt
t	Tt	tt

DIAGNOSIS

iTTP:

- LOW ADAMTS13 & ANTI-ADAMTS13 ANTIBODIES

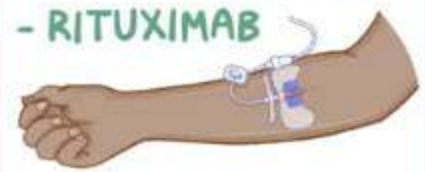
cTTP:

- ABSENCE of ANTI-ADAMTS13 ANTIBODIES

TREATMENT

iTTP:

- PLASMAPHERESIS
- RITUXIMAB

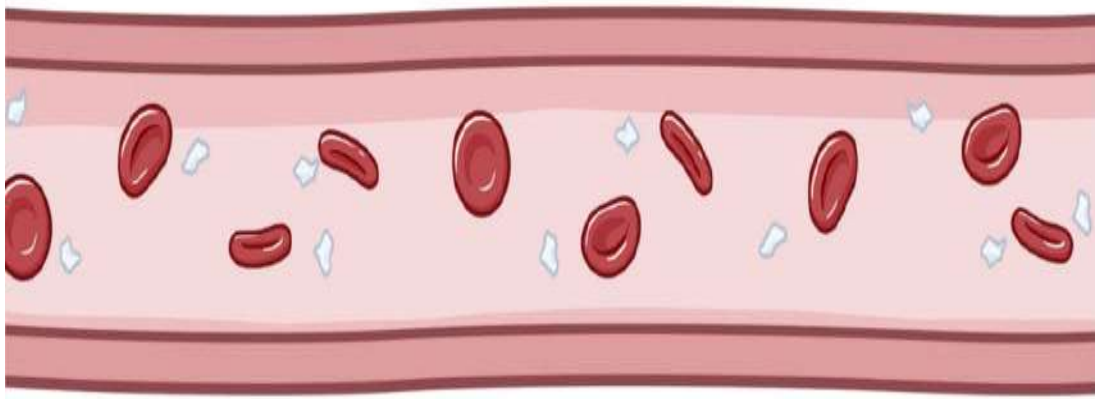


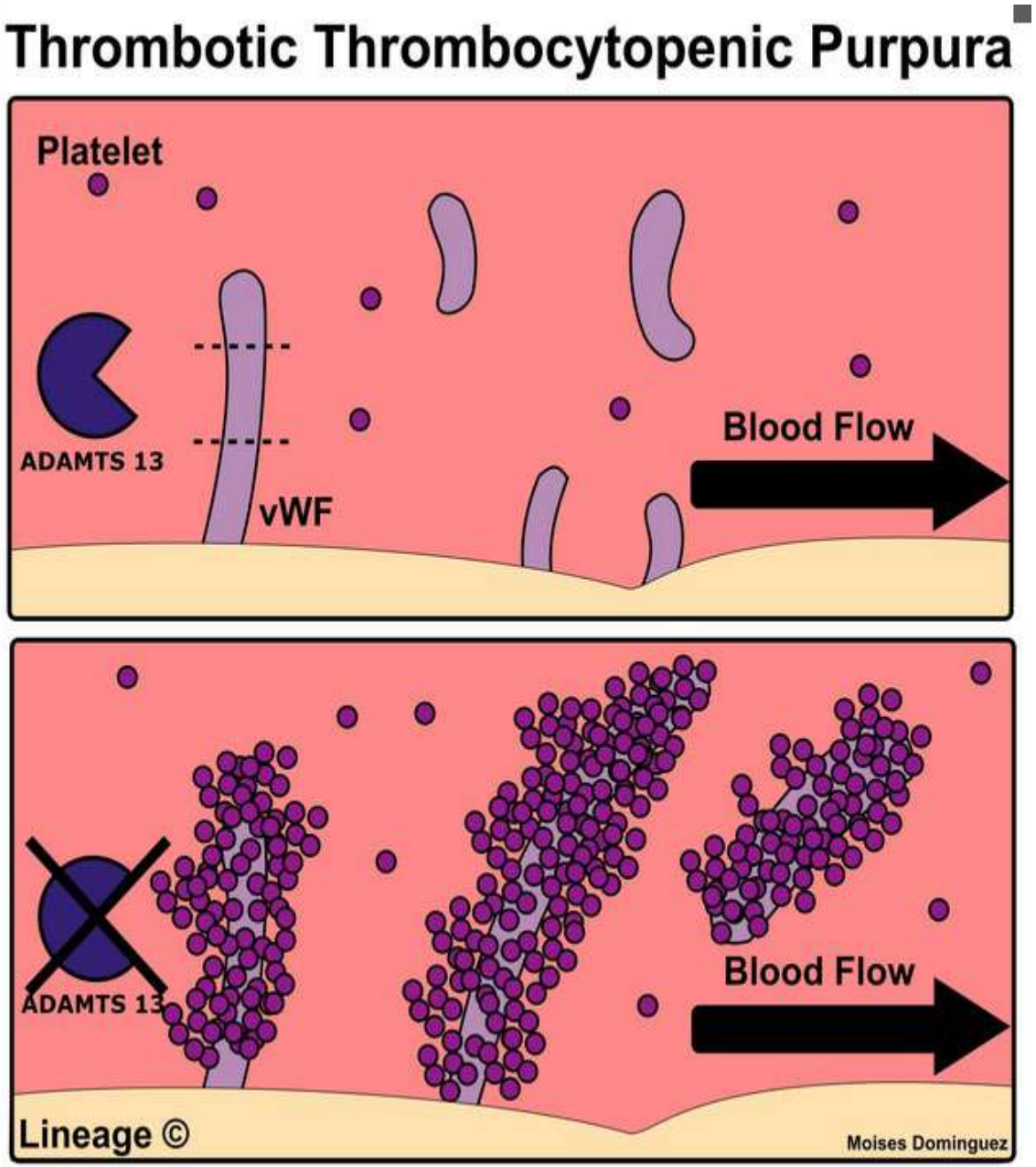
cTTP:

- PLASMA INFUSIONS

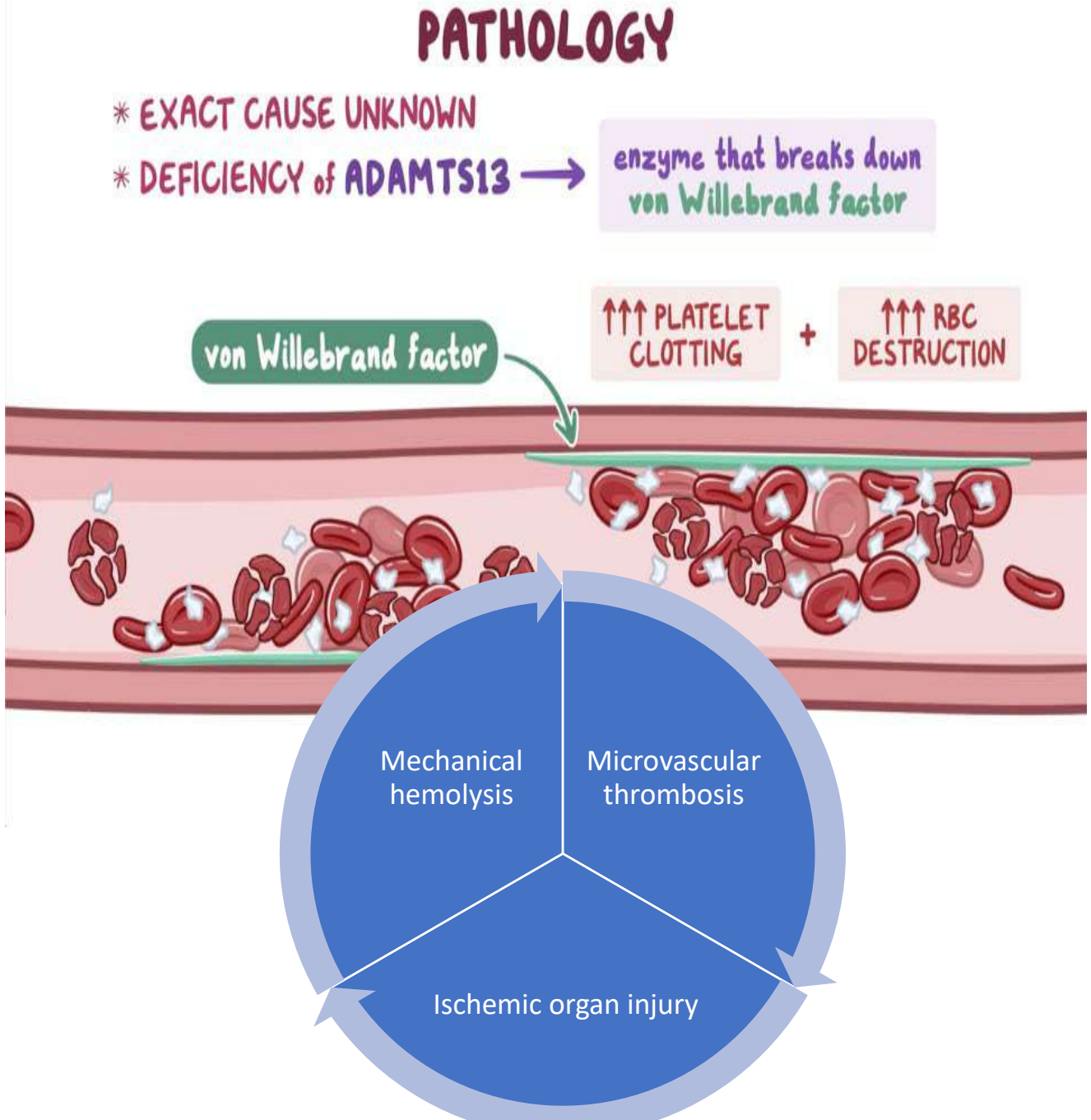
PATHOLOGY

* EXACT CAUSE UNKNOWN
* DEFICIENCY of ADAMTS13 → enzyme that breaks down von Willebrand factor





- iTTP is a thrombotic microangiopathy caused by the autoantibody-mediated absence or severe deficiency ofADAMTS13, a plasma metalloprotease necessary for cleavage of the ultralarge multimers of von Willebrand factor (VWF)
- In the presence of ADAMTS13, the newly synthesized and secreted ultralarge multimers of VWF are cleaved platelet-binding A1 domains hidden.
- In the absence of ADAMTS13, the ultralarge multimers of VWF persist in circulation
- The shear forces of flowing blood cause the ultralarge VWF multimers to unfold, exposing their A1 domains so that they become hyperadhesive for platelets.[3]



DIAGNOSIS

EVALUATE:

* SIGNS & SYMPTOMS

* MEDICAL HISTORY

* PHYSICAL EXAM

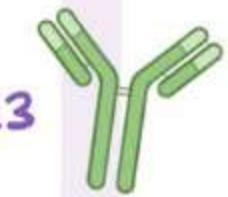
CONFIRM:

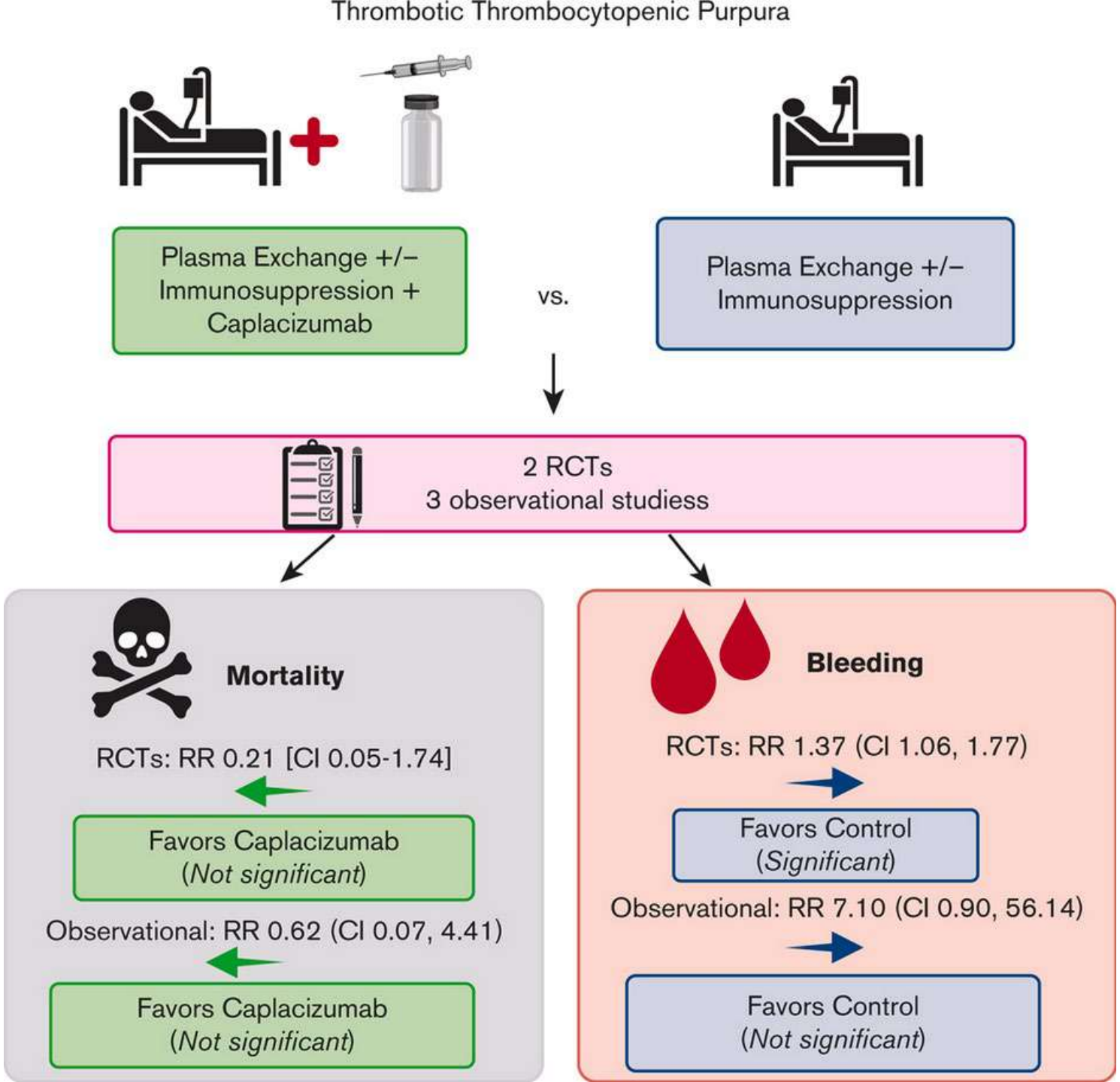
* BLOOD TESTS *

Deficiency of < 10% **ADAMTS13** activity

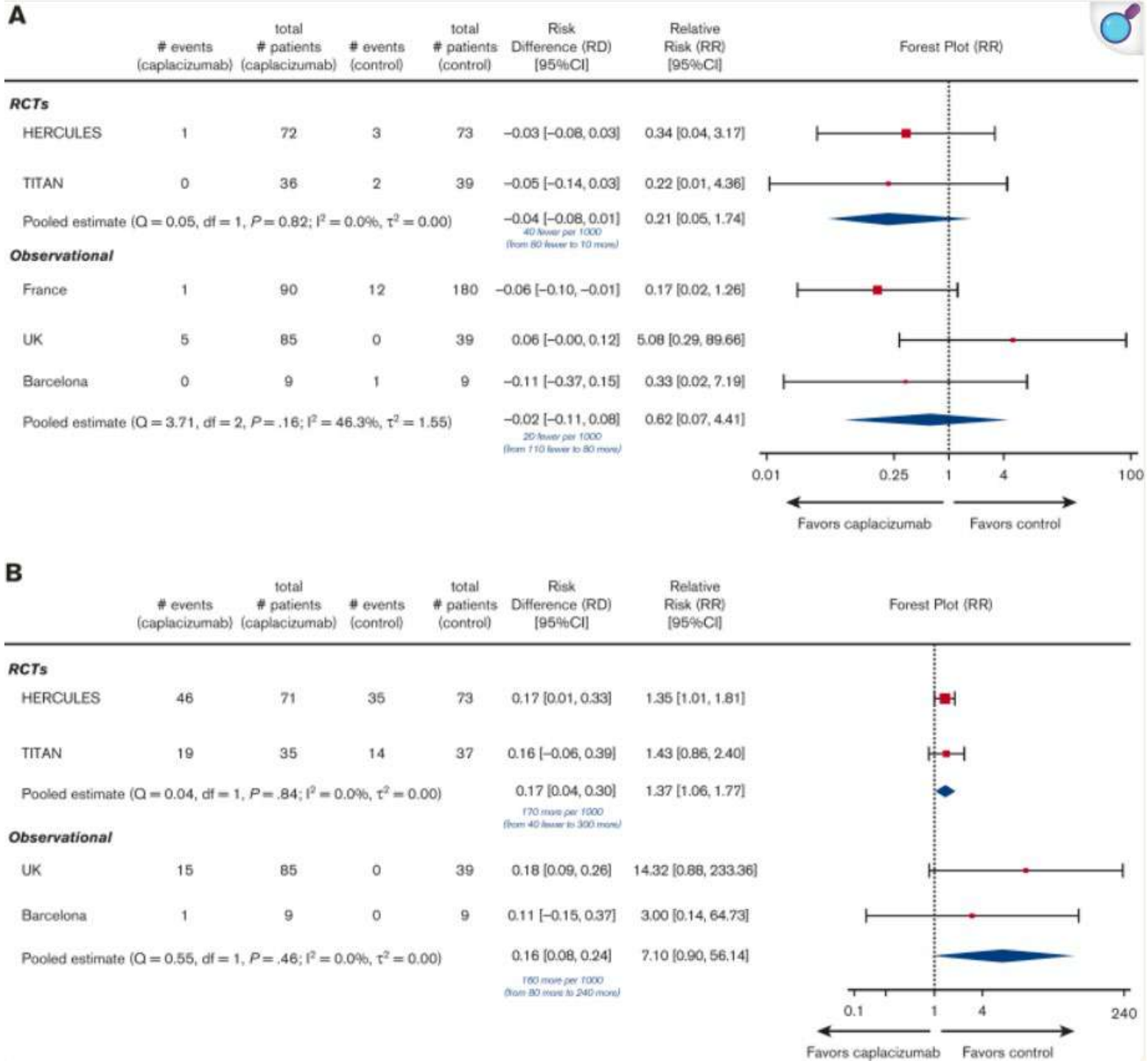
For iTTP:

Presence of **anti-ADAMTS13** antibodies





Adding caplacizumab to standard of care in thrombotic thrombocytopenic purpura: a systematic review and meta-analysis
Mia Djulbegovic



Adding caplacizumab to standard of care in thrombotic thrombocytopenic purpura: a systematic review and meta-analysis
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Secondary outcomes

Binary outcomes	Randomized controlled trials			Observational studies		
	Risk difference (95% CI)	Risk difference interpretation per 1000*	RR (95% CI)	Risk difference (95% CI)	Risk difference interpretation per 1000*	RR (95% CI)
TTP exacerbation	−0.29 (−0.42 to −0.14)†	290 fewer (from 420 fewer to 140 fewer)†	0.16 (0.07-0.47)†	−0.35 (−0.43 to −0.27)†	350 fewer (from 430 fewer to 270 fewer)†	0.10 (0.04-0.42)†
TTP relapse	0.14 (−0.00 to 0.27)	140 more (from equal to 270 more)	3.81 (1.58-14.28)†	0.00 (−0.29 to 0.29)**	equal (from 290 fewer to 290 more)	1.00 (0.07-13.64)**
Refractory TTP	−0.08 (−0.13 to −0.02)†	80 fewer (from 130 fewer to 20 fewer)†	0.11 (0.01-0.81)†	−0.22 (−0.45 to −0.03)†	220 fewer (from 450 fewer to 30 fewer)†	0.12 (0.02-0.61)†
Thrombosis	0.00 (−0.07 to 0.07)	equal (from 70 fewer to 70 more)	1.02 (0.40-2.63)	0.00 (−0.05 to 0.06)	equal (from 50 fewer to 60 more)	1.07 (0.57-2.03)
Major bleeding	0.02 (−0.02 to 0.07)	20 more (from 20 fewer to 70 more)	1.73 (0.39-7.07)	0.00 (−0.19 to 0.19)**	equal (from 190 fewer to 190 more)**	1.00 (0.02-45.13) **
Intracranial bleeding	0.00 (−0.03 to 0.03)	equal (from 30 fewer to 30 more)	1.04 (0.15-7.25)	Not reported		

Continuous outcomes	Mean difference (95% CI)	Mean difference interpretation	Mean difference (95% CI)	Mean difference interpretation
Time to platelet count recovery (d)	−0.66 (−0.90 to −0.43)†	0.66 d fewer (from 0.90 fewer to 0.43 fewer)†	−4.84 (−7.91 to −1.76)†	4.84 d fewer (from 7.91 fewer to 1.76 fewer)†
Hospital LOS (d)	−6.00 (−8.92 to −3.08)†	6 d fewer (from 8.92 fewer to 3.08 fewer)†	−9.06 (−18.96 to 0.84)	9.06 d fewer (from 18.96 fewer to 0.84 fewer)
Duration of TPE (d)	−3.60 (−3.82 to −3.38)†	3.60 d fewer (from 3.82 fewer to 3.38 fewer)†	−6.63 (−11.83 to −1.43)†	6.63 d fewer (from 11.83 fewer to 1.43 fewer)†

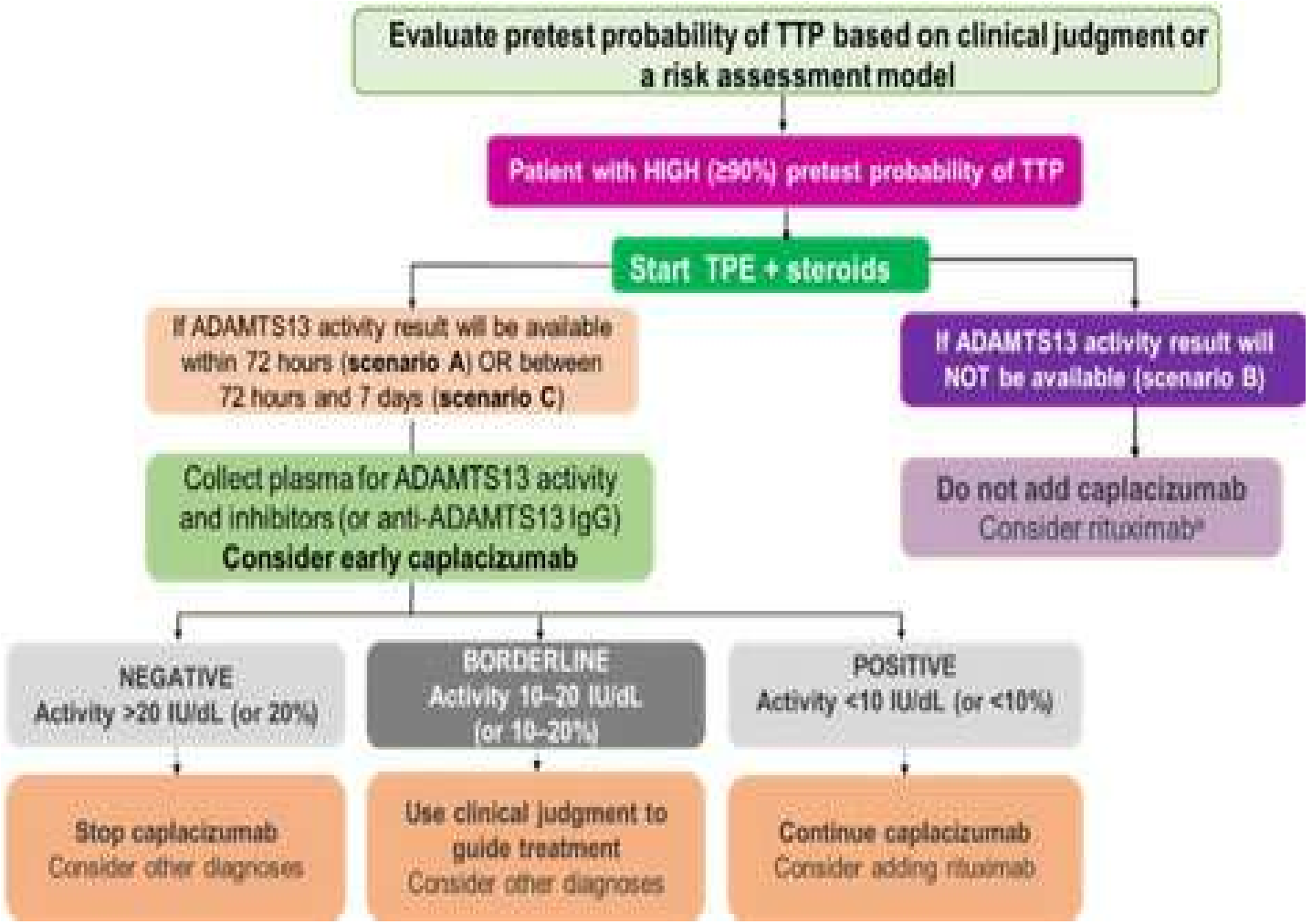
Adding caplacizumab to standard of care in thrombotic thrombocytopenic purpura: a systematic review and meta-analysis
Mia Djulbegovic

In observational studies, bleeding risk was not significantly increased (RR, 7.10; 95% CI, 0.90-56.14).

Addition of caplacizumab was associated with **a significant reduction in refractory iTTP and exacerbation risks** and shortened response time but increased relapse risk. Frontline addition of caplacizumab does not significantly reduce all-cause mortality compared with SOC alone, although it reduces refractory disease risk, **shortens time to response**, and improves exacerbation rates at the expense of increased relapse and bleeding risk.

Adding caplacizumab to standard of care in thrombotic thrombocytopenic purpura: a systematic review and meta-analysis
Mia Djulbegovic

Suggested Diagnostic Strategy: High Pretest Probability of aTTP



- ADAMTS13 testing : ideally in <72 hours; acceptable <7 days
- Plasmic score

Platelet count <30,000/microL

One or more indicators of hemolysis:
Reticulocyte count (percentage) >2.5%; or
Haptoglobin undetectable; or
Indirect bilirubin >2.0 mg/dL [>34 mcmol/L]

No active cancer in the preceding year

No history of solid organ or hematopoietic stem cell transplant

Mean corpuscular volume (MCV) <90 femtoliters

International normalized ratio (INR) <1.5

Creatinine <2.0 mg/dL [<177 mcmol/L]

ISTH Guidelines for the Diagnosis and Management of aTTP (iTTPa)

Revised outcome definitions for iTTP and their clinical implications

Category	Outcome	Definition	Management implications
Response	Clinical response	Sustained platelet count ≥150 × 10^9/L and LDH <1.5 times ULN and no clinical evidence of new or progressive ischemic organ injury.	Preremission implications
Exacerbation	Clinical exacerbation	After a clinical response and before a clinical remission, platelet count decreases to <150 × 10^9/L (with other causes of thrombocytopenia excluded), with or without clinical evidence of new or progressive ischemic organ injury, within 30 d of stopping TPE or anti-VWF therapy	In general, TPE may be discontinued and patients may be discharged from the hospital soon after they achieve a clinical response.
			Persistent severe ADAMTS13 deficiency after a clinical response is associated with an increased risk of clinical exacerbation.
			Immunosuppression (e.g., corticosteroids, rituximab) may be used to induce an ADAMTS13 remission.
			Use of anti-VWF therapy (e.g., caplacizumab) until attainment of ADAMTS13 remission is protective against clinical exacerbation.
Remission	Clinical remission	Sustained clinical response with either no TPE and no anti-VWF therapy for ≥30 d or with attainment of ADAMTS13 remission (partial or complete), whichever occurs first.	Postremission implications
	Partial ADAMTS13 remission	ADAMTS13 activity ≥20% to <LLN.*,†	ADAMTS13 remission (partial or complete) is always accompanied by clinical remission.
	Complete ADAMTS13 remission	ADAMTS13 activity ≥LLN.	However, clinical remission may occur with or without an ADAMTS13 remission.
Relapse	Clinical relapse	After a clinical remission, platelet count decreases to <150 × 10^9/L (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury. A clinical relapse must be confirmed by documentation of severe ADAMTS13 deficiency.	Patients in clinical remission who do not achieve an ADAMTS13 remission or who experience an ADAMTS13 relapse are at increased risk of clinical relapse.
	ADAMTS13 relapse	After an ADAMTS13 remission (partial or complete), the ADAMTS13 level decreases to <20%.*,†	In such patients, preemptive immunosuppression (e.g., rituximab) may be used to attain an ADAMTS13 remission, thereby reducing the risk of clinical relapse.

Adding caplacizumab to standard of care in thrombotic thrombocytopenic purpura: a systematic review and meta-analysis
Mia Djulbegovic

Novel aptamer to von Willebrand factor A1 domain (TAGX-0004) shows total inhibition of thrombus formation superior to ARC1779 and comparable to caplacizumab. Haematologica. 2020

The development and characterization of a long acting anti-thrombotic von Willebrand factor (VWF) aptamer. J Thromb Haemost. 2020

- The primary efficacy and safety outcomes

✓all-cause mortality

✓treatment-emergent bleeding

- Secondary outcomes

✓exacerbation

✓Relapse

✓refractory iTTP

✓time to response.

Drug-induced thrombotic microangiopathy (DITMA)

- 10%–13% of all thrombotic microangiopathy (TMA) cases
- 20%–30% of secondary TMAs, just behind pregnancy-related and infection-related f
- complement genetic pathological mutations are rarely involved in DITMA (2/122, 1.6%) forms
- a treatment approach for DITMA, ***drug withdrawal*** and the role of therapeutic plasma-exchange (***TPE***), ***rituximab***, and ***anti-complementary therapy***.
- the mechanism of endothelial damage induced by different drugs is heterogeneous and it can involve ***direct endothelial damage***, ***alteration of ADAMTS-13 activity*** or ***deregulation of different endothelial biological pathways*** (such as VEGF and NF-kB pathways)

Drug-induced thrombotic microangiopathy: An updated review of causative drugs, pathophysiology, and management. T. Mazzierli

Drug-induced thrombotic microangiopathy (DITMA)

Calcineurin inhibitors (CNIs) can induce thrombotic microangiopathy (TMA), especially tacrolimus.

Proteasome inhibitors can also induce

Chemotherapeutic drugs	Targeted cancer drugs	Immunosuppressive drugs	Antibiotics and antivirals	Other drugs
Daunorubicin	Alemtuzumab	Adalimumab	Ciprofloxacin	Onasemnogene abeparvovec
Docetaxel	Moxetumomab pasudotox	Certolizumab pegol	Levofloxacin	Clopidogrel
Gemcitabine	Imatinib mesylate	Cyclosporine A	Metronidazole	Bupropion
Lomustine	Lenvatinib	Tacrolimus	Penicillin	Valproic acid
Mitomycin C	Nintedanib	Interferon (alpha, beta,polycarboxylate)	Rifampicin	Estrogen/ Progesterone
Oxaliplatin	Palbociclib	Leflunomide	Sulfisoxazole	Hydroxychloroqu
Pegylated liposomaldoxorubicin	Pazopanib	Muromonab-CD3 (OKT3)	Trimethoprim-sulfamethoxazole	Oxycodone hydrochloride ER
Pentostatin	Regorafenib	Sirolimus	Famciclovir	Oxymorphone ER
Tamoxifen	Sunitinib	Everolimus	Valacyclovir	Quetiapine
Trastuzumab	Bevacizumab			Quinine
Vincristine	Ramucirumab			Simvastatin
Lomustine				
Bortezomib				Illicit drugs and toxic substances
Carfilzomib				Cocaine
Ixazomib				Ecstasy
				Trielina

Thrombotic Microangiopathy Associated with Calcineurin Inhibitors: A Real-World Analysis of Postmarketing Surveillance Data X. Yu et al

Drug-induced thrombotic microangiopathy: An updated review of causative drugs, pathophysiology, and management. T. Mazzierli

Transplant-associated thrombotic microangiopathy

- Severe complication post transplant
- High mortality rate 50-75%
- Endothelial dysfunction due to multiple triggers
- Outstanding questions regarding pathophysiology, diagnosis, treatment options

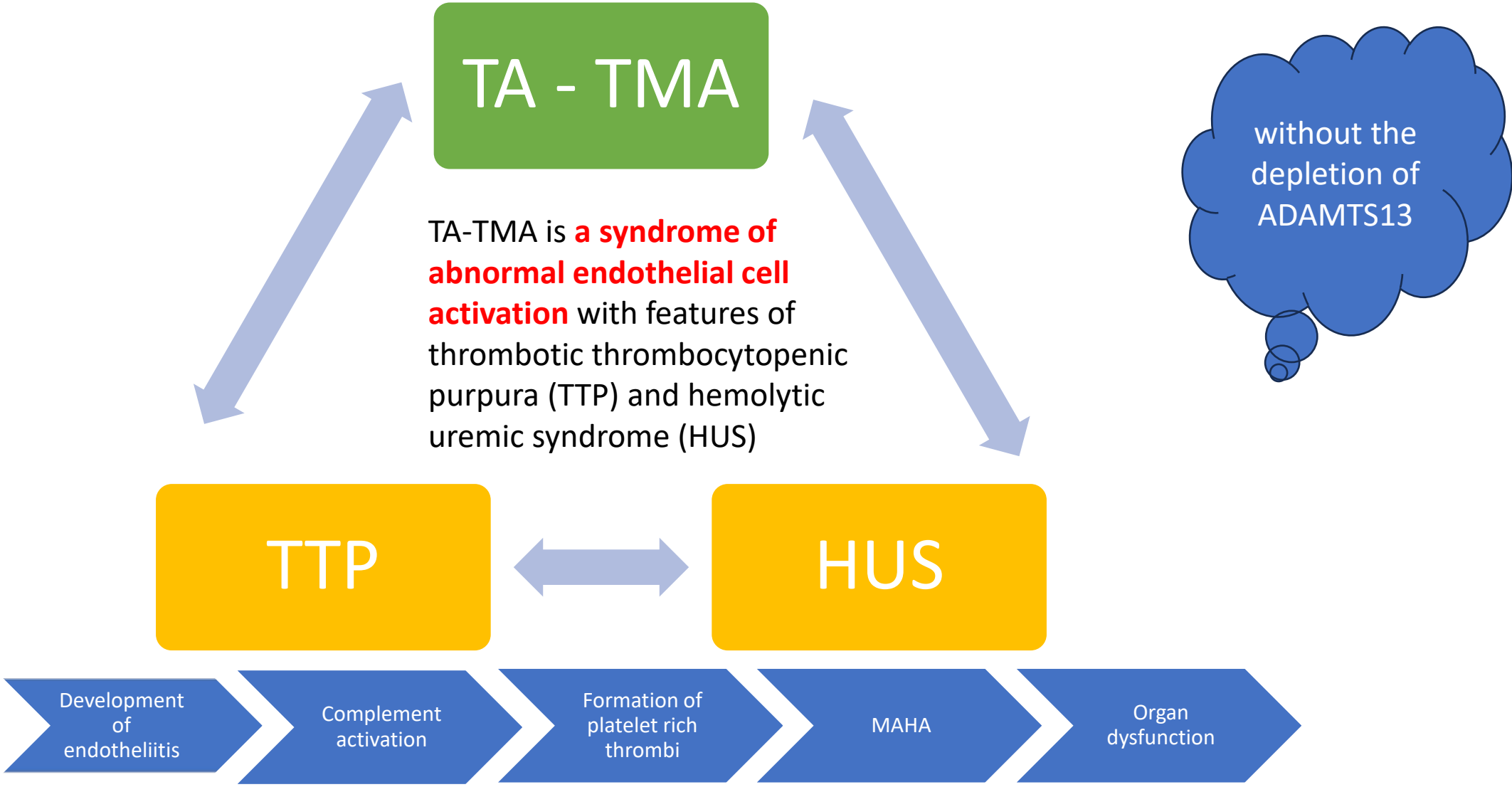
Gavriilaki E et al EBMT 2017

Transplant-associated thrombotic microangiopathy

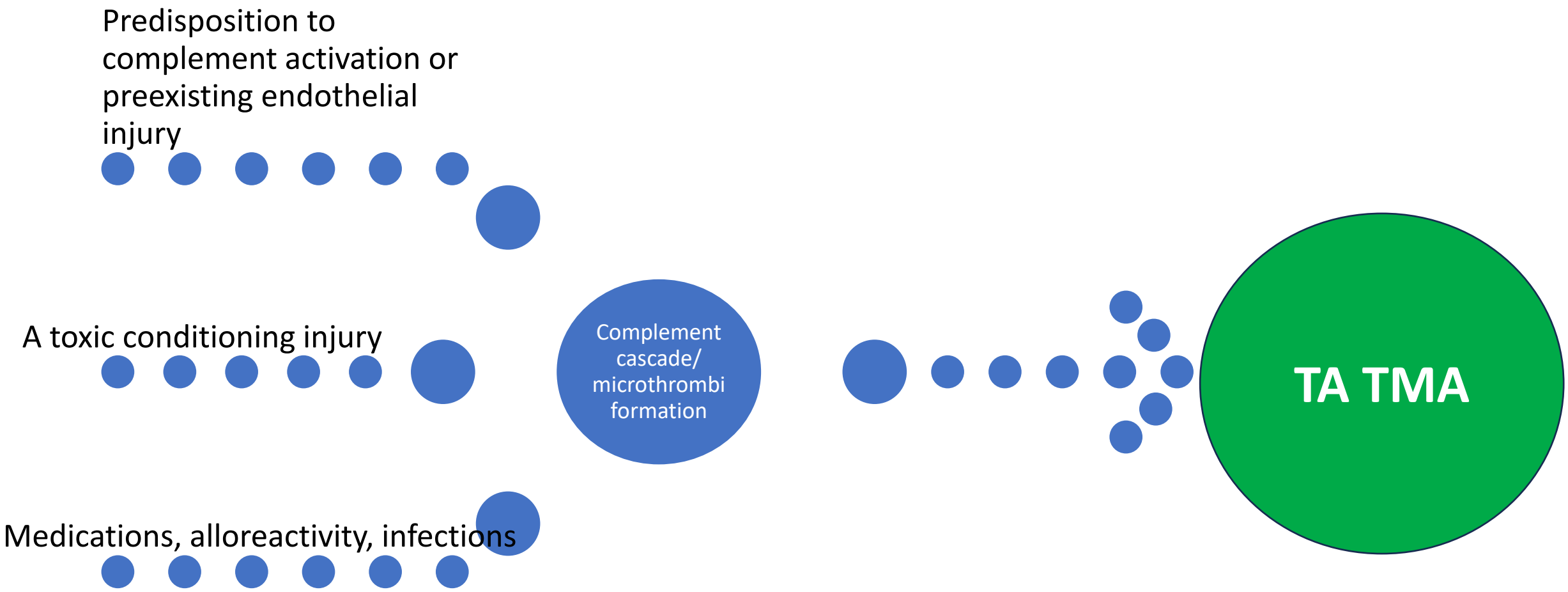
Clinical or laboratory marker	CTN-TMA [19]	IWG-TMA [71]	City of Hope (COH)[f] [76]	Overall-TMA, Cho et al. [50]	Joint Study Group, Uderzo et al. [73]	TA-TMA by Jodele et al.[g] [15]
Schistocytosis	≥2/HPF	>4% (8/ HPF)	Yes	≥2/HPF	>1–2/HPH	Yes
Negative direct and indirect Coombs test	Yes	–	–	Yes	Yes	–
Concurrent renal and/or neurologic dysfunction without other explanations[a]	Yes	–	SCr > 1.5 × baseline	–	Proteinuria and hypertension	Proteinuria and hypertension
Decrease in serum haptoglobin	–	Yes	–	Yes	–	–
De novo thrombocytopenia[b]	–	Yes	Yes	Yes	Yes	Yes
De novo anemia[c]	–	Yes	–	Yes	Yes	Yes
**Increase in serum LDH*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
**Hypertension[d]*	–	–	–	–	*Yes*	*Yes*
**■Proteinuria[e]*	–	–	–	–	*Yes*	*Yes*
■Terminal complement activation (Elevated sC5b-9)	–	–	–	–	*Yes*	*Yes*

Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis. Young et al

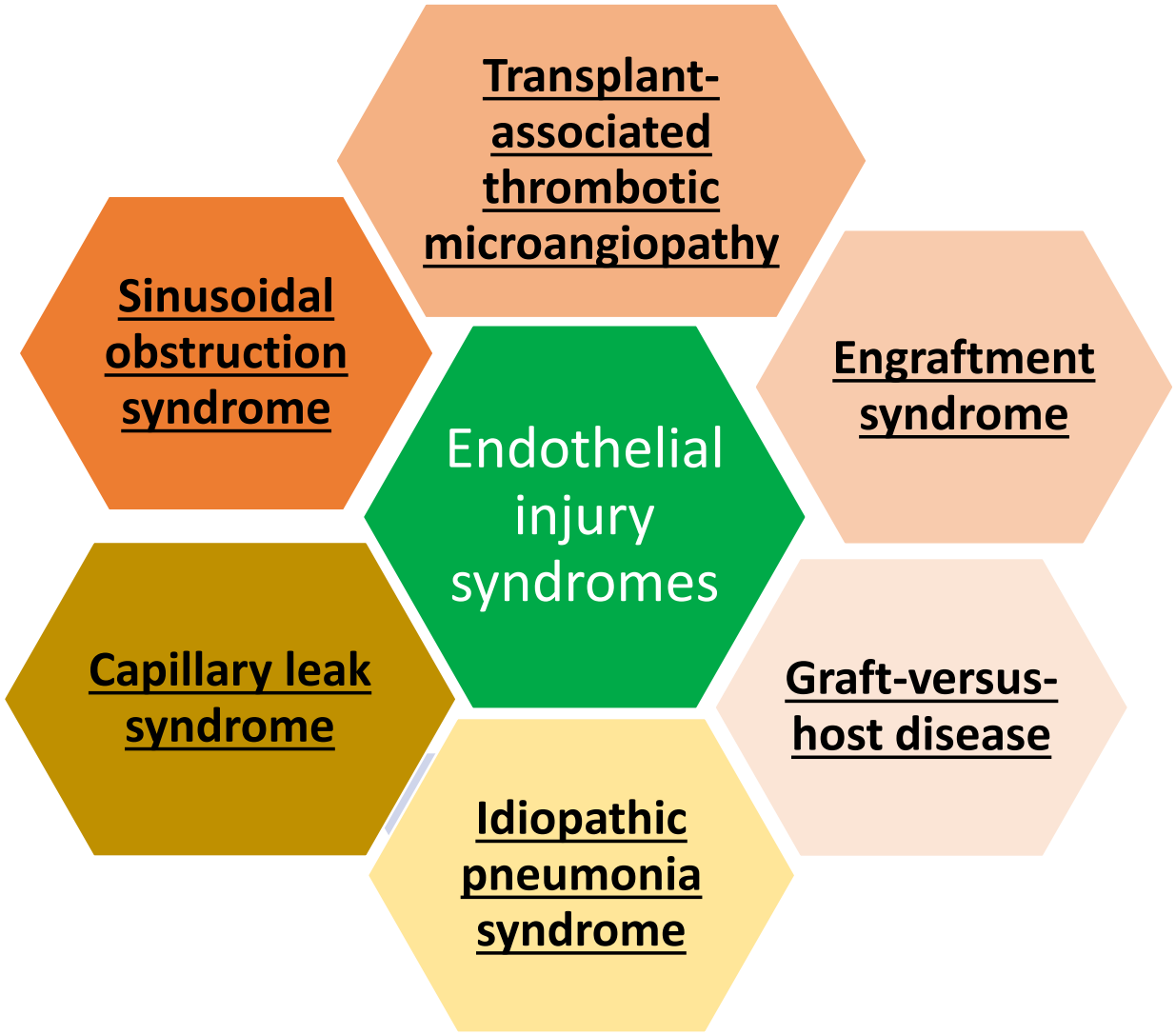
Transplant-associated thrombotic microangiopathy- Pathophysiology



Transplant-associated thrombotic microangiopathy- Pathophysiology



Endothelial injury syndromes in allogenic Stamm cell Transplantation



HSCT-TMA Harmonization Panel: Diagnostic criteria

Modified Jodele criteria for the diagnosis of HSCT-TMA based on Delphi consensus recommendations[1]	
Biopsy-proven disease (kidney or GI) or	
Clinical criteria: must meet ≥4 of the following 7 criteria within 14 days at 2 consecutive time points	
Anaemia[a]	Defined as one of the following: 1. Failure to achieve transfusion independence for pRBCs despite evidence of neutrophil engraftment 2. Hemoglobin decline from patient's baseline by 1 g/dL 3. New onset of transfusion dependence Rule out other causes of anaemia, such as AIHI and PRCA
Thrombocytopenia[a]	Defined as one of the following: 1. Failure to achieve platelet engraftment 2. Higher than expected platelet transfusion needs 3. Refractoriness to platelet transfusions 4. ≥50% reduction in baseline platelet count after full platelet engraftment
Elevated LDH	>ULN for age
Schistocytes	Present
Hypertension	>99th percentile for age (<18 yr), or systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg (≥18 yr)
Elevated sC5b-9	≥ULN
Proteinuria	≥1 mg/mg rUPCR

[a]Clarification from published Jodele et al. criteria.[2] AIHI, autoimmune haemolytic anaemia; BP, blood pressure; GI, gastrointestinal; HSCT-TMA, haematopoetic stem cell transplant-associated thrombotic microangiopathy; PRCA, pure red cell aplasia; pRBC, packed red blood cell; rUPCR, random urine protein to creatine ratio; ULN, upper limit of normal.

1. Schoettler ML *et al. Transplant Cell Ther.* 2023;29:151–63; 2. Jodele S *et al. Blood.* 2014;124:645–53.

HSCT-TMA Harmonization Panel: Risk stratifications and Multi-organ Dysfuction

HSCT-TMA risk stratification

Standard-risk TMA	High-risk TMA
Peak LDH <2 × ULN	Peak LDH >2× ULN[a]
Spot rUPCR <1 mg/mg	Spot rUPCR ≥1 mg/mg
KDIGO stage 1 AKI	Any organ dysfunction developing in the setting of TMA except KDIGO stage 1 AKI
Normal sC5b-9	Elevated sC5b-9 (>ULN)
	Concurrent acute GVHD grade 2–4
	Concurrent systemic infection (bacterial or viral)[a]

International consensus risk stratification is a modification of Jodele et al.[2]

Definitions of multi-organ dysfunction in HSCT-TMA

Organ	Manifestations
Renal	≥50% reduction in GFR from pre-HSCT conditioning value calculated by serum creatinine or cystatin-C or increase in serum creatinine ≥2× baseline
Pulmonary	Any need for positive-pressure ventilation (non-invasive or invasive) for ≥24 hours in the absence of definite aetiology (i.e. adenovirus pneumonia, fluid overload, or severe sepsis), diffuse alveolar haemorrhage
Cardiovascular	Pulmonary hypertension diagnosed by a cardiologist using cardiac catheterization, or pulmonary hypertension diagnostic criteria on echocardiography
Serositis	Clinically significant serositis (pleural or pericardial effusions or ascites) requiring medical therapy (i.e. diuretics) or drainage in the absence of other causes (e.g. VOD/SOS, congestive heart failure)
Central nervous system	Confusion, altered mental status, seizures with or without imaging evidence of posterior reversible encephalopathy syndrome
GI	GI bleeding and/or intestinal strictures requiring medical or surgical interventions

Multi-organ dysfunction as defined by Jodele et al.[2]

[a]Additional risk factor. AKI, acute kidney injury; GFR, glomerular filtration rate; GI, gastrointestinal; GVHD, graft-versus-host-disease; HSCT-TMA, haematopoetic stem cell transplant-associated thrombotic microangiopathy; KDIGO, kidney disease improvign global outcomes; LDH, lactate dehydrogenase; ULN, upper limit of normal; rUPCR, random urine protein to creatine ratio; TMA, thrombotic microangiopathy; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

1. Schoettler ML *et al. Transplant Cell Ther.* 2023;29:151–63; 2. Jodele S *et al. Blood Rev.* 2015;29:191–204.

Ongoing clinical trials in HSCT-TMA

Intervention	Target	ClinicalTrials.gov identifier	Study phase	Study status*	Sponsor
Narsoplimab	MASP-2	NCT05855083[1]	Phase 2	Recruiting	Omeros
Ravulizumab	C5	NCT04543591[2]	Phase 3	Recruiting	Alexion Pharmaceuticals
		NCT04557735[3]	Phase 3	Recruiting	Alexion Pharmaceuticals
Nomacopan (Coversin)	C5 and LTB4 inhibition	NCT04784455[4]	Phase 3	Recruiting	AKARI Therapeutics
Pegcetacoplan	C3	NCT05148299[5]	Phase 2	Recruiting	**Sponsor**: Swedish Orphan Biovitrum **Collaborator**: Apellis Pharmaceuticals, Inc.

*Correct as of February 2024.

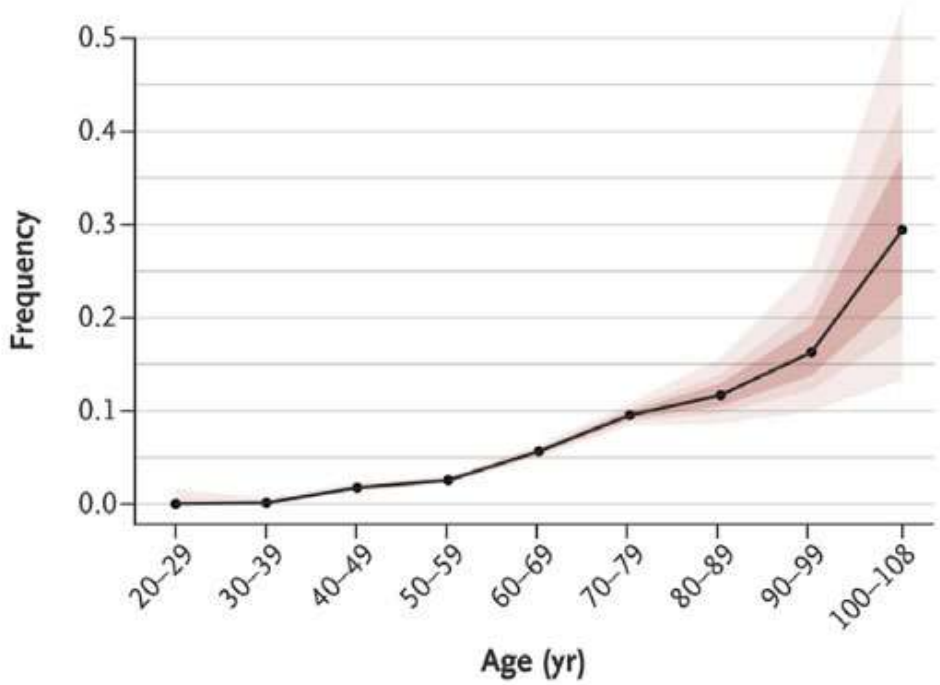
HSCT-TMA, haematopoetic stem cell transplant-associated thrombotic microangiopathy; LTB4, leukotrien B4; MASP-2, mannan-binding lectin serine protease 2.
1. ClinicalTrials.gov. URL: https://classic.clinicaltrials.gov/ct2/show/NCT05855083 (accessed 8 February 2024); 2. ClinicalTrials.gov. URL: https://clinicaltrials.gov/study/NCT04543591 (accessed 8 February 2024); 3. ClinicalTrials.gov. URL: https://clinicaltrials.gov/study/NCT04557735?term=NCT04557735&rank=1 (accessed 8 February 2024); 4. ClinicalTrials.gov. URL: https://clinicaltrials.gov/search?term=NCT04784455 (accessed 8 February 2024); 5. ClinicalTrials.gov. URL: https://clinicaltrials.gov/study/NCT05148299?term=NCT05148299&rank=1 (accessed 8 February 2024).

Clonal Hematopoesis and endothelial injury

Clonal hematopoiesis is defined as

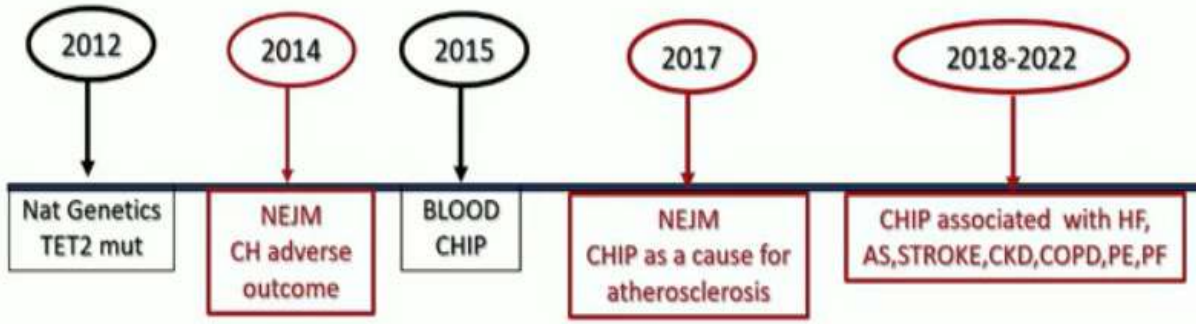
the presence of clonally expanded blood cells

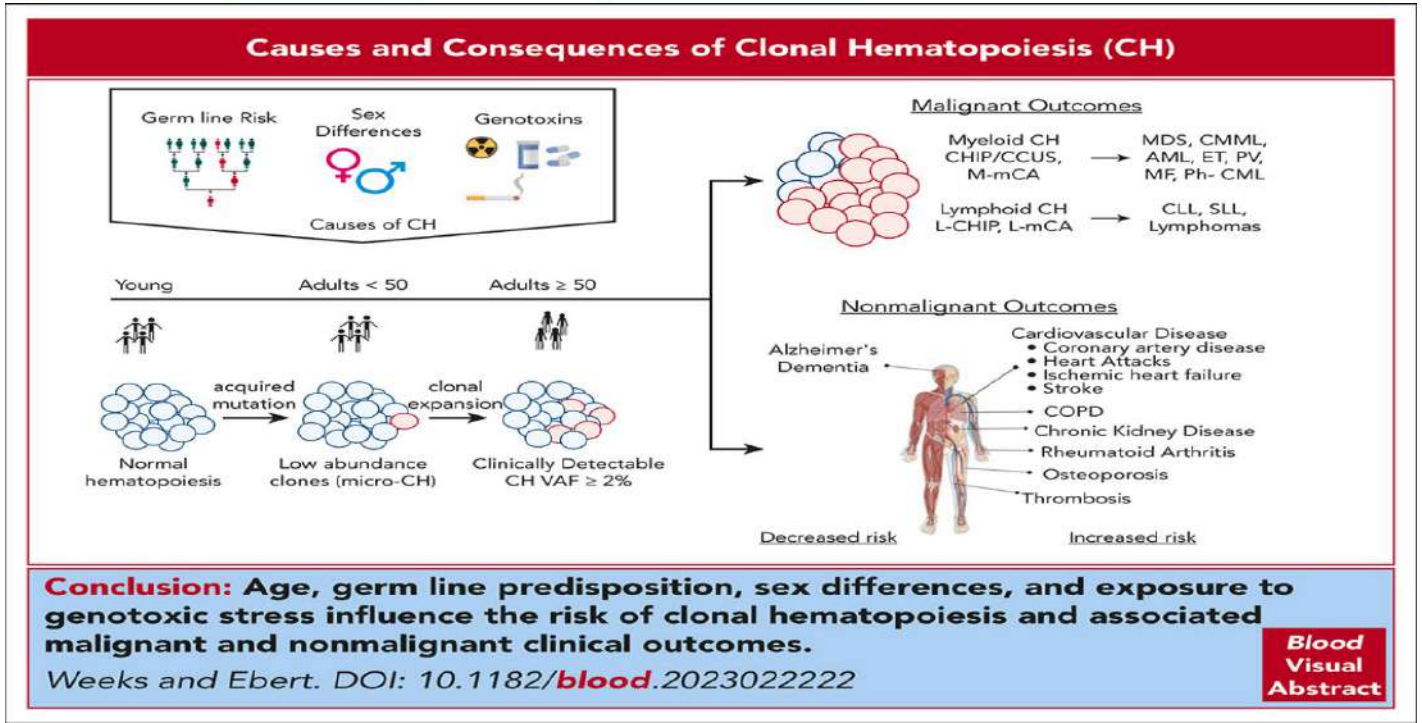
without the evidence of hematological malignancy



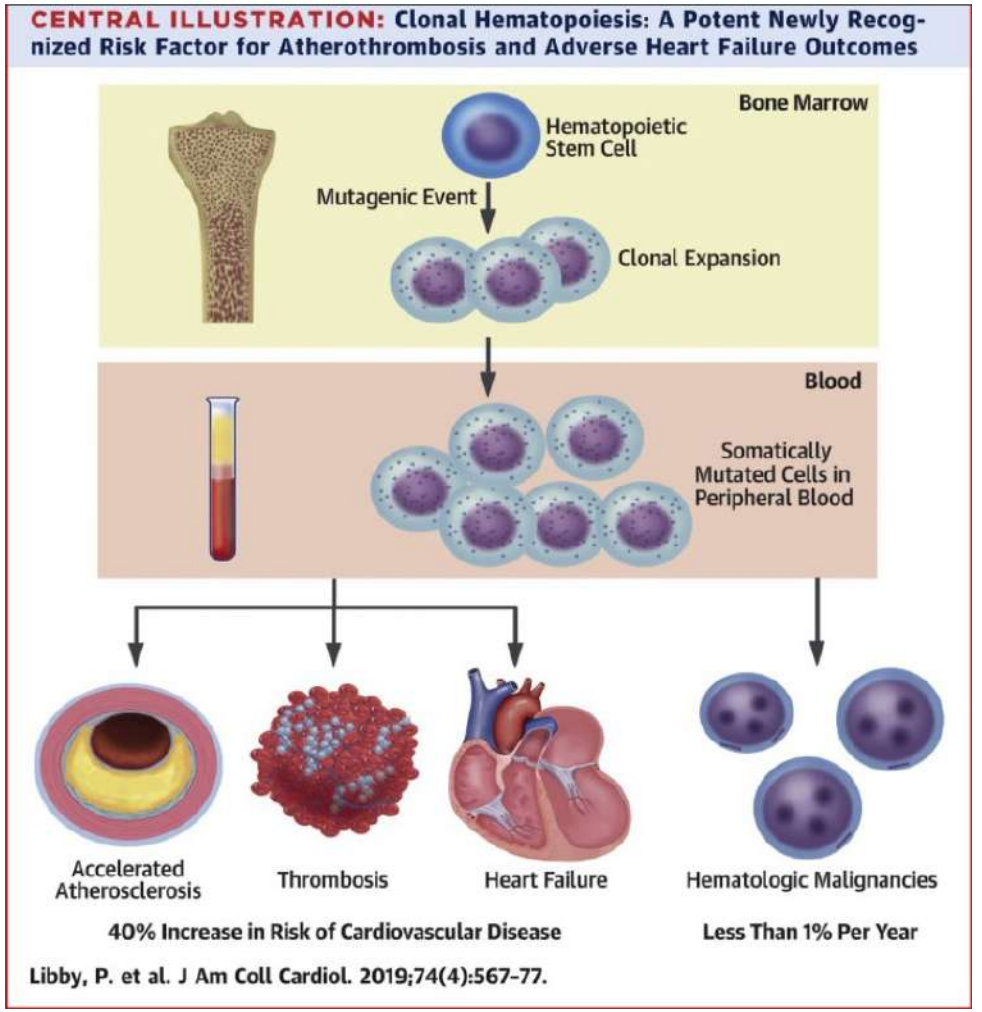
No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

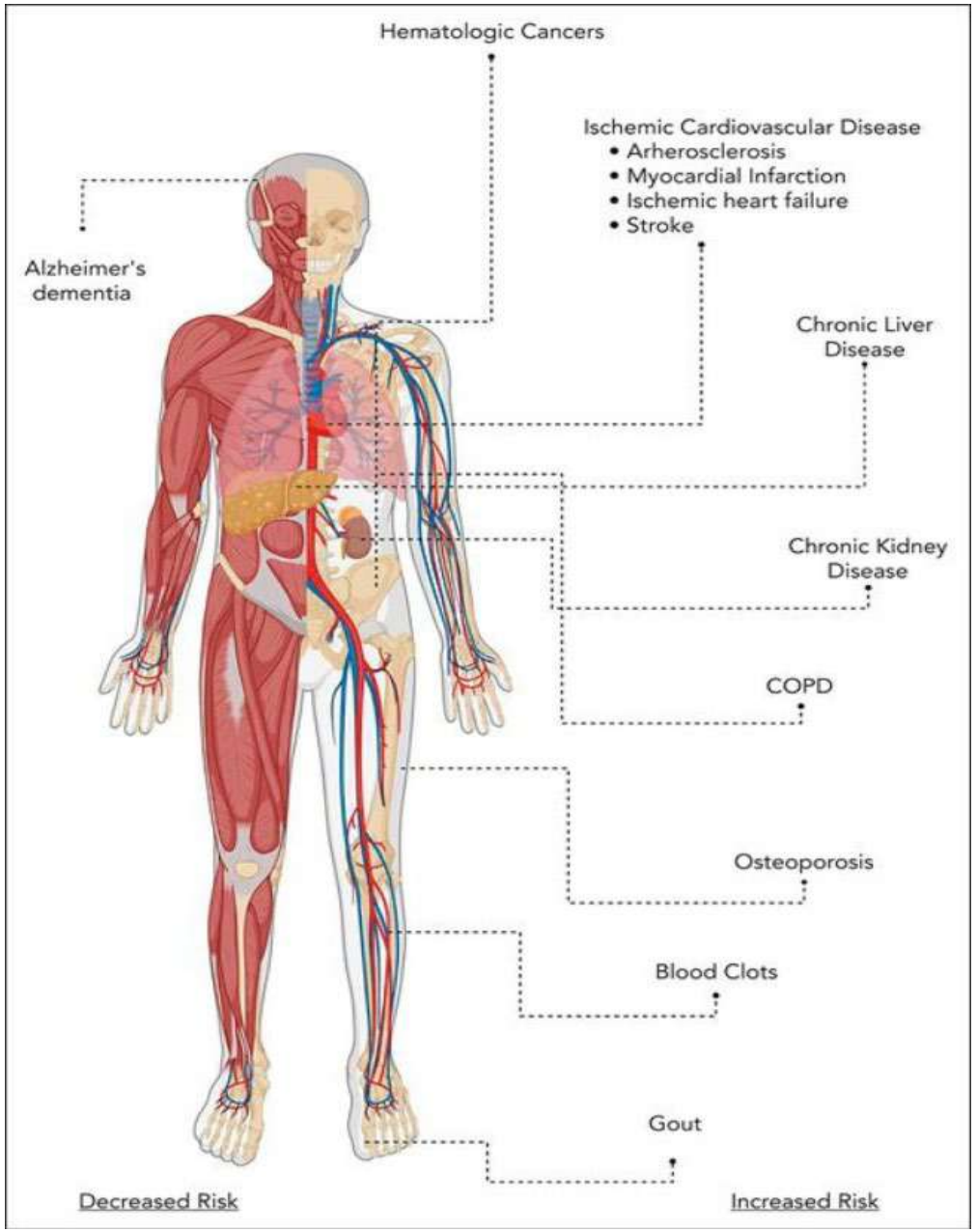
Clonal hematopoiesis: Time line…





CHIP: Increased incidence and more aggressive phenotypes of select age-related nonmalignant diseases





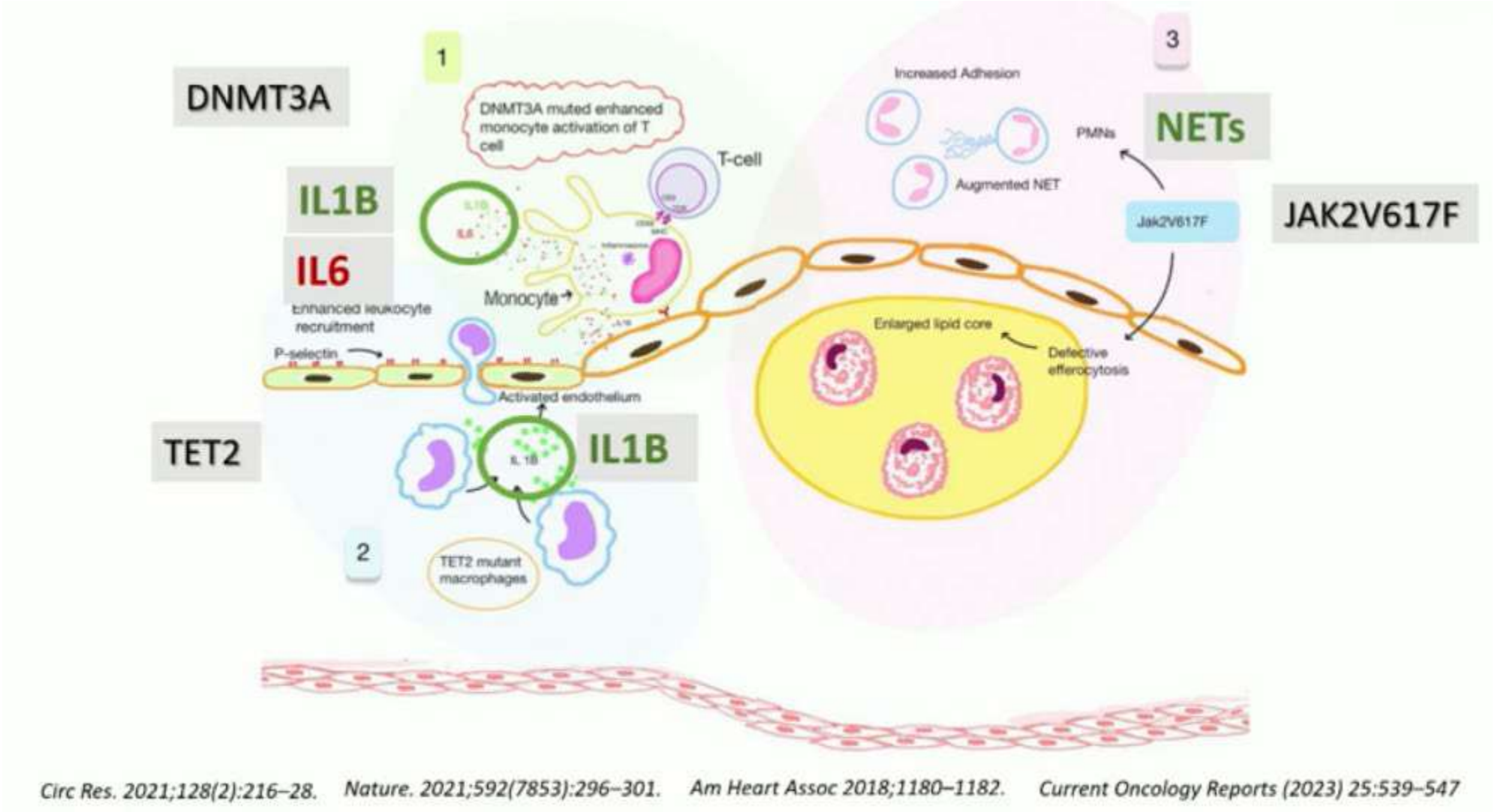
e.g. chronic liver disease

- *JAK2*-mutant CH
- *TET2*-mutant CH

A higher incidence of gout in CHIP/CCUS is driven by the exaggerated IL-1β signaling in response to urate crystal exposure in *Tet2*-deficient compared with in *Tet2*-proficient animals

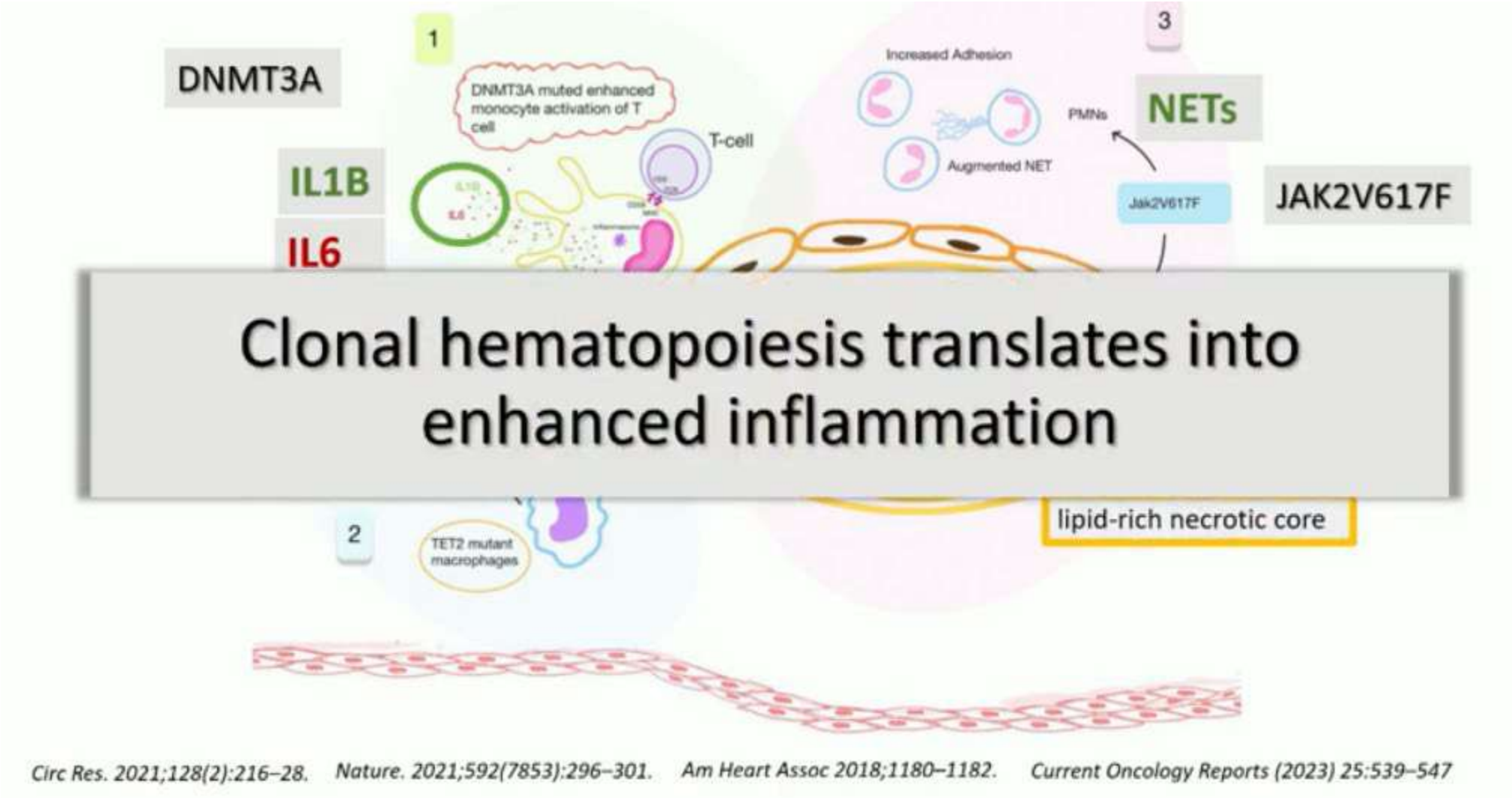
Causes and consequences of clonal hematopoiesis. Lachelle D. Weeks, Benjamin L. Ebert

CHIP: Development of atherosclerosis



Circ Res. 2021;128(2):216–28. *Nature. 2021;592(7853):296–301.* *Am Heart Assoc 2018;1180–1182.* *Current Oncology Reports (2023) 25:539–547*

CHIP: Development of atherosclerosis



Circ Res. 2021;128(2):216–28. *Nature. 2021;592(7853):296–301.* *Am Heart Assoc 2018;1180–1182.* *Current Oncology Reports (2023) 25:539–547*

A hematologist will focus on specific laboratory findings to diagnose TMA and differentiate its causes:

- **Complete Blood Count:** Reveals low hemoglobin (anemia) and low platelet count.
- **Peripheral Blood Smear:** The hallmark is the presence of fragmented red blood cells called **schistocytes**.

New medicines for thrombotic angiopathy (TMA) include **caplacizumab** for acute TTP, which speeds up remission by preventing platelet clumping. For other types of TMA, new and emerging treatments target the complement system, such as **ravulizumab** (a long-acting eculizumab), and experimental therapies like **narsoplimab** for certain types of TMA are under review. Additionally, **rituximab** can be used to prevent relapses in some cases

- Thrombotic angiopathy in clonal hematopoiesis (CH) is a serious complication where the presence of CH increases the risk of developing a thrombotic microangiopathy (TMA) syndrome.
- This occurs because certain mutations associated with CH, particularly those in the *JAK2* gene, are linked to a higher risk of thrombosis.

Increased thrombotic risk → **Endothelial damage** → **TMA as a downstream effect**

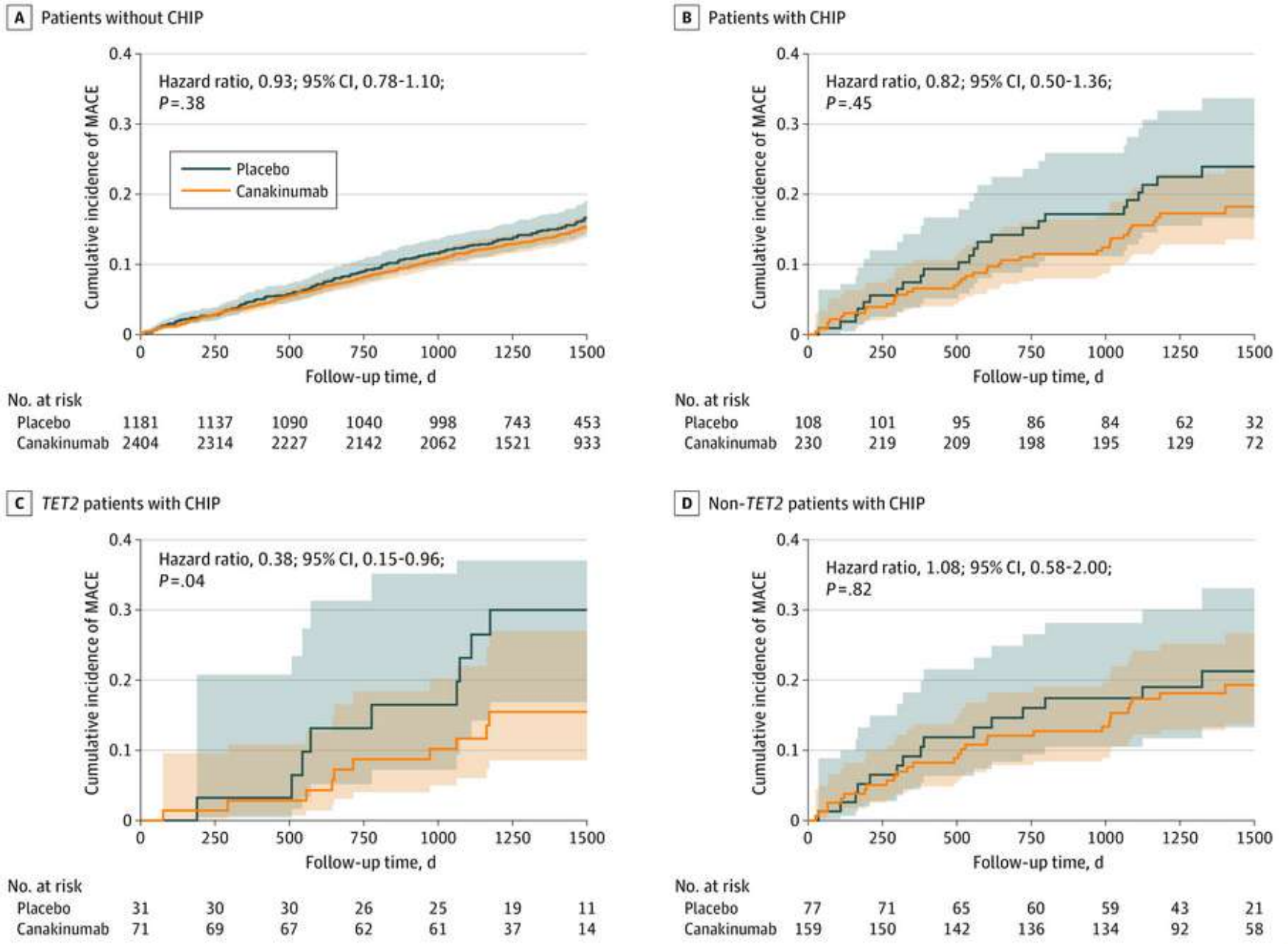

THE
END

TET2-Driven Clonal Hematopoiesis and Response to Canakinumab

An Exploratory Analysis of the CANTOS Randomized Clinical Trial

Eric C Svensson [1,2], Aviv Madar [1,3], Catarina D Campbell [1], Yunsheng He [1,4], Marc Sultan [1,5], Margaret L Healey [1], Huilei Xu [1], Katie D'Aco [1,6], Anita Fernandez [1], Clarisse Wache-Mainier [1], Peter Libby [7], Paul M Ridker [7,8], Michael T Beste [1,✉], Craig T Basson [1,2]

Η κλωνική αιμοποίηση απροσδιόριστου δυναμικού (CHIP) σχετίζεται με αυξημένο κίνδυνο αθηροσκληρωτικής καρδιαγγειακής νόσου και πειράματα σε ποντίκια υποδηλώνουν ότι το CHIP που σχετίζεται με την απώλεια λειτουργίας Tet2 σε κύτταρα μυελικής σειράς επιταχύνει την αθηροσκλήρωση μέσω της σηματοδότησης αυξημένης ιντερλευκίνης (IL) 1β.



Association of Canakinumab and Placebo With Incident Major Adverse Cardiovascular Events (MACE) According to *TET2* Clonal Hematopoiesis of Indeterminate Potential (CHIP) Status.

Kaplan-Meier curves are displayed for the rate of MACE in placebo and canakinumab-treated patients (50-, 150-, and 300-mg doses combined) without CHIP (A), patients with CHIP (B), *TET2* patients with CHIP (C), or non-*TET2* patients with CHIP (D). A Cox proportional hazard model was used to calculate hazard ratios with covariates of age, time to last myocardial infarction, and baseline $\log_2$(high-sensitivity C-reactive protein).

MACE (the primary end point in the CANTOS trial defined as a combination of myocardial infarction, stroke, or cardiovascular death)

A Phase Ic Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics Following 4 Weeks of NLRP3 Inhibition With Selnoflast inParticipants With Coronary Artery Disease

- **NLRP3 Inhibitors**: An ongoing Phase Ic clinical trial is studying the use of an NLRP3 inhibitor (selnoflast) in patients with coronary artery disease and elevated C-reactive protein, with a specific substudy evaluating its effects in subjects with pathogenic *TET2* variants. This trial aims to determine if targeting the inflammatory pathway specific to CHIP can reduce cardiovascular risk.

The association between clonal hematopoiesis and heart failure. Mutations in hematopoietic stem cell progenitor cells give rise to clones that expand over time.

(1) Factors stimulate clonal proliferation;

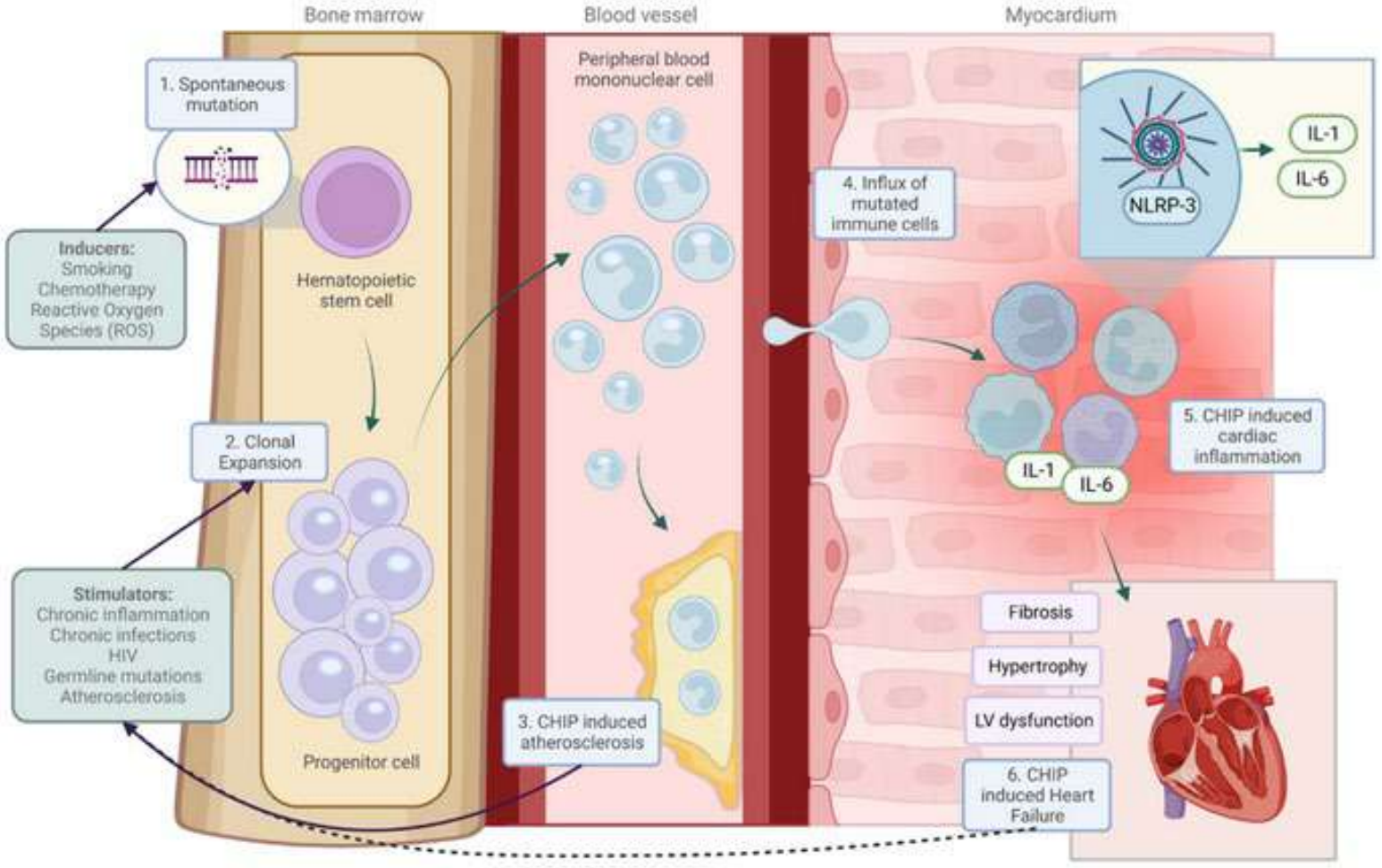
(2) consequently, these mutated cells enter the bloodstream and myocardium and cause atherosclerosis,

(3) or impair cardiac function.

(4) An inflammasome/interleukin 1/6-mediated response

(5) is central to clonal hematopoiesis-induced heart failure.

(6) Heart failure could be a driver of clonal proliferation, as indicated by the dashed line. Solid lines are based on published results.

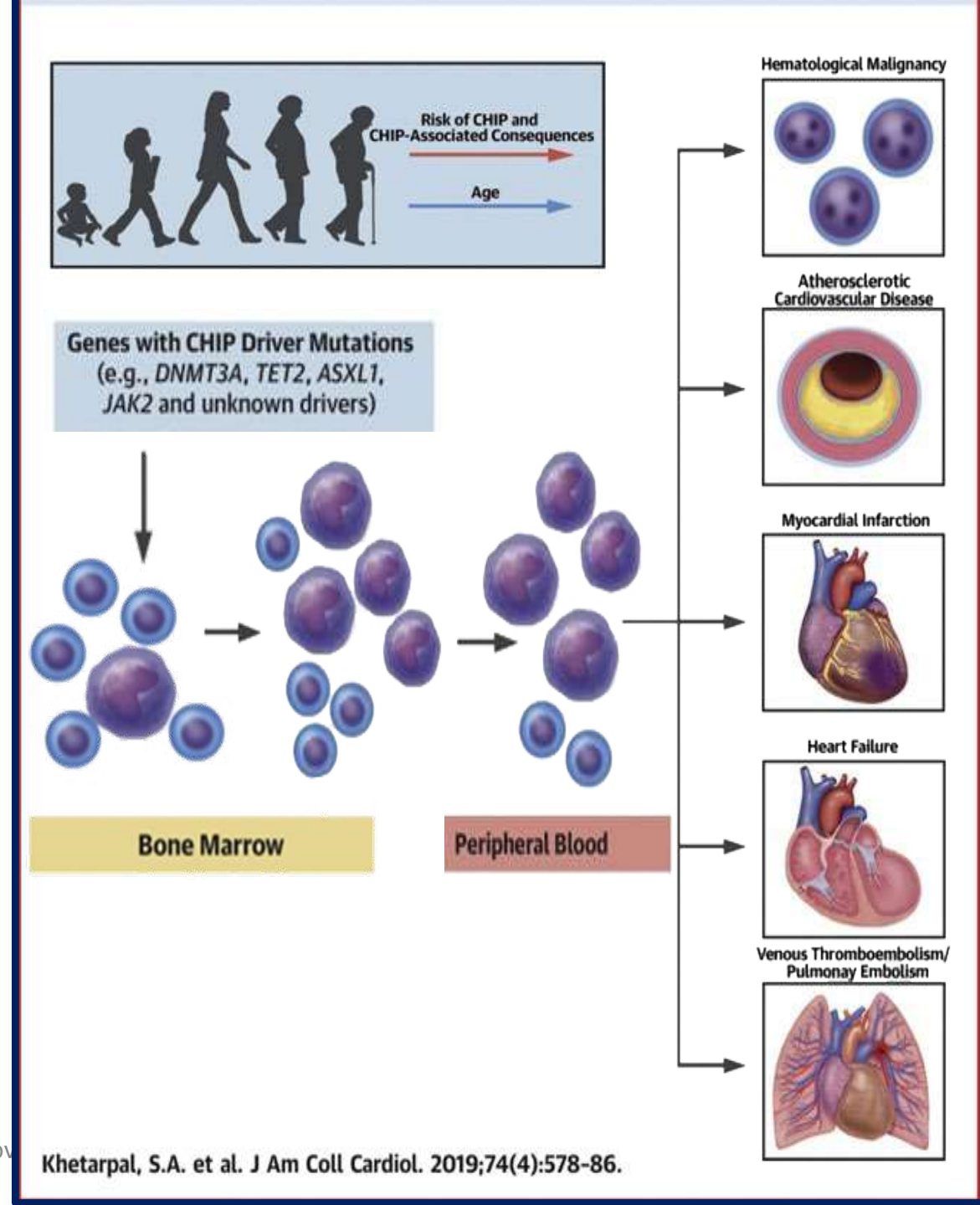


Thrombotic, Cardiovascular, and Microvascular Complications of Myeloproliferative Neoplasms and Clonal Hematopoiesis (CHIP): A Narrative Review

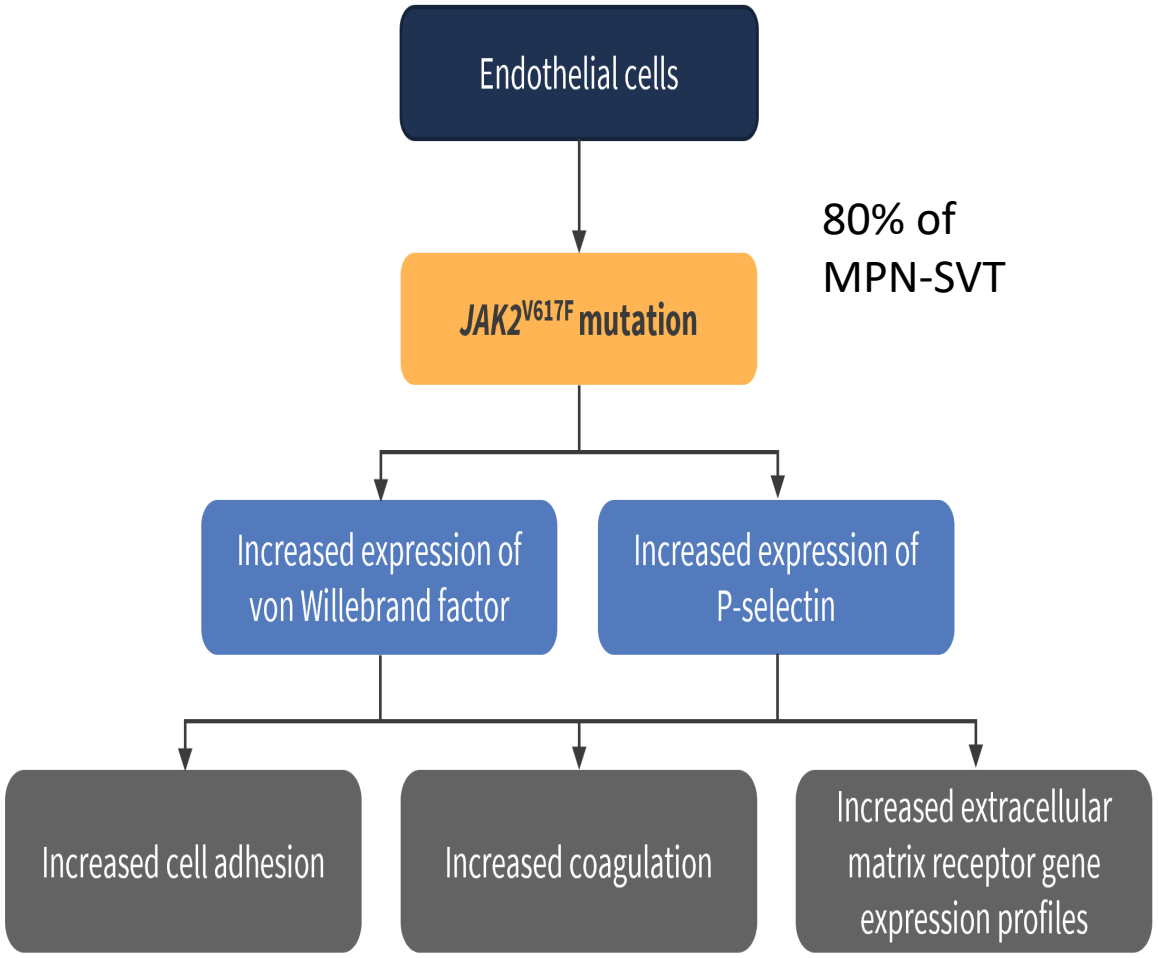
CHIP-associated SVT

- Mutations in the ***D****NMT3A*, ***T****ET2* and ***A****SXL1* (**DTA**) genes have ability to regulate the effect of DNA methylation and modulate gene expression.
- Mutations in *DNMT3A* gene modulate the expression of various genes involved in the inflammation response, therefore favouring the development of thrombosis.
- Mutations of DTA genes have been reported to increase thrombotic risk in PV patients.
- Presence of at least one of DTA mutations has 6-fold higher risk of vascular event.

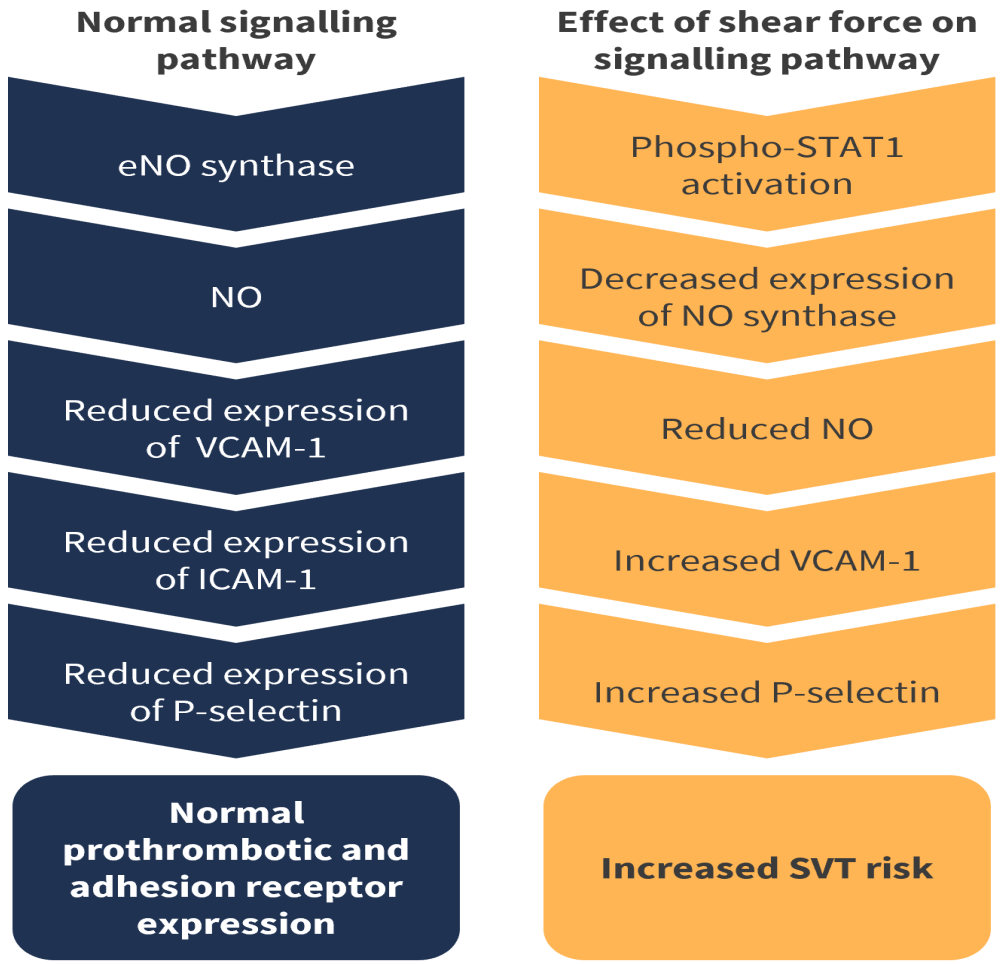
Segura-Díaz et al. Thrombotic Risk Detection in Patients with PV: The Predictive Role of DNMT3A/TET2/ASXL1 Mutations. Cancers 2020



Risk factors for SVT



80% of MPN-SVT



Author	Patient (age)	Causative drug	Disease	Serological markers	Renal biopsy (immunofluorescence staining)
Li Cavoli [2011] [S18]	F, 36	IFN-β	Multiple sclerosis	NA	chronic TMA IF: IgM and C1q ++,mesangial
Broughton [2011] [S19]	F, 53	IFN-β	Multiple sclerosis	normal C3 and C4 levels	subacute TMA IF: C3++
Olea [2012][S20]	F, 37	IFN-β	Multiple sclerosis	NA	chronic TMA IF: negative
Nerrant [2013] [S21]	F, 38	IFN-β	Multiple sclerosis	normal C3 and C4 levels normal ADAMTS13	acute TMA IF: IgM
Piccoli [2016][S22]	M, 31	IFN-β	Multiple sclerosis	Normal C3 and C4 levels	acute TMA, collapsing glomerulopathy IF: negative
Allinovi [2017] [S23]	M, 35	IFN-β	Multiple sclerosis	Low C3 levels and normal C4 levels; normal ADAMTS13	acute TMA IF:C3++,subendothelial and capillary wall
Gianassi [2019] [S24]	F, 55	IFN-β	Multiple sclerosis	low C3 levels and normal C4 level; normal ADAMTS13	acute TMA IF: C3+, capillary wall
Parisi [2020][S25]	M, 39	IFN-β	Multiple sclerosis	normal C3/C4 levels normal ADAMTS13	acute TMA IF: IgG +
Allinovi [2021] [S26]	M, 38	IFN-β	Multiple sclerosis	low C3 level and normal C4 levels	TMA IF: C3++, capillary wall
Murugapandian [2015][S27]	F, 74	Gemcitabine	Ovarian carcinoma	Normal C3 and C4 levels	Acute TMA IF: negative
Krishnappa [2018] [S28]	F, 69	Gemcitabine	Pancreatic adenocarcinoma	Low C3 and C4 levels; normal ADAMTS13	Acute TMA IF:C3++, capillary wall
Burns [2020][S29]	M, 39	Gemcitabine	Pancreatic adenocarcinoma	Normal C3 and C4 levels; normal ADAMTS13	Acute TMA IF:C3+++,C1q+ in capillary wall
Grall [2021][S30]	12 patients	Gemcitabine	Pancreas, ovarian, lung and uterine adenocarcinoma	8 patients: normal C3 and C4 levels 4 patients: low C3 All patients: normal ADAMTS13	TMA IF: all patients C5b9 +++ in tubule, glomerulus and capillary wall
Etta [2020][S31]	M, 44	Clopidogrel	Unstable angina	Normal C3 and C4 levels	Acute TMA IF: negative
Mizuno [2021] [S32]	M, 75	Bortezomib	Multiple myeloma	Normal C3 and C4 levels; normal ADAMTS13	MPGN and TMA IF: IgG +++
Hobeika [2014] [S33]	M, 62	Carfilzomib	Multiple myeloma	Normal C3 and C4; normal ADAMTS-13	TMA and podocytopathy IF: C3, C1q +++, IgM and fibrin in interlobular artery
Yamada [2019] [S34]	F, 77	Ramucirumab	Colic adenocarcinoma	Normal C3 and C4	Acute TMA IF: C1q and IgM++ in mesangium and capillillary wall
Ozawa [2019][S35]	9 patients	Ramucirumab and bevacizumab	Colon, rectum, lung and brain cancer	NA	Acute TMA IF: all patients C4+/++, 4 patients C3+, 5 patients C3 negative
Nakano [2021] [S36]	M, 71	Ramucirumab	Cecal cancer	NA	TMA and collapsing glomerulopathy IF: C3 ++, C4, C1q, IgA, IgM and IgG + in mesangium and capillary wall
Pellé [2011][S37]	M, 77	IO anti-VEGF	Age-related macular degeneration	Normal C3 and C4; normal ADAMTS-13	TMA IF: negative
Touzani [2019] [S38]	M, 72	IO anti-VEGF	Glaucoma	Normal C3 and C4; normal ADAMTS-13	TMA IF:C3++ in capillary wall
Hanna [2020][S39]	M, 59	IO anti-VEGF	Diabetic retinopathy	NA	Chronic TMA IF: negative
	F, 43		Diabetic retinopathy	NA	Acute TMA IF: negative
	M, 77		Diabetic retinopathy	NA	Chronic TMA IF: negative
Miller [2019][S40]	F, 70	DCR-MYC (short interfering RNA)	Breast adenoid cystic carcinoma	NA	Chronic TMA IF: negative
Eremina [2008] [S41]	6 patients	Bevacizumab	Hepatic, lung carcinoma, pancreatic and ovarian cancer	NA	TMA IF: 4 negative and 2 IgA++ patients
Roncone [2007] [S42]	M, 59	Bevacizumab	Renal cell carcinoma	NA	Chronic TMA IF: IgG, IgA, IgM, C3 ++ in mesangium and capillary wall
Toriu [2019][S43]	M, 88	Bevacizumab	Colorectal cancer	Normal C3 and C4; normal ADAMTS-13	Acute TMA IF: C3 and IgM ++ in mesangial and capillary wall
Morimoto [2021] [S44]	M, 68	Bevacizumab	Ovarian carcinoma	Normal C3 and C4	TMA IF: IgG, IgA, IgM, C3, C4, and C1q ++ in subendothelium and mesangium
Yilmaz [2016][S45]	M, 15	Polychemotherapy	Osteosarcoma	Normal C3 and C4; normal ADAMTS-13	Acute TMA IF: IgG, IgA, IgM, C3, C4, and C1q ++
Morita [2022][S46]	M, 79	Imatinib	Chronic myeloid leukemia	NA	Chronic TMA and podocytopathy IF: negative
Patel [2008][S47]	5 patients	Sunitinib	GIST, epithelioid hemangio-endothelioma and teratocarcinosarcoma	NA	TMA IF: negative
Bollée [2009][S48]	F, 44	Sunitinib	Malignant skin hydro adenoma	normal C3 and low C4; normal ADAMTS-13	Acute TMA IF: IgM, IgG, IgA, C3 and C1q ++ in mesangium and capillary wall
Jha [2013][S49]	M, 60	Sunitinib	Clear-renal cell carcinoma	NA	Acute TMA IF: IgM+
Nieto-Rios [2021] [S50]	M, 74	Sunitinib	GIST	Normal ADAMTS-13	Chronic TMA and podocytopathy IF: negative
Hyogo [2018] [S51]	F, 70	Lenvatinib	Papillary thyroid carcinoma	NA	Chronic TMA IF: negative
Hasegawa [2020] [S52]	M, 69	Nintenatib	Pulmonary idiopathic fibrosis	Normal C3 and C4; normal ADAMTS-13	Acute TMA IF: IgM+
Maruyama [2018] [S53]	M, 31	Pazopanib	Rhabdomyosarcoma	NA	Acute TMA IF: IgA, IgM, C3, C4, C1q ++ along the glomerular basement mebrane