Neuropsychiatric Presentations of Hypercoagulability



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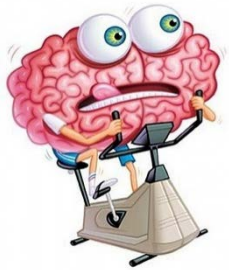
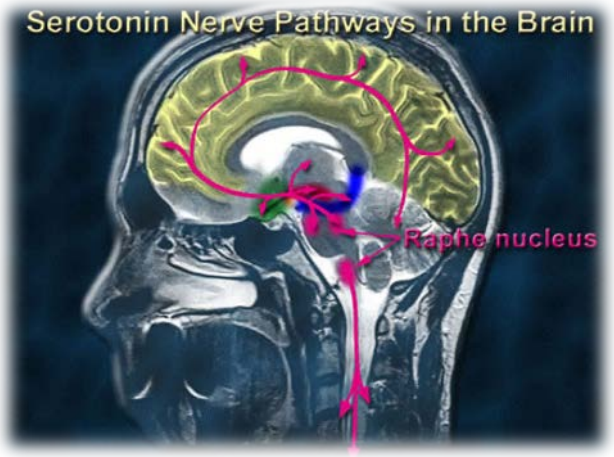
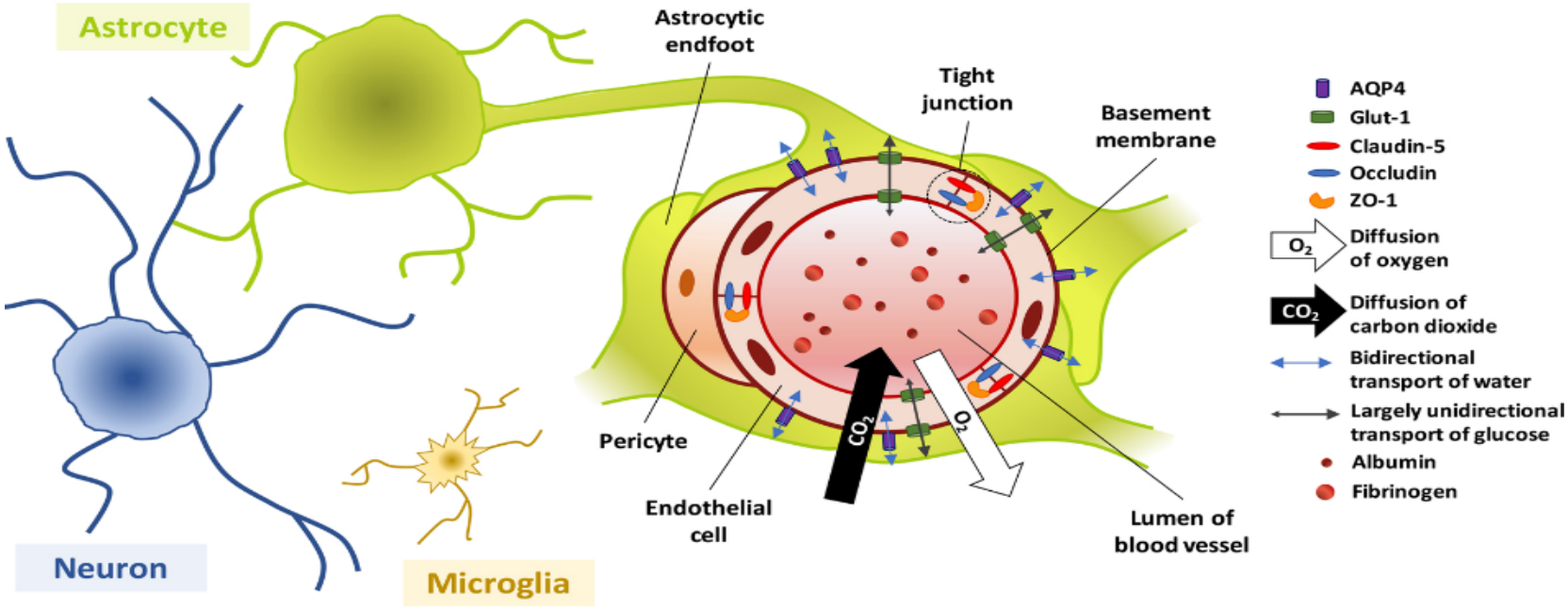


Brain Physiology

- Brain vasculature is uniquely programmed to protect CNS tissues and respond to their metabolic demands.
- Neuron-microvascular interactions at the neurovascular unit are essential for normal functioning of the CNS and maintenance of hemostasis.



del Zoppo Semin Thromb Hemost, 2013



Neurovascular unit:

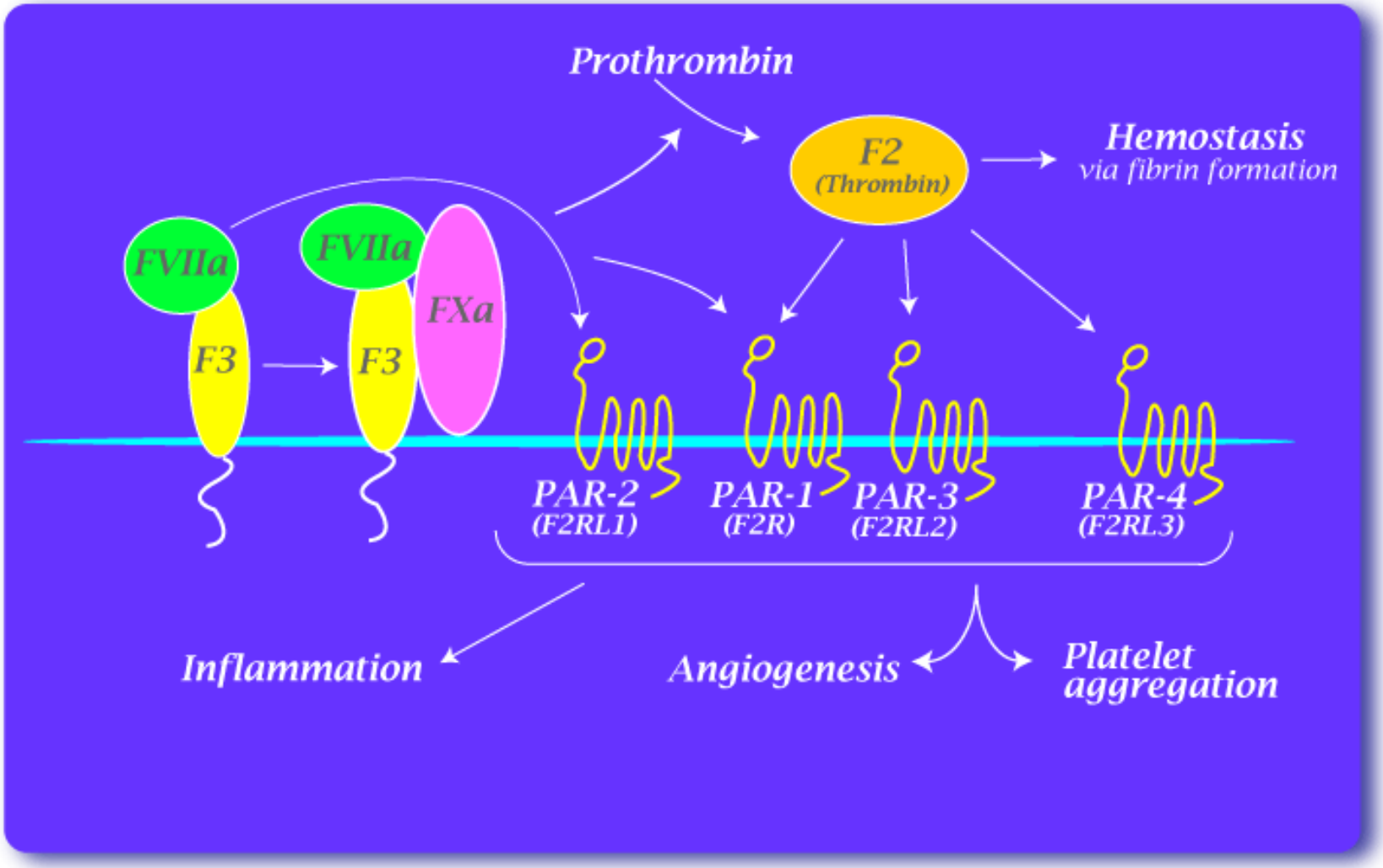
Neurons, Astrocytes, Microglia, Pericytes and Endothelial cells *with the cells being arranged around cerebral blood vessels*.

Coagulation and Brain

- Perivascular expression of TF and serine protease inhibitors can affect vascular and tissue injury.
- Coagulopathy occurs locally within the microvasculature of the ischemic territory at-risk.
- Components of the plasminogen activator system are involved in CNS development,plasticity,inflammation,extracellular- matrix remodeling and neuronal signaling.

del Zoppo Semin Thromb Hemost, 2013

PARs Activation

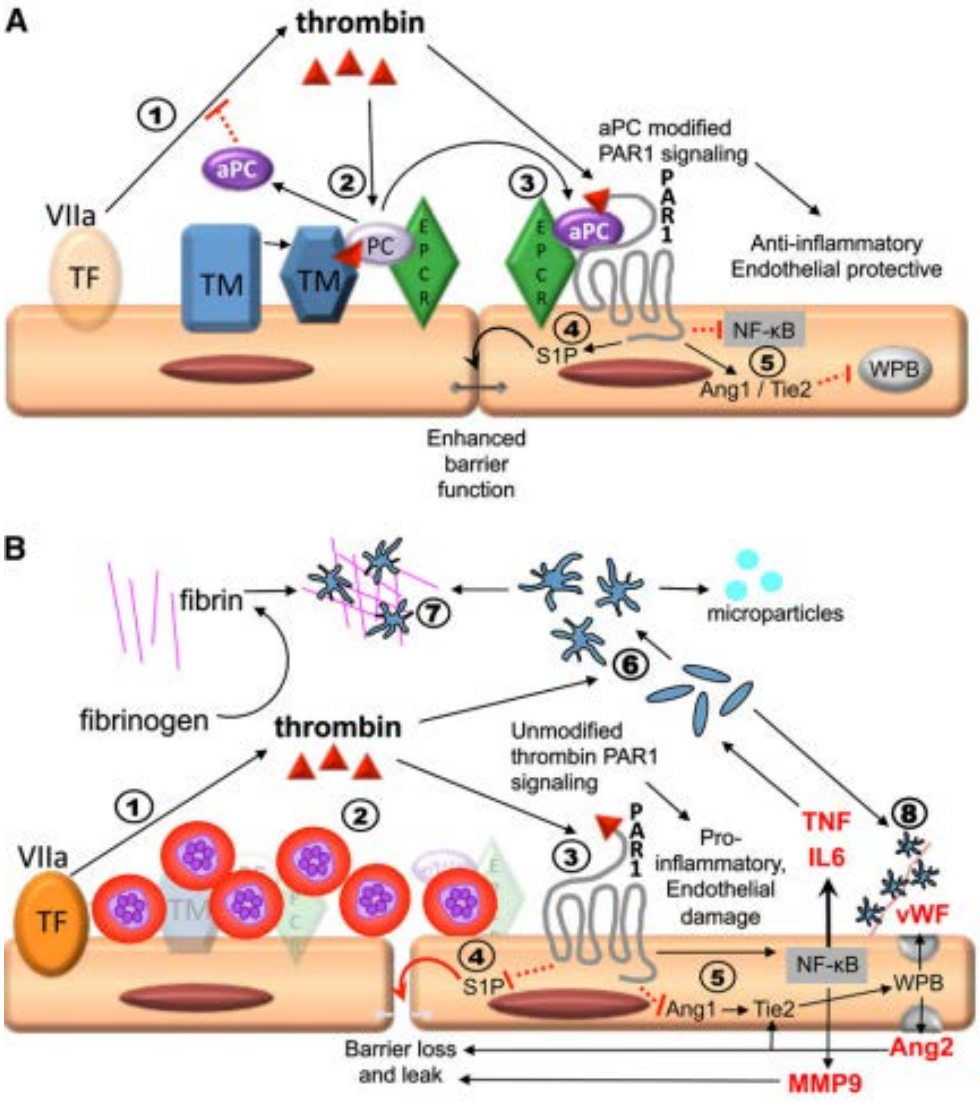


Coagulation in CNS Inflammatory Diseases

- Thrombin and other proteases can stimulate brain inflammation through the protease activated receptors.
- PAR-1 is located in the synapses and its excessive activation leads to blocks in nerve conduction.
- Coagulation-like pathways play a significant role in the pathogenesis of inflammatory diseases in the CNS and present a target for therapeutic strategies.

Chapman Semin Thromb Hemost ;2013,2025

Loss of endothelial protein C receptors links coagulation and inflammation to parasite sequestration in cerebral malaria in African children



Moxon Blood 2013

Coexistence of Hereditary Homocystinuria and Factor V Leiden — Effect on Thrombosis

Authors: Hanna Mandel, M.D., Benjamin Brenner, M.D., Moshe Berant, M.D., Nurith Rosenberg, Ph.D., Naomi Lanir, Ph.D., Cornelis Jakobs, Ph.D., Brian Fowler, Ph.D., and Uri Seligsohn, M.D. Author Info & Affiliations

Published March 21, 1996 | N Engl J Med 1996;334:763-768 | DOI: 10.1056/NEJM199603213341204

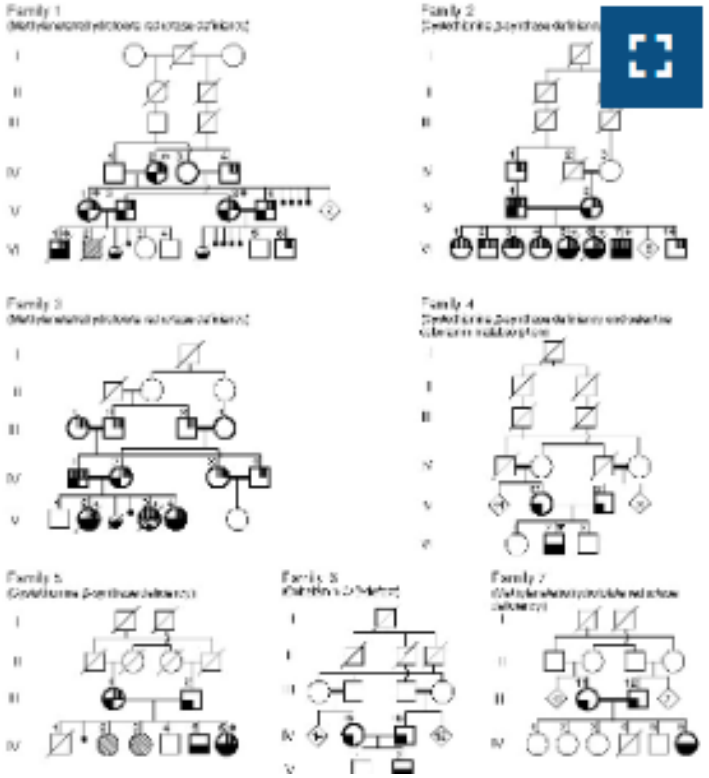


Table 2. Association between Mutated Genotypes for Homocystinuria and Factor V Leiden and the Occurrence of Thrombosis in 33 Subjects from the Seven Families Studied.

Genetic Association		No. of Subjects	Thrombosis	No Thrombosis
Homocystinuria	Factor V Leiden			
Homozygote	Homozygote	1	1	
Homozygote	Homozygote or heterozygote	3	3	
Homozygote	Heterozygote	3	2	1*
Homozygote	Normal genotype	4		4
Obligate heterozygote	Heterozygote	8	3†	5
Obligate heterozygote	Normal genotype	7		7
Obligate heterozygote	Homozygote	2		2
Not determined	Homozygote	5	1‡	4
All subjects		33	10	23

*This subject (Subject V-4 in Family 3) was an 18-month-old child treated with warfarin from birth.

†These three subjects were women who had recurrent abortions, low-birth-weight babies, and placental infarctions. One woman (Subject IV-2 in Family 1) was a grandmother who was considered to be heterozygous for homocystinuria on the basis of a high fasting plasma homocysteine level.

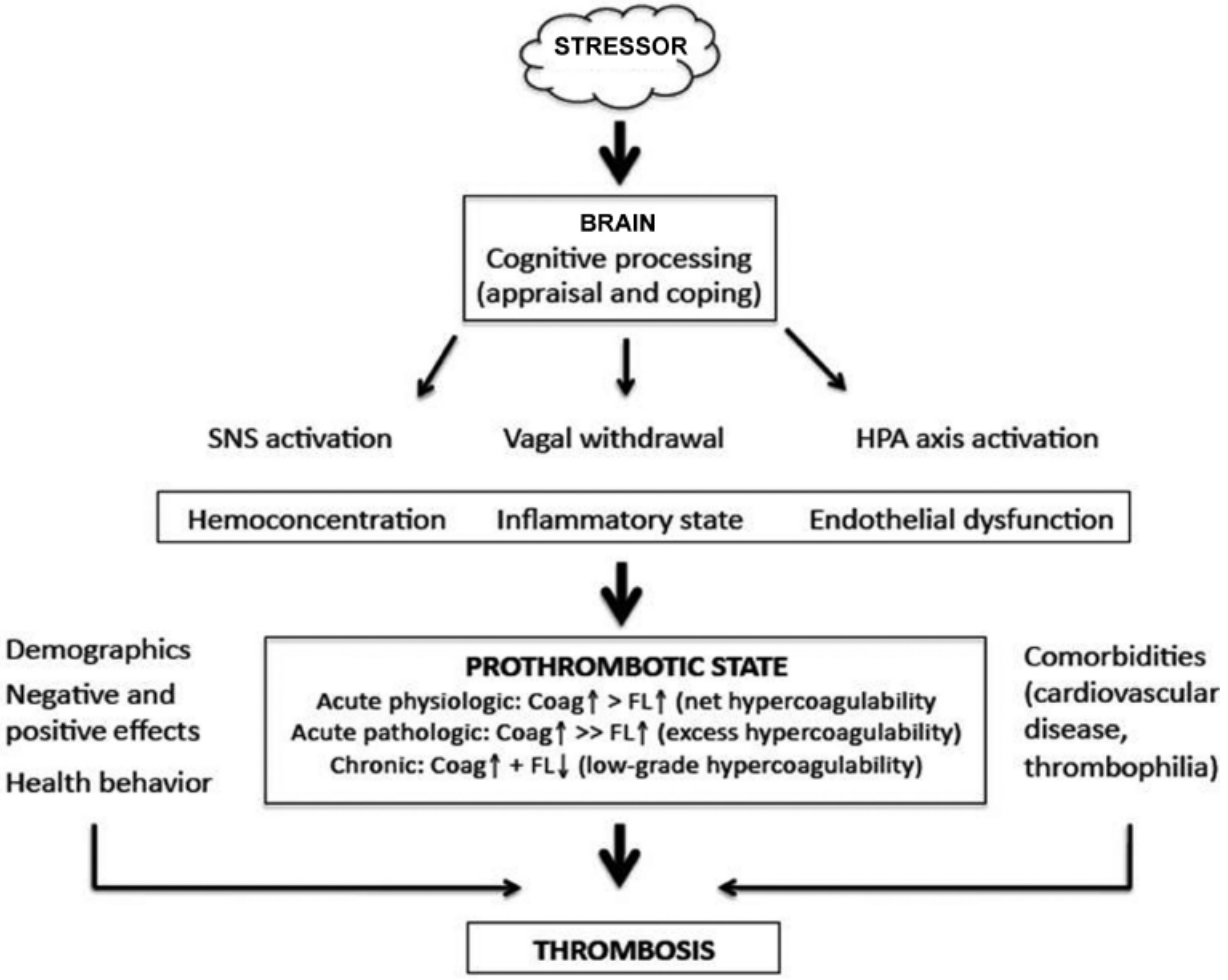
‡This subject (Subject V-3 in Family 3) had congenital diarrhea, and thrombosis was induced by central venous catheterization.

Stress and Thrombosis

- Cohort studies demonstrate an association between stress and a hypercoagulable state in athero-thrombosis and venous thromboembolism.
- Mendelian randomization studies suggest that these associations are partially causal.
- Mechanisms : activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, along with vagal withdrawal. Hormones involved: catecholamines, cortisol and vasopressin.

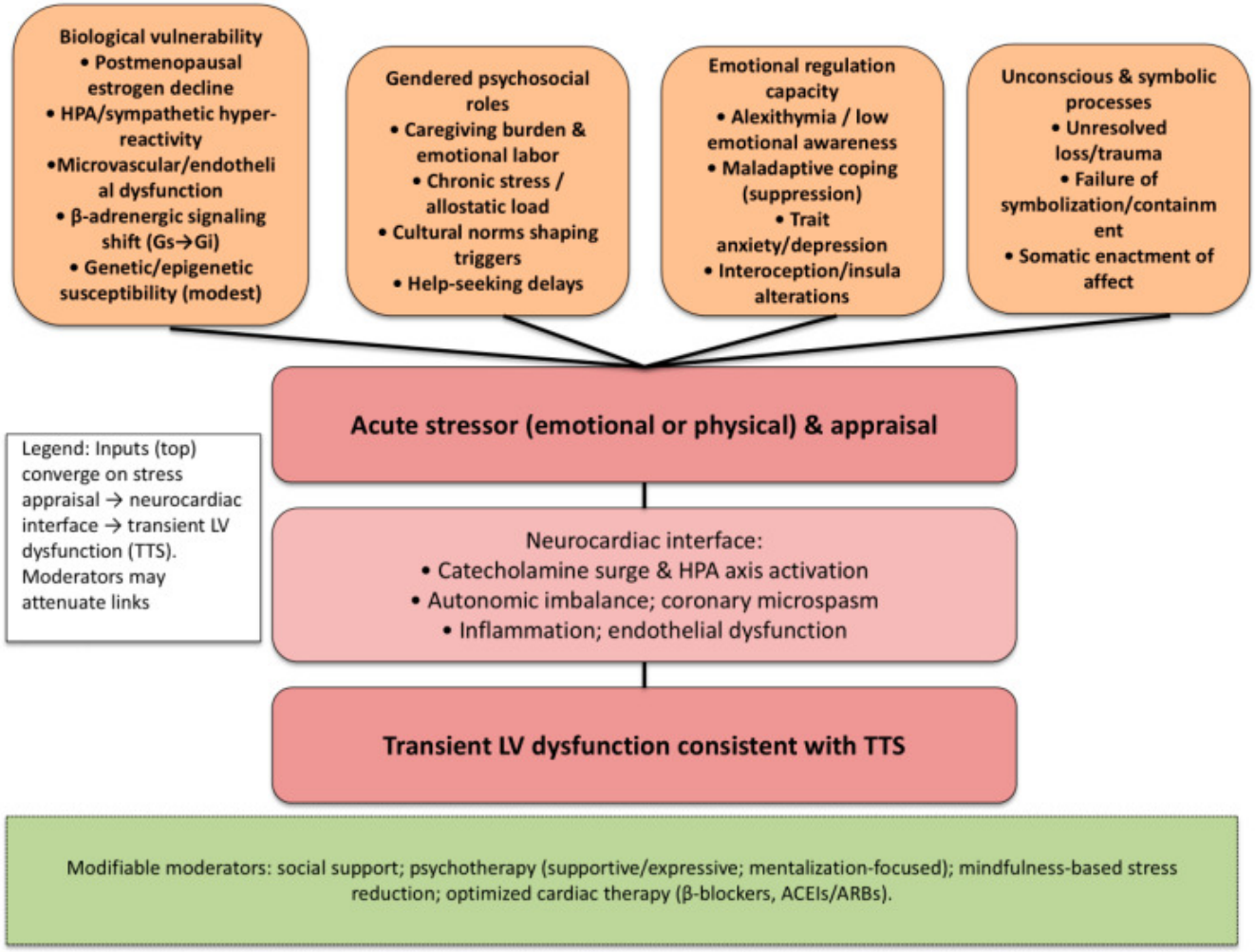
Von-Kanel, STH 2025

Mechanisms of Stress and Hemostasis



Von Kanel Sem Thromb Hemost, 2025

Takotsubo Cardiomyopathy



Chronic Stress and Hemostasis

- The hypothalamic–pituitary adrenal axis and autonomic dysfunction are important regulators of hemostatic activity in chronic stress.
- Restoring normal hemostatic function with bio-behavioral and pharmacological interventions bears the potential of decreasing thrombotic risk.

Bentur Semin Thromb Hemost. 2018

Case Presentation

- A 25 years old female presented with post-partum depression after CS of 1500gr baby at 35 weeks of gestation .
- At 30 years she presented with Ischemic Stroke.
- APLA Syndrome was diagnosed .

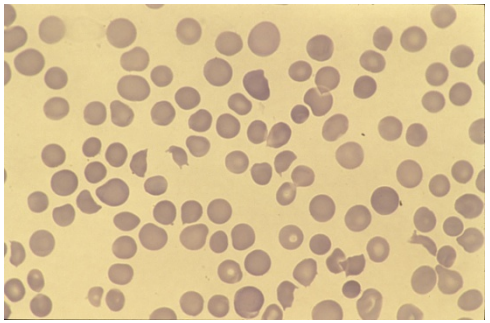
Antiphospholipid Antibodies

- *Strong associations*:
  - Venous thromboembolism
  - Arterial thrombosis, especially stroke and TIA
  - Microvascular thrombosis
  - Poor pregnancy outcome

- *Some others*:

  Thrombocytopenia

  Haemolytic anaemia [Immune and MAHA]



Livedo reticularis

Atherosclerosis

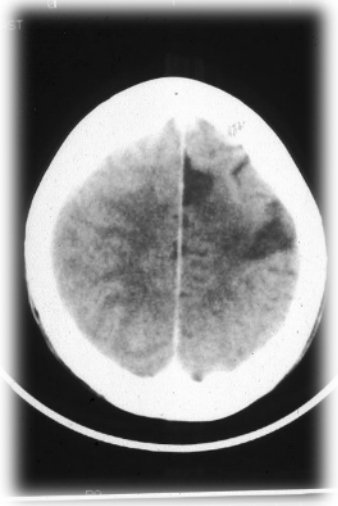
How do APLA Cause Thrombosis?

- Interference with protein C/S
- Inhibition of fibrinolysis
- Induction of tissue factor expression
- Activation of endothelium
- Inhibition of clearance of apoptotic cells
- Promotion of platelet aggregation
- Complement activation

CNS Manifestations of APS

- Arterial stroke
- Venous thrombosis

- Cognitive deficit
- MS-like disease
- Chorea
- Sensorineural deafness
- Transverse myelopathy
- Ocular thrombosis



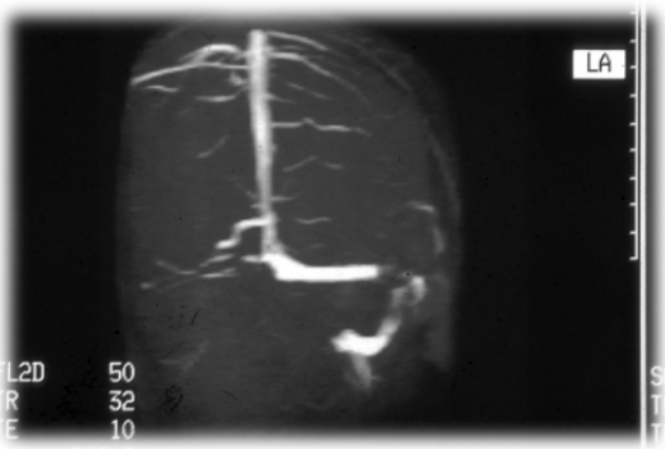


Table 1 Associations between antiphospholipid antibodies and central nervous system morbidities

1. Neurologic syndromes
   - Thrombotic mechanism: APS syndrome
     - Stroke
     - Early-onset multi-infarct dementia
     - Transient ischemic attack
       - Amaurosis fugax
       - Transient paresthesias
     - Cerebral vein thrombosis
   - Other nonsystemic thrombosis-related mechanisms
     - Optic neuropathy/atrophy
     - Epilepsy
     - Chorea and dystonia
     - Cognitive dysfunction
     - Nonvascular dementia
2. Psycho-psychiatric syndromes
   - Hyperactivity and behavioral abnormalities
   - Depression and mania: bipolar disorders
   - Psychosis
3. Neurologic symptoms possibly associated with or mimicked by aPL
   - Multiple sclerosis
   - Transverse myelitis
   - Idiopathic intracranial hypertension

Gris & Brenner Sem Thromb Hemost, 2013

APLA and Psychosis
Systematic Clinical Studies

Firer M.,1994	Ariel, Israel	Case-control	28 multicase families with schizophrenia	aCL IgGs and IgM more common in patients
Schwartz M., 1998	Haïfa / Acre, Israel	Before / after neuroleptic treatment	34 patients, acute psychosis	Increased incidence of LA and aCL Abs
Schwartz M., 1999	Haïfa / Acre, Israel	Long-term neuroleptic treatment	50 patients, schizophrenia	aPL Abs: 50%, LA, aCL Abs
Hoirisch-Clapauch S, 2014	Brazil, Rio de Janeiro	Case-control	70 schizophrenia adults, 90 age-matched conrols	aPL Abs: 30%, *multiple or high-titer Abs were refractory to therapy*
Canoso RT, 1990	USA, Brocton, MA	Case-control	184 chronic male psychiatric patients taking neuroleptics	aPL Abs: 70% *vs.* 9%. Phenothiazines: polyclonal IgM.
Samoud S, 2024	Tunisia, Tunis	Case-control	80 drug-free schizophrenic patients, 80 healthy controls	31% *vs.* 5%, Higher levels of aCL IgM, High prevalence of aCL-IgA and of aβ2GP1-IgA

APS-Multiple Sclerosis-like Presentation

- It is sometimes difficult to differentiate APS from multiple sclerosis (MS), as some initial clinical presentations of APS can mimic MS, which often leads to a miss-diagnosis.
- Nearly a third of aPL-positive patients heard their doctor mentioning at any stage a possible diagnosis of MS in a hospital audit.

Hughes Postgrad Med J, 2003

APS-Multiple Sclerosis-like Presentation

- Screening of 70 classic MS and 100 non-classic MS cases with unusual clinical features revealed a high proportion of aCL-positive patients in the non-classic MS group.
- In the study of 161 MS cases, aPL-positive MS patients did not seem to differ from aPL-negative MS patients in terms of age at onset, presenting signs and symptoms, neurological findings, or disease course.

Karussis, Ann Neurol, 1998
Tourbah , Arch Neurol, 1998

APS -Psychosis

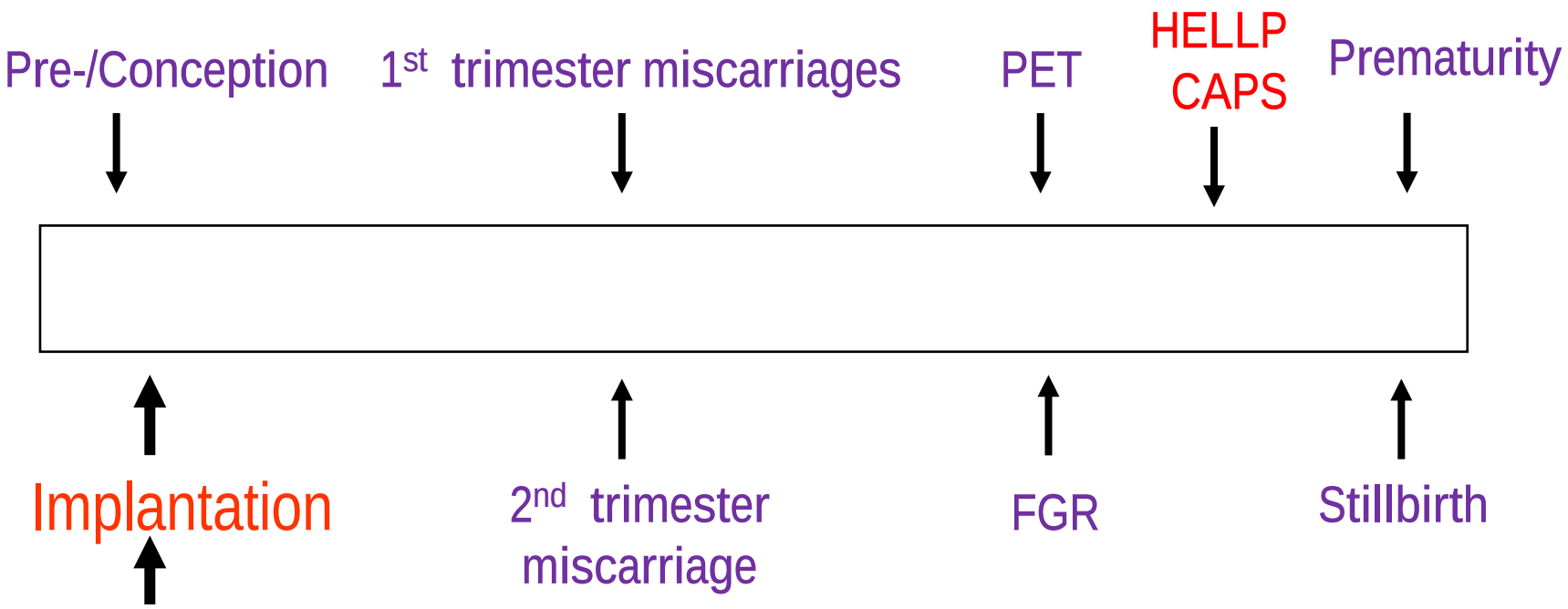
- APS may present as psychosis many years before the occurrence of somatic symptoms [Purcell et al Nature 2009]
- Psychosis can present in both primary and secondary APS.
- Psychiatrists should consider SLE in the differential diagnosis of psychosis occurring during pregnancy {Siu et al East Asian Arch Psychiatry 2010]
- Catatonia is now considered to be a manifestation of SLE and its pathogenesis in this instance may related to the affinity of aPL antibodies for the basal ganglia [Pustilinik et al J Psychaitr 2010]

APS -Medications

- Antithrombotic therapy, while useful for primary and secondary prevention of vascular events, has not been evaluated in neuropsychiatric settings of APS patients.
- Steroids occasionally used in APS may aggravate neuropsychiatric presentations.
- Likewise, anti-malarial medications can sometimes induce aPL and neuropsychiatric manifestations.

Lim JAMA, 2006
Panichpisal Curr Rheumatol Rep, 2012
Schneider Travel Med Infect Dis, 2013

Pregnancy Complications of APS



Increased risk for future thrombosis and neuropsychiatric disorders
in obstetric APS patients

World J Biol Psychiatry 2019; 20(1):51-63.

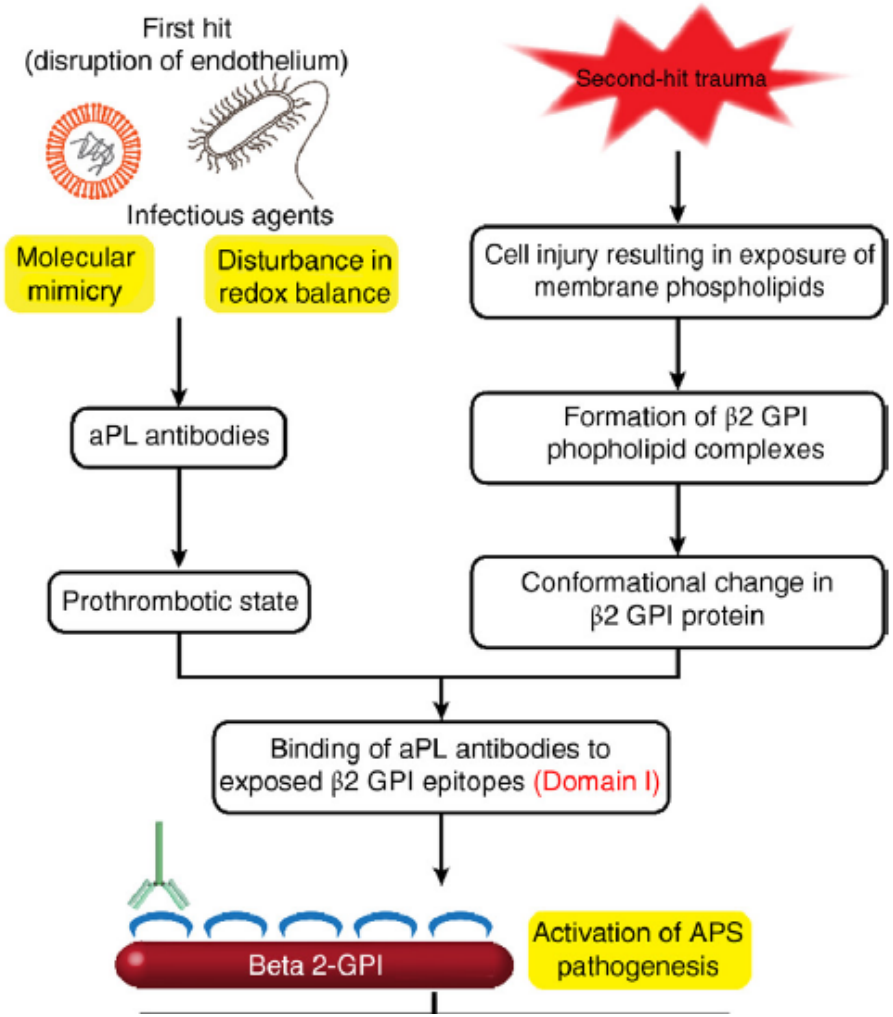
FV Leiden positive women *vs.* Controls: NS

oAPS women *vs.* Controls:

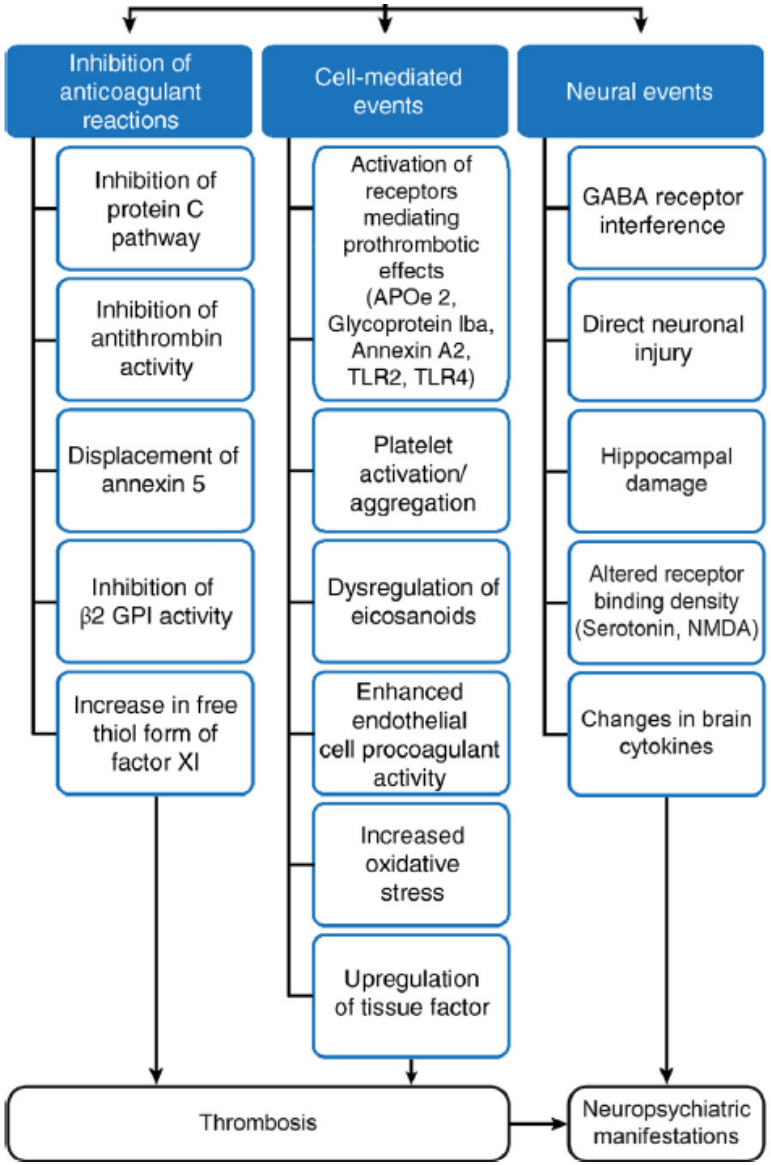
	RR
Mood disorders	
Recent depressive episode	1.54 (1.19-1.99)
At least one mood disorder	**1.57 (1.26-1.95)**
Anxiety disorders	
Panic disorder	1.67 (1.09-2.57)
Agoraphobia	1.78 (1.02-3.10)
At least one anxiety disorder	**1.65 (1.37-1.98)**
Mood *or* anxiety disorders	**1.68 (1.45-1.94)**
Alcohool	**2.52 (1.11-5.70)**

Positive aPLAb	aOR *	95%C.I.	P
At least one mood disorder:			
Lupus Anticoagulant	1.99	1.39-2.85	<0.0001
Anticardiolipin IgG	0.62	0.42-0.94	0.0223
aβ2GP1 IgG	4.49	2.86-7.06	<0.0001
At least one anxiety disorder:			
Lupus Anticoagulant	1.46	1.05-2.03	0.0230

World J Biol Psychiatry 2019; 20(1):51-63.



Rege & Mackworth-Yong, Translational Developmental Psychiatry, 2015



Rege & Mackworth-Yong, Translational Developmental Psychiatry, 2015

When to Suspect Antiphospholipid Syndrome in Psychiatry

- Atypical psychiatric presentation
- Treatment-resistant psychiatric illness
- Cognitive dysfunction and dementia
- Abnormal involuntary movements with or without the use of antipsychotics
- Migraines
- History of DVT in patients <50 years of age
- History of pulmonary embolism with or without the use of antipsychotics
- Stroke or TIA in patients <50 years of age
- Livedo reticularis
- Recurrent early miscarriages
- Raynaud's phenomenon
- Diagnosis of SLE
- Unexplained white matter hyperintensities (WMHs) on MRI in patients <50 years of age

Rege & Mackworth-Yong, Translational Developmental Psychiatry, 2015

APS & Brain-Therapy

- Despite Maximum anticoagulation, a significant proportion of patients with APS develop new lesions, mainly WML, cortical and basal ganglia infarcts.
- The linear WML lesions encountered in APS patients could potentially represent venous infarcts, illustrating the combined venous and arterial aetiology of APS strokes.
- There is a need for optimization of anticoagulation therapy to minimize the frequency of new lesions and associated disability

Svrckova, EPOS 2017

VTE in Psychiatric Patients

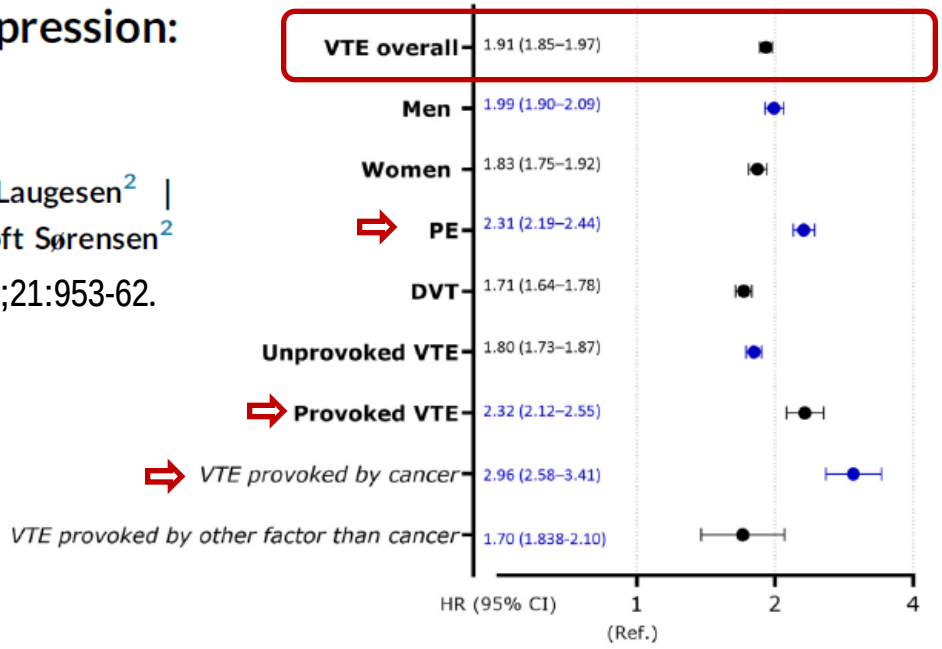
	Disease	Mechanism	Coagulation abnormality
Comorbidities	Obesity and metabolic Syndrome ~30%	Endothelial dysfunction Inflammation	Fibrinogen, VWF, increased Reduced fibrinolysis: reduced tPA and PAI-I
	Diabetes (>9%) (atherosclerosis, CVD)	Oxidative stress Inflammation Endothelial dysfunction Enzyme glycation	Fibrinogen, FVII and TF, FVIII, VWF, and FX are increased AT is reduced Reduced anticoagulant pathway
	COPD	Multifactorial Inflammation, immobilization	Venous stasis Procoagulant state
Lifestyle	Smoking (>40%)	Endothelial injury High oxidative stress Inflammation	Platelet aggregation enhanced Protein C complex depressed Fibrinogen, VWF increased
	Sedentary life	Immobilization	Venous stasis
	Substance abuse	Illicit drugs Alcohol	
	Adherence and compliance	Reduced	
Disease course	Catatonia, restraining	Immobilization, inflammation	Venous stasis, procoagulant state
Primary coagulation dysfunction	Suspect connection to the *etiopathogenesis* of the psychiatric disorder	Genetic, epigenomic, Proteomic Not yet understood	Protein S deficiency tPA reduced and its polymorphism AT dysfunction
Antipsychotic drugs	Second-generation atypical drugs: risperidone, olanzapine, and quetiapine are potent procoagulants	Inflammation Metabolic syndrome Biochemical effects Sedation	Platelet aggregation Fibrinogen and VWF are increased. Not yet understood

Geris, STH 2025

Venous thromboembolism and risk of depression: a population-based cohort study

Helle Jørgensen[1,2,3] | Erzsébet Horváth-Puhó[2] | Kristina Laugesen[2] | Sigrid K. Brækkan[1,3] | John-Bjarne Hansen[1,3] | Henrik Toft Sørensen[2]

J Thromb Haemost 2023;21:953-62.



Danish nationwide registries

Individuals with incident VTE: n=64,596 (1996-2016)
Matched* comparison cohort: n=322,999

Followed for 3 years;
depression: any related hospital admission
≥ 1 prescription of antidepressants

* Birth year, sex and calendar year of VTE

HR adjusted on socioeconomic status (education and income), obesity, cancer, coronary heart disease, diabetes, stroke, COPD, acute kidney failure, alcohol- and drug-related disorders, dementia, surgery, trauma 3 months prior to VTE, Charlson Comorbidity Index Score and comedication,

VTE is globally associated with an increased risk of depression, especially after PE and provoked VTE.

Risk of Depression after Venous Thromboembolism in Patients with Hematological Cancer: A Population-Based Cohort Study

Daniel Steiner[1,2] Erzsébet Horváth-Puhó[2] Helle Jørgensen[3] Kristina Laugesen[2,4] Cihan Ay[1]
Henrik Toft Sørensen[2]

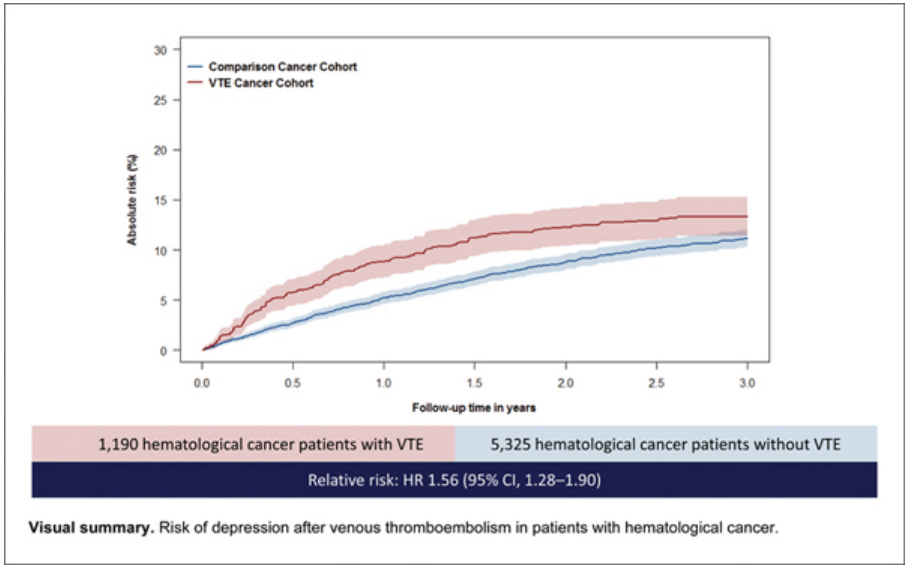
Danish nationwide registries

1995-2020:

individuals with
haematological cancer and incident VTE
(6 months before-1 year after diagnosis)
n=1,190

matched* comparison cohort,
haematological cancer without VTE
n=5,325

* Birth year, sex and calendar year of VTE



Visual summary. Risk of depression after venous thromboembolism in patients with hematological cancer.

HR adjusted on cardiac disease, COPD, diabetes mellitus, acute and chronic kidney disease, liver disease, obesity, stroke, inflammatory bowel disease, hypertension, Any mental heralth disorder, surgery or trauma 3 months prior to VTE,

Thromb Haemost 2025;125:255-64.

Polygenic risk of major depressive disorder as a risk factor for venous thromboembolism

Joey Ward,[1] Ngoc-Quynh Le,[2] Suryakant Suryakant,[3] Jennifer A. Brody,[4] Philippe Amouyel,[5] Anne Boland,[6,7] Rosemary Bown,[8] Breda Cullen,[1] Stéphanie Debette,[3] Jean-François Deleuze,[6,7,9] Joseph Emmerich,[10,11] Nicholas Graham,[1] Marine Germain,[3] Jana J. Anderson,[1] Jill P. Pell,[1] Donald M. Lyall,[1] Laura M. Lyall,[1,7] Daniel J. Smith,[1,12] Kerri L. Wiggins,[4] José Manuel Soria,[2] Juan Carlos Souto,[13] Pierre-Emmanuel Morange,[14] Nicholas L. Smith,[15-17] David-Alexandre Trégouët,[3] Maria Sabater-Lleal,[2,18] and Rona J. Strawbridge[1,18,19]

Blood Adv 2023;7:5341-50.

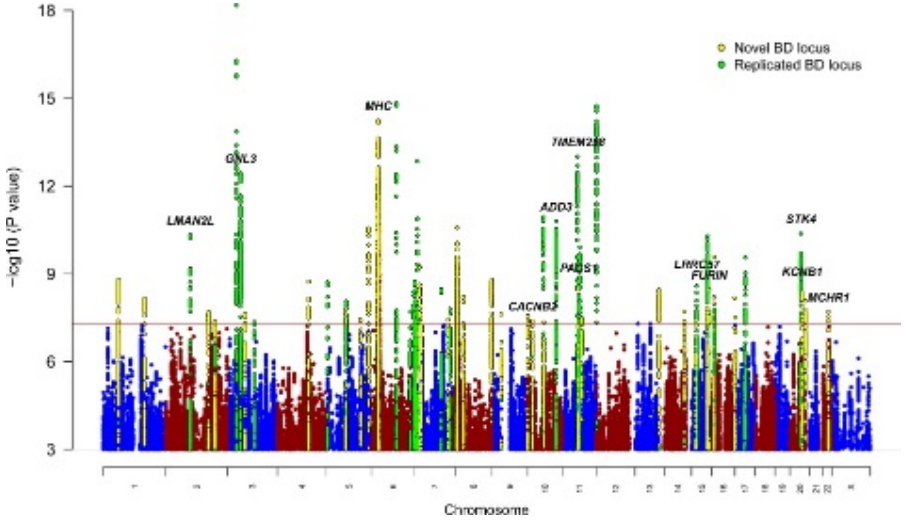
Key Points

- Genetic regulation of MDD and VTE was correlated.
- Genetic predisposition to MDD was associated with an increased risk of VTE.

Genetic predisposition to major depressive disorder
(44 variants: Nat Gen 2021;53:817-29)
is an independent risk factor for VTE.

Similar results are observed
when considering family history (first-degree relatives)
of major depressive disorder
instead of polygenic risk scores for major depressive disorder.

Consider family history of mental illness
when assessing the risk of VTE



The risk for psychiatric disorders in offspring from thrombosis-prone pedigrees in Sweden: a nationwide family study

Bengt Zöller | Jan Sundquist | Kristina Sundquist | Henrik Ohlsson

Res Pract Thromb Haemost 2025;9:e102692.

Regression of the mean rates of VTE across each pedigree cluster on each of the measured individual variables

VTE	All individuals, β*	Male group, β*	Female group, β*
Psychiatric disorders	**0.078 (0.06 ; 0.09)**	**0.040 (0.02 ; 0.065)**	**0.120 (0.099 ; 0.140)**
Depression	0.035 (0.02 ; 0.046)	NS	**0.050 (0.036 ; 0.068)**
Anxiety disorders	0.040 (0,029 ; 0,05)	NS	**0.060 (0.047 ; 0.078)**
Mood disorders	0.030 (0.02 ; 0.04)	NS	**0.049 (0.03 ; 0.065)**
Behavioral syndromes	0.025 (0.016 ; 0.03)	0.020 (0.006 ; 0.03)	**0.030 (0.02 ; 0.046)**
Substance use disorders	0.020 (0.01 ; 0.03)	NS	**0.048 (0.036 ; 0.060)**
Schizophrenia	NS	NS	NS

* β coefficients: interpreted as the increase/decrease in the variable being studied *for each pecentage-unit increase in VTE in the pedigree.*

" Offspring of pedigrees with a high density of VTE, ***especially female VTE density***, are at slightly increased risk for different psychiatric disorders "

Case Presentation

- 28 YO woman with 3 successive pregnancy loss (8,10,16 weeks).
- Family history: DVT in 2 uncles and grandfather on her mother side
- Mother with depression
- Thrombophilia work-up:

Protein S levels in the patient and several family members: 20-30U/dl

How would you manage this case in pregnancy ?

Antepartum and Postpartum LMWH

Clinical Manifestations of Prothrombin G20210A Mutation

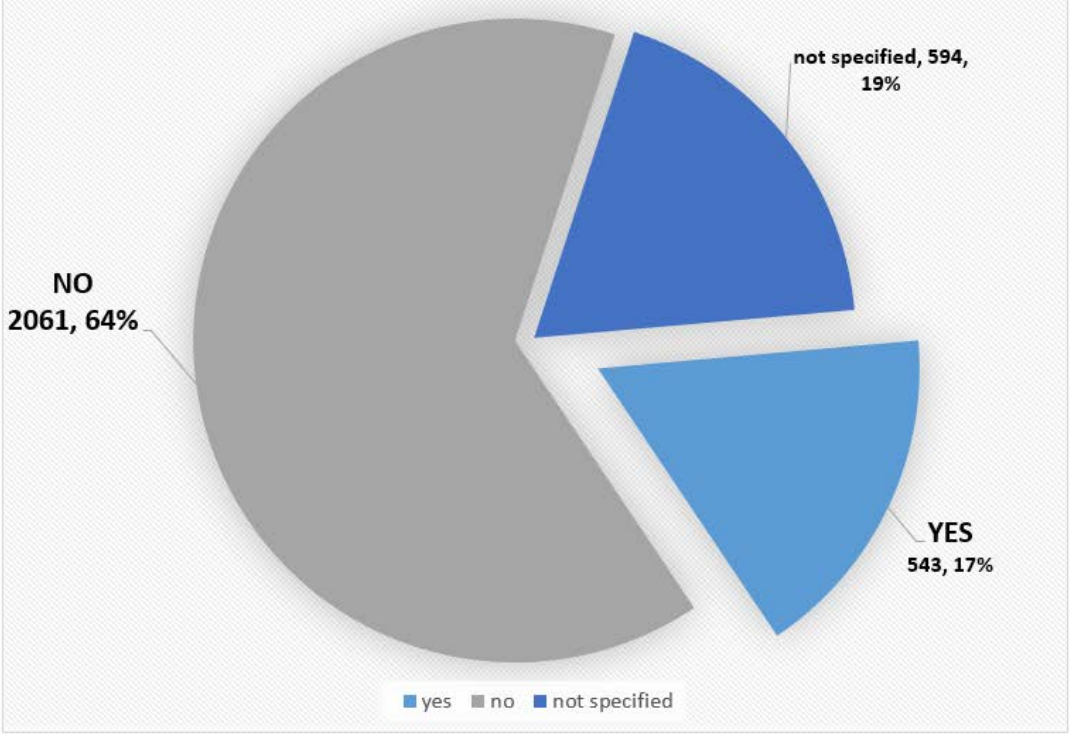
	Homozygous N=30	Heterozygous N=95	Non-carriers N=114
VTE events (%)	15 (50)*	26 (27.4)	19 (16.7)
Recurrent VTE events (%)	6 (20)*	10 (11)	4 (4)
Obstetric complications (%)	12 (66.7)*	14 (23.7)*	14 (21.9)
Neuropsychiatric symptoms (%)	8 (24)†	10(10.5)	12(8)

*$p<0.01$

†$p<0.05$

Tzoran Am J Hematol; 2017

VTE Patients – Psychotropics Use RMC Data



Psychotropic Drugs use and Outcome in Patients Receiving AC Therapy

Patients on psycho-tropics at baseline had:

A similar risk for VTE recurrences (adjusted HR: 0.81; 95% CI: 0.58-1.12),

Risk for major bleeding (adjusted HR: 1.15; 95% CI: 0.97-1.35),

A higher risk for **intracranial bleeding** (adjusted HR: 1.83; 95% CI: 1.32-2.53) or **death** (adjusted HR: 1.44; 95% CI: 1.32-1.57).

Marchena PJ, Thromb Haemost. 2020

Conclusions

- APLA are associated with a wide range of neurological, psychological, and psychiatric manifestations.

- Precise interactions between various antiphospholipid/cofactor autoantibodies (aβ2GP1, anti-prothrombin and anti-annexin A5) and cell-surface receptors on brain endothelial cells, neurons, astrocytes, and glial cells remain to be elucidated.

- Recent indications support a potential neuro-psychiatric impact of hypercoagulability.
- Systematic studies, focusing on the categorization of psychiatric syndromes according to molecular pathogenesis are warranted.

- Data from such studies may pave the way for new therapeutic developments.

Table 1 Mechanisms involved in neuro-psychiatric disease states

	Cell types in brain	Coagulation factors	Ischemia/inflammation	Associated disease
Dementia	Astrocytes,[9] microglia[20,23]	Thrombin[23,43,81,82], FXII, FXI, prekallikrein[89,90]	Complement system,[89,90] Bim,[87] histones, ROS[94]	AD, vascular dementia
Depression	Neurons, glia?	TF, FVII, FX[97–99]	APS, ICAM-1, antiribosomal P antibodies[100]	SLE[100]
Psychosis	Neurons, glia	Low levels of tPA,[105,106] protein S deficiency[106]	High cytokine levels, hyperhomocysteinemia[105]	SLE, APS[105]
MS	Microglia,[66–68] astrocytes[70]	Fibrinogen,[66,67] thrombin[71]	ROS,[66] TF, protein C inhibitors, cytokines[70]	

Khoury, Chapman, STH 2025

Future Agenda



Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Are the antiplatelet and profibrinolytic properties of selective serotonin-reuptake inhibitors relevant to their brain effects?

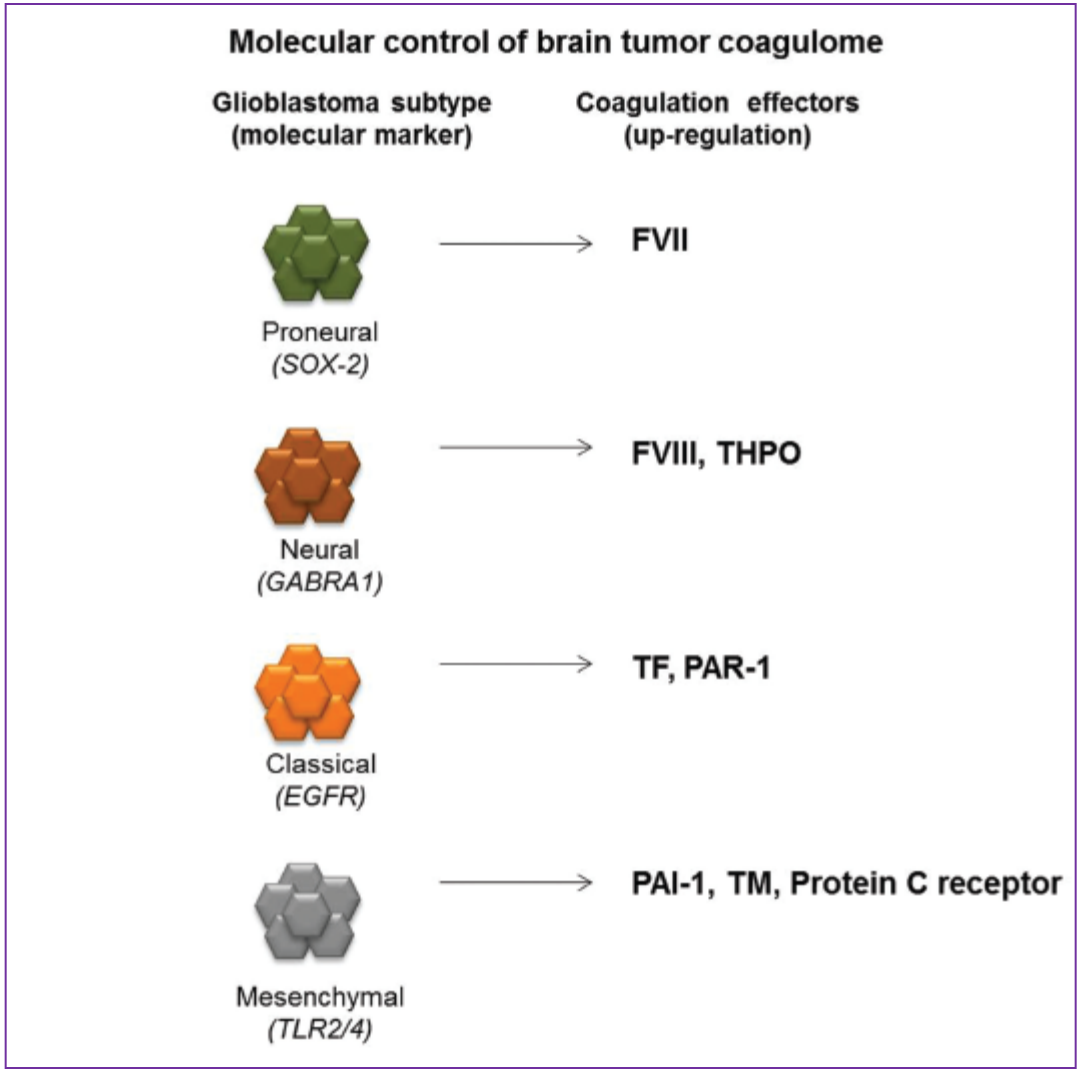
Silvia Hoirisch-Clapauch [a], Antonio E. Nardi [b], Jean-Christophe Gris [c], Benjamin Brenner [d,*]

- Role of severe types of thrombophilia in Psychiatric disorders
- Can we prevent vascular dementia ?
- Effects of antiplatelets / anticoagulants on depression?
- Effects of anticoagulants on psychosis?

Thank you !

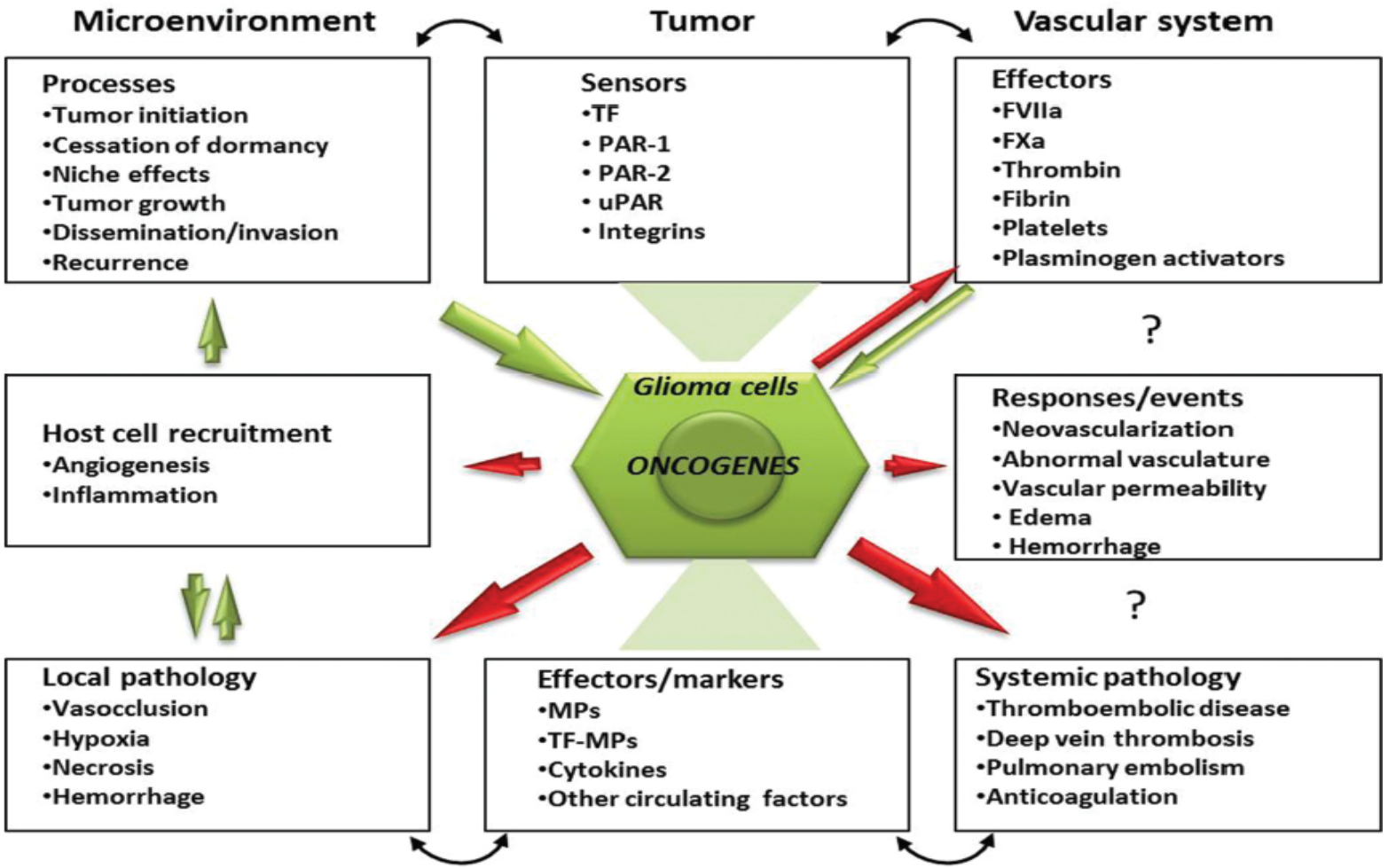


Molecular Control of Brain Tumor Coagulome



Magnus & Rak, Sem Thromb Hemost 2013

Procoagulant network in development of brain tumours (glioma as paradigm)



Magnus & Rak, Sem Thromb Hemost; 2013

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