

Stroke in the Young

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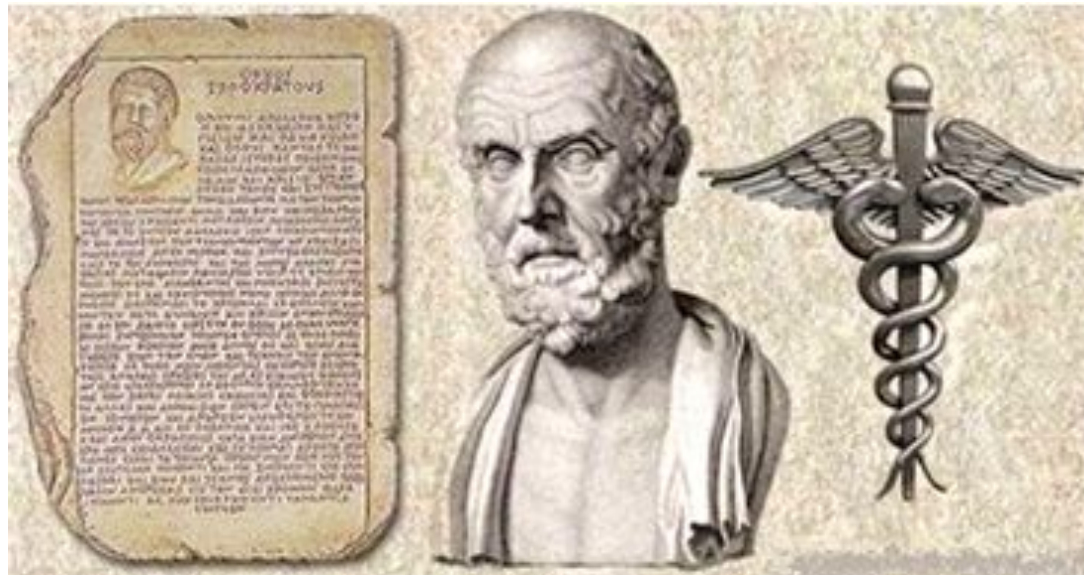
RWJ Barnabas
HEALTH



**Community
Medical Center**

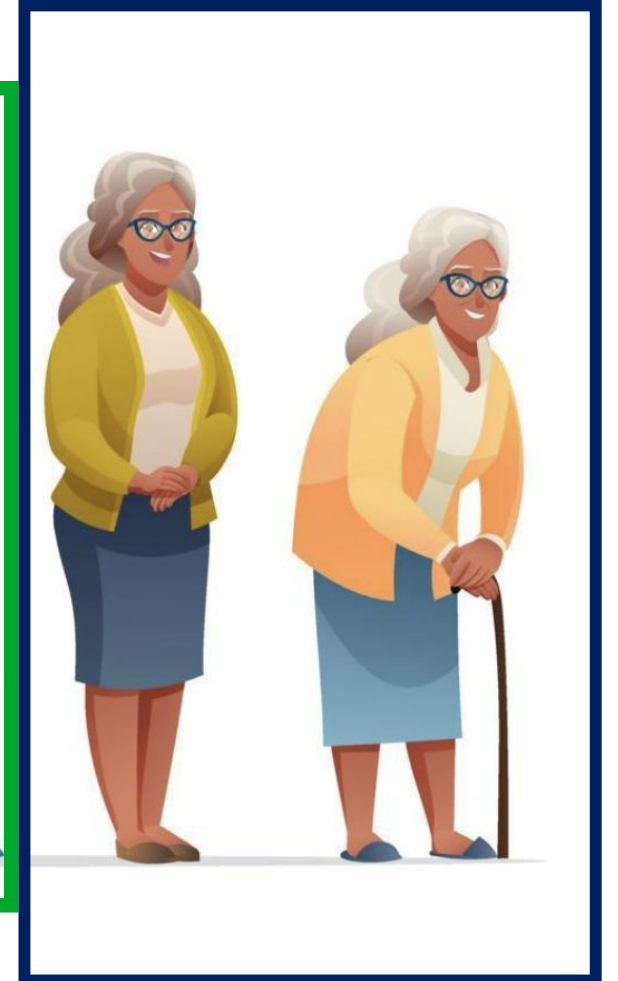
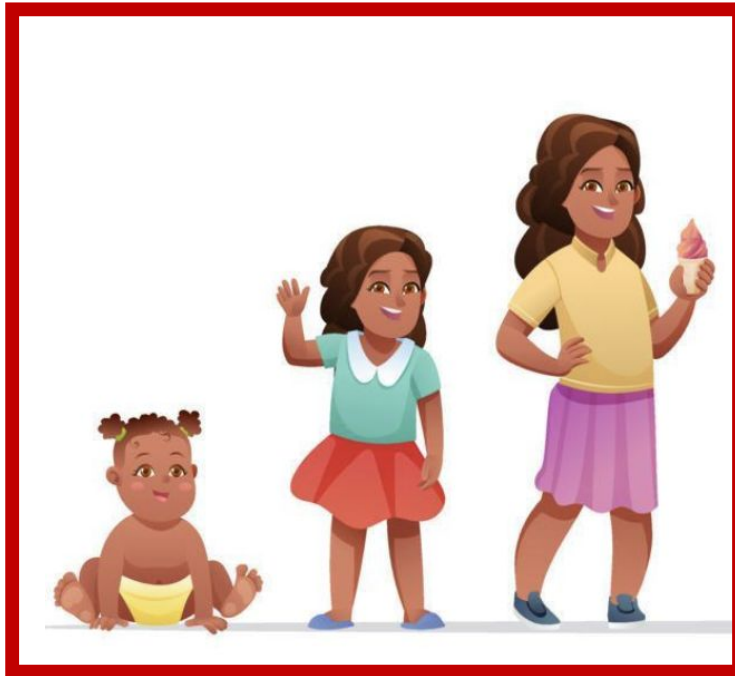
Stroke by Definition

- Originally termed "apoplexy" (Greek for "struck down by violence")
- Historically, described and recorded recorded dates back over 2,400 years to Hippocrates (400 BC)...

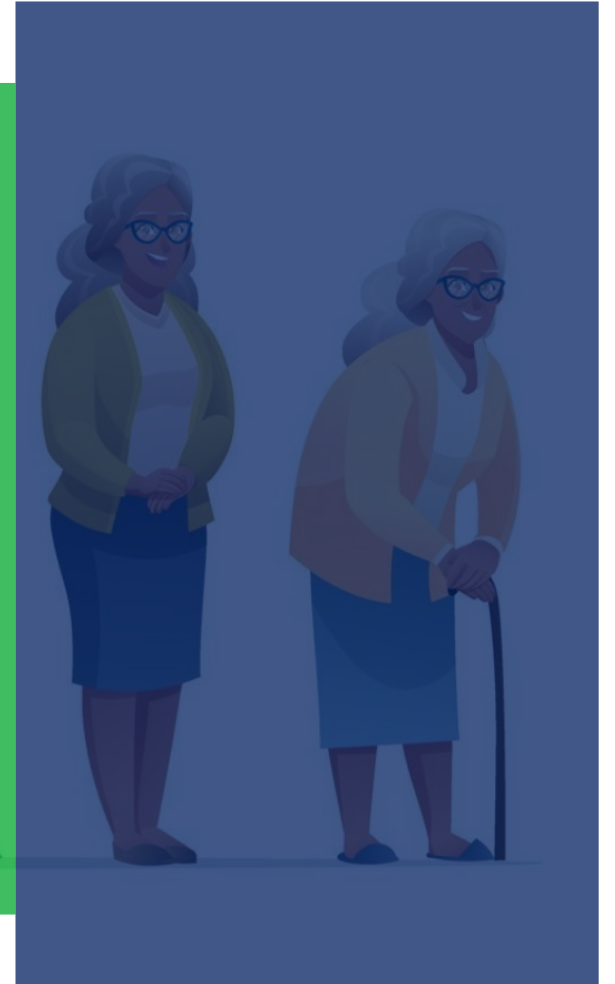
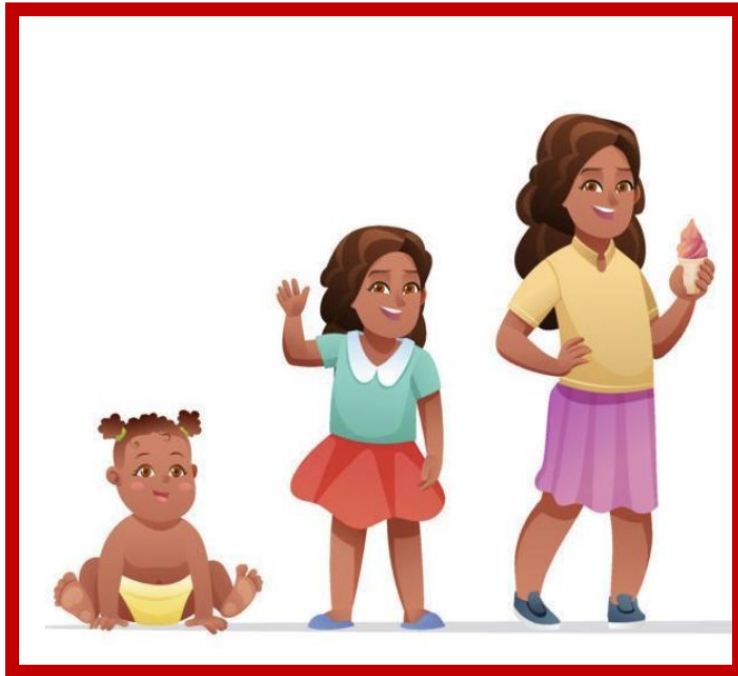


no treatments

Epidemiology of Stroke



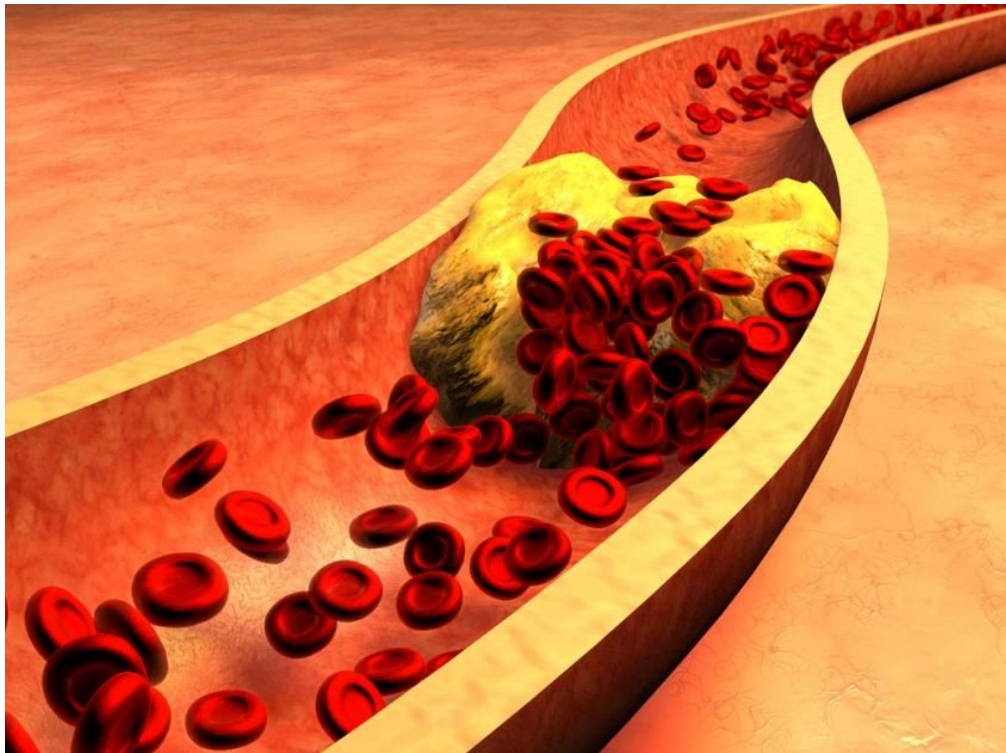
Epidemiology of Stroke



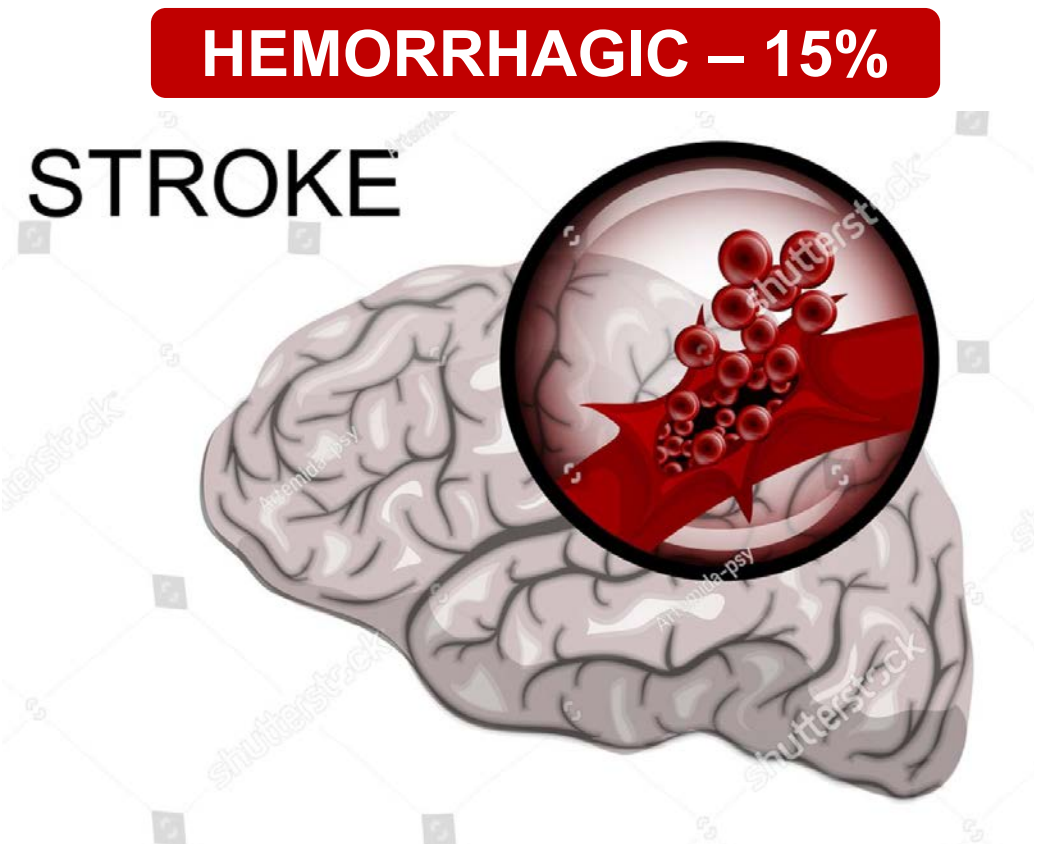
Perinatal to Adolescents

- Perinatal stroke develops between 20 weeks gestation and 1 month of age
 - Unfortunately, in many cases it may be diagnosed later than onset leading to limited therapies
 - While inclusive of many disorders, acute ischemic stroke is the most common presentation

Types of Stroke



ISCHEMIC – 85%



Perinatal to Adolescents

- Childhood stroke develops between 30 days and 18 years of age
 - Acute Ischemic Stroke
 - Hemorrhagic stroke
 - Sinovenous thrombosis.

Perinatal to Adolescents

- Perinatal stroke more frequent than childhood
 - Estimated as high as one per 1100 live births, worldwide
 - Childhood stroke based on multiple population-based studies of stroke in children between 1970 and 2010s found an incidence of 1 per 40,000 children
 - This encompasses all stroke types (AIS, ICH, VTE)

Challenges in Diagnosis

- Perinatal / Infant stroke can be difficult to identify



Challenges in Diagnosis

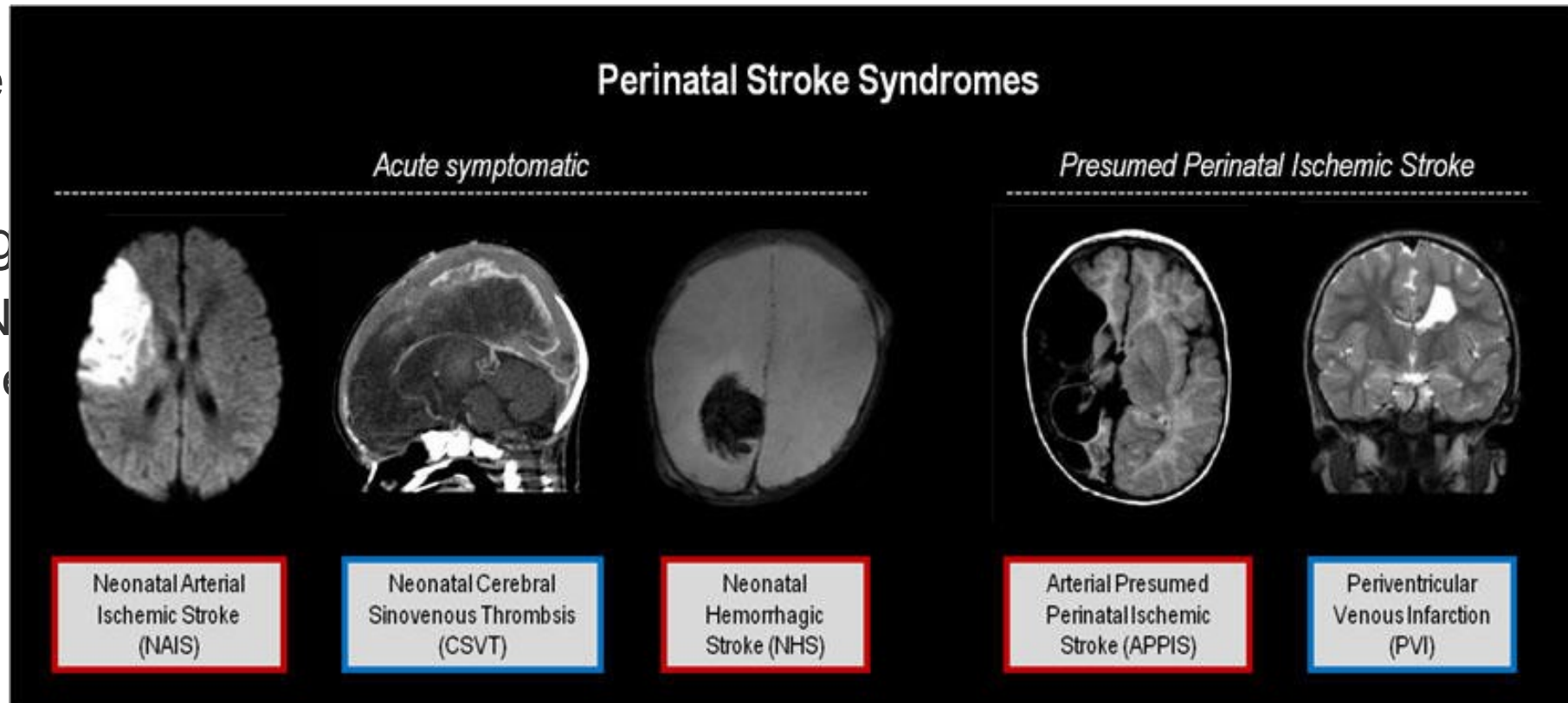
- Most common presentation for infants
 - Seizures
 - Obtundation / Lethargy
 - Failure to Thrive

Challenges in Diagnosis

- Due

- Diag

- N
 - s



Challenges in Diagnosis

- Most common presentation for children
 - Can still present with seizures
 - Frequently focal seizures, e.g., motor, visual aura, etc.
 - Also commonly seen - hemiplegia
 - Not always recognized emergently!

Challenges in Diagnosis

- Studies evaluated commonly used adult stroke assessments in children presenting to the emergency department
 - Cincinnati Prehospital Stroke Scale (CPSS)
 - Recognition of Stroke in the Emergency Room (ROSIER)
- Findings demonstrated poorer sensitivity and greater variability in scoring leading to overall limitations in utility

Challenges in Diagnosis

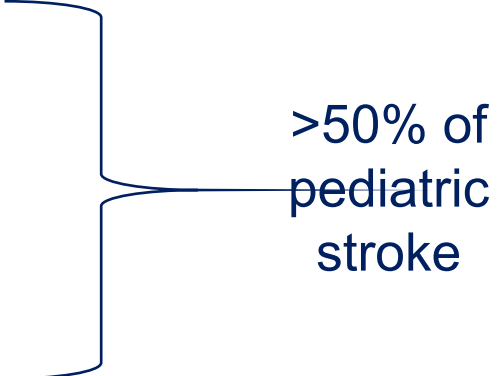
Instructions	Scoring Definition
1a. Level of Consciousness: For children age 2 yrs and up, the investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation. <i>For infants age 4 months up to age 2 years, multiply the score for this item by three, and omit scoring items 1b and 1c.</i>	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues. <i>Modified for children, age 2 years and up. A familiar Family Member must be present for this item: Ask the child "how old are you?" Or "How many years old are you?" for question number one. Give credit if the child states the correct age, or shows the correct number of fingers for his/her age. For the second question, ask the child "where is XX?", XX referring to the name of the parent or other familiar family member present. Use the name for that person which the child typically uses, e.g. "mommy". Give credit if the child correctly points to or gazes purposefully in the direction of the family member. Omit this item for infants age 4 months up to age 2 years. See comment under item 1a.</i>	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes (<i>For children > age 2 years, this command to open and close the eyes is suitable and can be scored as for adults.</i>) and then to grip and release the non-paretic hand. <i>For children > age 2 years, substitute the command to grip the hand with the command "show me your nose" or "touch your nose".</i> Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored. <i>Omit this item for infants age 4 months up to age 2 years. See comment under item 1a.</i>	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly

Categorization of Pediatric Stroke

Childhood Arterial Ischemic Stroke Standardized Classification and Diagnostic Evaluation (CASCADE)

- Developed by the International Pediatric Stroke Study (IPSS) investigators to categorize childhood strokes according to the underlying cause

Categorization of Pediatric Stroke

1. Small vessel arteriopathy
 2. Unilateral focal cerebral arteriopathy (FCA)
 3. Bilateral cerebral arteriopathy
 4. Aortic/cervical arteriopathy
 5. Cardioembolic
 6. Other
 7. Multifactorial
- 
- >50% of pediatric stroke

Categorization of Pediatric Stroke

Arterial dissections are the most common cause of extracranial arteriopathies in children

- Tear in the intimal layer or rupture of the vasa vasorum and hemorrhage into the medial layer
- Such a tear causes platelet activation, clot formation which either occludes the vessel or embolizes material intracranially

Cat

- Intr
ag

- Ex

☰

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Roughhousing is good for kids' brains



Screenshot

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(zuranolone) capsules Ⓞ
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Find out more →

Please see full Prescribing Information, including Boxed Warning and Medication Guide.

at least 12 hours after taking each dose during your 14-day treatment course of ZURZUVAE

- You may not be able to tell on your own if you can drive safely or tell how much ZURZUVAE is affecting you
- Decreased awareness and alertness [central nervous system (CNS) depressant effects]. ZURZUVAE may cause sleepiness, drowsiness, slow thinking, dizziness, confusion, and trouble walking
- Because of these symptoms, you may be at a higher risk for falls during treatment with ZURZUVAE

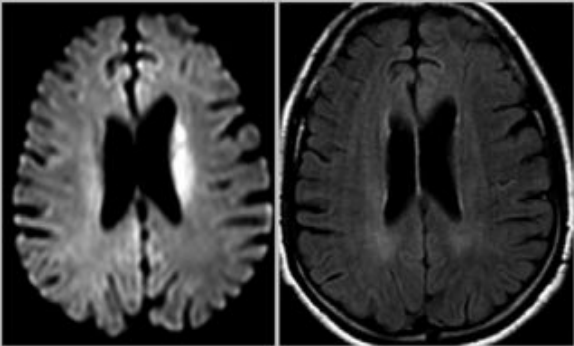
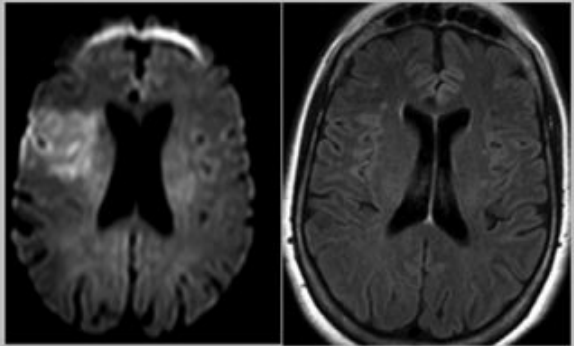
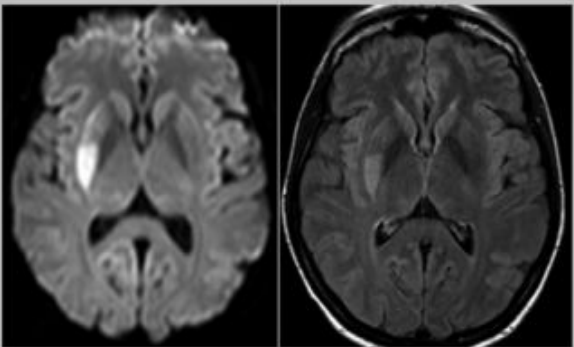
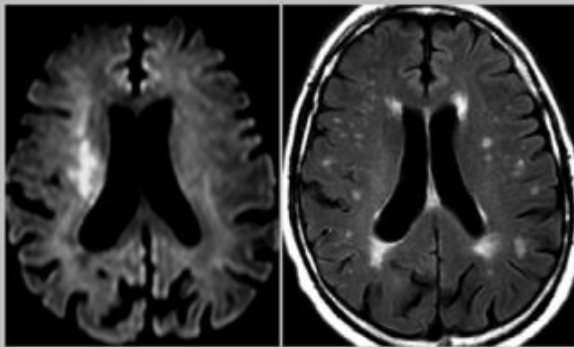
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Evaluation of Pediatric Stroke

ED presentation and mechanisms of triage/transfer to centers with dedicated pediatric expertise are critical

- Stroke screening tool in the ED (based on time of onset and symptoms)
- Code Stroke / Brain Attack protocol initiation
- Standardized emergent imaging

Evaluation of Pediatric Stroke

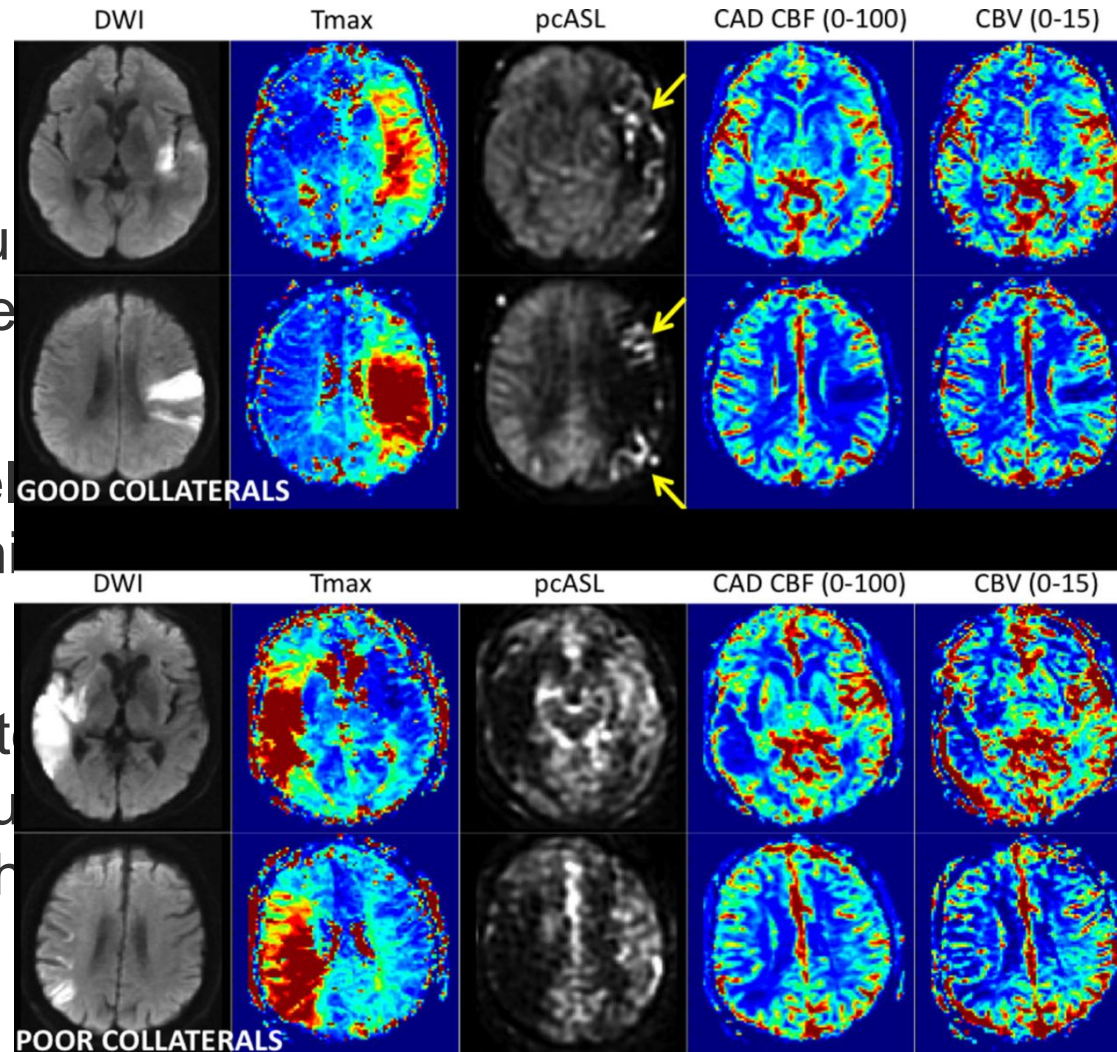
	No FLAIR signal change	Cortical FLAIR change
Negative FLAIR		
	Evident FLAIR signal change	Subtle FLAIR signal change
Positive FLAIR		

e in children because it

Mnemonic	Abnormal	T1	T2
It Be	Hyperacute	I	B
IdDy	Acute	I	D
BiDdy	Early Subacute	B	D
BaBy	Late Subacute	B	B
DooDoo	Chronic	D	D

Evaluation

- Imaging is helpful for selecting patients for acute treatment
- Arterial spin labeling (ASL) is more commonly used in children than adults
- Several ASL techniques are available. ASL is more commonly used in children than adults because it does not require IV contrast and has a lower risk of contrast-induced nephropathy



and selecting

technique that is com

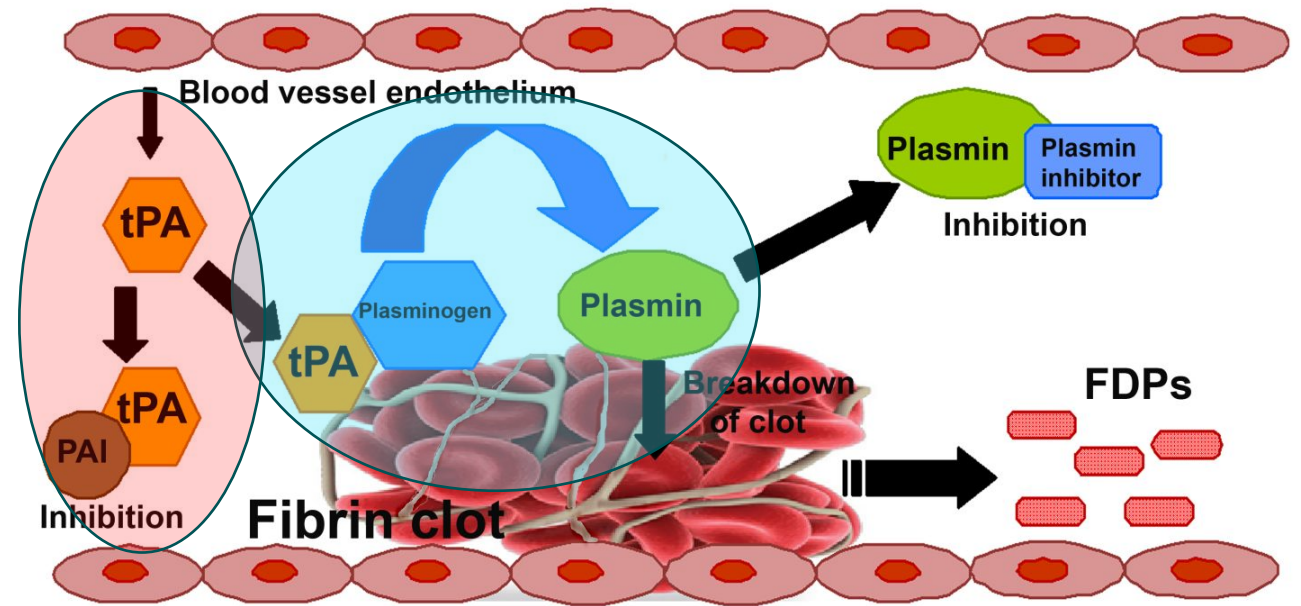
the cerebral perfusion
not require IV
compared to adults

Treatment of Pediatric Stroke

- Perennial dictum in every medical school pediatric rotation...
- “KIDS ARE NOT SMALL ADULTS”

Medication Therapies

- tPA is secreted by the blood vessel endothelium
- PAI-1 cancels out tPA
- Such balance is critical to ensuring thromboembolic complications do not occur



Treatment of Pediatric Stroke

- Perennial dictum in every medical school pediatric rotation...
 - “KIDS ARE NOT SMALL ADULTS”
 - Younger children have lower levels of endogenous tPA and higher levels of Plasminogen Activator Inhibitor-1 (PAI-1) compared with older children and adults
- The Thrombolysis In Pediatric Stroke (TIPS) trial (2009) was a multicenter prospective safety and dose-finding study of IV tPA in childhood stroke
 - Closed prematurely due to lack of participant accrual

Treatment of Pediatric Stroke

- TIPS did establish framework for further evaluation / study for pediatric stroke evaluation
- TIPSTER study (2020)
 - Retrospectively analyzed the safety of IV thrombolysis for acute stroke in 26 children at prior TIPS sites
 - Estimated 2.1% rate of symptomatic intracranial hemorrhage after thrombolysis in children (no real ICH, only two with epistaxis)
 - As Intracranial Hemorrhage rates range to 6.4% in adult studies, IV thrombolysis for acute stroke is at least as safe in children when compared to adults

Treatment of Pediatric Stroke

- tPA remains rare in pediatric stroke, but is given in 5-7% of patients presenting without contraindication
 - Adults range between 6-10%, with 90% treated if presenting within window to comprehensive stroke centers
 - Time window, dosing regimen, benefit, TNK to tPA comparison all remain without sufficient data to draw informed conclusions

Treatment of Pediatric Stroke

Mechanical Thrombectomy

- More data suggests thrombectomy in pediatric patients provides benefit without increased risk

Treatment of Pediatric Stroke

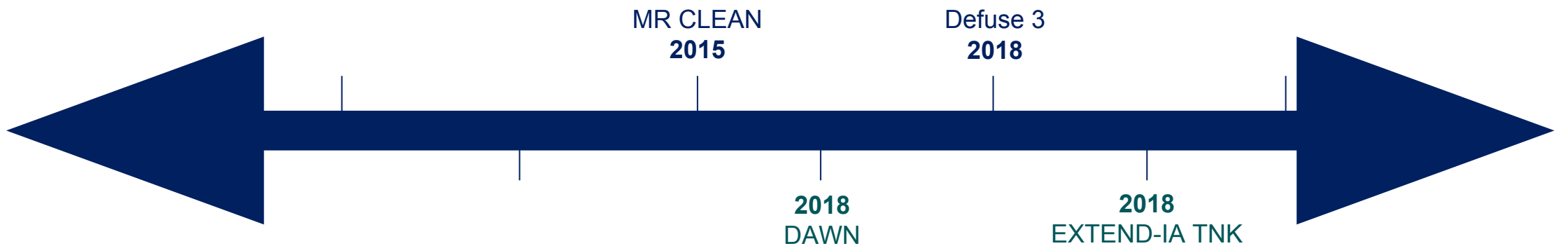
- Save-ChildS study (2019)
 - 73 children who underwent thrombectomy for acute ischemic stroke
 - 1 patient developed symptomatic intracranial hemorrhage (1.4%)
 - Meta-analysis of data and other studies later showed between 53 and 90% clinical improvement in symptoms for thrombectomy patients (NNT for adults 2-3)

Treatment of Pediatric Stroke

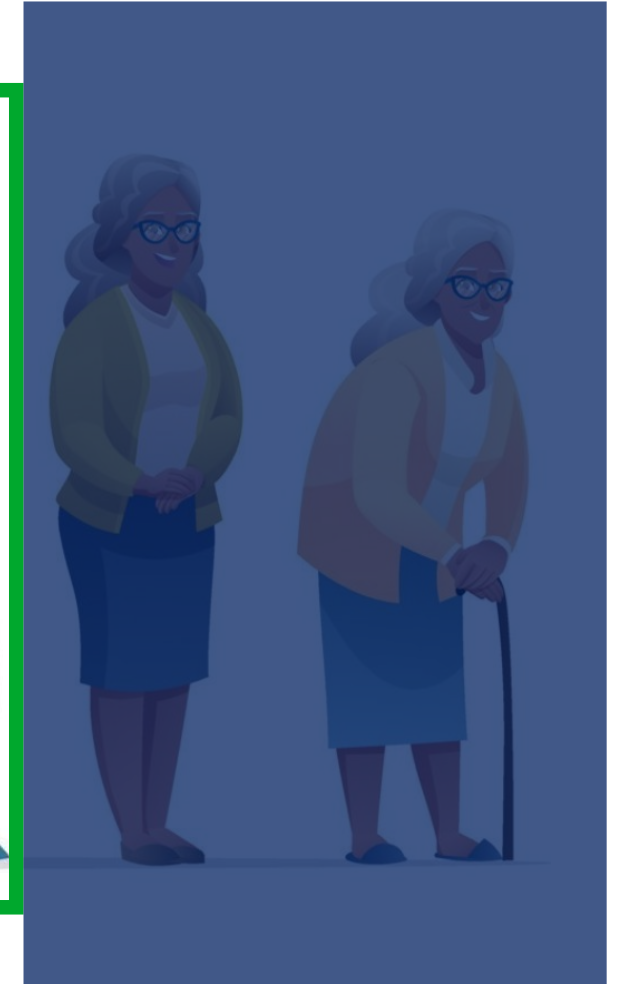
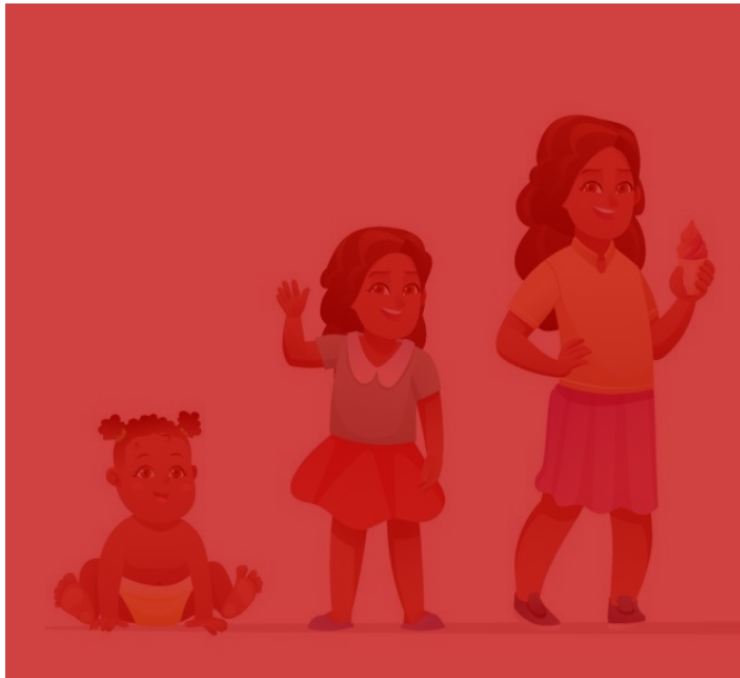
- National Inpatient Sample (2022)
 - 190 children treated with thrombectomy
 - No patient with contrast-induced kidney injury
 - No patient with periprocedural iatrogenic ischemia or hemorrhage

Treatment of Pediatric Stroke

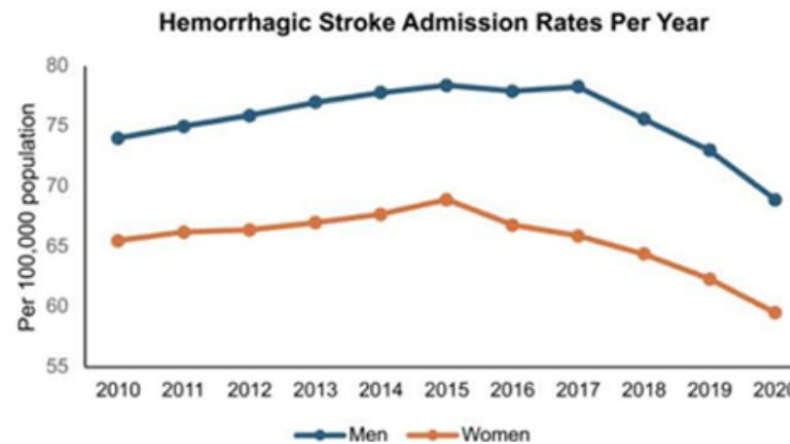
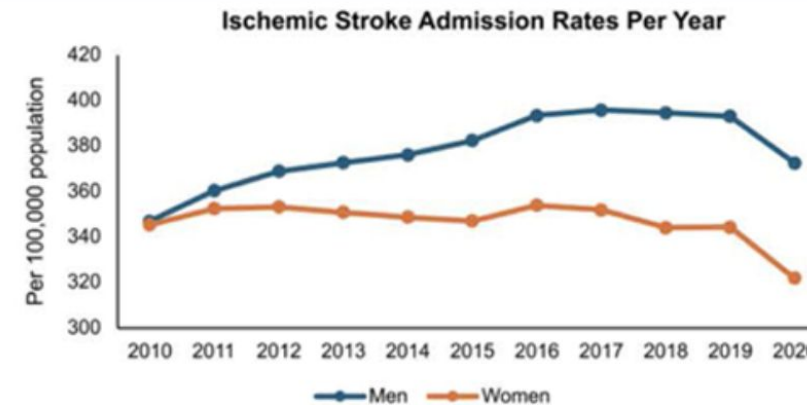
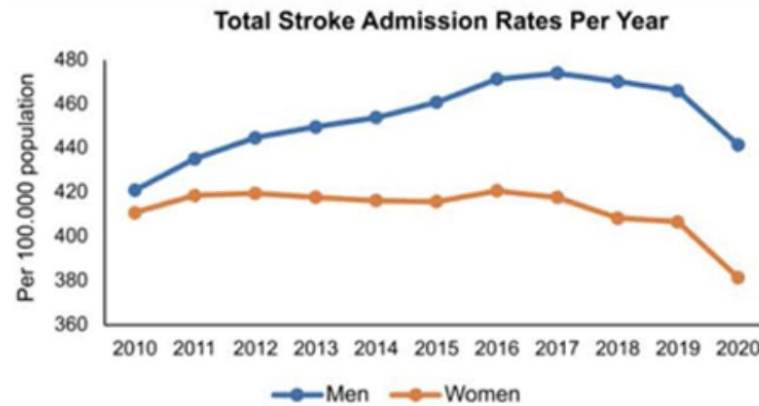
- Cross-sectional data derived from the “Kids’ Inpatient Database”
 - Thrombectomy was used in 1.2% of children admitted for acute ischemic stroke in 2009
 - Thrombectomy was used in 3.0% of similar children admitted for acute ischemic stroke in 2019



Epidemiology of Stroke

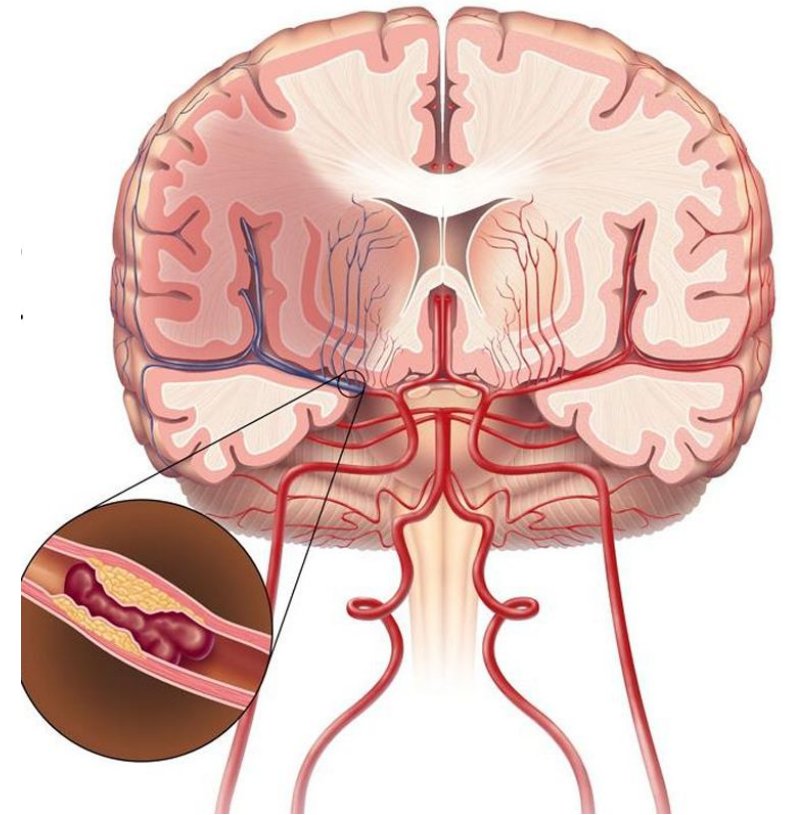


Epidemiology of Stroke



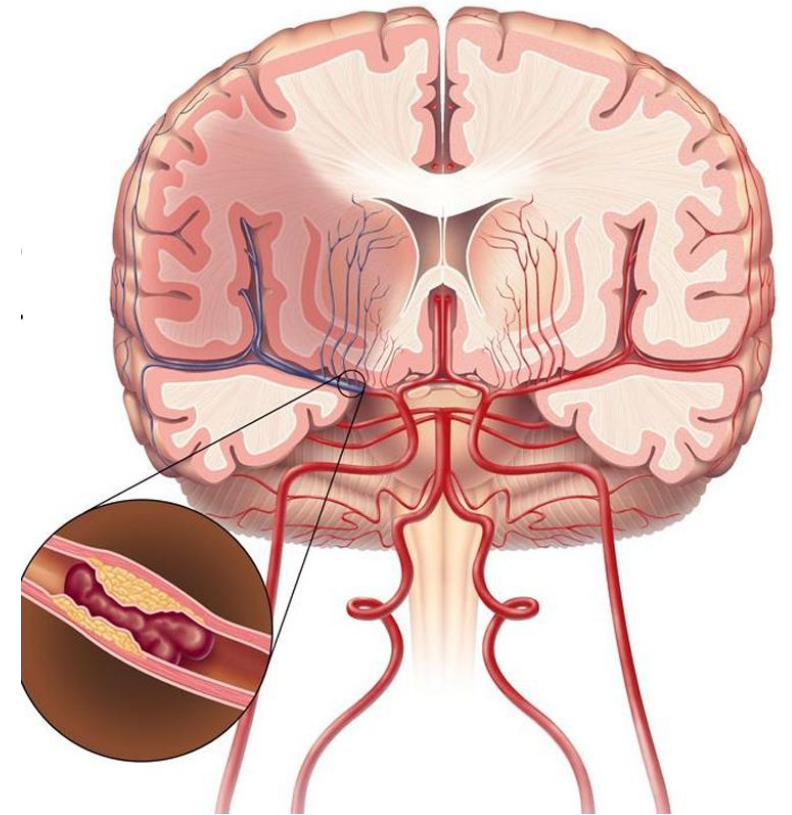
How Stroke Varies in the Young Adult

- Unlike Age > 45, Young women are at a disproportionately increased risk of ischemic strokes compared with their male counterparts
 - 44% more women ≤ 35 years old with ischemic strokes than men
 - Between ages 35 – 45 years old, proportion narrows



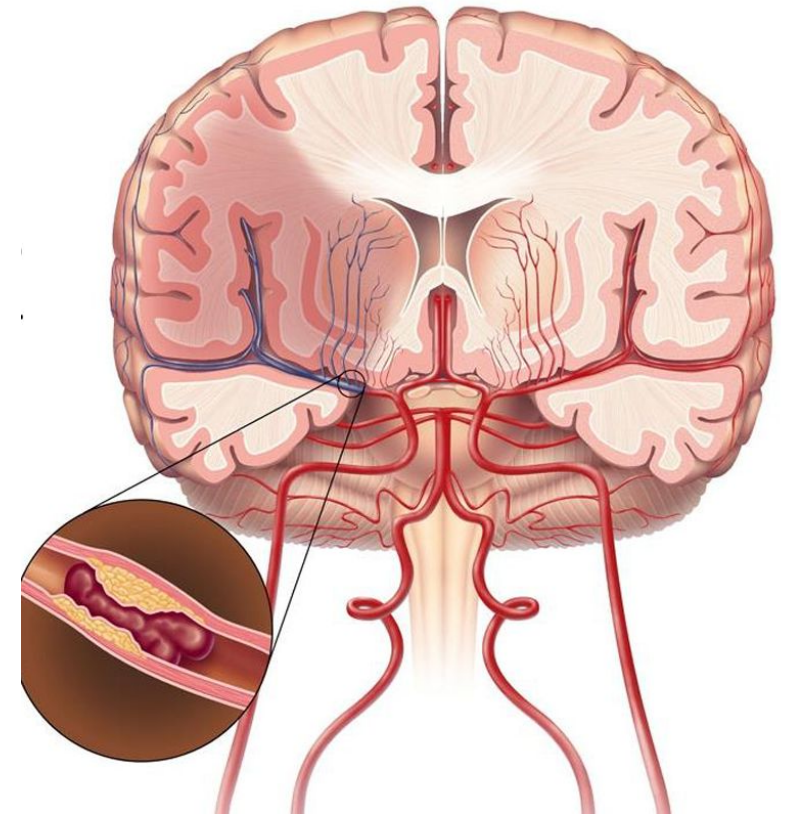
How Stroke Doesn't Vary in the Young Adult

- Unfortunately, ethnic variability in stroke is consistent between older and younger
- Northern Manhattan Stroke Registry
 - African Americans were 2.4 times more likely to experience stroke than white
 - Hispanics were 2.5 times more likely to experience stroke than white



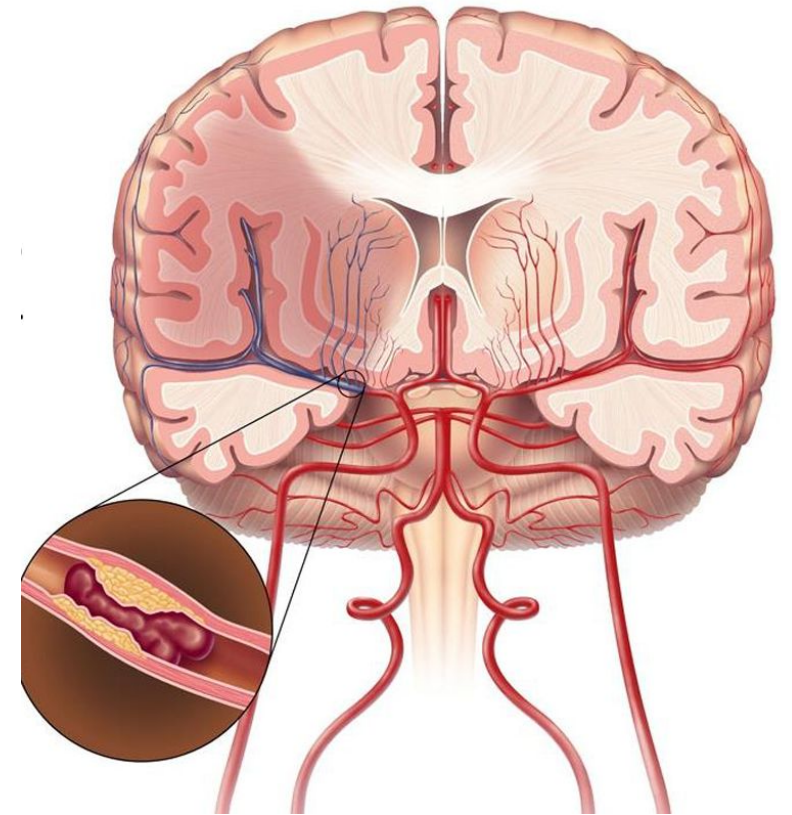
How Stroke Doesn't Vary in the Young Adult

- Baltimore Stroke Registry
 - Rates of Hemorrhagic and Ischemic Stroke both are higher in African Americans
 - > 2 times more frequent in Ischemic
 - > 3 times more frequent in Hemorrhagic



How Stroke Doesn't Vary in the Young Adult

- Baltimore Stroke Registry
 - AA patients also poorer in outcome, and 30-day post stroke mortality
 - Patient populations had same access and rates of treatment with medical and surgical therapies



Stroke Risk Factors

Stroke in Young Adults

- Defined as age < 50 years
- Estimated to account for 10–14% of all strokes
- Rate of stroke increasing over past decades

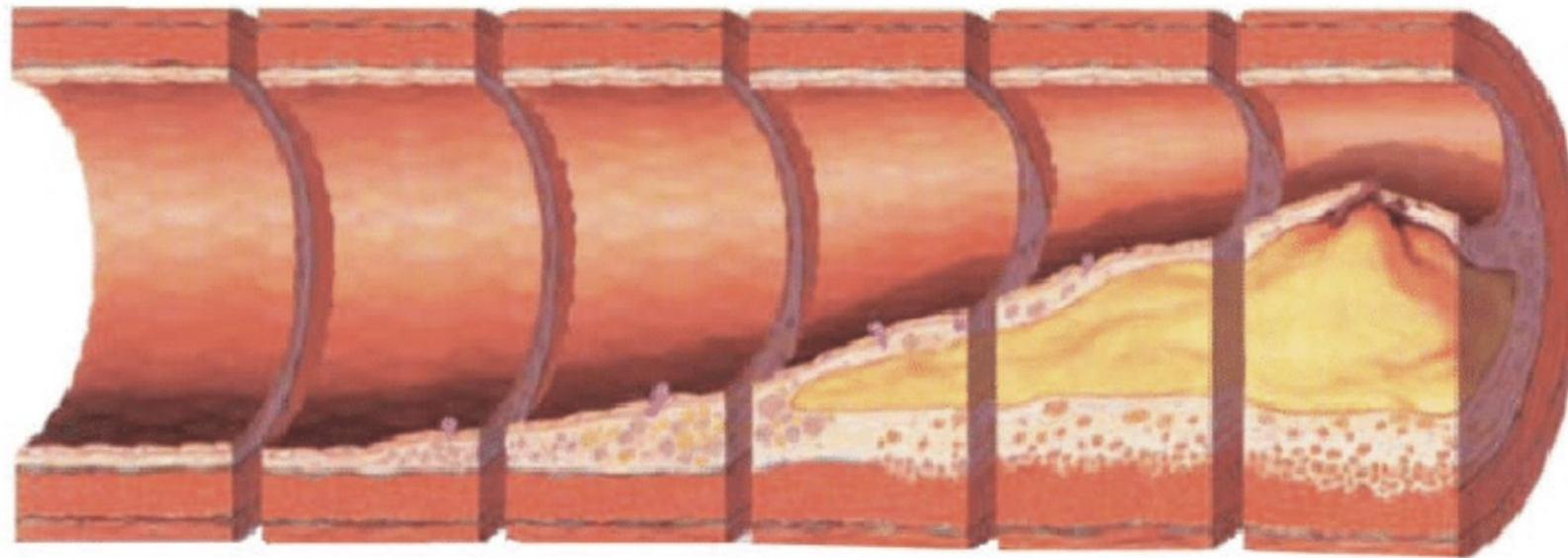
Irreversible

- Age
- Male Gender

Incidence of stroke for ages 20–44

- 17 per 100,000 US adults (1993)
- 28 per 100,000 US adults (2015)

Why is Stroke Uncommon in Young



Normal
Vessel

Fatty
Streaks

Fibro-fatty Plaque

Vulnerable
Plaque

- This progression takes years-to-decades
- Can speed up in HIV, inflammatory disease, or with genetic mutations

Stroke Prevalence in the United States

Prevalence of these risk factors **DOUBLED** each decade from 2000-

Traditional risk factors



Hypertension



Hypercholesterolemia



Smoking



Obesity



Diabetes mellitus

Stroke in Young Adults



Unique risk factors



Migraine



Pregnancy and postpartum



Oral contraceptives



Illicit drug use



Hypercoagulable state

Elements which are more prevalent in the less than 50-year-old

Estrogen Medications, a Brief History



1914

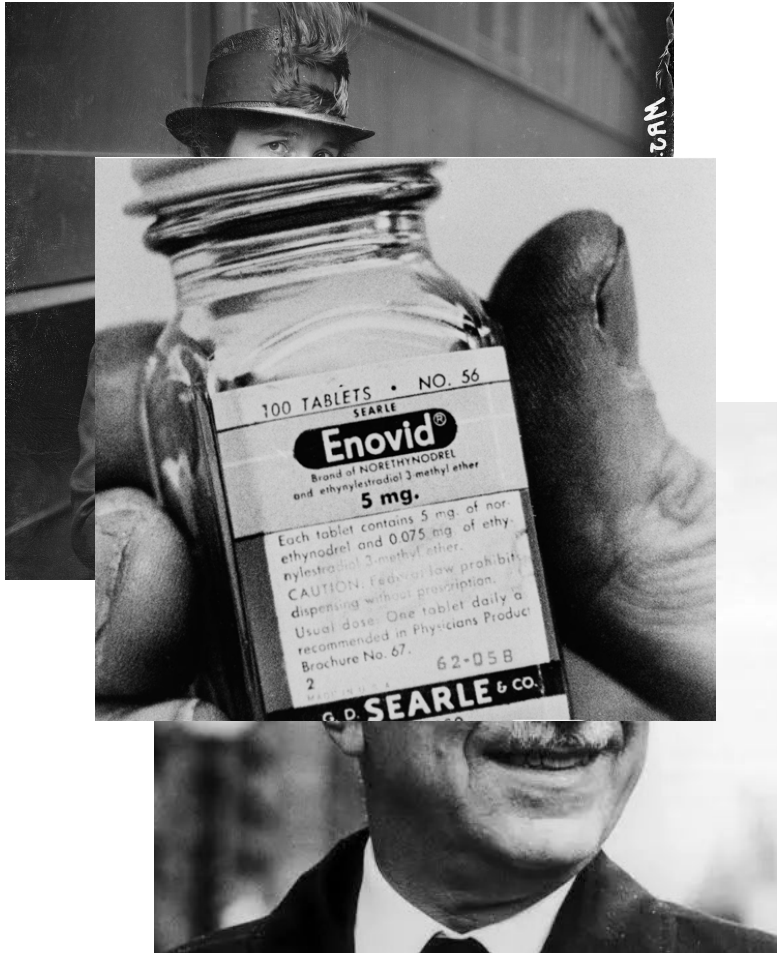
Margaret Sanger begins advocating for women to avoid pregnancy when they are ill or experiencing poverty in her journal *The Woman Rebel*

She coined the term "birth control"

1923

Margaret Sanger opens the Birth Control Clinical Research Bureau, the first legal birth control clinic, in Manhattan

Estrogen Medications, a Brief History



1950s

Dr. Gregory Pincus, biologist focusing on mammalian reproduction began work with support of Sanger to produce hormonal based therapies to prevent conception

1950s

Pincus begins clinical trials of the estrogen based oral contraceptive pill in Puerto Rico, Haiti, and Mexico City. Women in these trials often experienced severe side effects.

Estrogen Medications, a Brief History

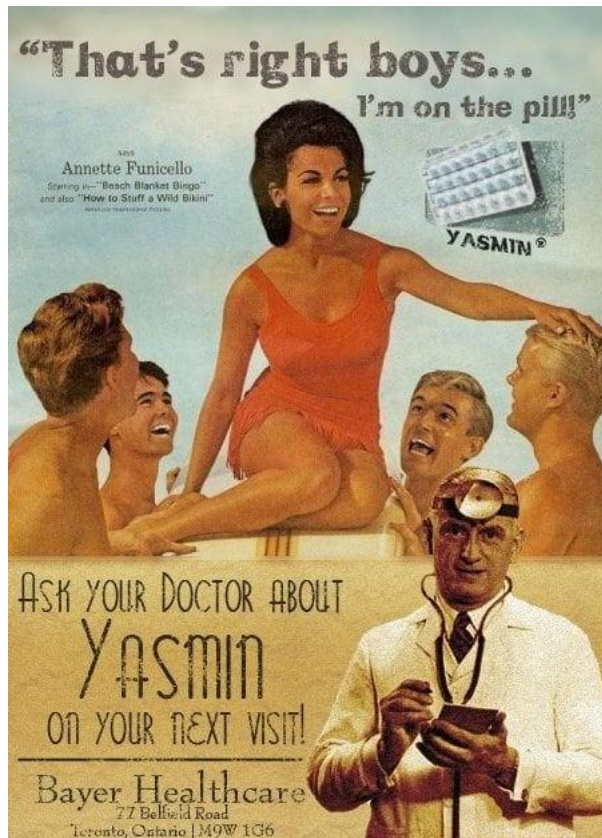


May 1960

ENOVID was approved by the FDA for menstrual regulation, with a warning label that said it stopped ovulation.

Commentary later by Sanger - "...in other words, the real purpose of the drug was listed as if it were a side effect.

Estrogen Medications, a Brief History



How Yaz Helps Women in Acne Treatment

Yaz contains a combination of two hormones, ethinyl estradiol and drospirenone. Ethinyl estradiol is a form of estrogen, while drospirenone is a progestin with anti-androgenic properties.

FACTS

By regulating hormone levels in your body, the active ingredients in Yaz can help bring about hormonal balance.

Yaz can keep those pesky pimples at bay by controlling sebum, unclogging pores, and reducing inflammation.

Clearer skin in 3 - 6 months!

As with any medication, it's essential to consult a doctor to determine if Yaz is the right choice for you.



Slynd
(drospirenone) tablets, 4mg

Your health is unique to you. **Make sure your birth control is too.**

Use our Doctor Discussion Guide.

Estrogen Medications - Hypercoagulability

Unfortunately, over the past ~70 years, we have learned the use of systemic estrogen therapies are associated with higher rates of stroke in younger women and post-menopausal women

- Oral Contraceptive Pills (OCP) with estrogen have been known to be associated with up to **three times the risk of stroke** - World Health Organization (WHO)

Estrogen Medications - Hypercoagulability

JAMA meta-analysis of studies performed between 1960-1999 of over 803 studies, narrowed to 16 high quality analyses

- Stroke was **present at a rate of 2.75 times** in those women using high-dose, estrogen-based OCPs for stroke compared to those not taking estrogen-based medications (RR, 2.75; 95% CI, 2.24-3.38)

Estrogen Medications - Hypercoagulability

JAMA meta-analysis of studies performed between 1960-1999 of over 803 studies, narrowed to 16 high quality analyses

- Lower dose relative risk was 1.93 (95% CI, 1.35-2.74) for low-estrogen preparations in population-based studies
- Findings suggested an additional 4.1 ischemic strokes per 100,000 nonsmoking, normotensive women using low-estrogen OCs
- Progestin-only did not convey any increased relative risk of stroke

Estrogen Medications - Hypercoagulability

NEJM published a large population based Danish study (n = 1,626,158 women)

- Risk of stroke increased **by a factor of 1.3 to 2.3** with those that included ethinyl estradiol at a dose of 30–40 µg
- Risk of stroke increased **by a factor of 0.9 to 1.7** with oral contraceptives that included ethinyl estradiol at a dose of 20 µg
- Reduced risk since 2000 can be partially attributed to decreased ethinyl estradiol dosing and alternate formulations without estrogens

Hypercoagulability – Estrogen Medications

Two common causes of stroke in younger women and post-menopausal women relate to the use of estrogen therapy

- Reduced risk since 2000 can be partially attributed to decreased ethinyl estradiol dosing and alternate formulations without estrogens
- However, comorbidities increase risk of stroke in patients with any estrogen-based formulation
 - Diabetes
 - Tobacco abuse
 - Undiagnosed underlying hypercoagulability

Hypercoagulability – Estrogen Medications

Hormone Replacement Therapy and Estrogen-based OCPs are most associated with Venous Thrombosis / Thromboembolic disease

- Most commonly in first year of use
- More common in oral or transdermal therapy
- More common in women with undiagnosed underlying hypercoagulability

Hypercoagulability

Congenital hypercoagulable disorders

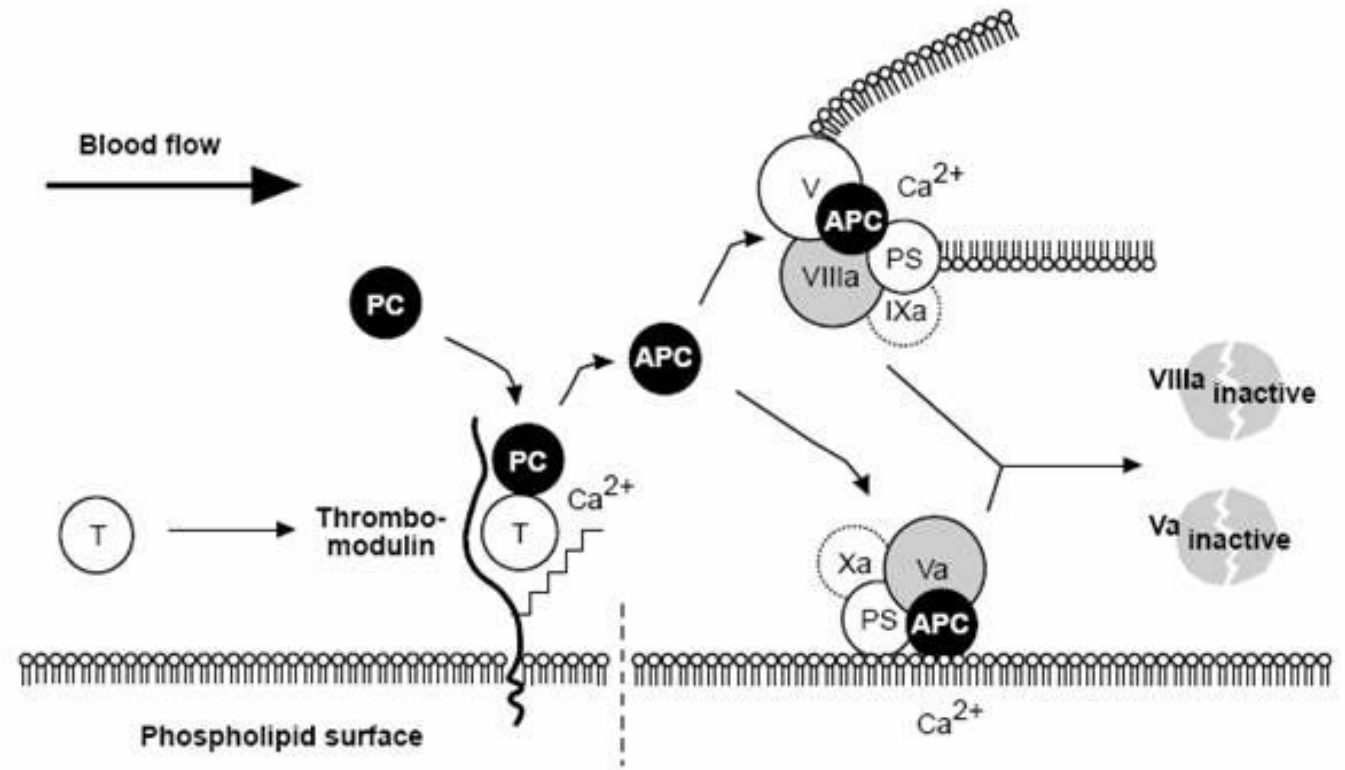
- Factor V Leiden (FVL)
- Protein C or S deficiency
- Prothrombin G20210A gene mutation

Acquired hypercoagulable disorders

- Antiphospholipid Syndrome (APLS)
- Malignancy
- Estrogen Therapy

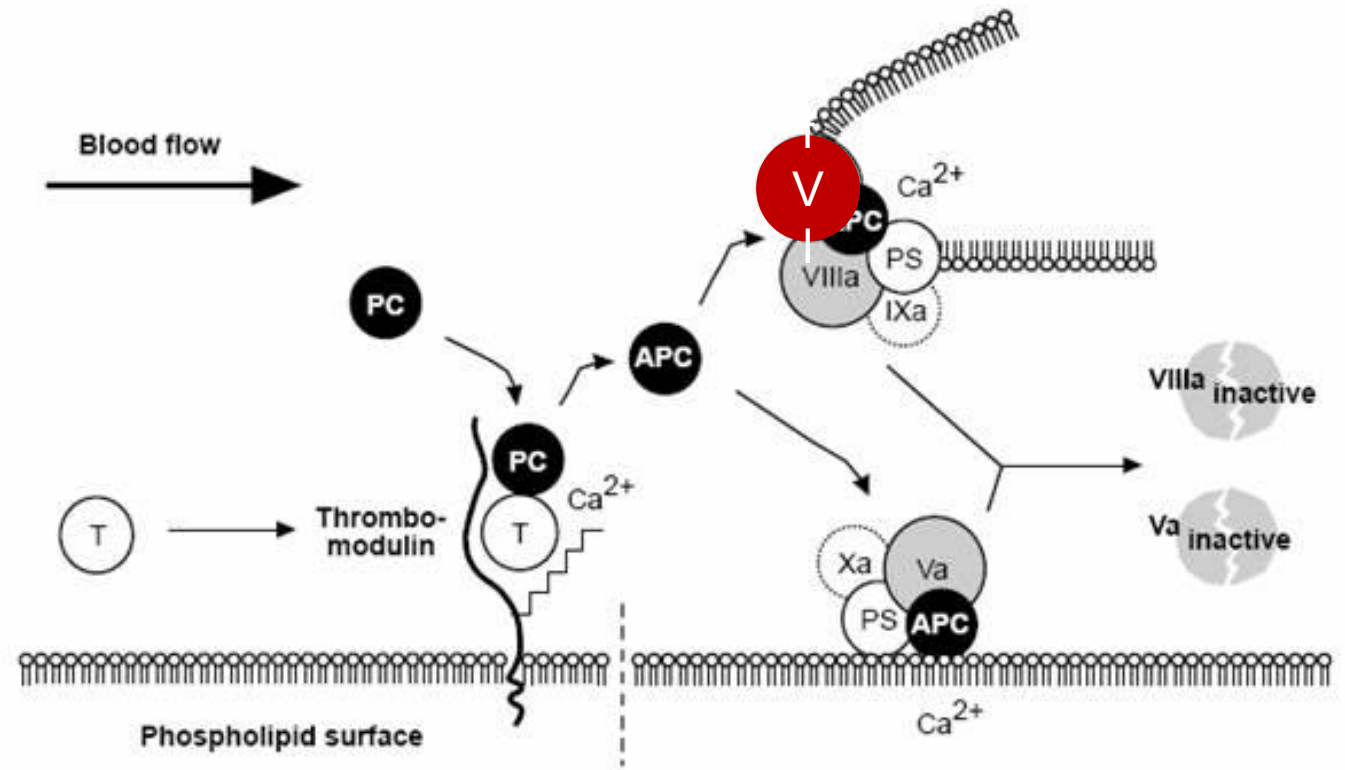
Hypercoagulability – Congenital Disorders

- Factor V Leiden
 - Polymorphism of Factor V which renders it resistant to APC



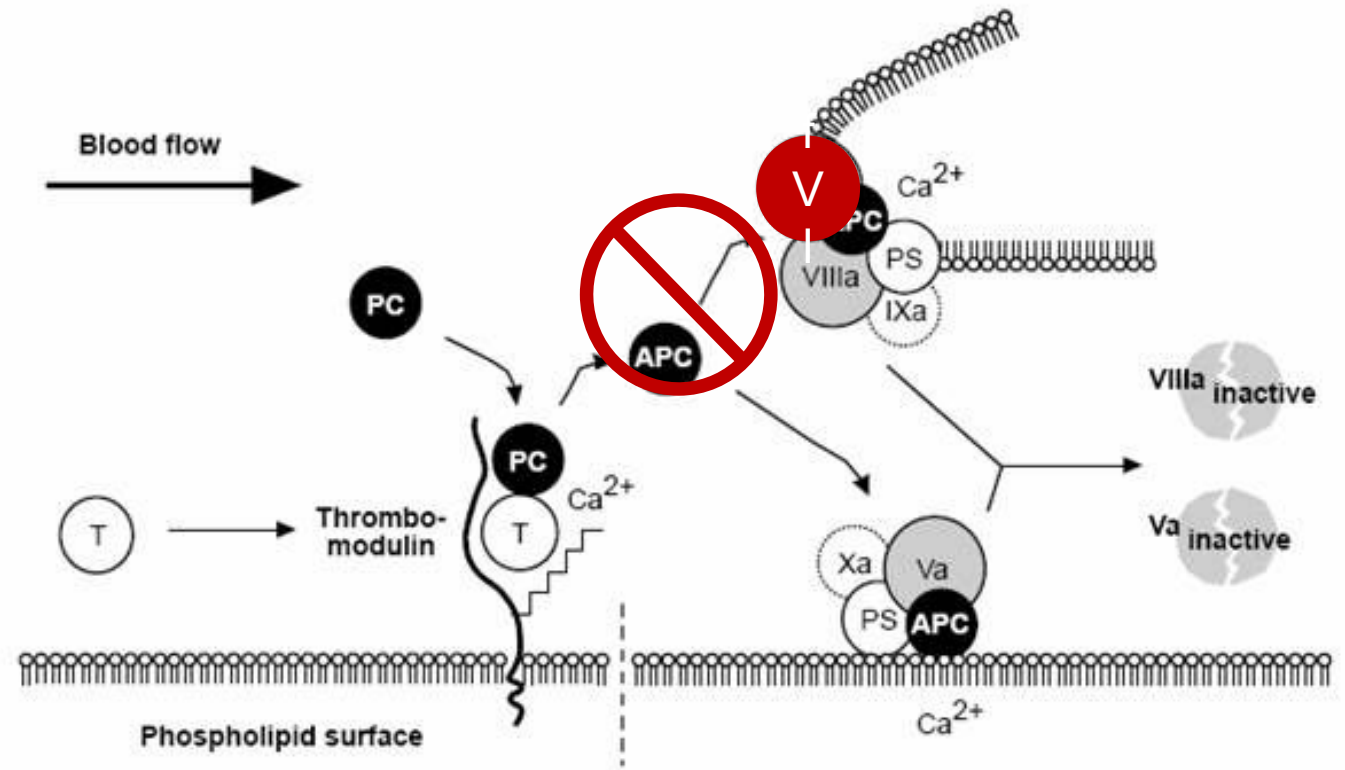
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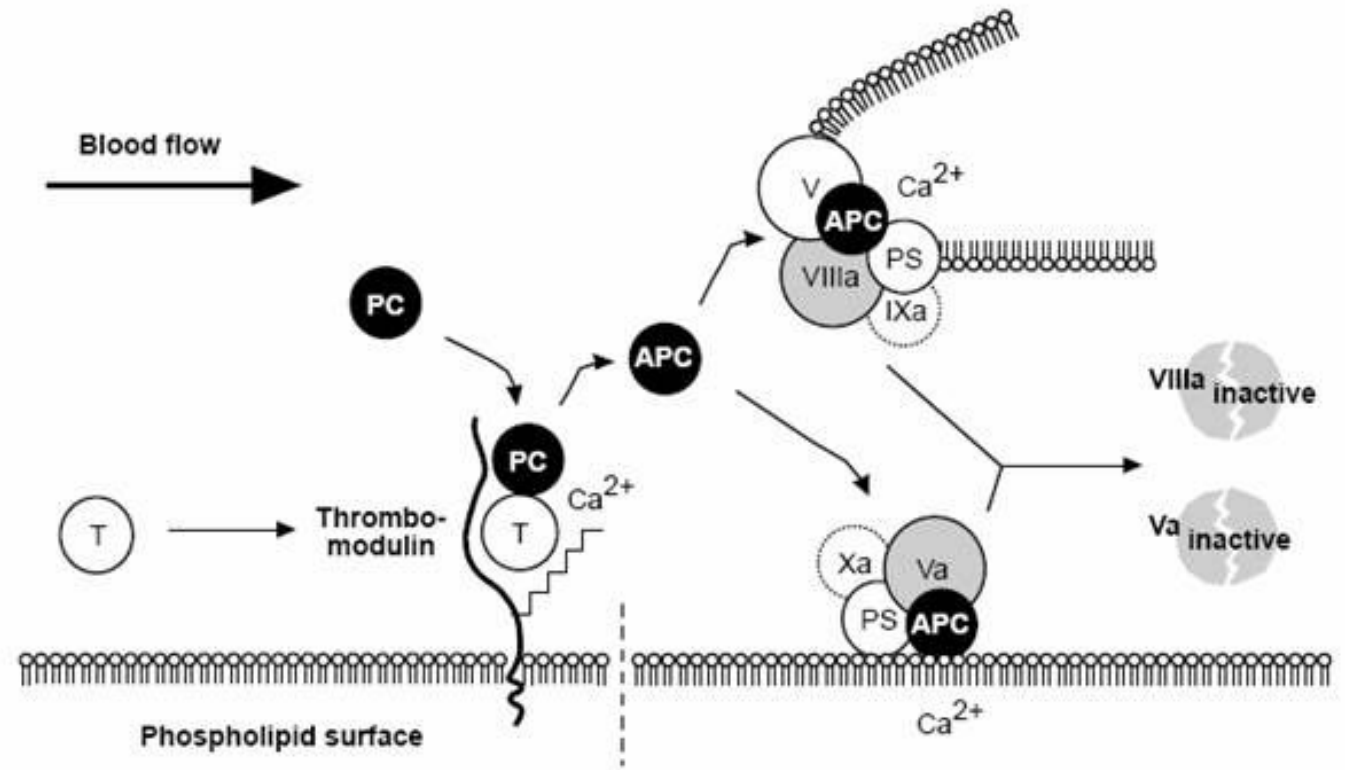
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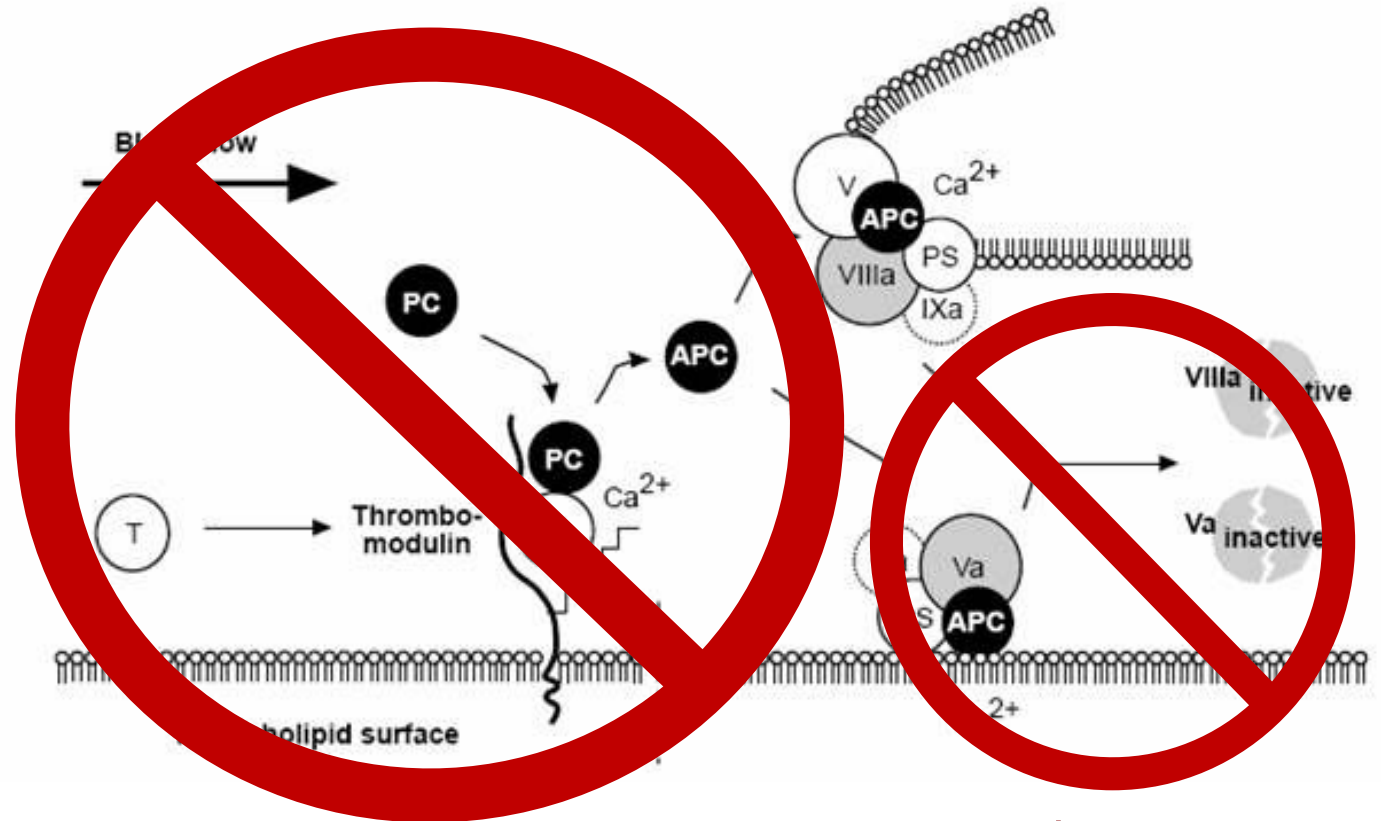
Hypercoagulability – Congenital Disorders

- Protein C Deficiency
 - Protein C binds with Thrombomodulin (T) / Thrombin (IIa) complex
 - Once activated (APC) it breaks down protein V and VIII



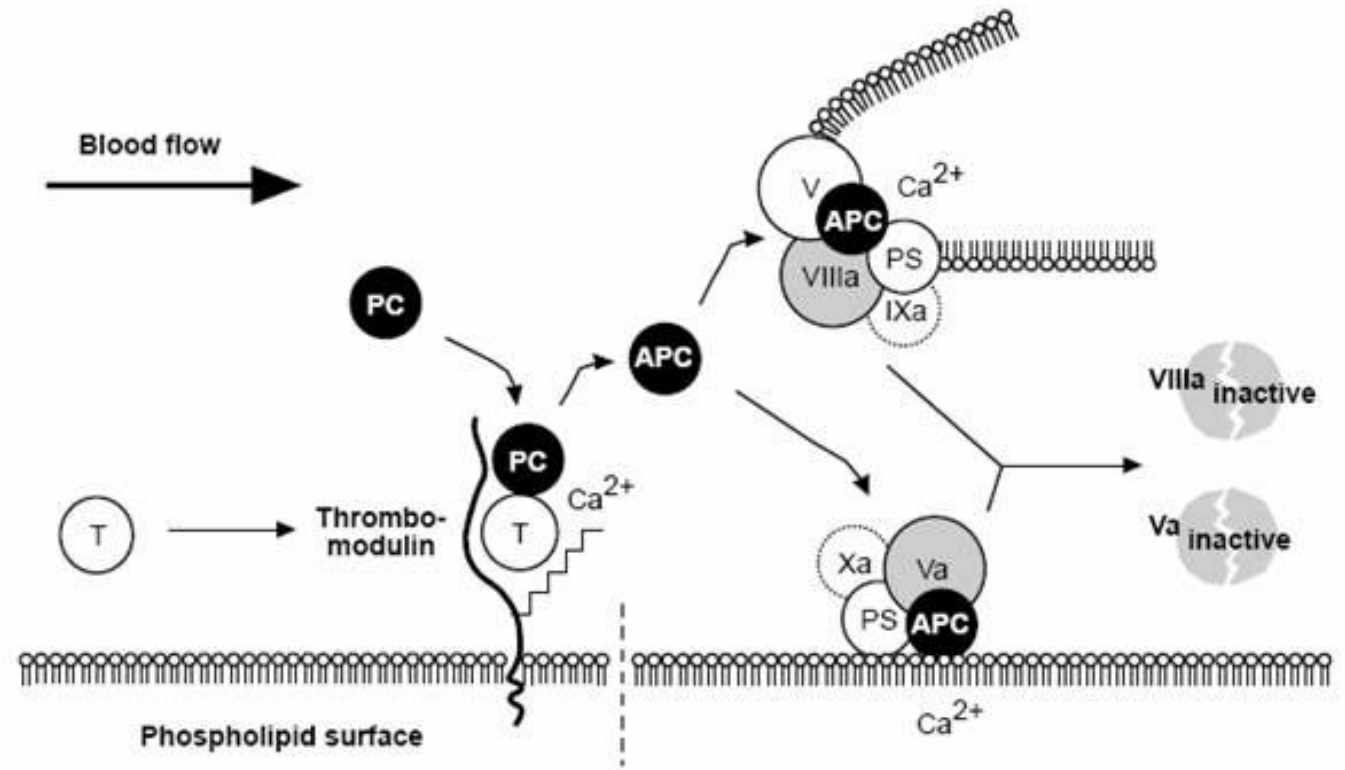
Hypercoagulability – Congenital Disorders

- Protein C Deficiency
 - With Protein C deficiency, less APC forms resulting in persistent thrombus formation



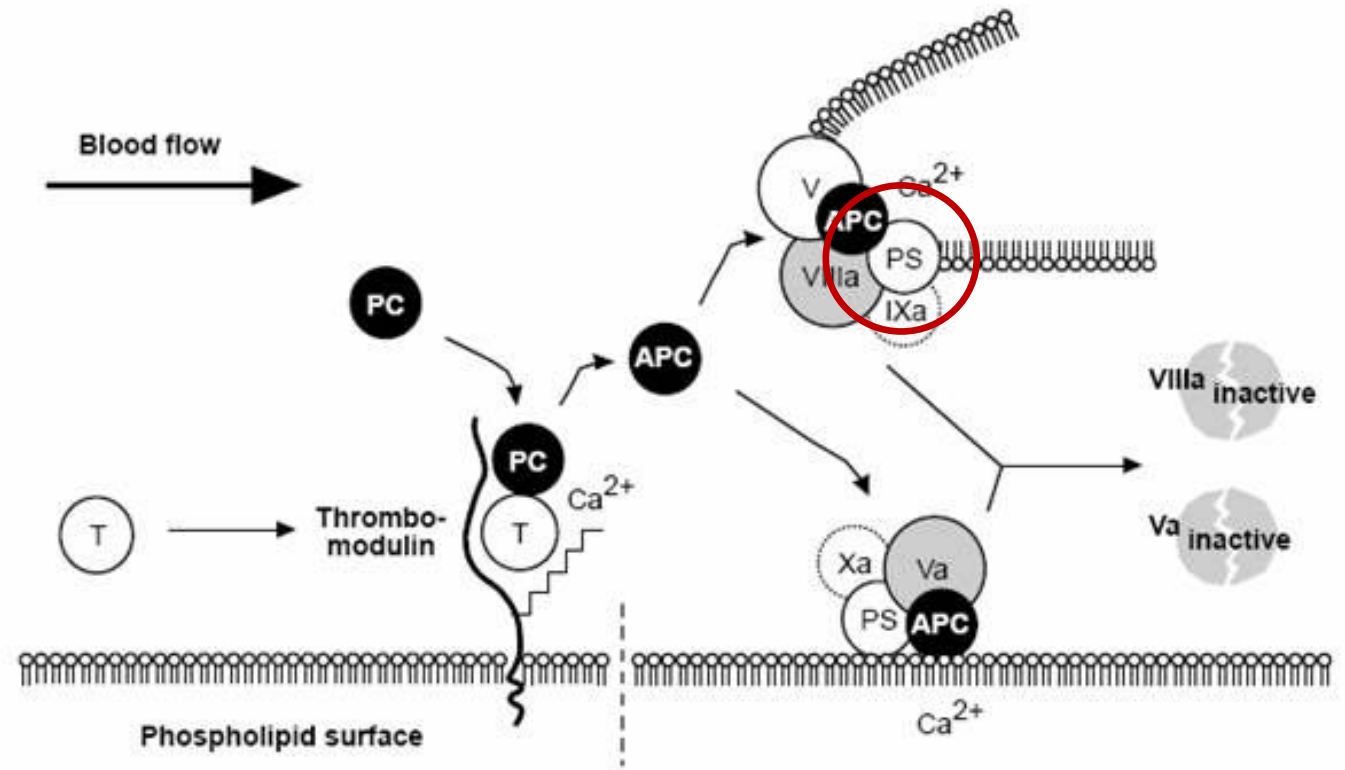
Hypercoagulability – Congenital Disorders

- Protein S Deficiency
 - Protein S acts as a cofactor to APC to inactivate V and VIII



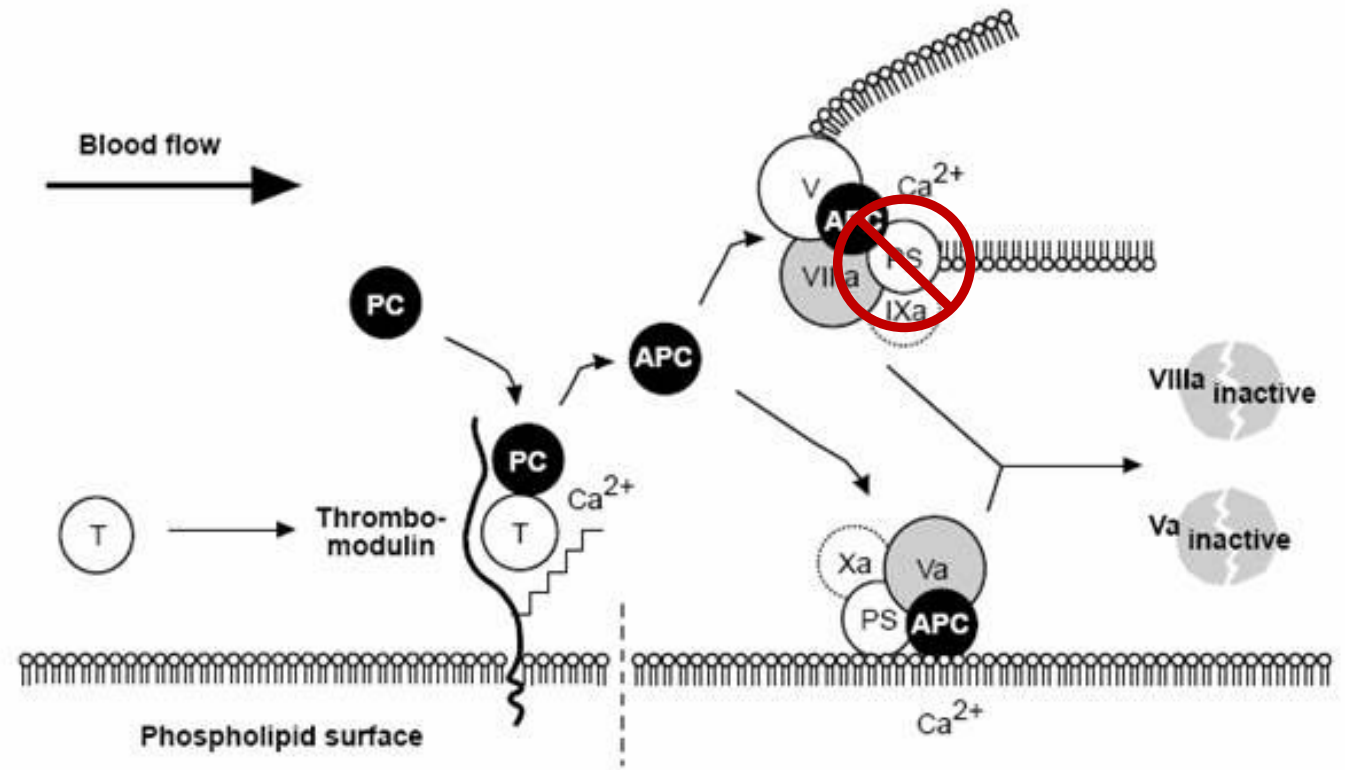
Hypercoagulability – Congenital Disorders

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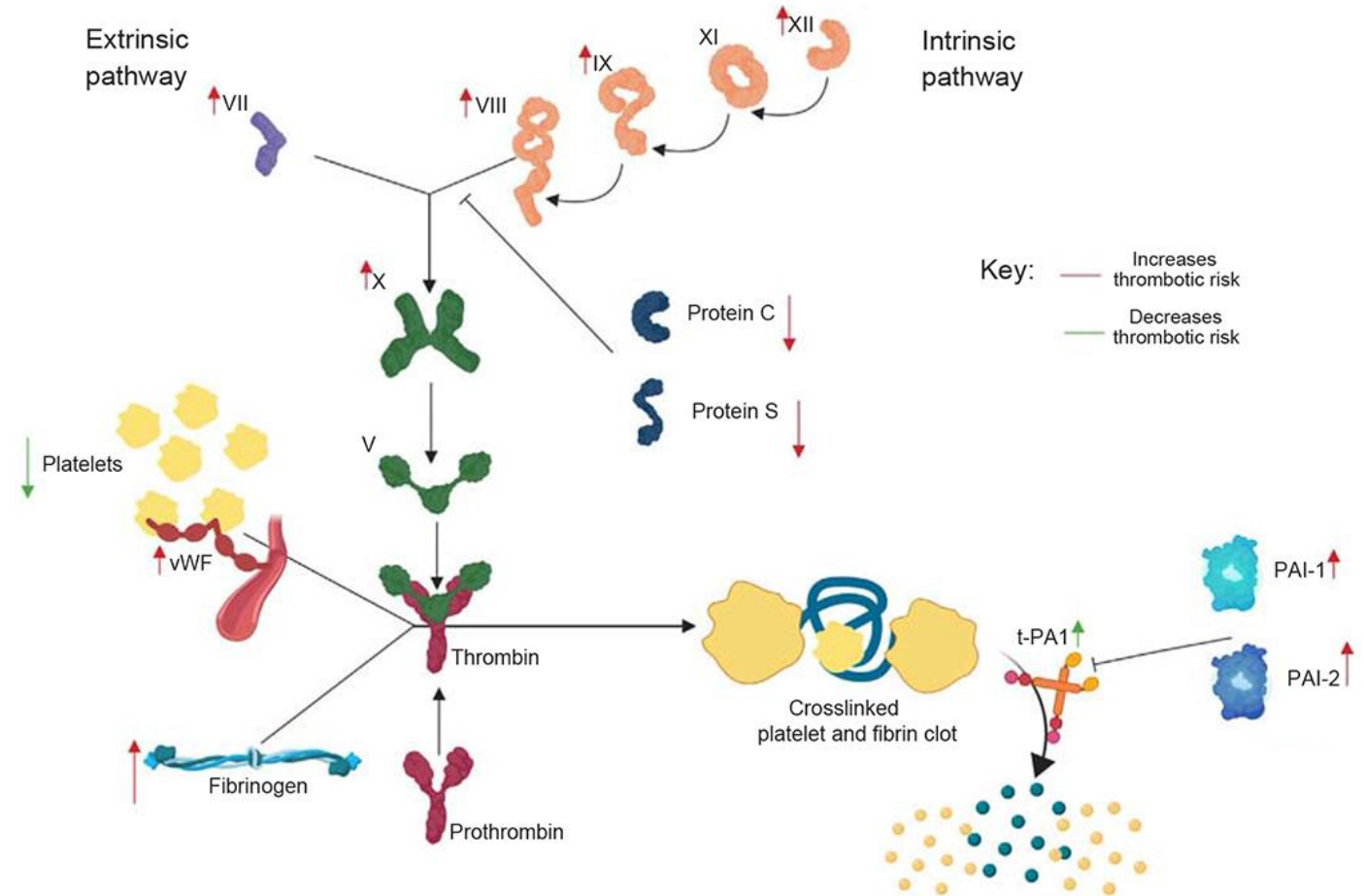
Hypercoagulability – Congenital Disorders

- Protein S Deficiency
 - Protein S acts as a cofactor to APC to inactivate V and VIII
 - Without Protein S, APC is less efficient in breaking down and inactivating VIII and V



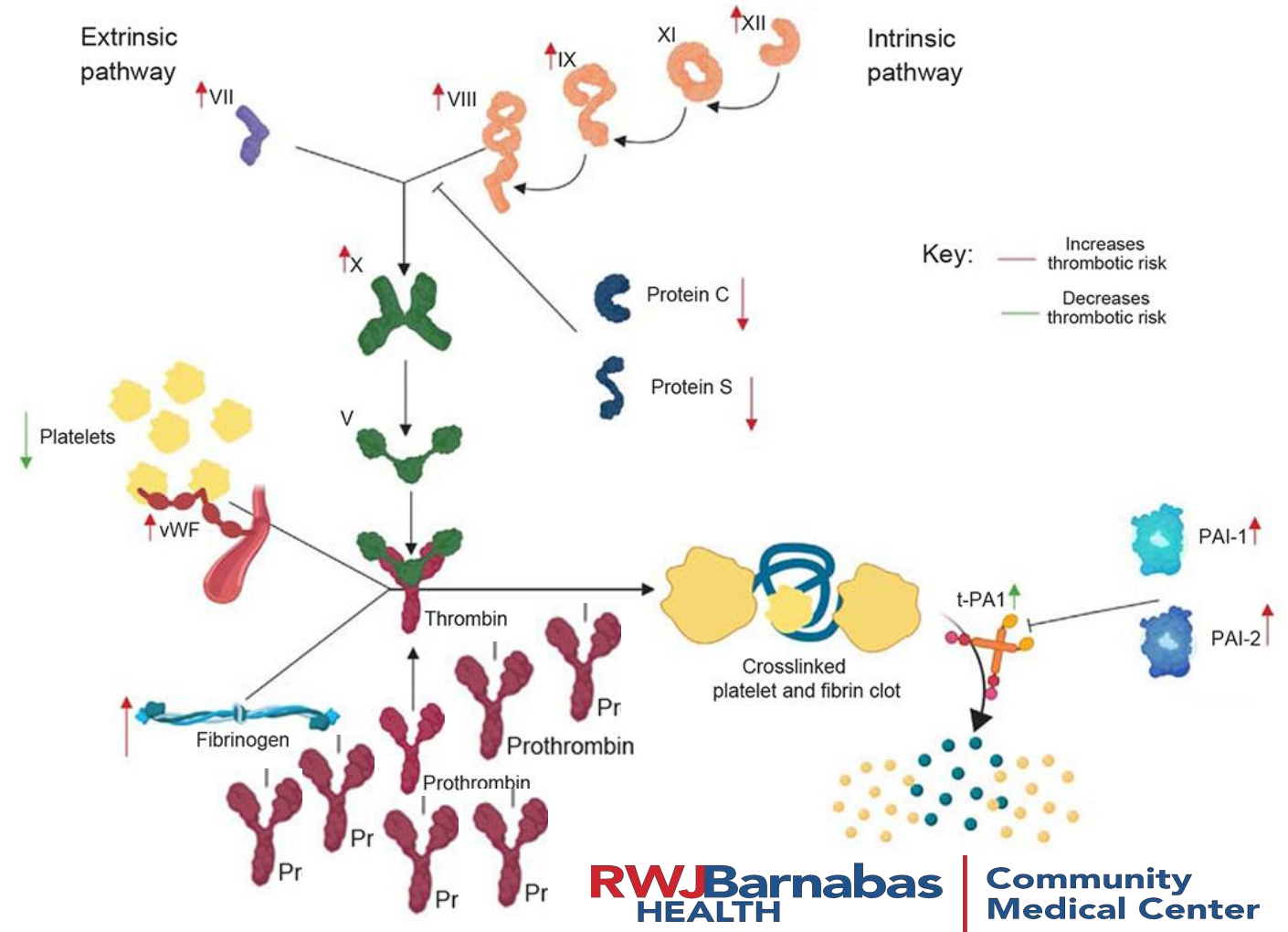
Hypercoagulability – Congenital Disorders

- Prothrombin g20210a
 - Genetic variant where prothrombin (II) is produced at elevated levels
 - Results in greater levels of thrombin upon cleavage and activation



Hypercoagulability – Congenital Disorders

- Prothrombin g20210a
 - Genetic variant where prothrombin (II) is produced at elevated levels
 - Results in greater levels of thrombin upon cleavage and activation



Hypercoagulability – Antiphospholipid Syndrome

Autoimmune disease which results from B-Cell mediated antibodies directed against phospholipid-binding proteins found in multiple organ systems

- Can be primary or secondary to other disease state
- Can be genetic
- Frequently causes thrombosis in Cerebral Veins or Lower Extremities

Hypercoagulability – Antiphospholipid Syndrome

- Three antibodies are evaluated in conjunction with the presence of thrombosis
 - Anticardiolipin, IgG or IgM (ELISA lab)
 - Anti- β 2 Glycoprotein, IgG or IgM (ELISA lab)
 - Lupus Anticoagulant (found in functional clotting assays)

Hypercoagulability – Antiphospholipid Syndrome

- Three antibodies are evaluated in conjunction with the presence of thrombosis
 - Anticardiolipin
 - Anti- β 2 Glycoprotein
 - Lupus Anticoagulant

If these are ALL present, DOACs are insufficient to prevent thrombosis, and heparin, LMWH, or warfarin must be employed as prophylaxis/treatment

Hypercoagulability – Antiphospholipid Syndrome

- Multiple studies, including TRAPS (2018) and Dufrost et al. (2018) show higher rates of arterial thromboembolism and recurrent VTE on patients with triple-positive APLS on DOAC
 - Mainstay therapy for these patients – Warfarin INR goal 2.0-3.0
 - Consider Heparin based therapies in the pregnant patient given warfarin teratogenicity
 - Unfractionated heparin (UFH)
 - Low Molecular Weight Heparin (LMWH)

Migraine Disorder

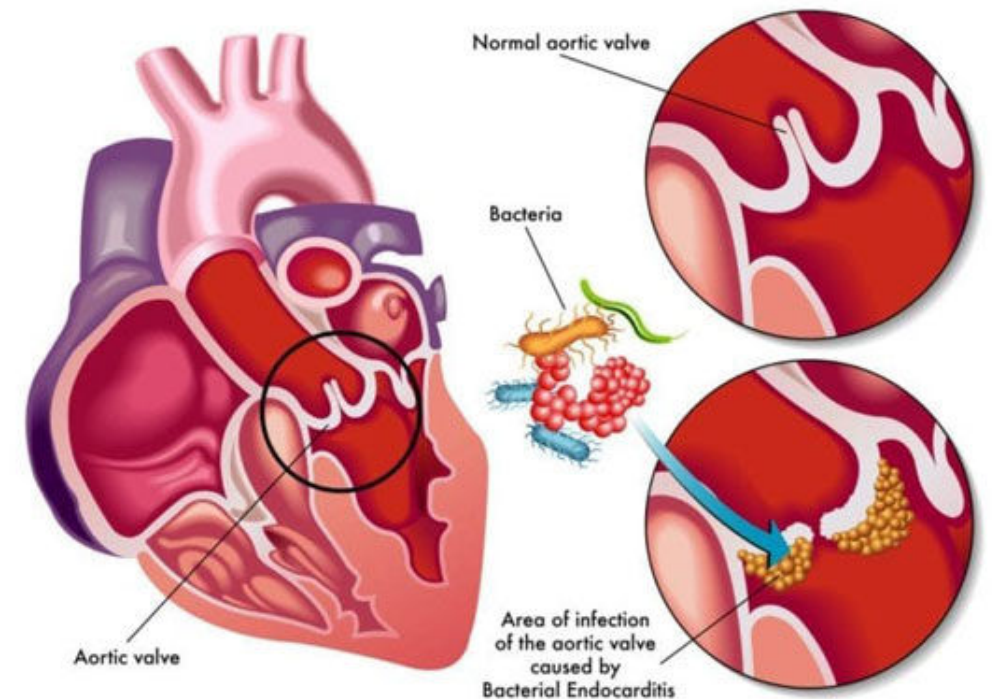
- Migraine predisposes patients to endothelial dysfunction and increased platelet activation
 - Presence of migraine WITHOUT aura places patient at a relative risk of 1.23 times compared to those without migraine
 - Presence of migraine WITH aura places patient at a higher relative risk of 2.16 times compared to those without

Migraine Disorder

- Other comorbidities in conjunction of migraine significantly increase risk of cardiovascular and cerebrovascular disease
 - Female Gender (RR 2.08, 95% CI 1.13 to 3.84)
 - No statistical increase in risk for male gender
 - Tobacco Abuse / Smoking (RR 9.09, 95% CI 4.22 to 19.34)
 - Oral Contraceptive Use (RR 7.02, 95% CI 1.51 to 32.68)

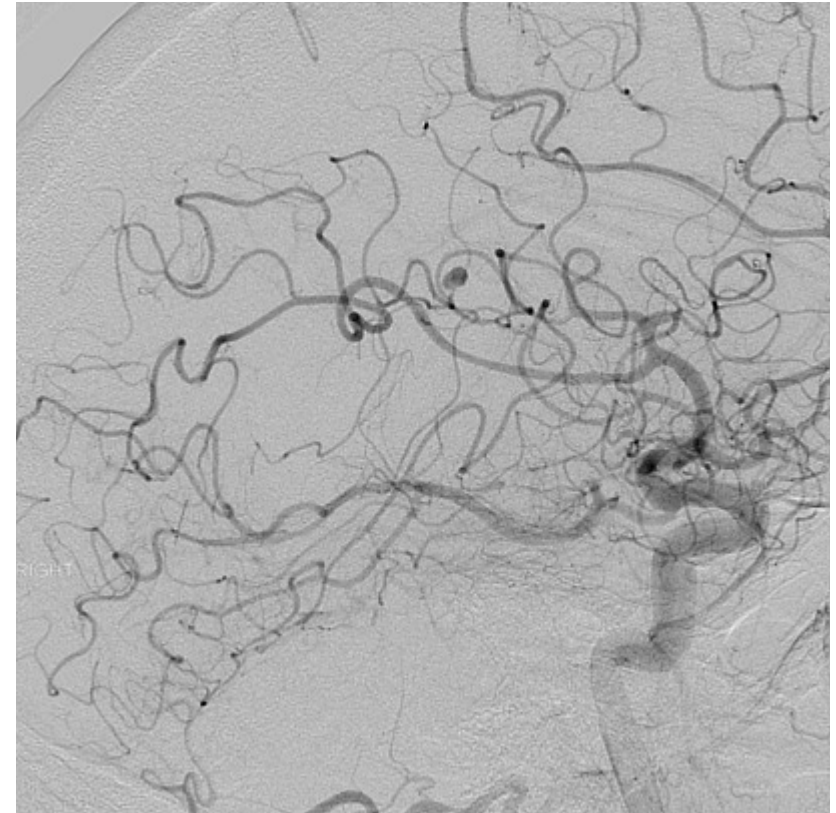
Cardioembolic – Bacterial Endocarditis

- Cause of Ischemic or Hemorrhagic stroke
 - Common – Staphylococcus (21-78%), Salmonella, and Pseudomonas
 - Can provoke embolism causing ischemia
 - Can also cause injury to intimal layer in both heart and cerebral vessels resulting in rupture



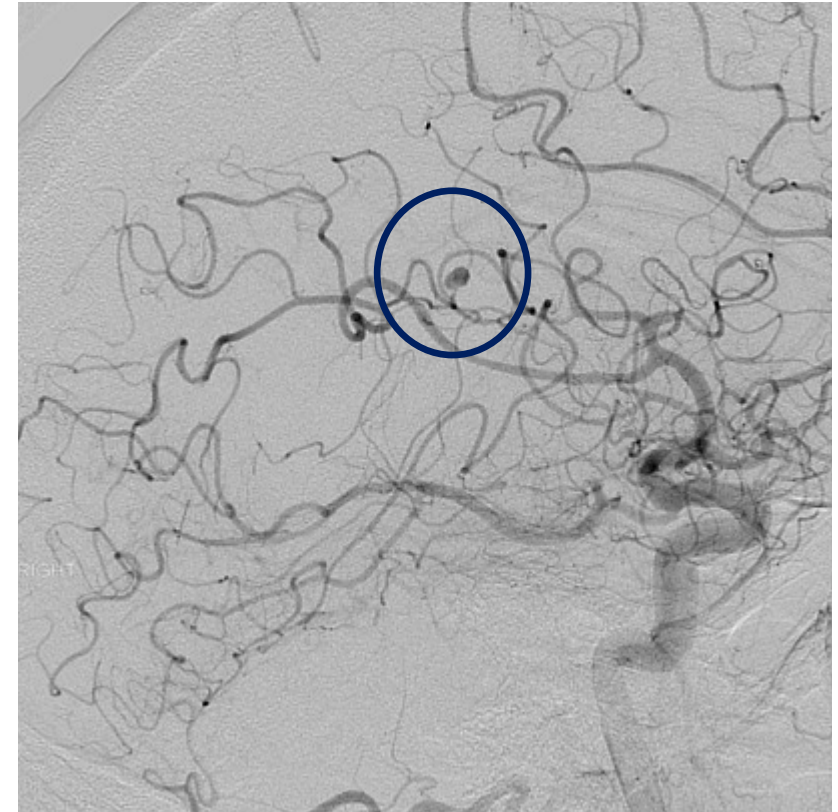
Infectious / IVDA Bacterial Endocarditis

- Cause of Ischemic or Hemorrhagic stroke
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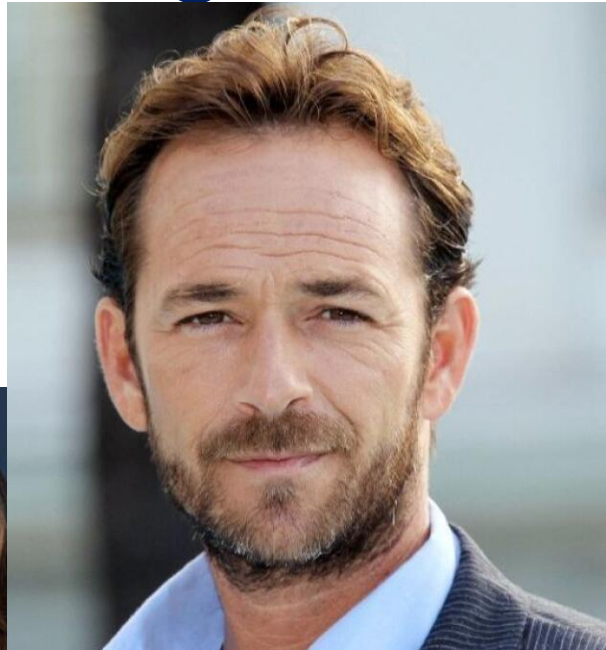
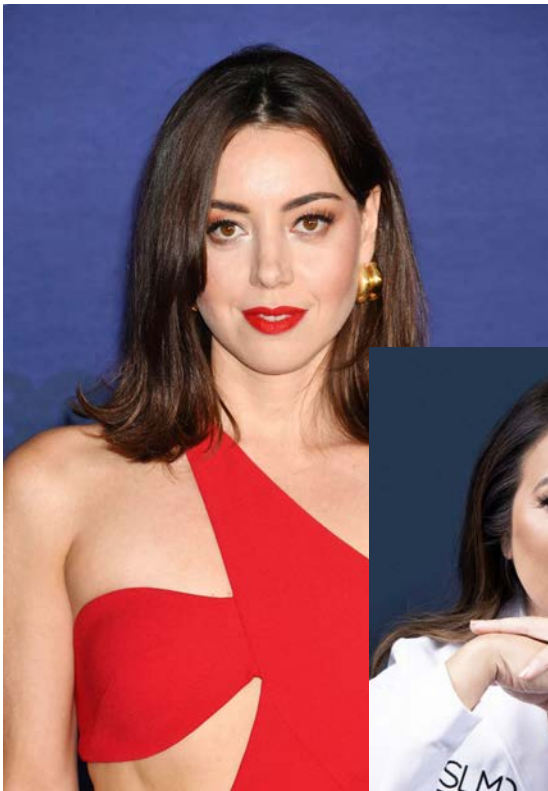


Infectious / IVDA Bacterial Endocarditis

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Stroke in the Young



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