Update on Antiplatelet Therapies for Stroke

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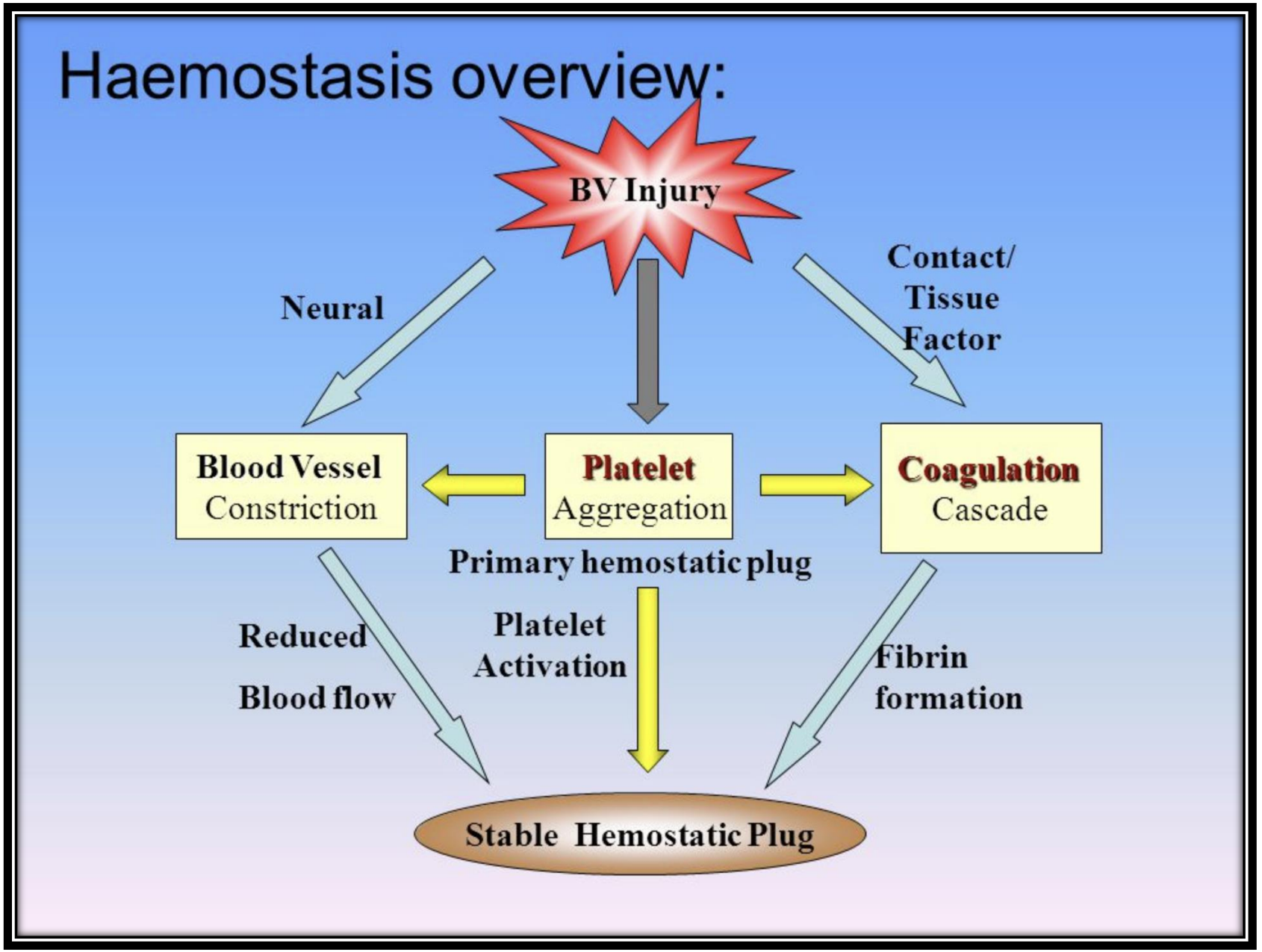
AdventHealth Shawnee Mission

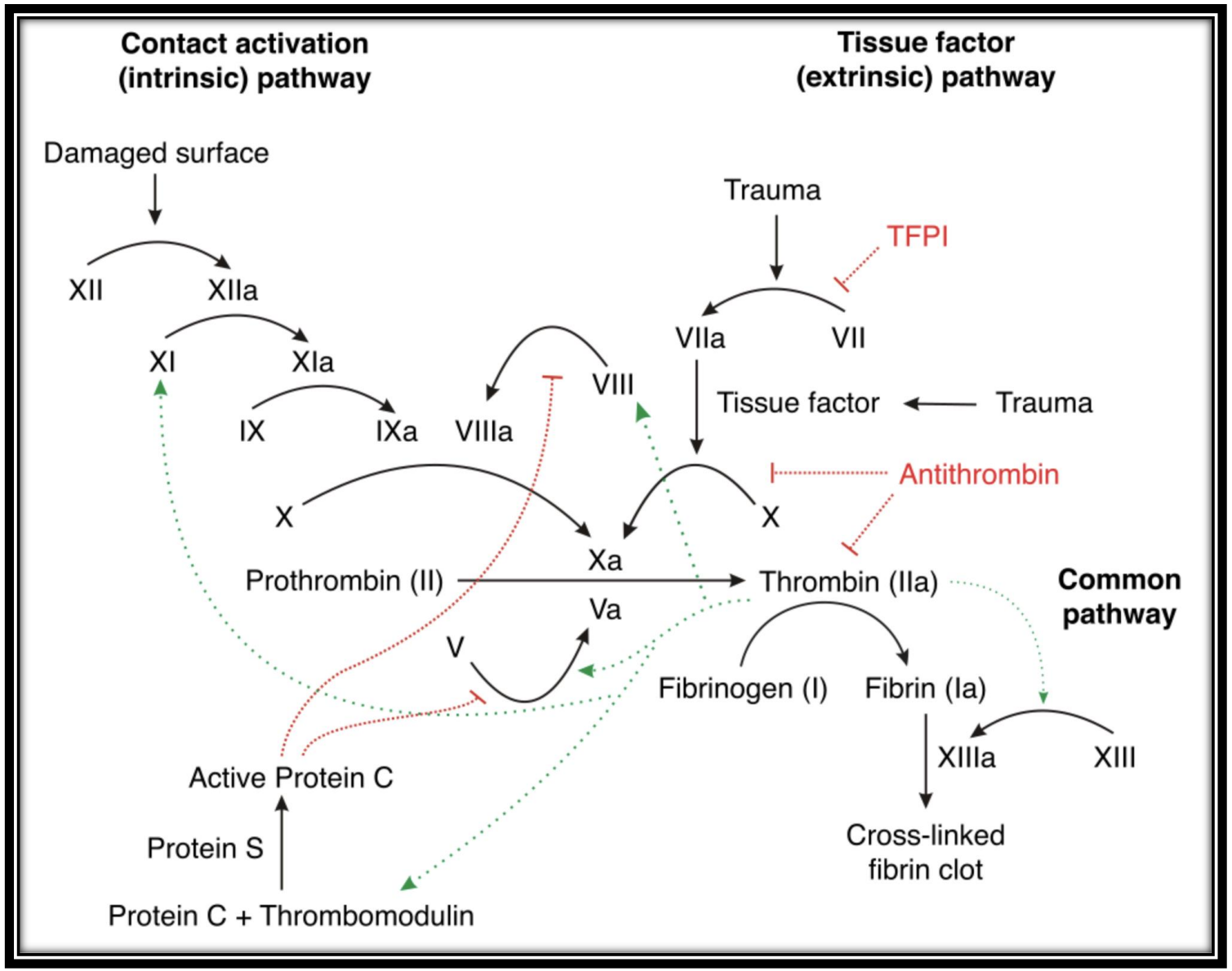
Talk Outline

- Brief review of coagulation and thrombosis
- Platelet physiology
- Anti-platelet agents
  - Aspirin
  - Clopidogrel
  - Ticagrelor
  - Other agents
  - Dual anti platelet strategies
- Prevention strategies
  - Primary prevention
  - Acute stroke intervention
  - Secondary prevention
- Future strategies

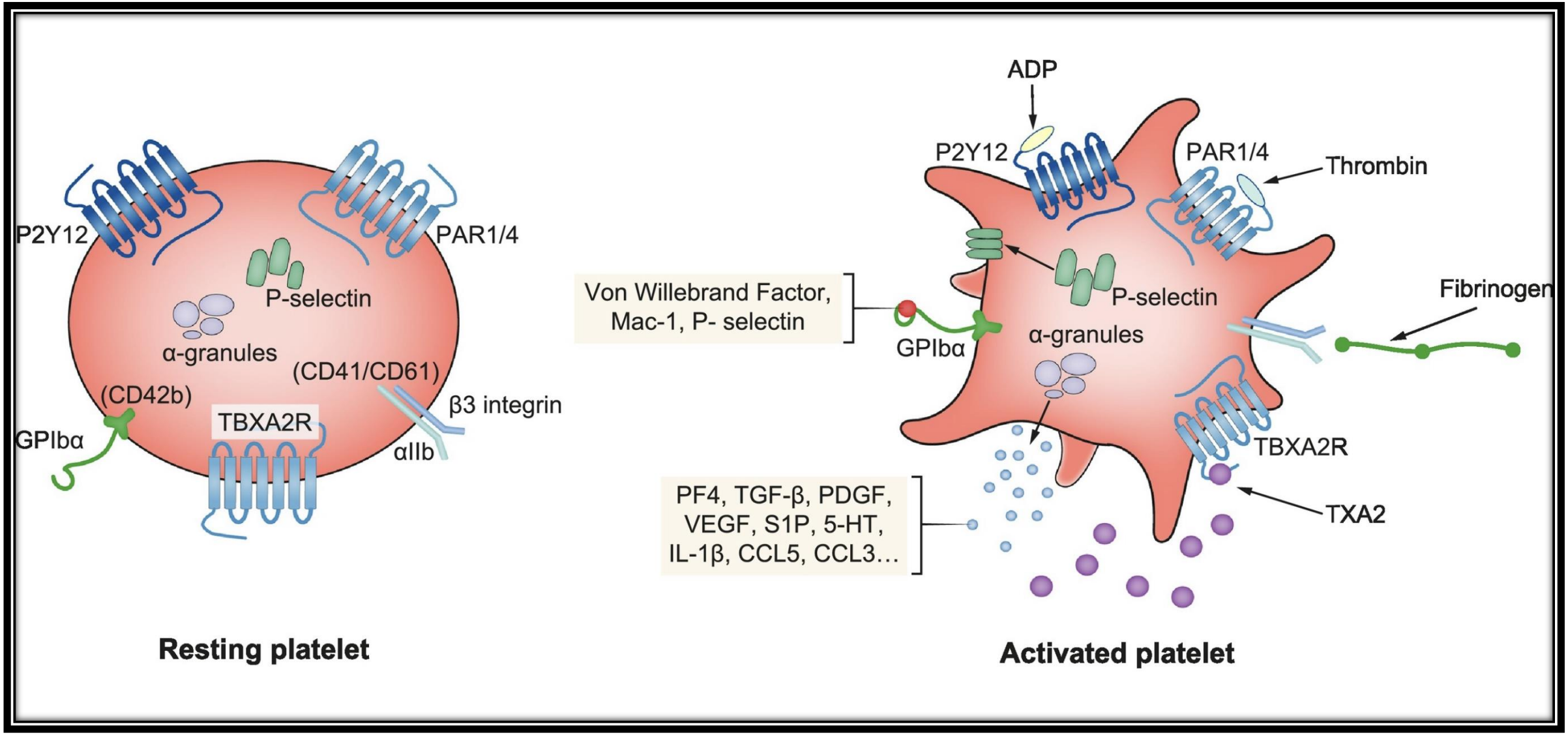
Haemostasis overview:

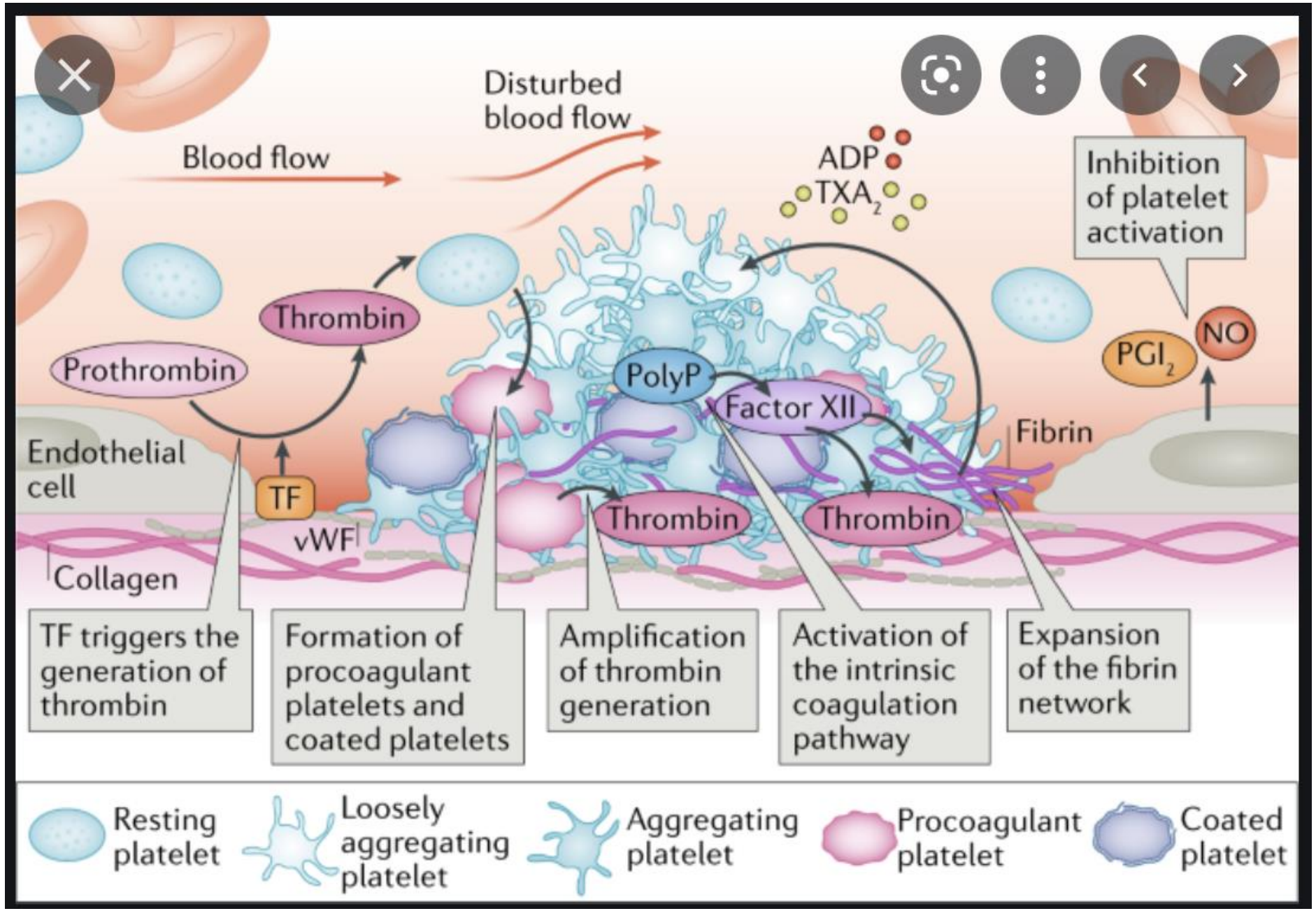


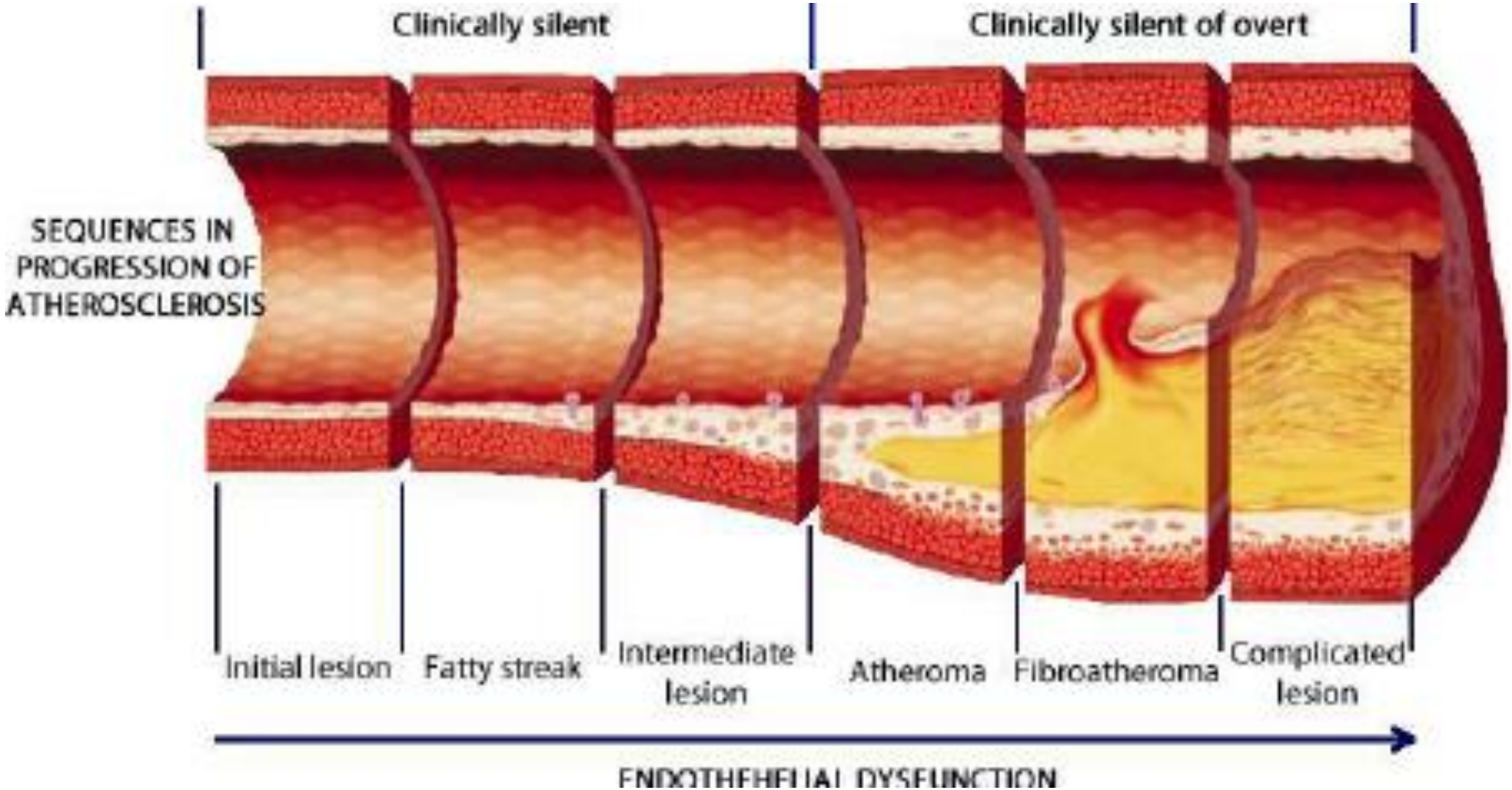
Clotting Cascade

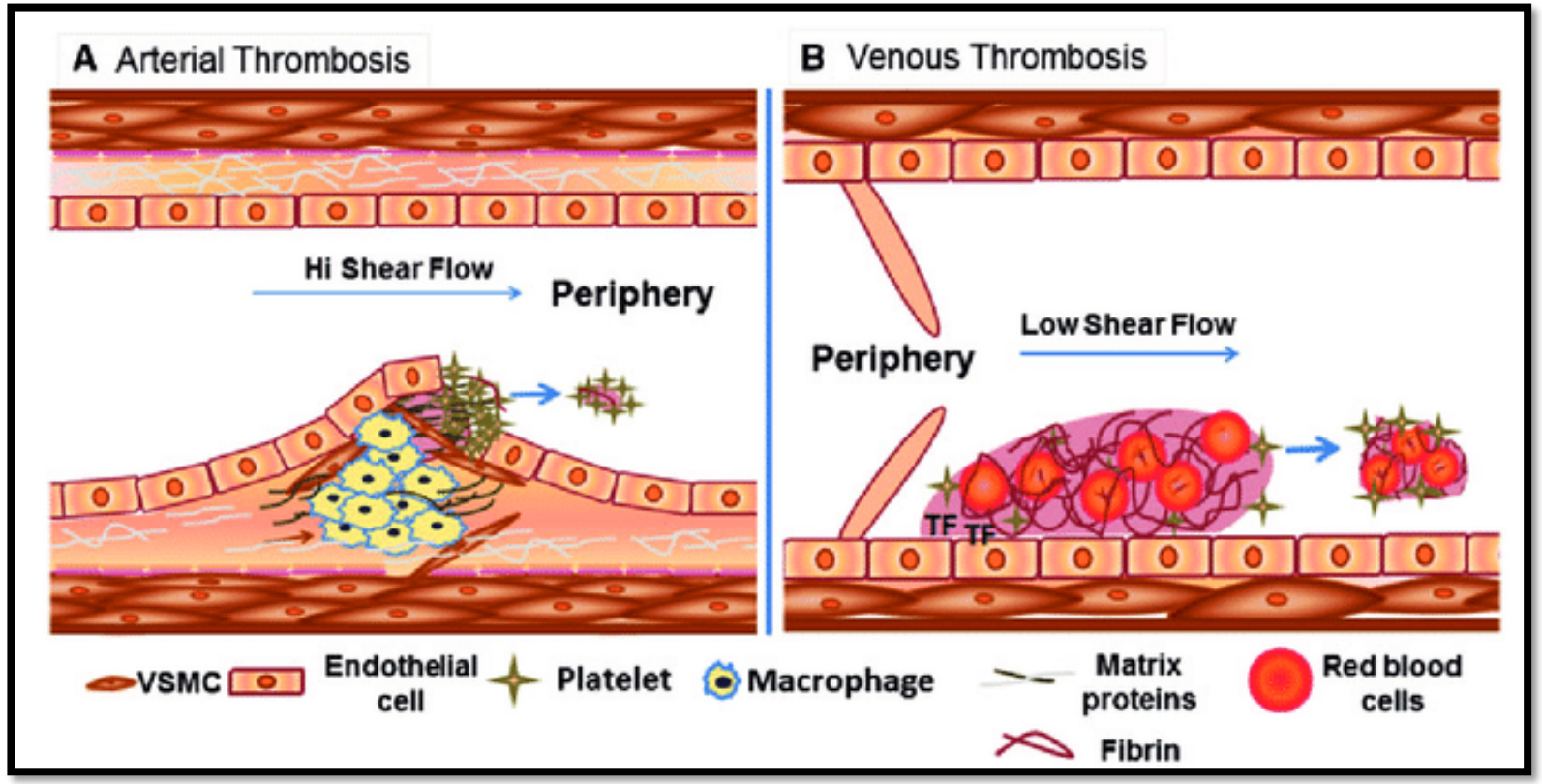


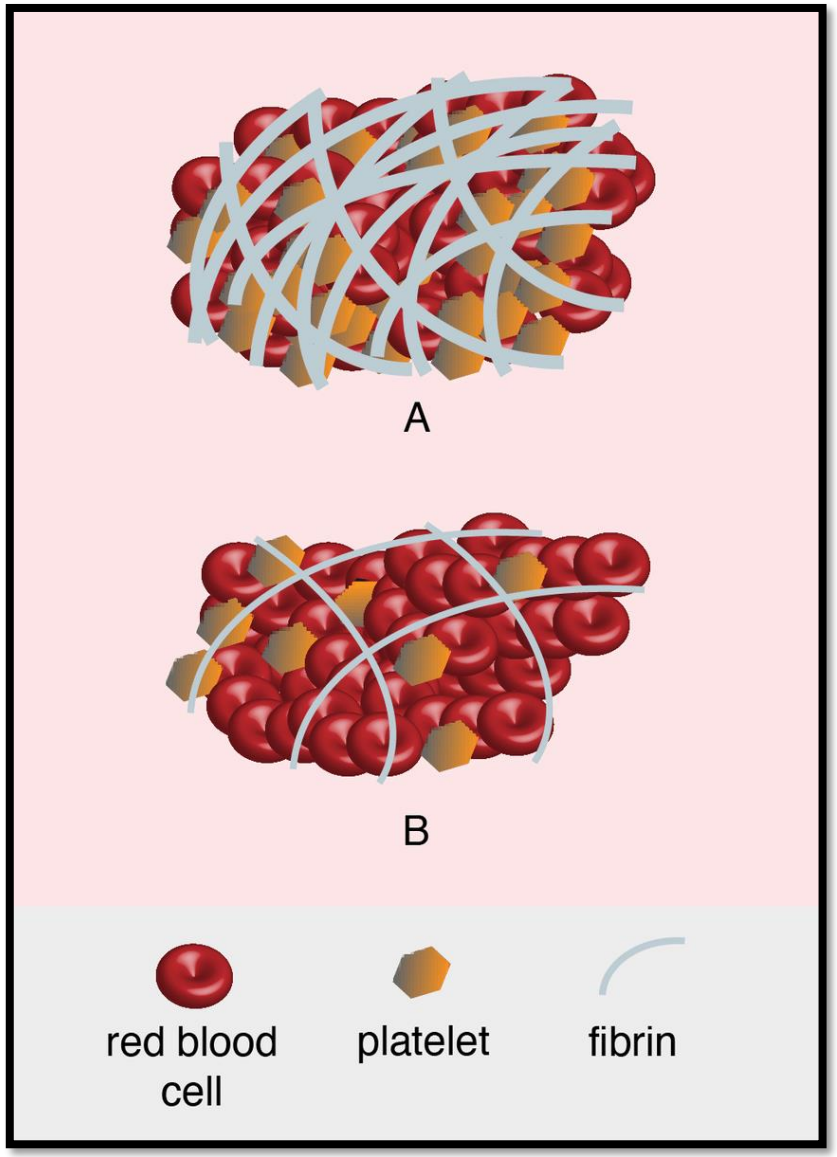
Platelet Activation



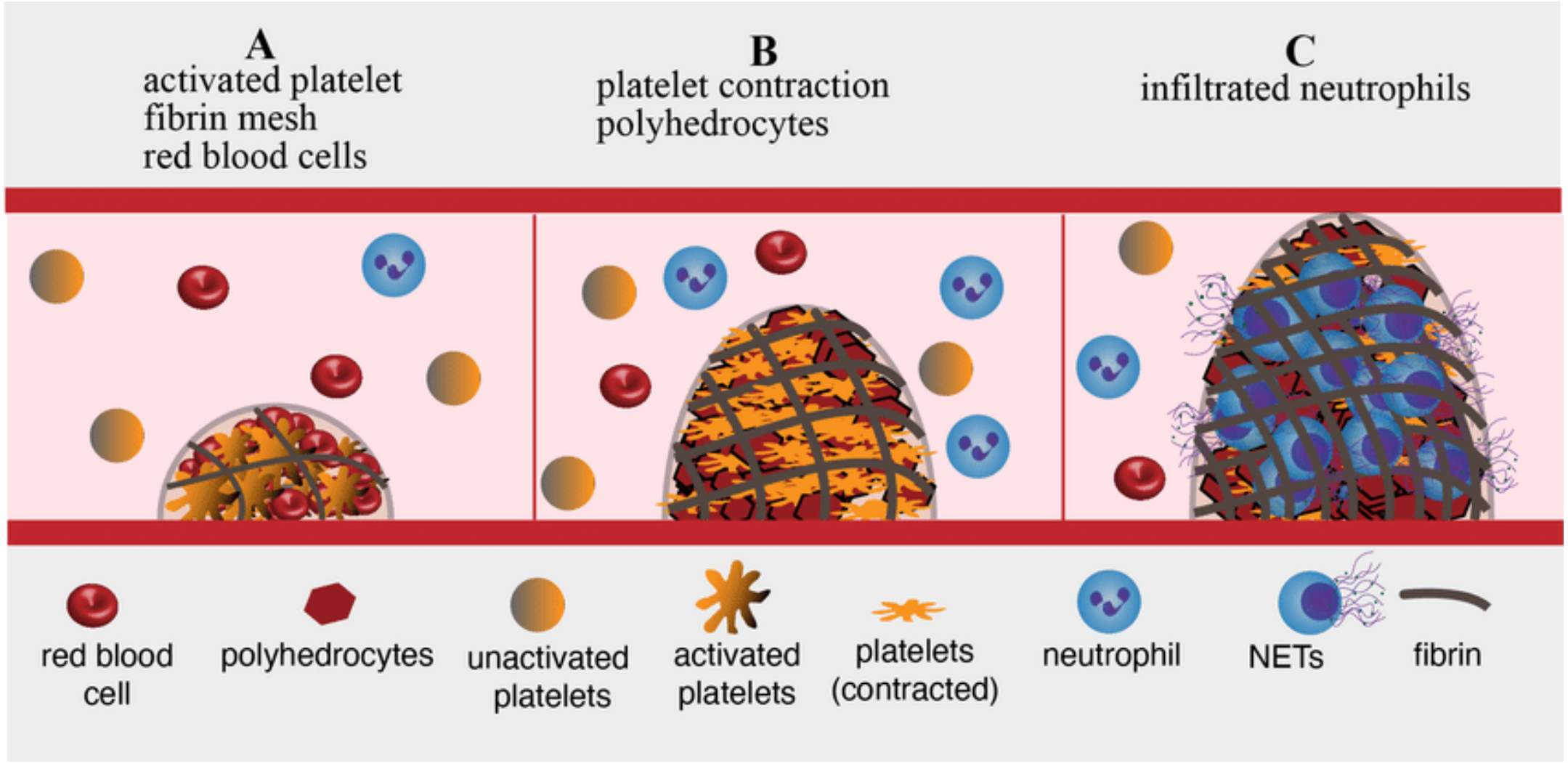

Disturbed blood flow
Blood flow
ADP
TXA_2
Inhibition of platelet activation
Thrombin
Prothrombin
PolyP
Factor XII
PGI_2
NO
Fibrin
Endothelial cell
TF
vWF
Collagen
Thrombin
Thrombin
TF triggers the generation of thrombin
Formation of procoagulant platelets and coated platelets
Amplification of thrombin generation
Activation of the intrinsic coagulation pathway
Expansion of the fibrin network
Resting platelet
Loosely aggregating platelet
Aggregating platelet
Procoagulant platelet
Coated platelet


Clinically silent
Clinically silent of overt
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
Initial lesion
Fatty streak
Intermediate lesion
Atheroma
Fibroatheroma
Complicated lesion
ENDOTHELIAL DYSFUNCTION

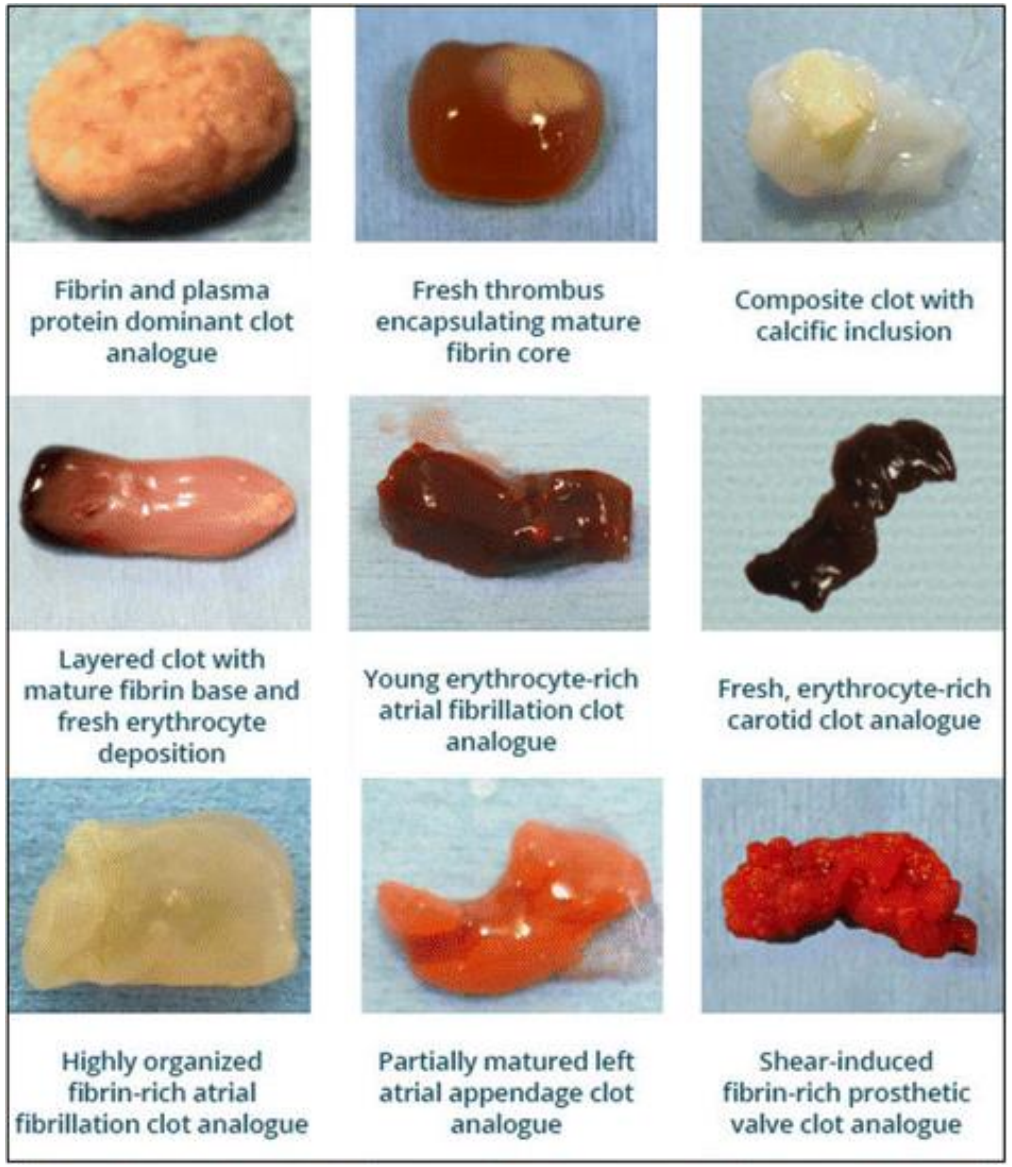


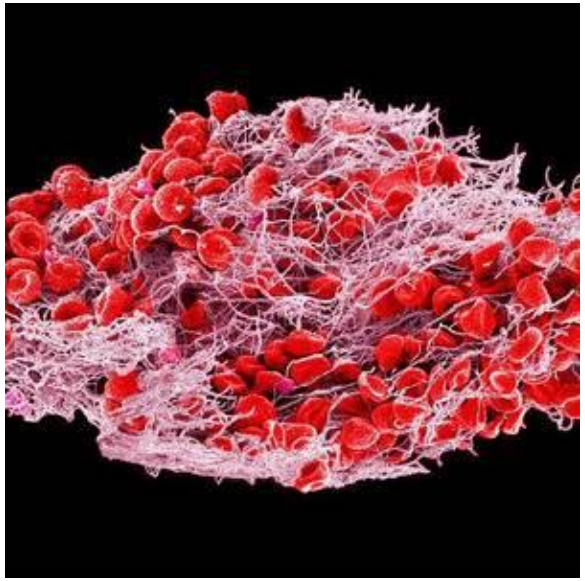


White Clot vs Red Clot

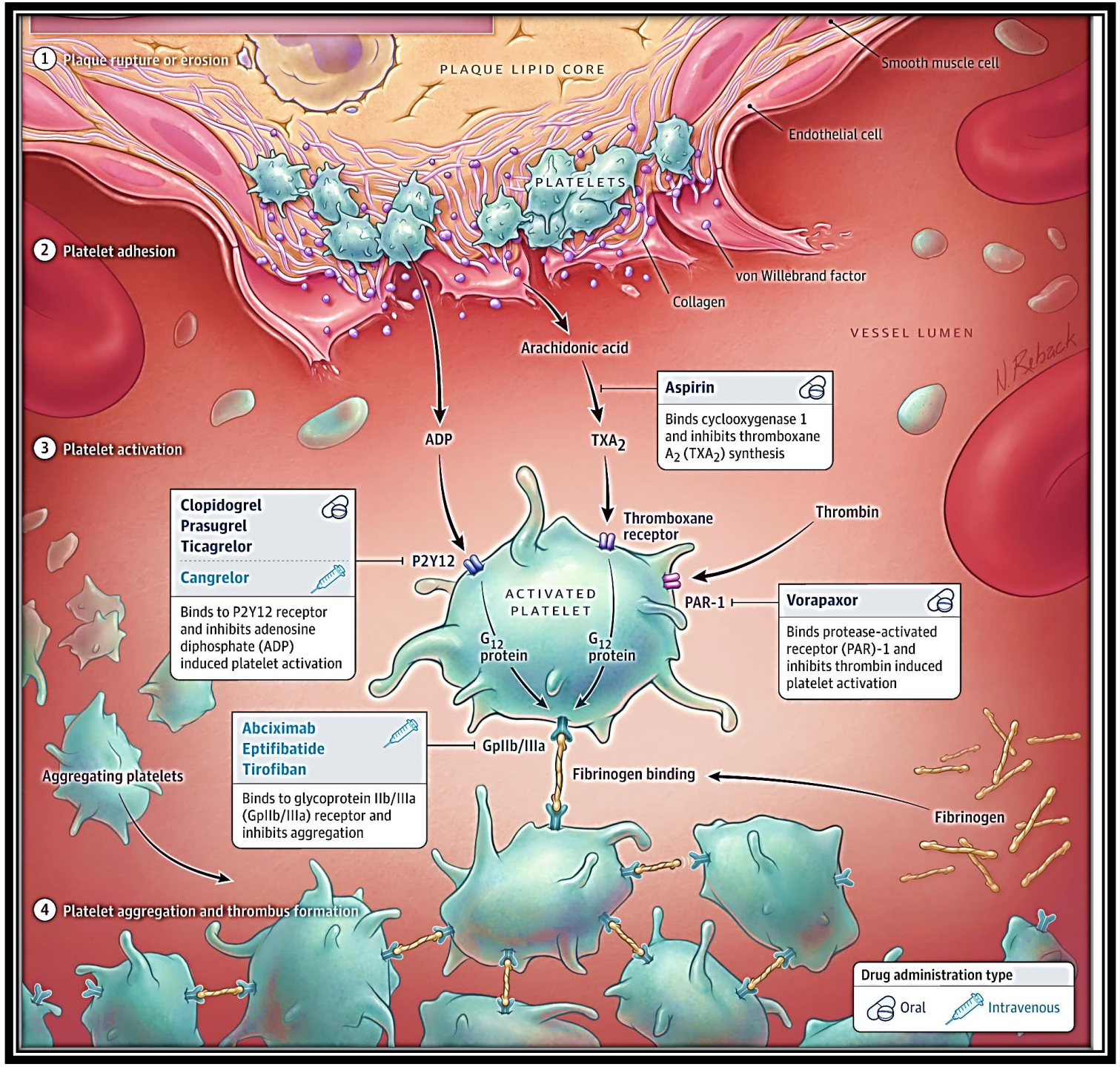


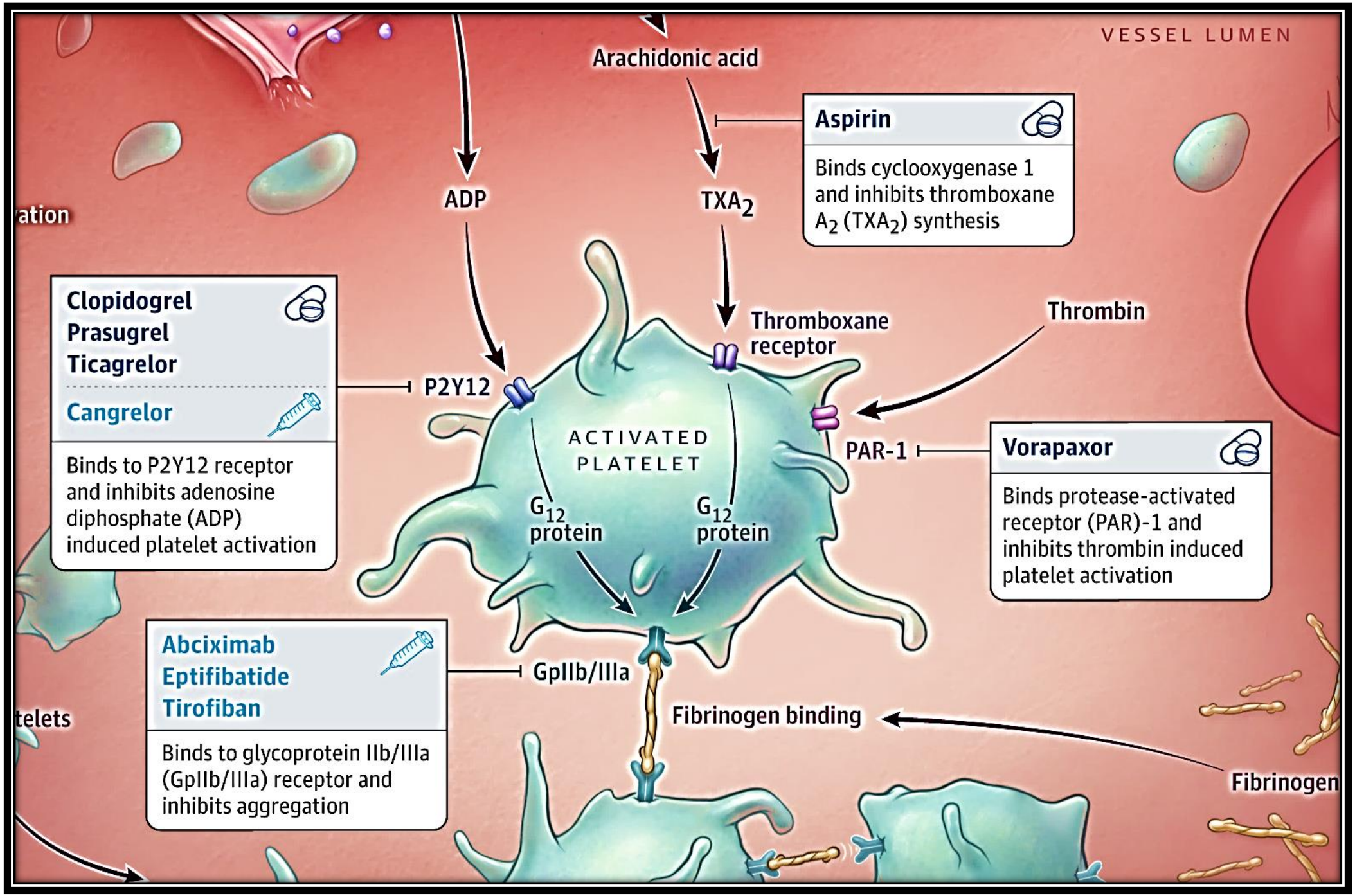
Thrombus Evolution with Time





Al-Ajlan, F.S., Qazi, E., Kim, C.K. *et al.* Multimodality CT based imaging to determine clot characteristics and recanalization with intravenous tPA in patients with acute ischemic stroke. *Neurovasc Imaging* **3,** 2 (2017). https://doi.org/10.1186/s40809-017-0026-9


1 Plaque rupture or erosion
PLAQUE LIPID CORE
Smooth muscle cell
Endothelial cell
PLATELETS
2 Platelet adhesion
von Willebrand factor
Collagen
VESSEL LUMEN
Arachidonic acid
Aspirin
Binds cyclooxygenase 1 and inhibits thromboxane A_2 (TXA_2) synthesis
3 Platelet activation
ADP
TXA_2
Clopidogrel
Prasugrel
Ticagrelor
Cangrelor
Binds to P2Y12 receptor and inhibits adenosine diphosphate (ADP) induced platelet activation
P2Y12
Thromboxane receptor
Thrombin
ACTIVATED PLATELET
PAR-1
Vorapaxor
Binds protease-activated receptor (PAR)-1 and inhibits thrombin induced platelet activation
G_{12} protein
G_{12} protein
Abciximab
Eptifibatide
Tirofiban
Binds to glycoprotein IIb/IIIa (GpIIb/IIIa) receptor and inhibits aggregation
GpIIb/IIIa
Aggregating platelets
Fibrinogen binding
Fibrinogen
4 Platelet aggregation and thrombus formation
Drug administration type
Oral
Intravenous


VESSEL LUMEN
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P2Y12
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ACTIVATED PLATELET
G12 protein
G12 protein
PAR-1
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Abciximab
Eptifibatide
Tirofiban
Binds to glycoprotein IIb/IIIa (GpIIb/IIIa) receptor and inhibits aggregation
GpIIb/IIIa
Fibrinogen binding
Fibrinogen

Aspirin

- Irreversibly blocks cyclo-oxygenase (COX) activity of prostaglandin (PG)H synthase 1 (COX-1) and 2 (COX-2)
- Induces permanent defect of thromboxane-A_2-dependent platelet function that includes platelet aggregation and causes vasoconstriction
- Peak half life is 15-30 minutes
- Loading dose: 160-325 mg; maintenance dose: 81 mg
- Risk of GI bleeding is dose dependent.
- Enteric coating slows half life to 3-4 hours & DOES NOT protect against GI bleeding
- Overall vascular RR by 19% but risk of hemorrhagic stroke RR 1.9 and GI bleeding RR 2.7)
  Antithrombotic Trialist's Collaboration Lancet 2009
- Other NSAIDs competitively bind to COS receptors but do not induce irreversible inhibition
  - NSAIDs should be taken 30 minutes after or 8 hours before ASA
- Possible other beneficial effects on endothelial cells and neutrophils
- Cost: ($6 /year)

Aspirin Treatment Failure

- Nonadherence
- NSAID interactions
- Enteric coating may cause decreased drug absorption (Grosser,T et al Circulation 2013;127:377-385)
- Possible role of dosage and patient weight
  - Pooled analysis for all vascular events (not stroke specific) suggested 75-100 mg for <70 kg and higher doses for >70 kg
- ?tachyphylaxis or genetic polymorphisms
- No difference in comparative effectiveness of 81mg vs 325 mg in 15K patients followed 2 years in secondary prevention Jones et al N Engl J Med 2021;384:1981-90
- High platelet turnover (eg atherosclerosis)
- Equivocal/low level evidence of possible benefit in switching to alternative antiplatelet agent

Clopidogrel

- One of the thienopyridines (with ticlopidine, prasugrel, & ticagrelor) which block the P2Y12 receptor leading to irreversible indirect platelet inhibition
- No data on treatment alone in acute stroke
- Secondary prevention: relative risk reduction compared to ASA of 7.3%
- Slightly lower risk of bleeding than ASA GI bleeding (.52% vs 0.72%) and

(intracranial hemorrhage (0.33% vs 0.47%)

- Prodrug: requires 2-step activation by 2 cytochrome P-450 enzymes
  - Theoretical concerns about drug interactions (esp PPIs) & genetic variations (65% Asians and 35% western populations have loss of function alleles)
  - Usefulness of genotyping is controversial; possibly of use in recurrent stroke on clopidogrel

- Cost: 15 cents/tablet or $54.75 year

Ticagrelor

- Not a prodrug
- Binds reversibly to P2Y12 receptor
- $T_{1/2}$ of 7-8 hours (must be dosed twice daily)
- More effective than clopidogrel in preventing MI, stroke or vascular death in ACS (PLATO trial)
- Increased efficacy when used with ASA
- Increased risk of bleeding

- Cost: ($403.56/mo with GoodRX; $4,843/year)

Other Antiplatelet Agents

- Dipyridamole & Cilostazol
- Block phosphodiesterase, resulting in decreased reputable of adenosine and elevated levels of cAMP and gAMP
- Prolong platelet survival, reduce inflammation, scavenge free radicals and produce vasodilation
- Dipyridamole used clinically chiefly in combination with aspirin
- Cilostazol marketed in US to treat peripheral vascular disease
  - Japanese trials have suggested benefit following carotid endarterectomy and in secondary stroke prevention
  - trial of cilostazol + either ASA or Clopidogrel for non lacunar stroke in progess
- Vasodilation associated with frequent complaint of headache as main s/e

Dual Antiplatelet Strategies

ASA + Dipyridamole

- No trials have tested it's role in acute ischemic stroke
- Risk of recurrent stroke .82 compared with ASA alone Halkes PH JNP 2008;79:1218-1223
- Disadvantages: twice daily dosing; headache: high noncompliance rate

ASA + Clopidogrel

- Increased risk of bleeding (.9% DAPT vs 0.4% ASA alone)Johnston SC et al N Engl J Med. 2018;379:215-225
- Short term benefit: current cut point is 21 days

ASA + Ticagrelor

- .79 hazard ratio of recurrent stroke vs ASA alone but 4 times as much bleeding and no overall significant effect of disability or death

Benefit vs Risk

Risk vs Benefit

- Bleeding risk is increased in:
  - Age over 65
  - BMI< 18.5
  - Diabetes
  - Prior bleeding
  - Taking oral anticoagulants

- Risk of bleeding can likely be decreased by adding a PPI
- Risk of ICH can likely be reduced with aggressive BP control

AntiPlatelet Therapy: Clinical Situations

- Primary Prevention
- Acute stroke management
- Secondary Prevention
  - Early
  - Late

Case 1

60 year old male treated for hypertension and diabetes with no history of vascular events or bleeding problems asks you if he should start taking aspirin to prevent a stroke or heart attack. You reply:

A. He should start 81 mg ASA a day
B. He should start 325 mg ASA a day
C. He should take enteric coated 325 mg ASA
D. His risk of bleeding outweighs his risk of benefit

Primary Prevention

Recommendation Summary

Population	Recommendation	Grade
Adults aged 50 to 59 years with a 10% or greater 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a 10% or greater 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

USPS Task Force summary 2016 doi: .org/10.7326/M16-0577

United States Preventative Services Task Force Recommendations 2016

Recommendation Summary

Population	Recommendation	Grade
Adults ages 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults ages 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.	C
Adults age 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults age 60 years or older.	D

2021 Draft Recommendations

Case 2

A 55 year old woman with BMI 33 and history of diabetes, hypertension and smoking is seen in the ER 6 hours after developing mild right hemiparesis and dysarthria (NIHSS 3).

She should be given:

A. ASA 81 mg now and daily
B. ASA 162 mg now and 81 mg daily
C. ASA 325 mg now and 81 mg daily
D. ASA 325 mg now and daily

Acute TIA/stroke: Early Treatment

Preventing early recurrent stroke

- Risk of recurrent stroke about 10% w/i 1st week Aspirin started w/I 48 hr of stroke may have marginal benefit
- Cilostazole & dipyridamole appear to be less effective
- Ticagrelor + ASA vs ASA (THALES study) showed decreased risk of stroke (hazard ratio 0.79) but 4 times increased risk of serious bleeding (28 vs 7)
- Ongoing CHANCE-2 trial is comparing ASA+clopidogrel vs ASA+ticagrelor in acute stroke/TIA

Halting neurological worsening (stroke in evolution)

- More common in vertebrobasilar infarcts; esp. multilobar
- 20-30% of lacunar infarcts will progress
- Other causes:edema, hydrocephalus, seizures, electrolyte imbalances & infection
- Only small trials; no obvious benefit

Acute TIA/stroke: Early Treatment (2)

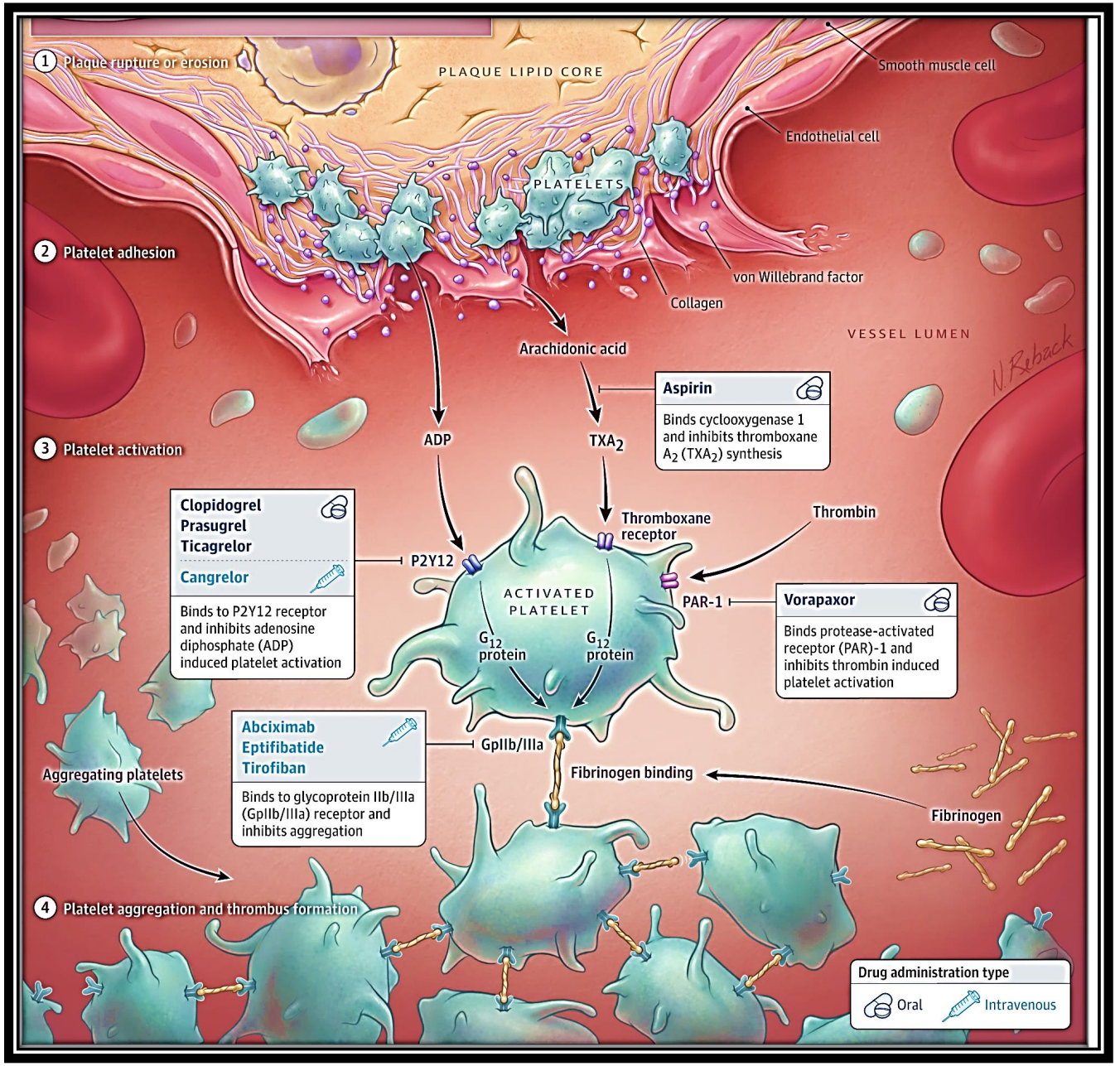
Augmentation of Acute Stroke Interventional Procedures

- Experience in PCI of acute MI
  - Often mix anticoagulants, IV antiplatelet drugs
- Little data yet of benefit/safety in acute stroke interventions

Coronary Artery Disease

- More experience with DAPT, ticagrelor & prasugrel
- DAPT advocated for 6-12 months after ACS and longer if high risk (eg multiple prior ACS episodes, diabetes & heart failure) if no increased bleeding risk (age>65, BMI<18.5, prior bleeding, oral anticoagulants)
- Prasurgel better than clopidogrel in ACS but associated with increased bleeding risk and **significant risk of stroke in patients with risk of stroke or TIA**
- Ticagrelor better than clopidogrel for 1 year but higher rate of bleeding and 10-20% experience non exertion all dyspnea in 1st week; increased risk of bleeding with ASA>100 mg/day vs <100 mg/day
- Several trials support d/c of ASA after 1-3 months of DAPT and continuing clopidogrel or ticagrelor vs DAPT for 1 year (equivalent benefit for recurrent ACS and decreased bleeding risk)

-Kamran,H et al JAMA 2021:325(15):1545-1555


1 Plaque rupture or erosion
PLAQUE LIPID CORE
Smooth muscle cell
Endothelial cell
PLATELETS
2 Platelet adhesion
von Willebrand factor
Collagen
VESSEL LUMEN
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GpIIb/IIIa
Aggregating platelets
Fibrinogen binding
Fibrinogen
4 Platelet aggregation and thrombus formation
Drug administration type
Oral
Intravenous

Acute TIA/stroke: Early Treatment (3)

- Cardiogenic embolism
  - Aspirin has modest benefit
  - Anticoagulants offer more robust protection; ? when to initiate
- DVT prophylaxis
  - ASA provides some benefit, but ASA guidelines prefer anticoagulation
- Dissection
  - ASA appears equivalent to heparin for dissection

Case 3

The 55 year old woman with BMI 33 and history of diabetes, hypertension and smoking admitted yesterday morning has improved (NIHSS now 1). Her work up has shown she had a small left internal capsule lacune. She wants to go home. In addition to smoking cessation and medication for her diabetes, hypertension and lipids, she should:

A. Take ASA 81 mg daily
B. Take ASA 325 mg daily
C. Take ASA 81 mg and Clopidogrel 75 mg daily for 21 days then stop one
D. Take ASA 81 mg and Clopidogrel 75 mg daily for 90 days

Acute TIA/Stroke (hospital discharge)

Single vs Dual anti-platelet therapy (ASA vs ASA+clopidogrel)

- 2021 systematic review (Brown DL et al. Stoke 2021;52:e468-e479)
- Based on 3 trials with early initiation (<1 week) and short-term treatment duration (<90 days) DAPT was superior to SAPT for prevention of recurrent ischemic stroke, any recurrent stroke and MACE in people with minor stroke or high risk TIA who were at low risk of bleeding
- Best benefit/risk is in the first 3 weeks
- Future research needed re:
  - Optimal time to start treatment
  - Whether patients with major stroke benefit
  - Whether certain genetic profiles modify the benefit of DAPT treatment
  - Whether agents other than ASA +clopidogrel (esp ASA+Ticagrelor) are better

Case 4

A 74 year old male is new to your practice. He is a former smoker who had a small right hemispheric stroke associated with RICA stenosis 4 months ago for which he underwent a successful CEA. His management should include:

A. ASA 81 mg daily
B. Clopidogrel 75 mg daily
C. ASA 81 mg daily and Clopidogrel 75 mg daily
D. No anti-platelet therapy

Long term Secondary Prevention

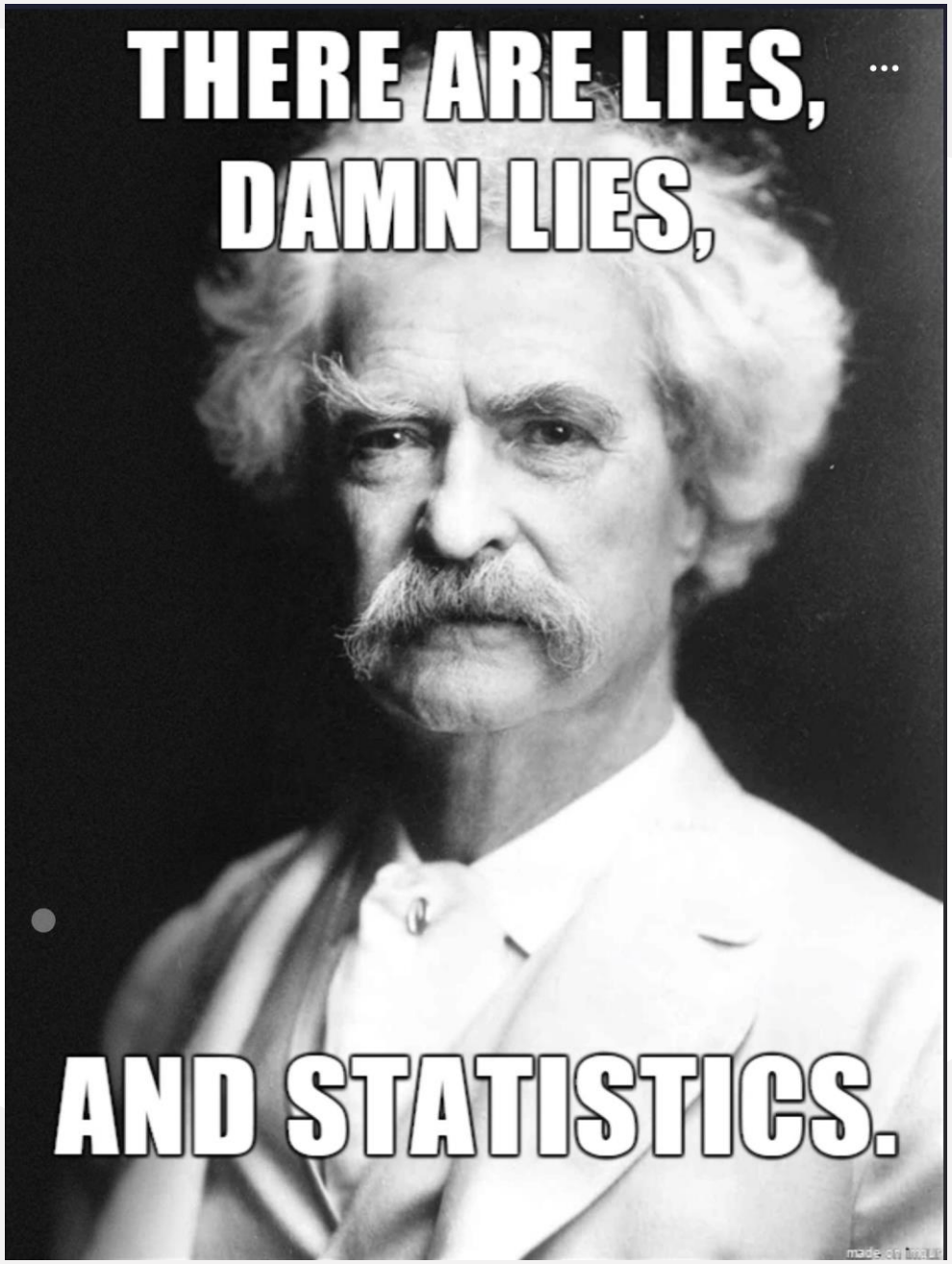
Special Subgroup Considerations

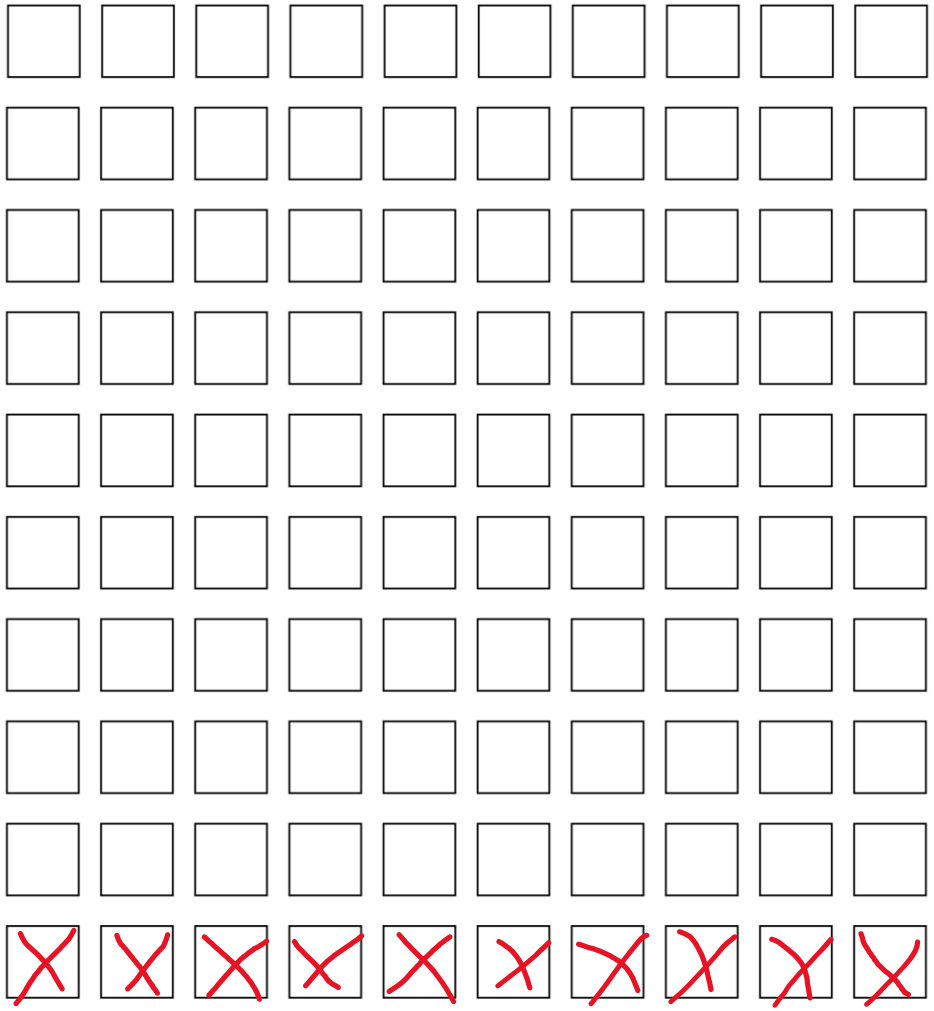
- Large vessel
  - Aortic Arch atherosclerosis: antiplatelet treatment (? Single vs dual) ASA 2021 guidlines
  - Internal Carotid Artery Stenosis (ICAS)
    - Benefit for ASA + Clopidogrel for 30 days but nonsignificant CHANCE trial
    - Risk of recurrence with ICAS extends well beyond 30 days
- Intracranial large vessel disease
  - SAMMPRIS used ASA/Clopidogrel for 90 days followed by ASA alone
- Small vessel disease
  - Single antiplatelet for long term treatment (no data for acute treatment and 20-30% progress)
  - Possible role for cilostazol
- Mixed pathologies: a fib + atherosclerosis
- After a stroke occurs while on ASA

Future Directions

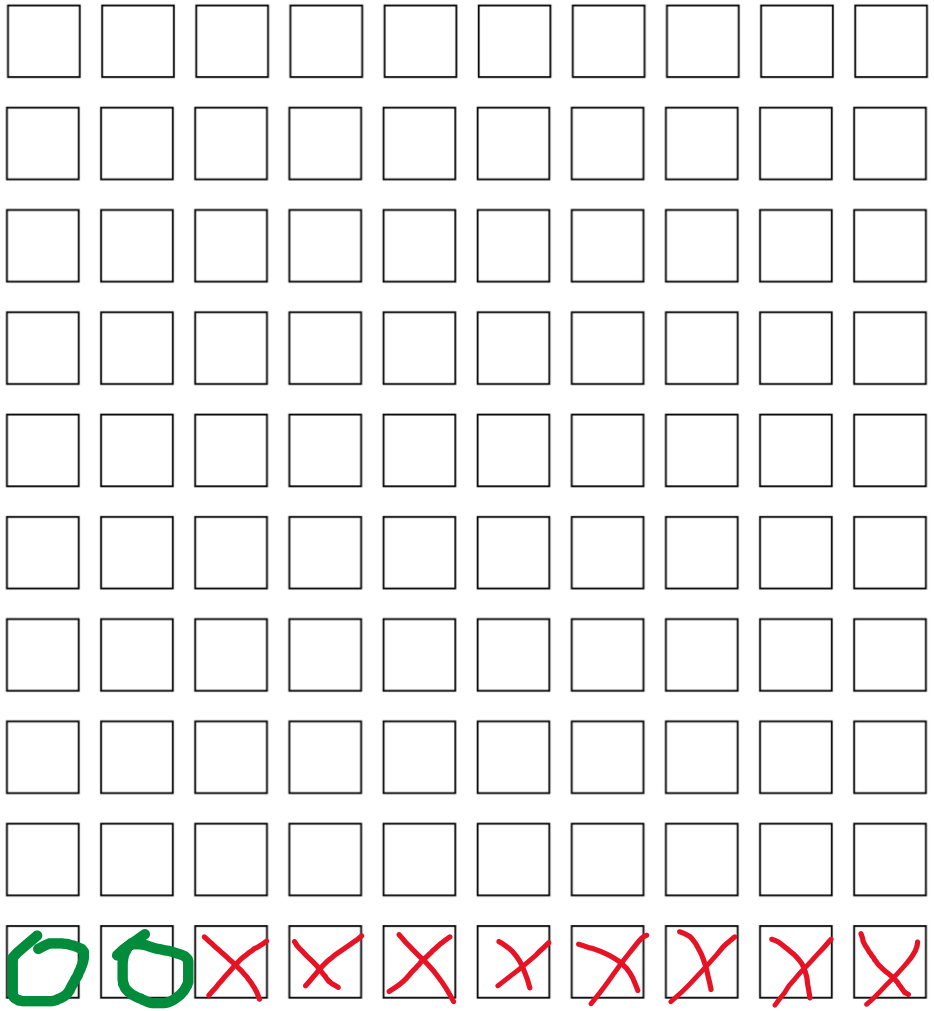
2021 ASA Guidelines for secondary prevention:

- Optimal combination of medications, timing of initiation & duration of DAPT
- Effectiveness & potential harm of DAPT in specific subgroups according to stroke subtype, genetic tests, other factors
- Benefit of switching anti-platelet agent for stroke patients already on 1 agent
- Effectiveness of DOAC’s compared with or in combination with anti-platelet therapy amount noncardioembolic ischemic stroke
- Role of IV anti-platelet therapy to augment acute interventional procedures

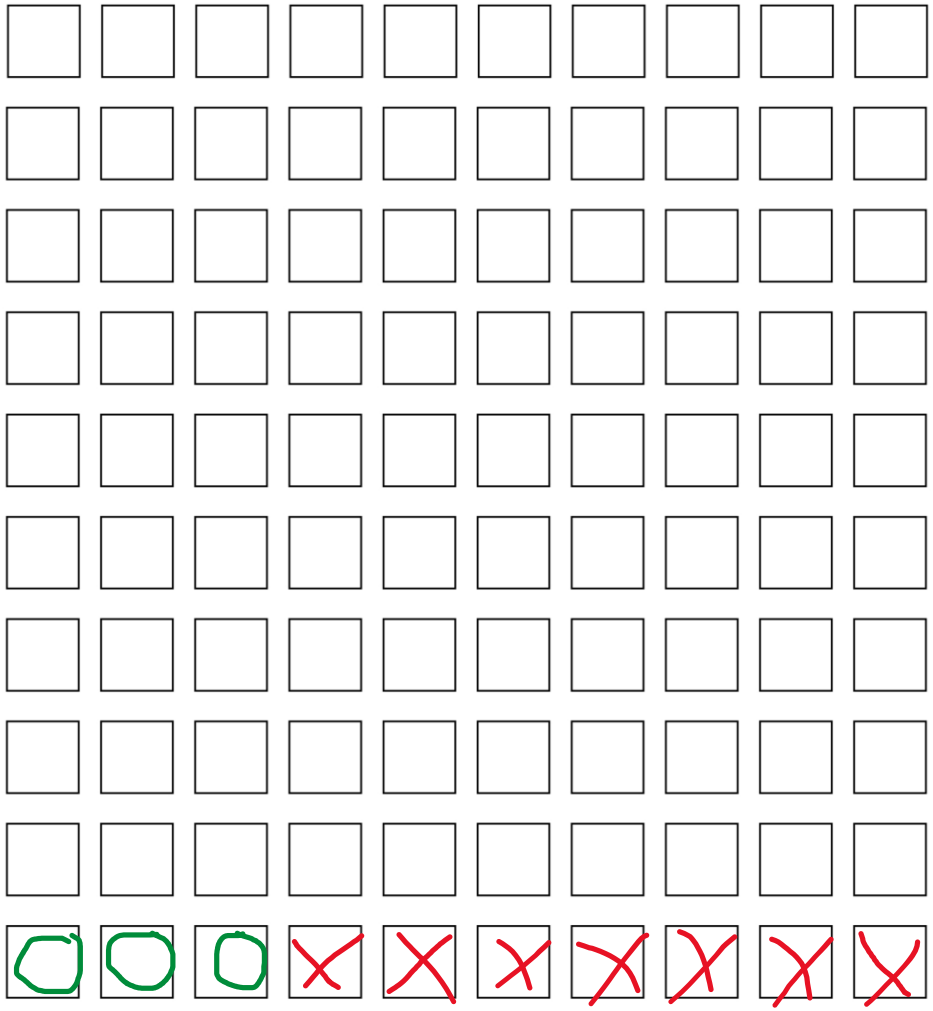

THERE ARE LIES,
DAMN LIES,
AND STATISTICS.



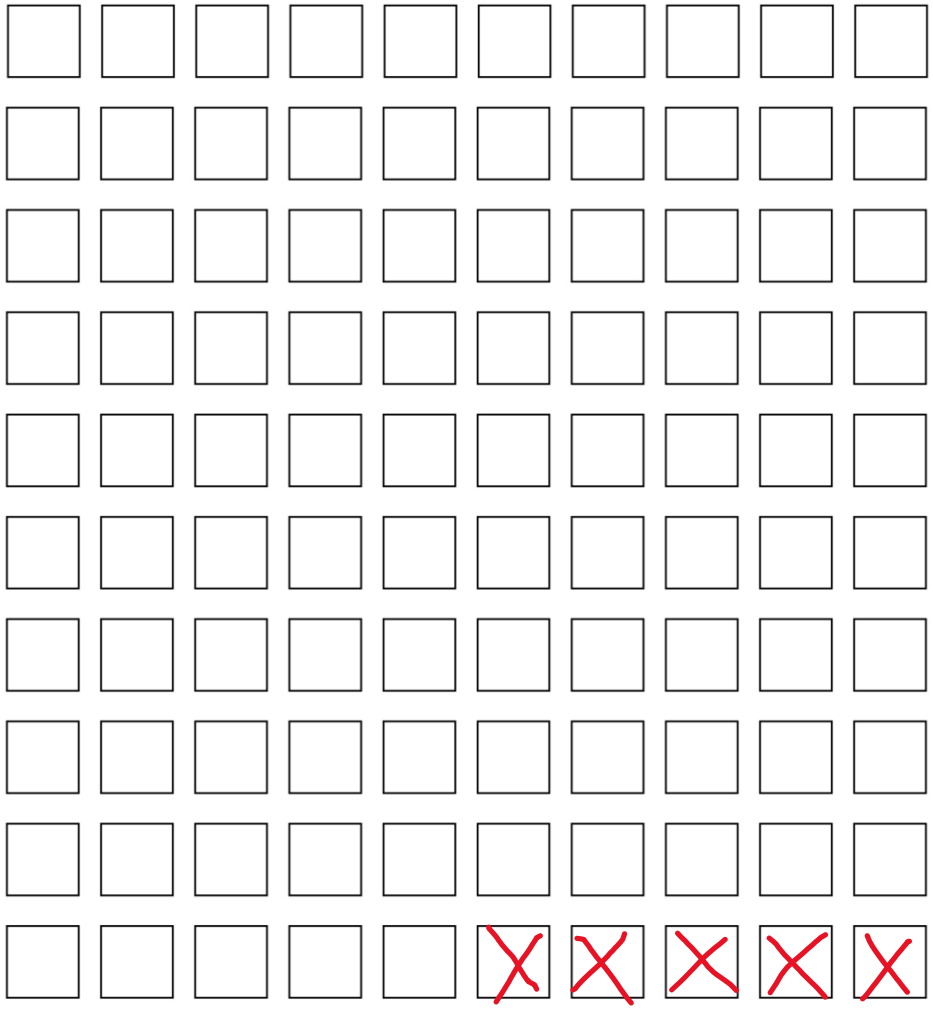
10% RISK OF STROKE



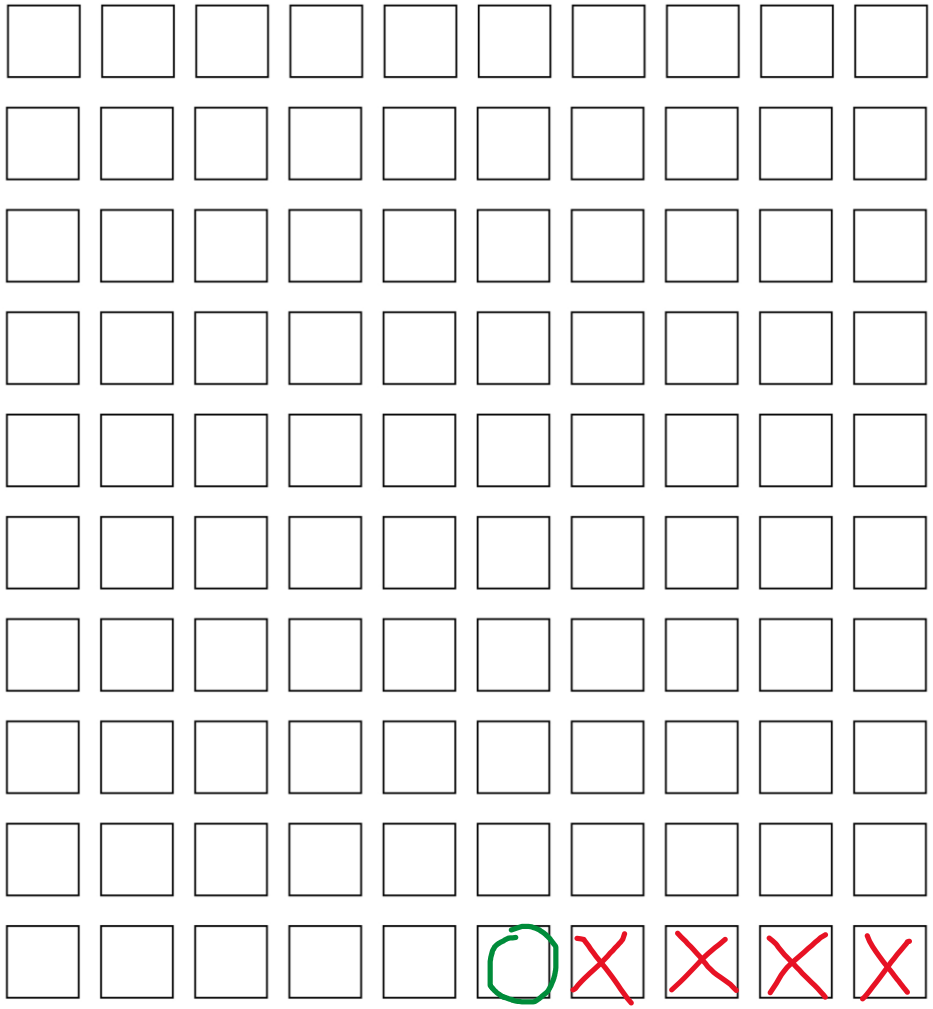
20% RISK REDUCTION



30% RISK REDUCTION



5% RISK

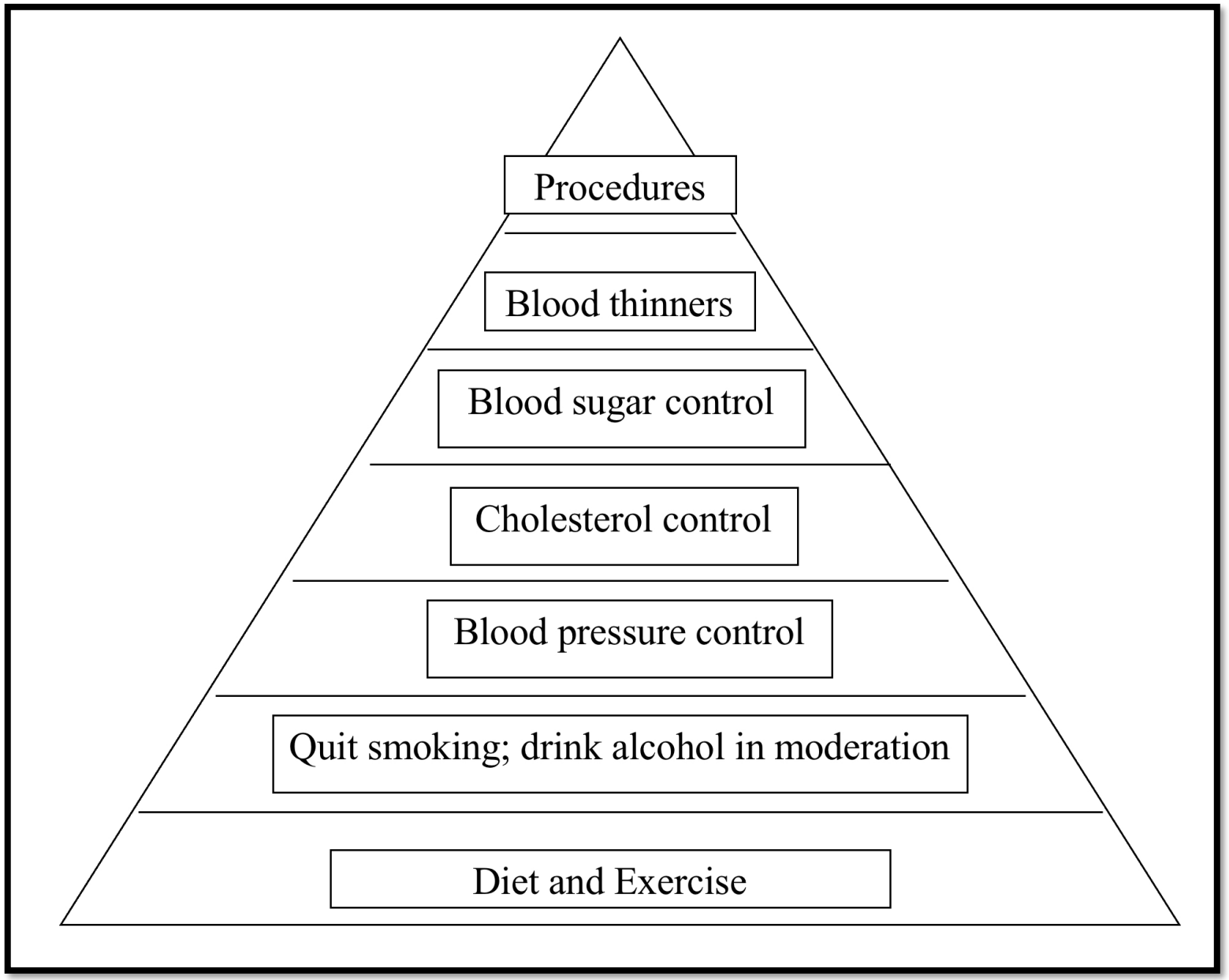


20% RISK REDUCTION

- **Overall, antiplatelet strategies decrease risk of stroke about 15-15%**
- **More potent therapies carry higher risks of bleeding**

- **We need to remember that this is only one of many strategies to help our patients decrease their stroke risk**

Stroke Prevention Pyramid



Summary

- Platelets play an important role in arterial thrombosis
- Decisions re: treatment depend on benefit/risk (primarily bleeding)
- Antiplatelet therapy is used for arterial thrombosis/emboli
- Anticoagulant therapy is superior for venous thrombosis and A fib
- Bleeding risk is increased in:
  - Age over 65
  - BMI< 18.5
  - Diabetes
  - Prior bleeding
  - Taking oral anticoagulants
- Risk of systemic bleeding can likely be reduced with PPI treatment
- Risk of ICH can likely be reduced with aggressive BP control

Summary (2)

- Antiplatelet therapy IS NOT recommended for primary prevention
- Aspirin (loading dose 180-365 mg/ maintenance 81 mg is recommended for acute stroke therapy)
  - Some evidence suggests better efficacy for 365 mg maintenance if weight >
- Aspirin plus Clopidogrel is recommended for the first 3 weeks after TIA and minor stroke
- Aspirin plus Ticagrelor MAY be an alternate option but bleeding risk is higher
- Long term treatment of large and small vessel disease favors single antiplatelet therapy