# ANTI-PLATELET MEDICATIONS

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Anti-platelet Medications | Mechanism of Action, Indications, Adverse Reactions, Contraindications

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## OUTLINE



## I) MECHANISM OF ACTION

### Hemostasis Overview

**Endothelial Cells**

- line the inner portion of blood vessels
- release chemicals such as **$PGI_2$** and **Nitric Oxide (NO)** that inactivate platelets to keep blood antithrombotic
- damaged vessel lining → ↓PGI2 and NO → ↓inhibition of platelet → ↑platelet that attach to endothelial lining

**von Willebrand Factor (vWF)**

- proteins that attach to the exposed collagen following endothelial damage
- made by endothelial cells and platelets

**Glycoprotein Ib (GPIb)**

- binds platelet to VWF

**Delta/ Dense granules**

- release platelet aggregation agents that call other platelets to the injured site
  - Serotonin (5HT)
  - ADP
  - $Ca^{2+}$
  - Thromboxane $A_2$ ($TXA_2$)

**Glycoprotein IIb/IIIa (GP IIb/IIIa)**

- protein complex on the surface of platelets [Trevor, Katzung, & Kruidering-Hall, 2015]
- when activated, aggregates platelets by binding to fibrin [Trevor, Katzung, & Kruidering-Hall, 2015]

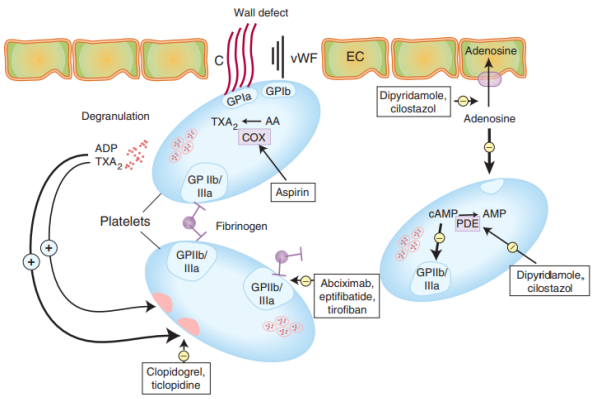


*Figure 1. Summary of Thrombus Formation and Mechanism of Action of Antiplatelet Medications*

[Trevor, Katzung, & Kruidering-Hall, 2015, p. 281, Fig. 34-3]

### (A) $TXA_2$ SYNTHESIS INHIBITORS

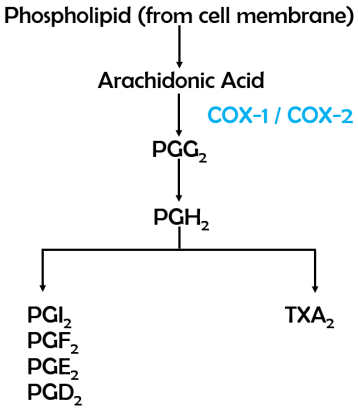


*Figure 2. $TXA_2$ Synthesis*

#### $TXA_2$ Roles

- Activate **$G_q$** pathway → activate **Phospholipase C (PLC)** → break down **$PIP_2$** into **$IP_3$** and **DAG**

**Inositol Triphosphate ($IP_3$)**
- Binds to endoplasmic reticulum-like network and stimulate protein channel to shuttle out $Ca^{2+}$
- Shuttled out $Ca^{2+}$ stimulates degranulation → release of ADP, 5HT, $Ca^{2+}$, $TXA_2$ → ↑platelet aggregation

**Diacylglycerol (DAG)**
- activate **Protein Kinase C (PKC)** → stimulate GP IIb/IIIa → stabilize platelet plug

#### Drug that Inhibits $TXA_2$ Synthesis

**Aspirin (ASA)**

- irreversibly **inhibits cyclooxygenase (COX) 1 and 2** that are responsible for the conversion of arachidonic acid to $PGG_2$, ultimately leading to decrease in $TXA_2$ production → ↓platelet aggregation & ↓stability of platelet plug

### (B) ADP RECEPTOR INHIBITORS

#### ADP Roles

a. bind to **P2Y12 receptor** on platelet surface → **activate $G_i$** pathway → inhibit **adenylate cyclase (AC)** →↓ATP →↓cAMP → ↓PKA → ↓phosphorylation of **VASP** into inactive form → ↑active VASP → ↑stimulation of GP IIb/IIIa → ↑platelet plug stability

**Adenylate cyclase**
- responsible for the conversion of ATP into cyclic AMP (cAMP); cAMP will then activate protein kinase A (PKA) that will phosphorylate active vasodilator stimulatory protein (VASP) into the inactive VASP-P

**VASP (active)**
- stimulate GP IIb/IIIa → ↑platelet plug stability

b. bind to P2Y12 receptor on platelet surface → **activate $G_q$** pathway → activate **Phospholipase C (PLC)** → break down **$PIP_2$** into **$IP_3$** and **DAG** (see discussion on $G_q$ in $TXA_2$)

### Drugs that block ADP receptor

- **block P2Y12** receptor leading to **inhibition of $G_i$ and $G_q$ pathways**, ultimately leading to decreased platelet aggregation and inhibition of GPIIb/IIIa
- **Thienopyridine Derivatives**
  - Converted in the liver to active metabolites that irreversibly inhibit ADP receptor [Trevor, Katzung, & Kruidering-Hall, 2015]
  - **Clopidogrel** (Plavix)
  - **Prasugrel** (Effient)
  - **Ticlopidine** – not commonly used anymore due to adverse drug reactions (ADRs)
- **Non-thienopyridine**
  - Does not require activation and reversibly inhibit ADP receptor [Trevor, Katzung, & Kruidering-Hall, 2015]
  - **Ticagrelor** (Brilinta)

## (C) GPIIB/IIIA INHIBITORS

- Inhibit GP IIb/IIIa interaction → ↓stability of platelet plug
  - **Abciximab**
  - **Tirofiban**
  - **Eptifibatide**

## (D) PHOSPHODIESTERASE-3 (PDE-3) INHIBITORS

- Inhibit PDE-3 (enzyme that breaks down cAMP)
  - ↓cAMP breakdown → ↑cAMP → ↑PKA → ↑phosphorylation of VASP →↓VASP active → inhibition of GPIIb/IIIa
  - **Cilostazol**
  - **Dipyridamole**

### Other Mechanism and Use of PDE-3 Inhibitors

- cause smooth muscle relaxation → dilate blood vessel → ↑ blood flow
- Use: **Peripheral Artery Disease**
- **Mechanism:**
  - Normal Physiology
    - In smooth muscles, adenosine binds to its receptor and activate $G_s$ → activates AC, which converts ATP to cAMP → activate PKA → phosphorylate myosin light chain kinase (MLCK) to its inactivated form MLCK-P → no smooth muscle contraction
  - Cilostazol and Dipyridamole
    - inhibit PDE-3 → ↓ cAMP breakdown → ↑ cAMP → ↑PKA →↑phosphorylation of MLCK → inhibition of smooth muscle contraction → smooth muscle relaxation → blood vessel dilation

# II) INDICATIONS

## (A) ACUTE CORONARY SYNDROME (ACS)

- Thrombus or blockade in the myocardial blood vessels
- **Types of ACS**
  1) Unstable Angina
  2) Non-ST Elevated Myocardial Infarction (NSTEMI)
  3) ST Elevated Myocardial Infarction (STEMI)

### Drug Combinations for ACS

- **ASA + Clopidogrel/ Prasugrel/ Ticagrelor/ *Abciximab (*only for high-risk patients)**

**High-risk patients**
- >75 y/o
- Diabetic
- ST segment deviations
- ↑↑Troponin
- Left Ventricular Ejection Fraction (LVEF) <40%
- Pulmonary Edema

### Potency of drugs (Most potent to least potent)

1) **Abciximab**
   - only give to high-risk patients
   - not commonly given since GPIIb/IIIa Inhibitors has the highest bleeding risk
2) **Prasugrel**
   - black box warning for bleeding
3) **Ticagrelor**
   - commonly used
4) **Clopidogrel**
   - commonly used
   - has risk of Thrombotic Thrombocytopenic Purpura (TPP)
   - some individuals may be poor metabolizers due to CYP2C19 mutation
5) **Aspirin**
   - Least bleeding risk

**Usual drug combos used in Percutaneous Coronary Intervention (PCI)**
- Long-term/ Post-PCI: ASA + Clopidogrel
- Pre-PCI: ASA + Ticagrelor
- High-Risk Patients Pre-PCI: ASA + Abciximab

## (B) CEREBROVASCULAR ACCIDENTS (CVA)

- Blood clots in brain, stroke
- **ASA + Clopidogrel** (given 3-4.5 hours **post-CVA**)

**Important!**
During **first 3-4.5 hours of CVA**
- give **tPA** (tissue plasminogen activator)

## (C) CAROTID ARTERY STENTING (PRE AND POST)

- Drug Combination: **ASA + Clopidogrel**

## (D) CORONARY ARTERY DISEASE PROPHYLAXIS

- **ASA** can prevent another MI or CVA

## (E) GIANT CELL ARTERITIS

- Inflammation of temporal arteries (vasculitis) increases risk of developing clots that can block the temporal artery branches, such as ophthalmic artery and arteries that supply muscles for mastication, leading to pain in temples, vision loss, or jaw claudication
- Drug: **ASA**

## (F) PERIPHERAL ARTERY DISEASE (PAD)

- Plaques or clots in the vessels of the leg occlude blood flow to the surrounding muscles leading to development of ulcers, gangrene, or claudication due to decreased oxygen supply
- Drug Combination**: ASA + Cilostazol**

## (G) PROPHYLAXIS OF COLORECTAL CANCER (LYNCH SYNDROME)

- **ASA** decrease risk of Colorectal cancer (especially Lynch Syndrome)
- **Lynch Syndrome**: tumors that form in different parts of body (colorectal, endometrial, ovarian, renal, pancreatic)

## (H) STRESS TEST

- Assessment of myocardial perfusion in CAD is usually done by exercise-induced stress test. If the patient cannot exercise, Dipyridamole can be used.
- **Dipyridamole** dilates myocardial vessels to see perfusion via imaging techniques. Dipyridamole increases blood flow of normal vessels, but stenotic vessels are not dilated.

**Important Dosage to Remember:**
**ASA**
- ACS: 325mg ASA chewed then swallowed
- CAD Prophylaxis: 80mg ASA/ day

**Clopidogrel**
- Loading dose of 300 mg, then 75mg/day

## III) ADVERSE DRUG REACTIONS (ADRS)

### (A) BLEEDING

6) Anterior Epistaxis – nosebleed
7) Gingival bleeding – bleeding in gums
8) Bleeding indications on skin
   a. Petechiae – pinpoint hemorrhage on skin
   b. Purpura – larger pinpoint hemorrhaging
   c. Ecchymosis – large bruising
9) Hematemesis- vomiting blood
10) Melena – upper GI bleed – dark or black feces
11) Hematochezia – lower GI bleed – red stool
12) Excessive Vaginal/Uterine Bleeding

#### Monitoring patients

- Look for signs of bleeding (physical exam)
- CBC to check for anemia
- Hemoccult to check for GI bleed

### (B) THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- Syndrome characterized by formation of small thrombi, platelet consumption and thrombocytopenia [Trevor, Katzung, & Kruidering-Hall, 2015]
- Associated with **Ticlopidine** and **Clopidogrel** use

#### Mechanism:

- **Normal Physiology**: VWF monomers fuse together forming multimers. Multimers can be broken down again into monomers via **ADAMS T13** enzyme.
- **Effect of Anti-platelets** (i.e., Ticlopidine and Clopidogrel)
  - ↓ ADAMS T13 level → ↑VWF multimers → platelets will stick to the multimers → ↑clots and ↓platelets (since they are consumed in the formation of clots)

**Conditions or Medications that ↓ADAMS T13**
- Antiplatelet medications (Ticlopidine, Clopidogrel)
- Lupus
- Chemotherapy (Gemcitabine, Cyclosporine)

#### Signs and Symptoms of TTP ("FAT-RN")

- **F**ever (> 100.4 ºF)
- Hemolytic **A**nemia due to breakdown of RBC
  - ↑LDH, ↑Bilirubin, ↓Haptoglobin
- **T**hrombocytopenia ↓platelets
- **R**enal damage
  - Basic Metabolic Panel (BMP) ↑Creatinine, ↑BUN
- **N**eurological Damage
  - Headache
  - Confusion

#### Treatment of TTP

- Plasmapheresis: clean blood by removing different substances
- Steroids to ↓inflammatory response
- Rituximab

## IV) CONTRAINDICATIONS

### (A) <19Y/O + FEVER RISK OF DEVELOPING REYE SYNDROME

- Never give **ASA**

#### Mechanism:

- **Normal Physiology**:
  - Hepatic mitochondria break down free fatty acids into acetyl-CoA via β-oxidation. Acetyl-CoA goes into the Krebs Cycle forming NADH and $FADH_2$ that stimulates the electron transport chain (ETC) to make ATP.
- If **Salicylates** (i.e., ASA) are given to patient:
  - Salicylates get metabolized by enzymes in the hepatic mitochondria, producing metabolites that inhibit β-oxidation, leading to ↓Acetyl-CoA → ↓NADH and $FADH_2$ → ↓ATP production
- **Viral infections**:
  - Viruses increase metabolism of salicylates → ↑salicylate metabolites → ↑ inhibition of β-oxidation → → → ↓ATP → ↓cell function → cell death
- **Detoxification in Liver**
  - Amino Acids can be degraded in the liver, forming ammonia ($NH_3$) as a product.
  - $NH_3$ is then metabolized and excreted via the Urea cycle in the hepatic mitochondria.
  - If there is liver failure (i.e., due to giving salicylates during viral infections), the liver would not be able to metabolize ammonia via the Urea cycle.
    - ↑ $NH_3$ in blood → $NH_3$ into CNS → $NH_3$ converts glutamate into glutamine in the astrocytes → astrocytes become osmotically active → swelling → **Encephalopathy**

**Signs and Symptoms of Encephalopathy**
- Vomiting
- Fatigue
- Seizures
- Coma
- Delirium

#### Reye Syndrome Triad

- <19y/o, febrile (possibly due to viral infection)
- Liver Damage (↑AST/ALT)
- Signs of Encephalopathy

**Remember:**
Aspirin increases the risk for Reye's syndrome, so giving ASA to <19y/o febrile patients is contraindicated.

### (B) THROMBOCYTOPENIA

- Low platelet count (<100,000)
- Contraindicated especially in **GPIIb/IIIa inhibitors i.e., Abciximab**

### (C) UNCONTROLLED BLOOD PRESSURE/ AORTIC DISSECTION

- High BP can tear tunica intima of blood vessels → **aortic dissection** → ↑ bleeding risk

### (D) BLEEDING

- GI bleed, perforated peptic ulcer
- Subarachnoid hemorrhage

### (E) TRAUMA/ SURGERY

## V) REVIEW QUESTIONS

1) **Which of the following is a GP IIb/IIIa inhibitor**?
   a. Clopidogrel
   b. Aspirin
   c. Ticlopidine
   d. Abciximab

2) **Which drug can be used in cardiac stress test?**
   a. Tirofiban
   b. Dipyridamole
   c. Prasugrel
   d. Eptifibatide

3) **What is the mechanism of action of Aspirin?**
   a. Inhibits PDE-3
   b. Blocks P2Y12 receptor
   c. Inhibits COX-1 and COX-2
   d. Inhibit GP IIb/IIIa

4) **What enzyme metabolizes Clopidogrel?**
   a. CYP2C19
   b. ADAMS T13
   c. PDE-3
   d. Adenylyl cyclase

5) **What is given to patients suffering from CVA during the first 3 to 4.5 hours?**
   a. Aspirin
   b. Clopidogrel
   c. tPA
   d. Ticlopidine

6) **Which enzyme is responsible for the conversion of ATP into cAMP?**
   a. Phospholipase C
   b. Adenylate Cyclase
   c. PDE-3
   d. Protein Kinase A

7) **Which drug is contraindicated in children with fever since it increases the risk of developing Reye's syndrome?**
   a. Clopidogrel
   b. Paracetamol
   c. Aspirin
   d. Tylenol

8) **Which of the following is given only in high-risk ACS patients?**
   a. Aspirin
   b. Clopidogrel
   c. Abciximab
   d. Cilostazol

9) **Loading dose of Clopidogrel**
   a. 325 mg
   b. 300 mg
   c. 80 mg
   d. 75 mg

10) **Which can be used for Peripheral Artery Disease?**
   a. Cilostazol
   b. Abciximab
   c. Tirofiban
   d. Clopidogrel

**CHECK YOUR ANSWERS**

## VI) REFERENCES


- Trevor, A., Katzung, B., & Kruidering-Hall, M. (2015). *Katzung & Trevor's Pharmacology Examination & Board Review*. McGraw Hill Education