

CHAPTER 13

ASPIRIN

- Action
- Aspirin Resistance
- Aspirin Dose
- Therapeutic Efficacy
 - Secondary prevention
 - Acute coronary syndromes
 - Primary prevention
- Limitations and Side Effects

Aspirin

- Aspirin should be administered indefinitely (for the rest of patient's life) to all patients with any form of CAD.
- Aspirin should be given acutely to all patients with ACS.
- Aspirin-protects against new cardiovascular events:
 - Reduces the severity of new episodes of ACS.
- Aspirin beneficial effects are through:
 - Antiplatelet action – less thrombus formation.
 - Antiinflammatory action – less ASO plaque progression.
 - Atherosclerotic plaque stabilizing effect-help prevent ACS.
- For primary prevention (individuals without a prior history of cardiovascular disease), aspirin is recommended only in high risk individuals (age older than 50 years with at least one risk factor for CAD).
- Aspirin dose of 75-150 mg/day will provide the same protection as high doses with less side effects.

ACTION

- Aspirin irreversibly inhibits cyclo oxygenase (COX) by acetylating a serine residue in the COX polypeptide (figure 13-1).
- COX converts arachidonic acid (AA) into the prostaglandin G2 (PGG2) which is the precursor of another prostaglandin PGH2.
- PGH2 is either converted into prostacyclin (PGI2) by prostacyclin synthase present in endothelial cells or converted into TXA2 by thromboxane synthase in platelets (figure 13-1).
- Platelets lack the ability to synthesize new proteins (they have no nuclei), as aspirin inhibits thromboxane synthase for the life span of the platelet, while vascular endothelial cells can generate new COX.
- Thromboxane acts only on one of the platelet activation pathways (figure 12-3), aspirin is unable to inhibit platelet activation by other stimuli such as thrombin that can activate platelets through TXA2 – independent pathways.
- Low doses of aspirin may selectively inhibit platelet synthesis of thromboxane, while maintaining endothelial cell synthesis of prostacyclin.
- In addition to antiplatelet activity aspirin have other effects:
 1. It reduces markers of inflammation (proinflammatory cytokines and CRP) in patients with chronic stable angina.
 2. It modifies the acute-phase inflammatory response to myocardial injury.

Aspirin provides greater benefit against subsequent coronary events when serum CRP is elevated with less benefit when serum CRP is normal.

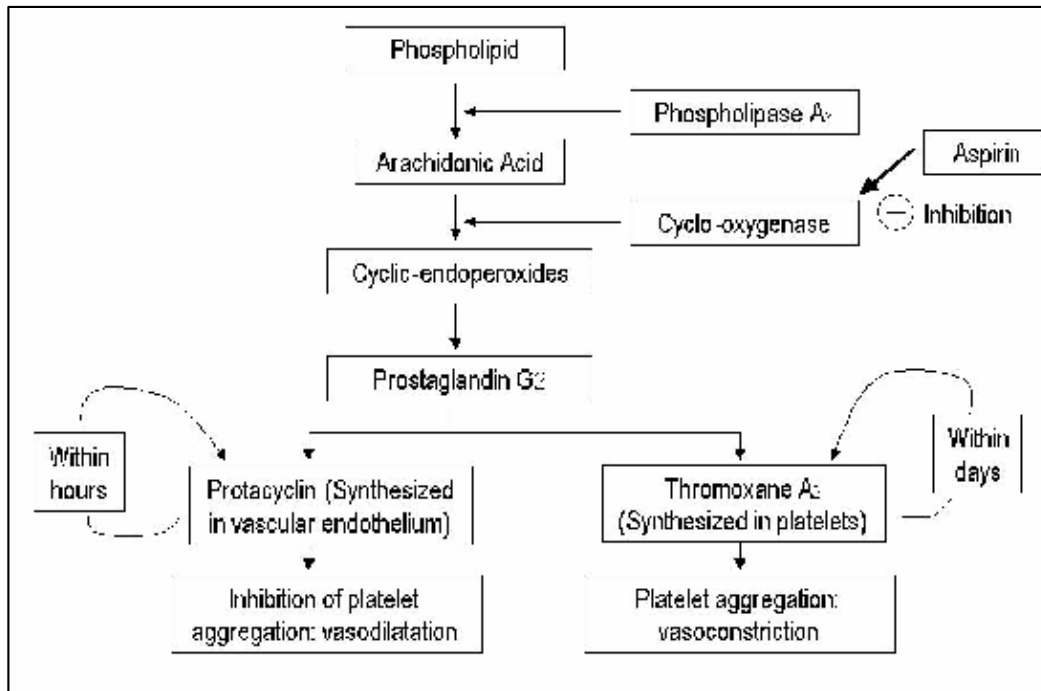


Figure 13-1: Antiplatelet Action of Aspirin (Modified After Taneja et.al 2004)

ASPIRIN RESISTANCE

- There is a group of patients who are not deriving any benefit from aspirin therapy at the usual doses.
- Aspirin resistance has been defined as failure of aspirin to prolong bleeding time or failure to reduce platelet aggregation or clinically as having a new cardiovascular event despite aspirin therapy.
- About 5-40% of patients have been reported to have aspirin resistance.
- The possible mechanisms for aspirin resistance are:
 1. Increased platelet activation that could override the inhibitory effect of aspirin.
 2. More macrophages in the plaques producing TXA₂ by synthesizing new COX-2 after inhibition by aspirin.
 3. Intrinsic platelet mechanism that allows TXA₂ production despite aspirin.
- Aspirin resistance is clinically relevant. Aspirin non-responders (platelet function test) had a 20-fold higher rate of cardiovascular death, MI or recurrent stroke over 2 years compared to aspirin responders. However, both the definition of aspirin resistance and its prognostic significance remain uncertain.
- Management of patients with aspirin resistance is possibly the substitution of aspirin by clopidogrel.

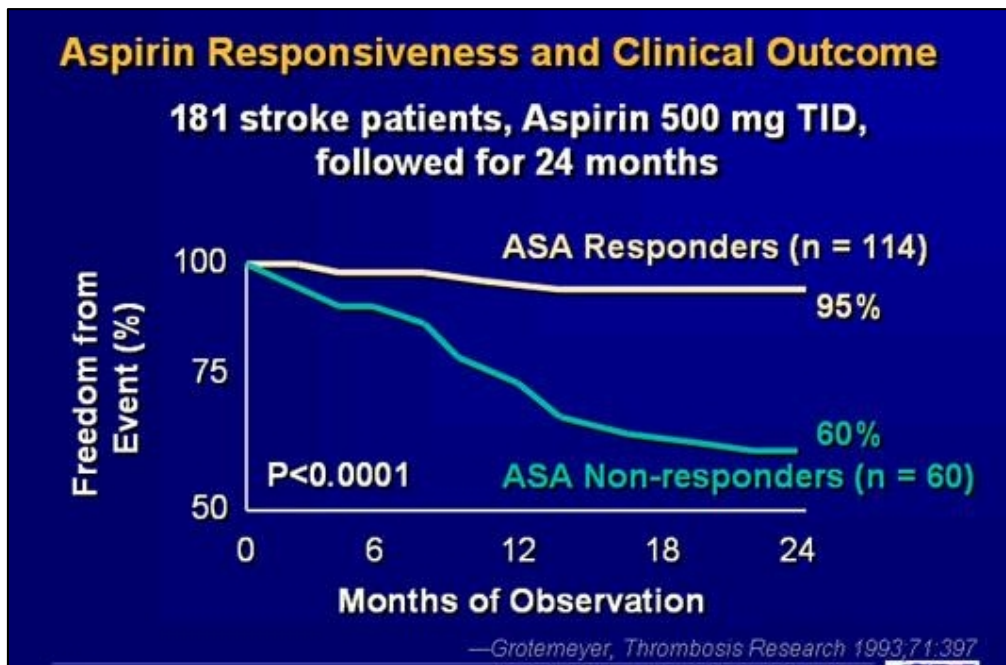


Figure 13-2 : Aspirin Responsiveness and Clinical Outcome

ASPIRIN DOSE

- Plasma levels of aspirin are detectable 20-30 minutes after administration of a single crushed or chewed dose, and platelet inhibition is achieved after approximately 60 minutes. Aspirin is readily absorbed in the stomach and small intestine.
- The dose-response effect of aspirin on platelet aggregation and TXA₂ production reaches a plateau at approximately 80mg. Lower doses can inhibit platelet aggregation with less frequency of gastrointestinal side effects.
- A dose of 75-150 mg/day will provide the same protection as higher doses while limiting toxicity.

THERAPEUTIC EFFICACY

Secondary Prevention

- Long term aspirin therapy reduces the risk of subsequent MI, stroke and vascular death among patients with prior cardiovascular disease (prior or acute MI, prior or acute stroke or TIA and other high risk groups such as UA, PVD, CABG, PCI, etc.) by approximately 22%.

Acute coronary syndromes (ACS)

- Aspirin is the drug of choice and should be administered to every patient with an acute MI and other ACS. Even among patients with a history of bleeding or other side effects of aspirin, the contraindications to its use in AMI are relative, not absolute.

- Aspirin should be given as an initial dose of 325 mg followed by 75 to 150 mg once a day. The first tablet should be chewed or crushed.
- Patients who develop gastrointestinal side effects are usually able to tolerate a lower and probably still effective dose.
- Patients who are unable to take aspirin should be treated with clopidogrel.
- Therapy should continue indefinitely.
- In addition to protecting against new cardiovascular events when given for secondary prevention and in improving outcomes when given acutely to patient with ACS, aspirin also appear to reduce the severity of new episodes. This is possibly due to less thrombus formation at the site of plaque rupture.
- *Prior Aspirin use in ACS*
 - In patients with a non-ST elevation ACS, prior aspirin use within the preceding seven days was associated with an increased risk of adverse effects.
 - This is a marker for more underlying vascular diseases, leading to higher event rates.
 - Recent aspirin use is one of the seven adverse predictors in the TMI risk score (see TIMI risk score).

**TIMI Risk Score in ACS without Persistent ST-elevation
Independent Predictors of Cardiac Adverse Events at 14 days**

- Age \geq 65 years.
- \geq 3 CAD risk factors.
- Coronary artery stenosis $>$ 50%.
- ST deviation.
- \geq 2 anginal events $<$ 24 hours.
- Aspirin in last 7 days.
- Elevated cardiac markers.

Primary Prevention

- Aspirin prophylaxis in patients without a prior history of cardiovascular disease is recommended in high risk individuals. However, the clear benefit on reducing the risk of a first MI must be weighed against potential risks e.g. a small increase in hemorrhagic stroke.
- One meta-analysis found that aspirin reduced all cardiovascular events by 15% and MI by 30% with a non significant 6% increase in the risk of stroke and a significant 69% risk of bleeding complications.

- The decision to recommend aspirin prophylaxis should rely on individual clinical judgment, taking into account the patient's cardiovascular risk profile. Risk scoring systems (e.g. Framingham Risk Score) can define the risk of cardiovascular event in the coming 10 years.
- Aspirin is strongly recommended for primary prevention if the 10 year risk is 6% or greater. Aspirin should be considered for men and women more than 50 years of age who have at least one risk factor for CAD (e.g. cigarette smoking, hypertension, diabetes, high cholesterol level, and a family history of MI) and have no contraindications for aspirin.
- Aspirin prophylaxis is worthwhile when the coronary event risk is > 1.5% per year. Aspirin is unsafe when the coronary event risk is 0.5% per year.
- Routine use of aspirin is not recommended for primary prevention in people free of a history of MI, stroke or TIA who are less than 50 years of age.
- Assessing the net effect of aspirin requires an estimation of the absolute risk of the individual patient for thrombotic or hemorrhagic complications (table 13-1)

Table (13-1): Benefit/Risk Ratio of Antiplatelet Prophylaxis with Aspirin

	Benefit (Number of patients in whom a major vascular event is avoided per 1000/year)	Risk (Number of patients in whom a major bleeding event is caused per 1000/year)	
Men at low to high CV risk	1-2	1-2	benefits and hazards are similar
Essential Hypertension	1-2	1-2	benefits and hazards are similar
Chronic stable angina	10	1-2	benefits greatly outweigh hazards
Prior MI	20	1-2	benefits greatly outweigh hazards
Unstable angina	50	1-2	benefits greatly outweigh hazards

Modified from Patrono et al in ESC expert document on antiplatelet drugs (2004).

LIMITATIONS AND SIDE EFFECTS

- Infrequent side effects with low-dose.
- Major side effects are gastrointestinal symptoms, which occur more frequent with higher aspirin doses and occur in about 40% of patients.
- Gastrointestinal bleeding can occur at any dose up to 5% per year, frank melena (1% per year) and hematemesis (0.1% per year).
- Aspirin may cause bronchospasm and angioedema in 4% of patients with adult onset bronchial asthma.
- Gout may be aggravated due to impaired urate excretion.