1) Permanent and irreversible inactivation of both COX-1 and COX-2 (cyclo-oxygenase) enzymes

2) COX-1 found in platelets, stomach, and kidney - more responsible for antiplatelet effect

3) COX-2 found in other blood cells, endothelial cells, and many organs – more responsible for analgesic and anti-inflammatory effects
4) Aspirin is 50-100 fold more potent in inactivating COX-1 than COX-2.

5) COX-1 (antiplatelet) is blocked permanently for the lifespan of the anucleate platelet (10 days).

6) COX-2 (pain and inflammation) is rapidly resynthesized in nucleated cells.

7) Thus antiplatelet action requires low dose and only once daily dosing and analgesic/anti-inflammatory effects require higher and more frequent doses.
ASPIRIN Pharmacokinetics

1) Rapidly absorbed in stomach and upper intestine
2) Peak plasma level 30-40 min. after ingestion of regular aspirin - 3-4 hr. after ingestion of enteric coated aspirin
3) Has 15-20 min. half-life in circulation
4) Evident platelet inhibition occurs after 1 hr. with regular aspirin
5) ~10% new platelets every day – aspirin exerts significant effect for ~1 week after being held
ASPIRIN

Adverse effects

GI hemorrhagic effects which depend on:

1) Dose
2) Duration of use
3) Use of other antithrombotic drugs

Enteric coated does not decrease GI adverse effects; use of PPI recommended

Always must weigh risks vs. benefit of GI effects

Should not be used in children <12 with fever due to higher risk of Reye’s syndrome
US Reye’s Syndrome Cases <18 yrs. old 1981-1997
ASPIRIN
Use in Various Settings

1) Atrial fibrillation
2) MI and stroke
3) Percutaneous Coronary Intervention (PCI) and Stents
4) CABG
5) PVD
6) Obstetric complications
7) DVT prophylaxis
8) Adjunctive with warfarin
9) Adjunctive with rivaroxaban
10) Other hematologic disorders
Aspirin use depends on:

1) whether AF is non-valvular or valvular

2) AF risk stratification
ATRIAL FIBRILLATION
Non-Valvular

High risk:

1) Sustained, persistent, or paroxysmal AF
2) Prior ischemic stroke
3) H/O TIA or systemic embolism
4) age > 75
5) impaired LV function or CHF
6) H/O HTN or DM
ATRIAL FIBRILLATION
Non-Valvular

Intermediate risk:
1) Persistent or paroxysmal AF
2) Age 65-75
3) no other risk factors

Low risk:
1) Persistent or paroxysmal AF
2) Age < 65
3) No other risk factors
ASPIRIN
Non-Valvular Atrial Fibrillation Indications

1) Less ASA now being recommended due to new agents

2) May use aspirin (75-325 mg/day) for CHA2DS2-VASc score of 1


3) May add low dose aspirin to warfarin if AF is accompanied by CAD
Aspirin indicated for:

1) Mitral valve prolapse pts with TIA’s at low dose

2) Pts with mechanical valves and additional cardiovascular risk factors

3) Aortic bioprosthetic valves in first 3 months after insertion at low dose (or warfarin) in all pts with bioprosthetic valves if in sinus rhythm
ASPIRIN
Established CV Indications

1) Prevention of primary and secondary stroke
2) Prevention of primary and secondary MI
3) Unstable angina
4) CABG and stent patency
ASPIRIN
CV Benefits

1) Thoroughly evaluated in >100 randomized trials in high risk patients
2) Found to prevent vascular death by ~15%
3) Prevents nonfatal vascular events by ~30%

*Antithrombotic Trials Collaboration BMJ 324:71-86, 2002*
Antithrombotic Trials Collaboration

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of trials</th>
<th>% Odds Reduction *</th>
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<tbody>
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<td>Acute MI</td>
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<td>Previous stroke/TIAs</td>
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<td>Coronary angioplasty</td>
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<td>Intermittent claudication</td>
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<td>23%</td>
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* for prevention of death, MI, and stroke

Antithrombotic Trials Collaboration BMJ 324:71-86, 2002
Primary prevention of CV events

1) Incidence of vascular events in low risk pts is lower and accrued benefits are less
2) ~1-3 events/yr prevented per 1000 pts treated
3) Must weigh against aspirin side effects
4) Women’s Health Study shows less benefit for MI than stroke at age <65 than for men
5) 2009 USPSTF recommended ASA for men age 45-79 and for women age 55-79 when MI benefit > GI bleeding

US Preventive Services Task Force Guidelines, 2009
Figure 2. The absolute risk of vascular complications is the major determinant of the absolute of antiplatelet prophylaxis. The data are plotted from placebo-controlled aspirin trials in clinical settings. For each category of patients, the abscissa denotes the absolute risk of experiencing a major vascular event as recorded in the placebo arm of the trial. The absolute benefit of antiplatelet treatment is reported on the ordinate as the number of subjects in whom an important vascular (i.e., nonfatal MI, nonfatal stroke, or vascular death) event is actually prevented by treating 1,000 subjects with aspirin for 1 year.
ASPIRIN
For Acute MI

Higher dose of chewable ASA (161-325 mg) initially* followed by 81 mg/d daily afterward


If pt is allergic to ASA (0.3% of pts)** or has high risk of GI bleeding, clopidogrel 300 mg* followed by 75 mg could be used daily

*Loading doses for more rapid platelet inhibition

**higher if pt has asthma, urticaria, nasal polyps, rhinitis
COUMADIN VS. ASA IN STROKE

1) Still no strong evidence that Coumadin is superior to antiplatelet agents for any stroke indication other than for atrial fibrillation.

2) Warfarin and Recurrent Systemic Stroke (WARSS) study (N=2206) showed no evidence for benefit of Coumadin (INR 1.4-2.0) over 325 mg ASA.

3) APASS study (N=1770) showed same for recurrent stroke prevention in patients with lupus anticoagulants (LACs).

4) Alternative anticoagulant may be a consideration in stroke pts with decreased mobility/paralyzed limb.
1) For non-cardioembolic ischemic stroke or TIA
   Class 1A
2) ASA dose - 50 to 325 mg po qd
   Class 1A
3) For pts who have ischemic stroke while already on ASA increasing dose provides additional benefit
   Class IIb C
4) Use with clopidogrel (Plavix) increases hemorrhage and is not recommended after minor ischemic stroke or TIA when started days to years after
   Class III A

ASPIRIN
Concomitant Use with NSAIDS

Incidence of CV events appears to be increased and antiplatelet effect of ASA lessened in pts with concomitant NSAID use especially:

1) When NSAID is a nonselective NSAID, i.e. has COX-1 activity

2) When NSAID is taken within 2 hrs. prior to ASA

If use of NSAID with ASA is necessary, recommendation is to use lowest possible dose for shortest period of time and use preferred or selective COX-2 inhibitor
ASPIRIN
Use pre-PCI and with stents

1) Pre-Rx with ASA reduces risk of thrombus formation, abrupt closure, and MI for PCI
2) Should usually be treated indefinitely with 81 mg of ASA after PCI and stenting
ASPIRIN
Use with CABG

1) Improves saphenous vein graft patency

2) Less clear benefit for internal mammary bypass grafts but recommended due to risk of co-existent vascular disease

Antithrombotic Trials Collaboration BMJ 324:71-86, 2002
Compared antiplatelet therapy (>90% ASA 81-325 mg) plus Coumadin vs. antiplatelet therapy alone in pts with peripheral arterial disease

Endpoints:
1) MI, stroke, or death from CV causes
2) MI, stroke, urgent arterial intervention, death from CV causes
Cumulative Incidence of the Coprimary End Points in the Two Treatment Groups

A

No. at Risk

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<tr>
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<th>Antiplatelet therapy</th>
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Days

P = 0.48

B

No. at Risk

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Days

P = 0.37

Cumulative Risk of Life-Threatening Bleeding Events, WAVE Trial, NEJM, 2007
ASPIRIN
Placental Insufficiency

1) Related to decreased placental blood flow due to vasoconstriction and/or thrombosis
2) Aspirin at low dose is associated with a ~15% decrease in 39 trials in pts with pre-eclampsia although results variable
3) No adverse effects on fetus noted
4) Aspirin usually started at 12 weeks gestation
Aspirin at low dose in conjunction with heparin has been associated with a reduction in miscarriage in this setting.

2) Aspirin usually started when pregnancy is discovered.

3) Aspirin alone is not beneficial.
<table>
<thead>
<tr>
<th>Regimen (References)</th>
<th>No. of Trials</th>
<th>No. of Patients</th>
<th>No. of Patients with DVT</th>
<th>Incidence, %</th>
<th>95% Limits</th>
<th>Reduction of Relative Risk, %</th>
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<td>Untreated control subjects (24-52, 70, 74, 75, 143-164)</td>
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*Pooled data from trials based on FUT.*
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Pooled data from trials based on routine phlebography.
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Pooled data from trials that used routine phlebography to screen for DVT.
ASPIRIN
For DVT

ASPIRE Trial

Aspirin to Prevent Recurrent Venous Thromboembolism

>27,000 pts with 1st unprovoked VTE after anticoagulant therapy for up to 4 yrs.

Brighton et al., NEJM, 2012.
B  Major Vascular Events

No. at Risk
Placebo  411  341  282  205  135
Aspirin   411  369  299  217  151

Hazard ratio, 0.66 (95% CI, 0.48–0.92)
P=0.01
ASPIRIN
Adjunctive therapy

1) May add aspirin when pts are warfarin failures in treatment for DVT

2) Aspirin has also been recommended at low dose in low risk pts with mechanical valves with PRIOR stroke or TIA in conjunction with warfarin to reduce ischemic stroke risk

OR can be added to pts with mechanical valves who develop a stroke or systemic embolism on adequate warfarin

OR can be increased to 325 mg if already on low dose ASA with warfarin and a mechanical valve who develop a stroke or systemic embolism

ASA plus Rivaroxaban in Stable CVD

Eikelboom et al., NEJM, 2017.

Rivaroxaban + aspirin vs. aspirin alone
Hazard ratio, 0.76 (95% CI, 0.66–0.86)
P < 0.001

Rivaroxaban alone vs. aspirin alone
Hazard ratio, 0.90 (95% CI, 0.79–1.03)
P = 0.12

Cumulative Risk of Cardiovascular Death, Stroke, or Myocardial Infarction

<table>
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<tr>
<th>Year</th>
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<tr>
<td>3</td>
<td>669</td>
<td>670</td>
<td>658</td>
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No. at Risk
1) There is variability in pt response due for heritable and acquired reasons

2) There are tests available to determine aspirin resistance

3) However, the correlation between test results and clinical outcomes remains controversial and testing is currently not generally recommended
ASPIRIN
Prevention of Colon Carcinoma

1) Both observational and randomized trials suggest a preventive effect against carcinoma of the colon
2) Doses as low as 75 mg/day appear to be effective although findings are inconsistent and optimal dose not established
3) Mechanism of anti-neoplastic effect is not clear
4) Need to gauge risk of bleeding against potential benefit in individual pts

Garcia-Albanaz, 2011
1) **In polycythemia vera**: ASA at low dose is recommended in pts with low or intermediate risk to prevent thrombotic complications in the absence of any bleeding contraindication.

2) **In essential thrombocytosis**: ASA is recommended at low dose in low or intermediate risk pts to prevent thrombotic complications in the absence of any contraindication although less strongly proven.

3) **Erythromelalgia sx** (painful erythematous discoloration of fingers or toes with warmth and burning) in pts with either disorder are often exquisitely sensitive to ASA.
ANTIPLATELET THERAPY
Aspirin Dosing

1) ASA doses at <75 not of clear benefit

2) Doses from 75-325 mg/d are of benefit but difficult to show that higher doses in that range are superior to 81 mg/d
ASPIRIN
Pre-operative Management

Usually recommend holding for 7 days to eliminate the antiplatelet effect if warranted by the specific procedure.

May need to delay elective noncardiac surgery in pts with stents due to concern for stent closure in early period (<30 days).
1) Combination of ASA extended-release dipyridamole (Persantine)

2) This combination has been shown to be superior to either ASA or dipyridamole alone in pts with ischemic stroke

2) May also be beneficial for pts sensitive to ASA

3) Dose: 100 mg qd

4) Has GI side effects and may cause angina or HA or steal syndromes due to vasodilatory properties with concern for pts with CAD
CLOPIDOGREL
Indications

1) To reduce the rate of MI and stroke, in conjunction with ASA, in pts with:
   - STEMI
   - ACS (Unstable angina/NSTEMI)

2) To reduce the rate of MI and stroke in pts with well established PAD and recent MI or stroke
CLOPIDOGREL
Mechanism of Action

1) 2nd generation thienopyridine derivative platelet antagonist

2) Has largely replaced ticlopidine (1st generation) due its greater potency and lower side effect profile

3) IRREVERSIBLY inhibits 40-60% of binding of ADP to P2Y12 receptor
CLOPIDOGREL
Pharmacokinetics

1) Rapidly absorbed

2) Evident platelet inhibition occurs several hrs. after single dose (delayed compared to ASA)

3) Half-life of ~7.7 hrs.

4) Metabolized by the liver

5) Levels may vary due to genetically determined rate of metabolism to active metabolite by CYP2C19 enzyme of the cytochrome P450 system

6) CYP2C19 may also be interfered with by certain drugs
CLOPIDOGREL
Drug Interactions

1) CYP2C19 enzyme inhibitors (reduce clopidogrel):
   - omeprazole and esomeprazole (PPI’s)
   - fluconazole and voriconazole (antifungals)
   - fluoxetine (SSRI)

2) INR’s rise in pts on warfarin with clopidogrel and raises bleeding risk

3) Use of clopidogrel with NSAIDS increases GI bleeding risk
CLOPIDOGREL
Adverse effects

1) Bleeding at slightly higher rate than ASA
2) TTP occurring in first 14 days after starting
   11 cases/3 million pts treated, requires plasmapheresis
3) In combination with ASA, major hemorrhage rate
   increases to 2%/yr., limiting combined use to when
   risk/benefit is weighed
4) Also more expensive
CLOPIDOGREL
Use with PCI and stents

1) Trial of pre-Rx and post-Rx with clopidogrel and ASA reduces risk of MI, death, and revascularization at same risk as ASA alone; might reserve this regimen for high risk pts only

2) For BMS at least 1 mo. post-stenting recommended

3) For DES at least 12 mos. recommended

4) Unless high bleeding risk, where dose reduction may length of rx may be truncated
CLOPIDOGREL RESISTANCE

1) Due to polymorphisms in CYP2C19 genes (occur in 2% of whites, 4% of AA’s, 14% of Asians)

2) Testing of genetics possible (not readily available); reactivity assay more available but of questionable validity, but considered to be reasonable in selected use

3) Probably more of a problem than with ASA
ANTIPLATELET THERAPY
Clopidogrel Dosing

For ACS: 300-600 mg loading dose, then 75 mg po qd

For recent MI, stroke, or PAD: 75 mg po qd
CLOPIDOGREL
Pre-operative Management

Usually recommend holding for 7 days to eliminate the antiplatelet effect if warranted by the specific procedure.

Package insert allows for 5 days; in clinical practice most recommend 7 days.

May need to delay elective noncardiac surgery in pts with stents due to concern for stent closure in early period (<30 days).
PRASUGREL
Mechanism of Action

1) 3rd generation thienopyridine platelet antagonist against P2Y12 receptor approved in 2009

2) Slightly different activation step in P-450 system results in more rapid inhibition of ADP binding to receptor
PRASUGREL
Pharmacokinetics

1) Rapidly converted to active metabolite
2) Peak plasma level reached within 30 min. after
3) Evident platelet inhibition in 15-30 min. after ingestion of loading dose
4) Maximal 60-70% platelet inhibition with 50% while on maintenance dosing, which is superior to clopidogrel
5) Exerts antiplatelet effect for 7-10 days
6) 75% excreted in feces; 25% in urine
PRASUGREL

Adverse effects

1) Its superior to clopidogrel pharmacokinetic effects lead to a significant increase in major bleeding and life-threatening bleeding in TRITON-TIMI trial

2) Carries black box warning from FDA

3) Risk very high in pts >75 yrs. or with wt. <60 kg

4) Not recommended in pts with age >75, with TIA or stroke, and dose reduction for pts <60 kg

5) TTP has also been reported in 1st 14 days after use as with clopidogrel
PRASUGREL
Indications

Selected pts undergoing PCI with:
1) Unstable angina or NSTEMI
2) STEMI
PRASUGREL
Dosing

Loading dose: 60 mg po
Maintenance: 10 mg po qd

If <60 kg consider maintenance dose reduction to 5 mg po qd
TICAGRELOR
Indications

1) Approved for use in Europe in 2010 and in the U.S. in 2011

2) Indicated to reduce CV death, MI, and stroke in pts with ACS or past h/o MI

3) Superior to clopidogrel for at least the first 12 months after ACS

4) Reduces the rate of stent thrombosis in pts stented for ACS
TICAGRELOR
Mechanism of Action

1) Is an antagonist of the P2Y12 ADP receptor preventing platelet activation
2) Does not require activation by CYP2C19
3) Binds REVERSIBLY to receptor in contrast to clopidogrel and prasugrel
1) Rapidly absorbed in GI tract
2) Peak plasma level at 1-3 hours
3) 50-60% inhibition of aggregation 2-4 hrs. after loading dose
4) Half life 6-13 hrs. requiring bid dosing
TICAGRELOR
Dosing

1) For ACS, starting dose is 180 mg po followed by 90 mg po bid during the 1\textsuperscript{st} year after ACS; after 1\textsuperscript{st} year reduce to 60 mg po qd

2) Ticagrelor effectiveness shown to be decreased in PLATO study with maintenance doses of ASA > 100 mg; must be used with low dose (75-100 mg) ASA

3) Not to be given with other P2Y12 inhibitor

4) May be given through NG tube
TICAGRELOR
Contraindications

1) In intracranial hemorrhage (ICH) because of high risk of recurrence of ICH
2) Platelet transfusion not shown to be of clinical benefit in reversing antiplatelet effect in normal controls
TICAGRELOR
Adverse effects

1) Dyspnea in ~14% of pts; may be self-limited; in PLATO trial led to d/c of drug in 0.9% of ticagrelor vs. 0.1% of clopidogrel pts; in PEGASUS trial 4.3% of ticagrelor vs. 0.7% on ASA

2) Platelet transfusion not shown to be of clinical benefit in reversing antiplatelet effect in normal controls

3) Stopping ticagrelor associated with increased risk of MI stroke and death

4) Avoid use in pts with severe hepatic impairment due to increased plasma ticagrelor concentration
Cangrelor

1) New PDY12 inhibitor approved in 2015
2) Only parenteral PDY12 inhibitor
3) Immediately reversible
4) Half-life 3-5 min.
5) Action offset in 1 hour
6) For pts undergoing PCI
7) Side effect is bleeding
8) Dose: 30 mcg/kg IV pre-PCI followed by 2 hr. infusion of 4 mcg/kg/min or duration of PCI
Figure 6

From Jemal, A. et al.
CA Cancer J Clin 2006;56:106-130.
Treatment algorithm for duration of P2Y12 inhibitor therapy in patients treated with PCI. Colors correspond to Class of Recommendation in Table 1.

Master treatment algorithm for duration of P2Y12 inhibitor therapy in patients with CAD treated with DAPT. Colors correspond to Class of Recommendation in Table 1.