School of Pharmacy
UNIVERSITY OF WISCONSIN-MADISON

Primary Prevention of Cardiovascular Disease and Antiplatelet Drugs

Andrea L. Porter, PharmD

Associate Professor (CHS)

University of Wisconsin – Madison School of Pharmacy

Clinical Pharmacy Specialist – Anticoagulation Clinic

William S. Middleton Veterans Memorial Hospital

Objectives

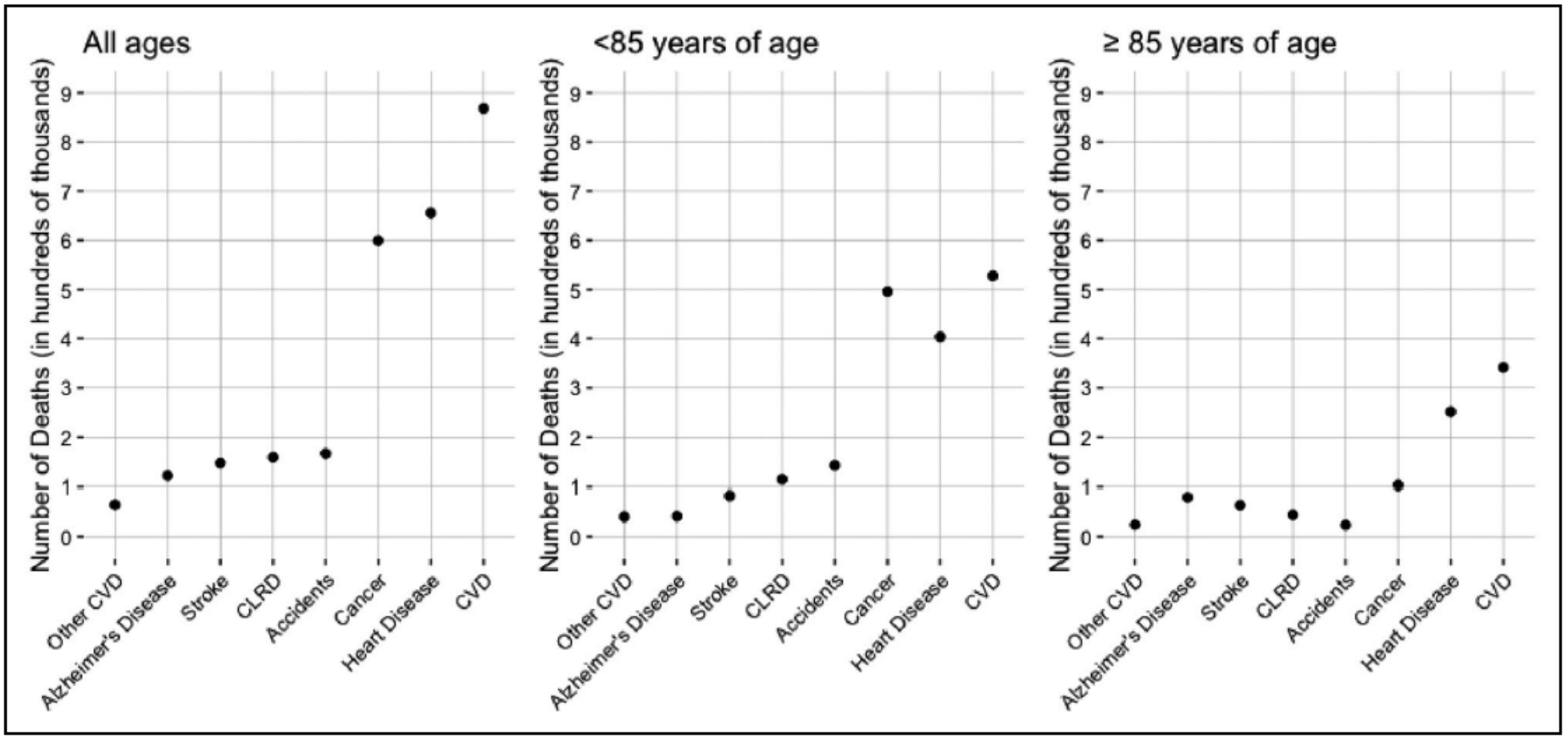
- Discuss primary and secondary prevention of CVD
- Explain the primary prevention of CVD guidelines related to antiplatelet therapy
- Discuss the place in therapy and indications for use, mechanism of action, dosing information, pharmacokinetics, common drug interactions, and common side effects for the oral antiplatelet agents used for primary and secondary prevention
- Describe which patients are at a higher bleeding risk and the prevention of GI bleeding in patients on oral antiplatelet agents

What is CVD?

- CVD includes:
  - Coronary heart disease (CHD) or ischemic heart disease (IHD)
    - Angina (chest pain)
    - Myocardial infarction (MI)
  - Stroke and transient ischemic attack (TIA)
  - Heart failure
  - Disease of aorta and arteries
    - Hypertension (HTN)
    - Peripheral artery disease (PAD)
  - Cardiac arrhythmia
  - Cardiomyopathy
  - Congenital heart disease
  - Rheumatic heart disease
- An estimated 126.9 million American adults (49.2%) have ≥1 types of CVD.

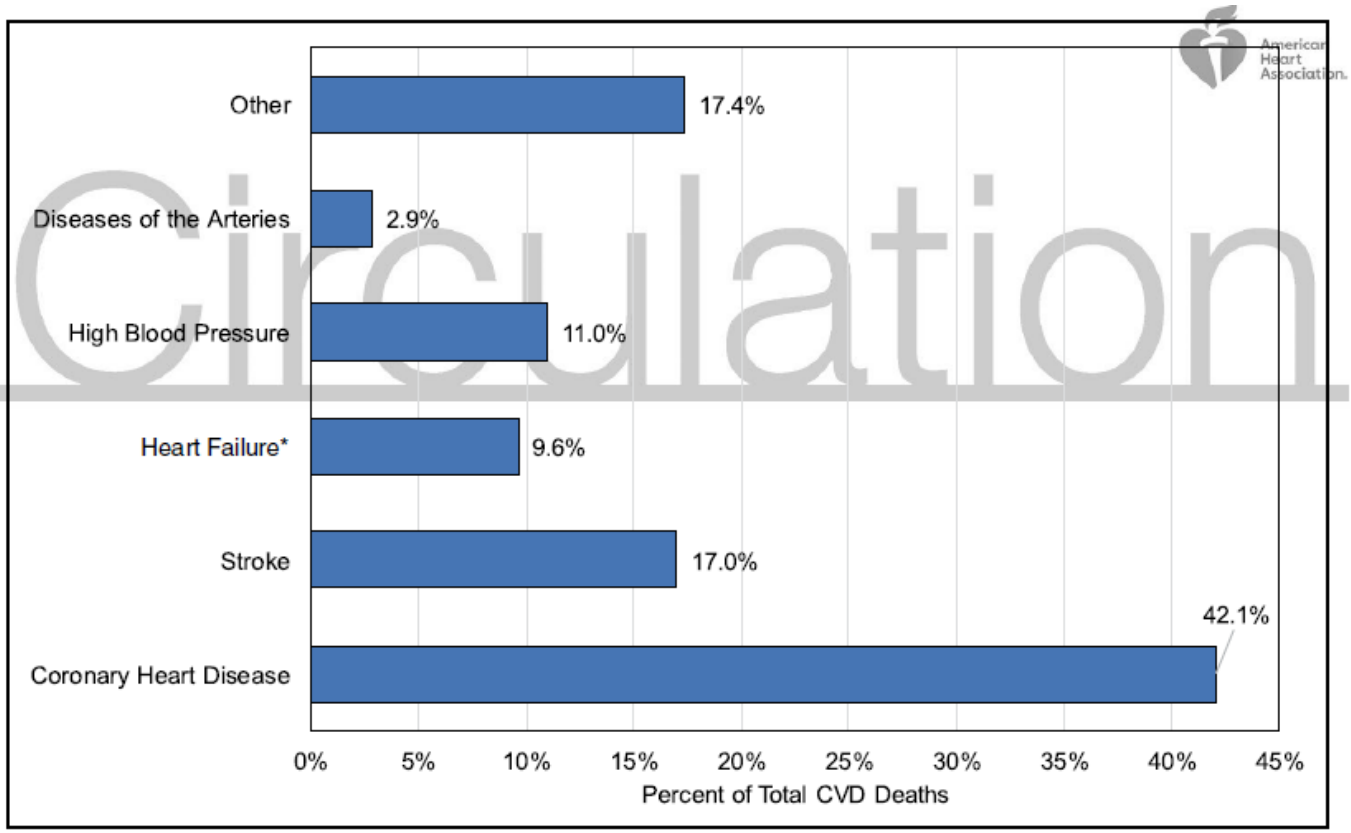
AHA Heart Disease and Stroke Statistics – 2021 Update

Cause of Mortality Comparison



AHA Heart Disease and Stroke Statistics – 2021 Update

CVD Death Breakdown



Percentage breakdown of deaths attributable to cardiovascular disease (United States, 2018).).

Source: NHLBI from National Center for Health Statistics reports and data sets.
AHA Heart Disease and Stroke Statistics – 2021 Update

Prevention of CVD

- Primary prevention:
  - Individuals with risk factors who have not yet developed clinically manifest CVD
- Secondary prevention:
  - Individuals with established coronary heart disease, cerebrovascular disease, or peripheral vascular disease

Source: WHO Prevention of Cardiovascular Disease

Primary Prevention of CVD

- Modifiable risk factors
  - Poor diet and nutrition
  - Smoking
  - Dyslipidemia and high cholesterol
  - Hypertension
  - Physical inactivity
  - Obesity and overweight
  - Diabetes
  - Heavy alcohol use
- Aspirin ??

Secondary Prevention of CVD

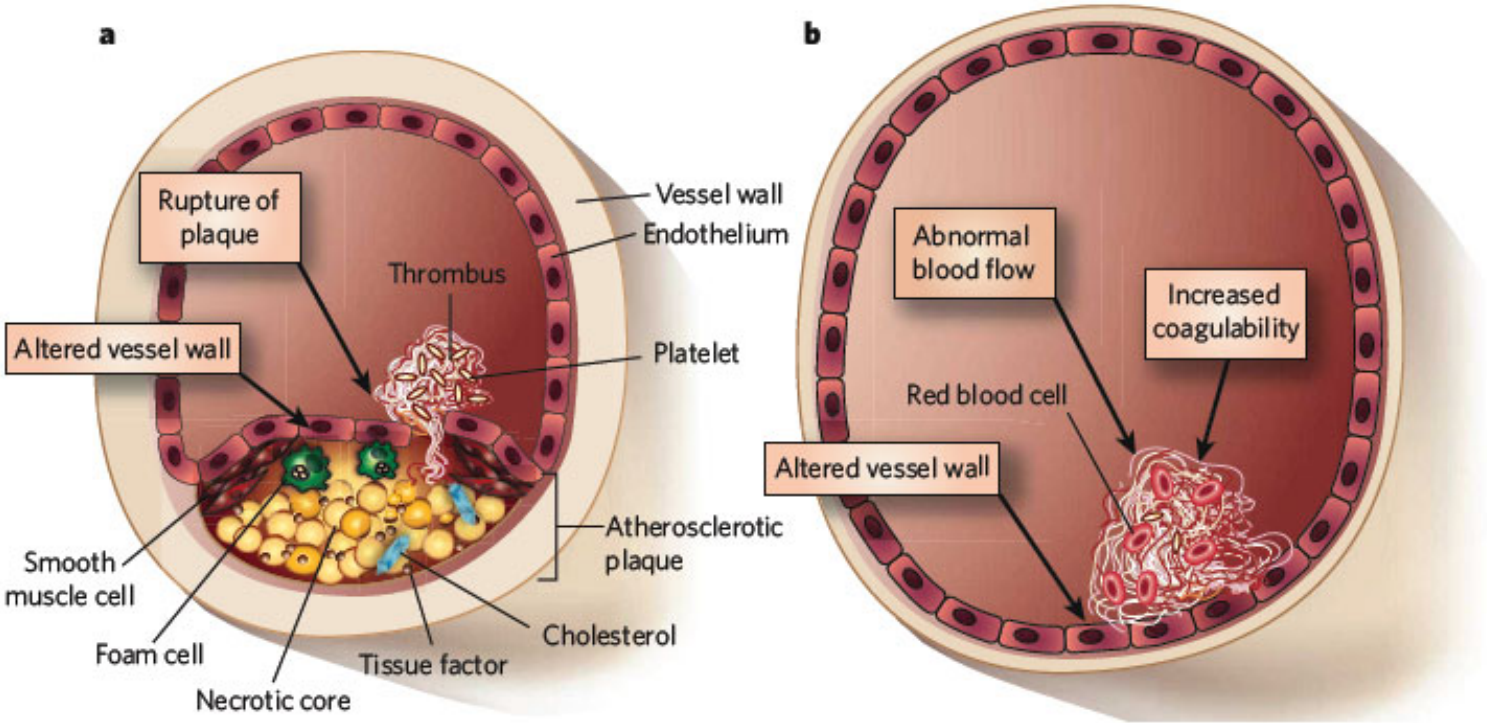
- Modifiable risk factors
- Antithrombotic therapy
  - Aspirin
  - $P2Y_{12}$ receptor blockers
  - Anticoagulants
- Other therapies:
  - Beta blockers
  - ACE inhibitors or ARBs
  - Influenza vaccine
  - Others depending on type of CVD

Aspirin: Primary Prevention of CVD

Yes or No?

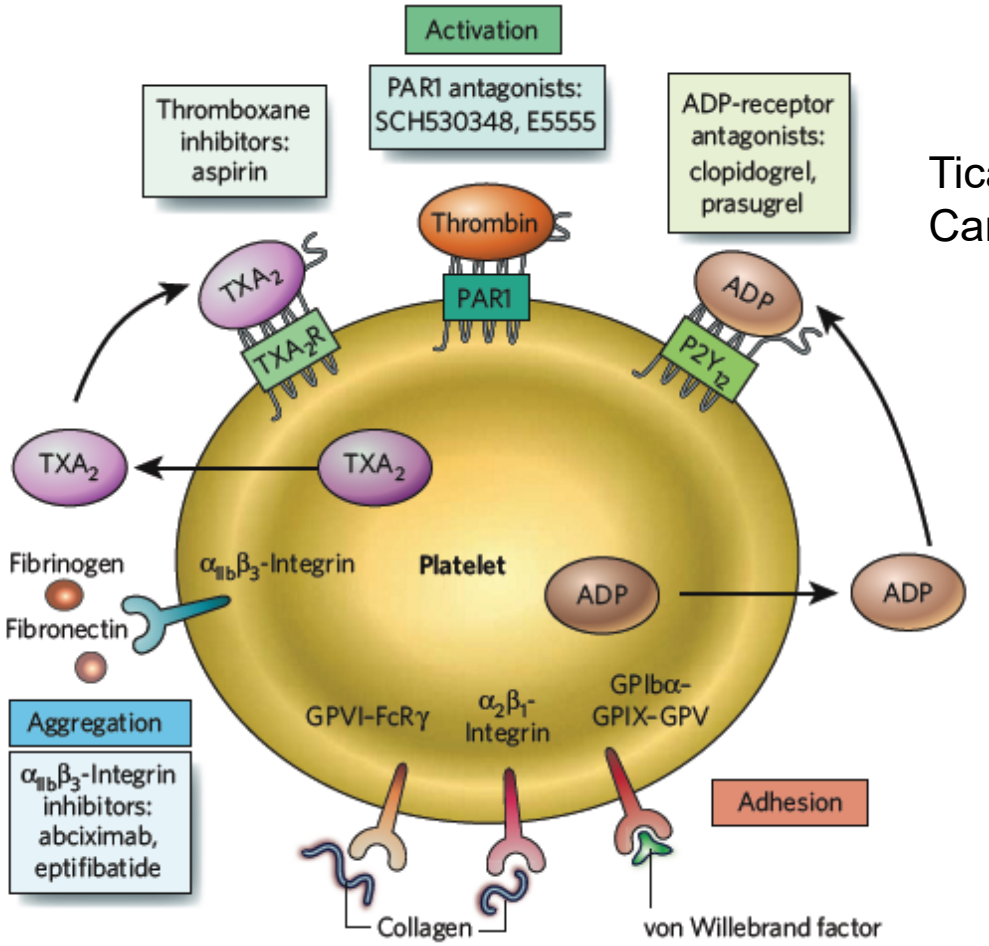
Arterial Thrombosis

Venous Thrombosis



Nature. 2008;451;914-918.

Antiplatelet Drugs

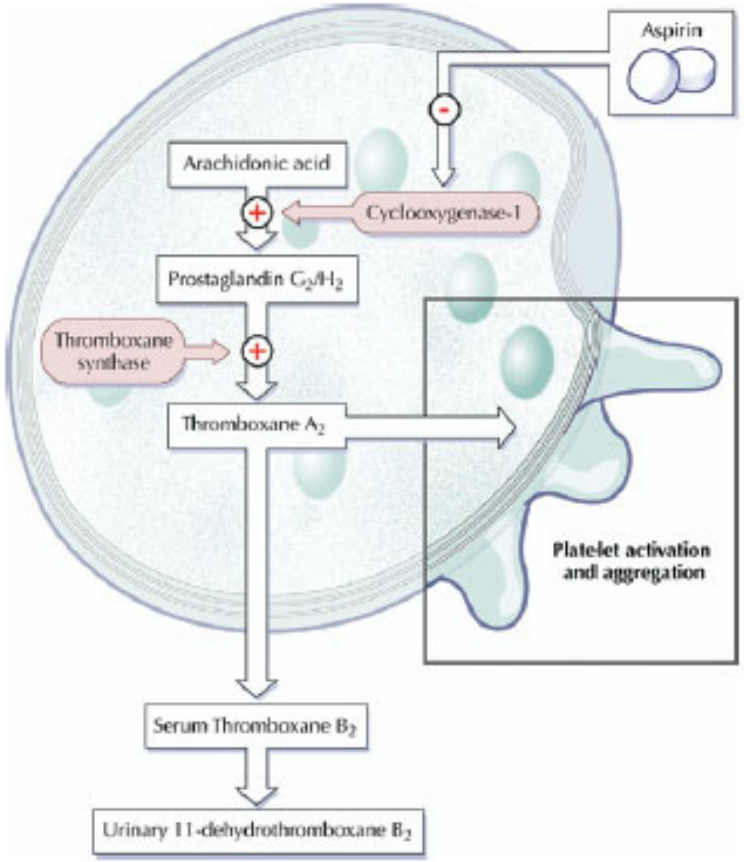


Ticagrelor
Cangrelor

GP IIb/IIIa Inhibitors

Nature. 2008;451;914-918.

Aspirin



- MOA: <u>irreversibly</u> inhibits cyclooxygenase (COX-1 and COX-2) via acetylation and thus decreases thromboxane A_2 (TxA_2) production which inhibits platelet aggregation


Demand
BAYER
BAYER
ASPIRIN
SAY "BAYER ASPIRIN" – Genuine
Unless you see the "Bayer Cross" on tablets, you are not getting the genuine Bayer Aspirin prescribed by physicians and proved safe by millions over 25 years for
Colds Headache Neuritis Lumbago
Pain Neuralgia Toothache Rheumatism
DOES NOT AFFECT THE HEART
Safe
Accept only "Bayer" package which contains proven directions.
Handy "Bayer" boxes of 12 tablets.
Also bottles of 24 and 100—Druggists.

Aspirin

- Indications (FDA approved)
  - Analgesic/antipyretic
  - Atrial fibrillation
  - Primary and secondary prevention of CAD
  - Stroke/TIA
  - PAD
- How supplied:
  - Tablet – regular, chewable, enteric-coated, buffered
    - Common strengths: 81mg, 325mg

Aspirin

- Rapidly absorbed in stomach and upper intestine
- Peak plasma levels:
  - 30-40 min regular ASA
  - 3-4 hours for EC
- Oral bioavailability
  - 40-50% for regular ASA
  - Much lower for EC
- Platelets inhibited for life of platelet (~10 days)
- 10-12% of circulating platelets replaced every 24hrs

Side Effects of Aspirin

- Bleeding
- GI toxicity
  - Gastric erosions, ulcers, and bleeding
  - Dose-dependent with doses 30-1300mg/day
- Intracranial hemorrhage (ICH)
  - <1% per year
- Hypersensitivity
  - Rhinitis, nasal polyps, and/or asthma
  - Urticaria/angioedema

Aspirin

- Monitoring:
  - CBC, fecal occult blood test
- Contraindications:
  - children <16 with viral illness (Reye's syndrome)
  - syndrome of asthma, rhinitis, nasal polyps
- Drug Interactions (DI):
  - other antithrombotics, thrombolytics, ibuprofen

Aspirin and Ibuprofen

- Ibuprofen interferes with antiplatelet activity of ASA (81mg, immediate release) when taken together
- Minimal risk with prn use of ibuprofen due to long-lasting effect of ASA on platelets
- Counseling pearls:
  - Patients should space ibuprofen at least 30 minutes after or more than 8 hours before ASA
- EC ASA – not a lot of evidence
- Other OTC NSAIDs – lack of evidence, should be viewed the same as ibuprofen
- APAP – appears to not interfere

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm

Aspirin Resistance

- Definition: High platelet reactivity associated with an increased risk of thrombotic events
- Treatment failure vs. Resistance vs. Nonresponse
- Possible causes of nonresponse:
  - Genetic polymorphism
  - Adherence
  - Use of EC ASA
  - Drug interactions
  - Increased COX-2 activity
- Options:
  - assess above possible causes
  - ? increase ASA dose
  - ? different antiplatelet

Chest. 2012;141;e94S.

Aspirin and Weight

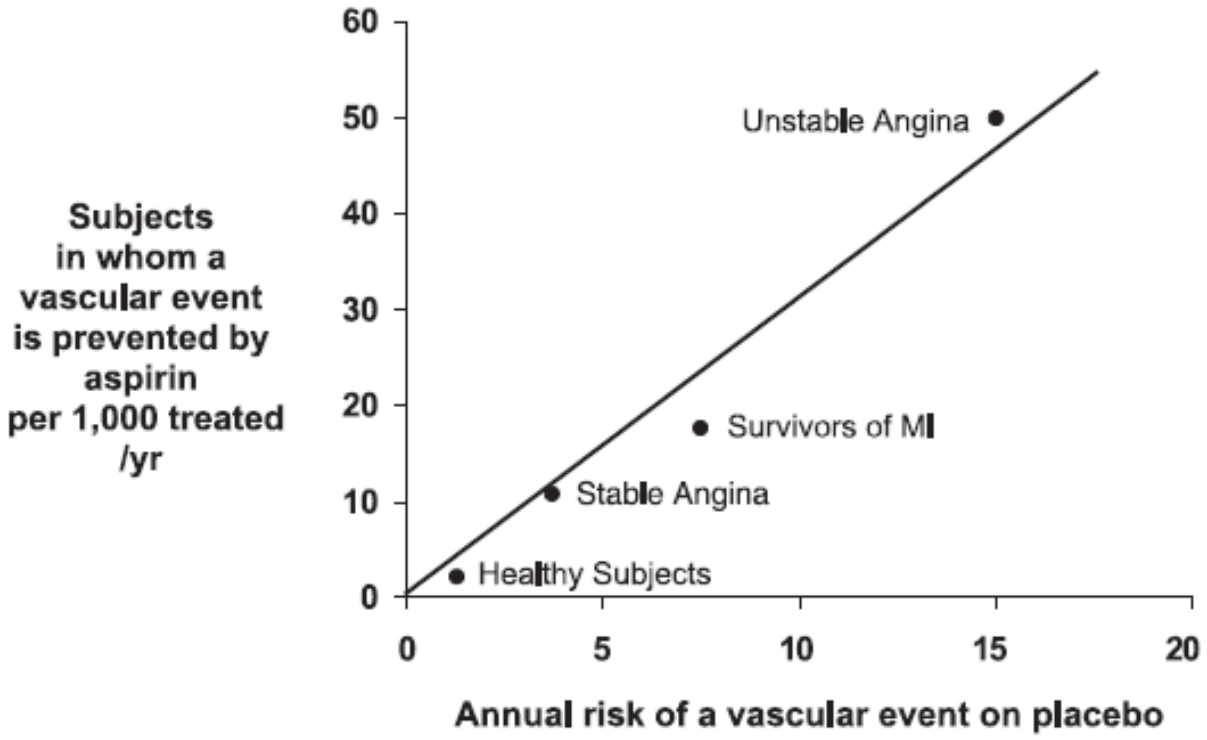
- 2018 meta-analysis evaluating impact of body weight on aspirin safety and efficacy
  - N=117,279
  - Aspirin for primary or secondary prevention
- Results:
  - Risk of major CV events with lower doses of aspirin (75-100mg) reduced in people weighing 50-69kg (HR 0.75, 95% CI 0.65–0.85)
    - Not in those weighing 70kg or more (HR 0.95, 95% CI 0.86–1.04)
      - Increased risk of fatality when treated with low-dose aspirin
  - Higher doses of aspirin (≥325mg) were effective in people weighing 70kg or more
  - Increased risk of major bleeding lost for patients who weighed 90kg or more
- Overall conclusion: do not recommend weight-based dosing of aspirin for primary or secondary prevention
  - Further studies needed at this time

Rothwell PM et al. Lancet. 2018;392(10145):387-399.

ASCEND Trial did not find a difference

NEJM. 2018;379:1529-1539

Absolute Risk of Vascular Complications is the Major Determinant of the Benefit of ASA Prophylaxis



CHEST. 2012 suppl 141(2):e100S.

Benefit vs. Harm of ASA

Clinical Setting	Benefits # of patients in whom a major vascular event is avoided per 1000/yr	Harm * # of patients in whom a major GI bleeding event is caused per 1000/yr
Low to high CV risk	1-2	1-2
Essential HTN	1-2	1-2
Chronic stable angina	10	1-2
Prior MI	20	1-2
Unstable angina	50	1-2

* Assumes comparability of other risk factors for upper GI bleeds, such as age and use of NSAIDs

CHEST. 2012 suppl 141(2):e99S.

Indirect Comparison of ASA Doses Reducing Vascular Events in High-Risk Patients

Aspirin Dose, mg/day	# of trials	# of patients	Odds Reduction, %
500-1500	34	22,451	19 ± 3
160-325	19	26,513	26 ± 3
75-150	12	6,776	32 ± 6
< 75	3	3,655	13 ± 8

Antithrombotic Trialists' Collaboration. BMJ. 2002;324:71-86.

Primary Prevention of CVD – **OLD Guidelines**

- CHEST Guidelines (2012)
  - For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

- AHA Prevention of CV Disease in Women (2011 Update)
  - Aspirin therapy can be useful in women 65 y of age (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke (Class IIa; Level of Evidence B) and may be reasonable for women 65 y of age for ischemic stroke prevention (Class IIb; Level of Evidence B).

Chest. 2012;141;e637S-e668S. *Circulation*. 2011;123:1243-1262.

Primary Prevention of CVD – FDA Statement (5/2014)

- "The FDA has reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke. In fact, there are serious risks associated with the use of aspirin, including increased risk of bleeding in the stomach and brain, in situations where the benefit of aspirin for primary prevention has not been established.
- The available evidence supports the **use of aspirin** for preventing another heart attack or stroke in patients who have already had a heart attack or stroke, or have other evidence of coronary artery disease, such as angina or a history of a coronary bypass operation or coronary angioplasty."

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm390574.htm

Primary Prevention of CVD – **OLD Guidelines**

- United States Preventive Services Task Force (USPSTF) – Aspirin to Prevent CV Disease and Colorectal Cancer (2016)

Population	Adults aged 50-59 y with a ≥ 10% 10-y CVD risk	Adults aged 60-69 y with a ≥ 10% 10-y CVD risk	Adults younger than 50 y	Adults aged 70 y or older
Recommend-ation	Initiate low-dose aspirin use Grade: B	The decision to initiate low-dose aspirin use is an individual one Grade: C	No recommend-ation Grade: I (insufficient evidence)	No recommend-ation Grade: I (insufficient evidence)

Ann Intern Med. 2016;164(12):836-845. doi:10.7326/M16-0577

Primary Prevention of CVD – **Current Guidelines**

- ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease (2019)

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (S4.6-1–S4.6-8).
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age (S4.6-9).
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (S4.6-10).

Primary Prevention of CVD – Guidelines

- Other guidelines:
  - American Diabetes Association
    - Low-dose aspirin for patients with type 1 or 2 diabetes who have a >10% 10-year CVD risk and not at an increased risk for bleeding
      - No recommended in men < 50 years, most women < 60 years who have low CVD risk (bleeding > benefits)

Primary Prevention of CVD

- Additional considerations
  - Decision should be made on an individual basis
  - Shared decision making with patient
  - Balance risk vs. benefit

Other Uses of Aspirin (doses, guidelines, etc.)

- To be discussed in future lectures …
  - Peripheral Artery Disease
  - Secondary Prevention (SIHD and ACS lectures)
  - Atrial Fibrillation
  - Stroke
  - Diabetes
  - Oncology

Question

- Which of the following statements is CORRECT about aspirin?
  a) Enteric coated and buffered aspirin are less likely to cause GI bleeding than regular aspirin.
  b) Both regular aspirin and enteric coated aspirin have similar time to peak plasma levels and bioavailability.
  c) Aspirin-related GI toxicity is dose dependent, with higher doses having more GI side effects.
  d) Children over the age of 16 with a viral illness should not take aspirin due to Reye's syndrome.

Main Points

1.

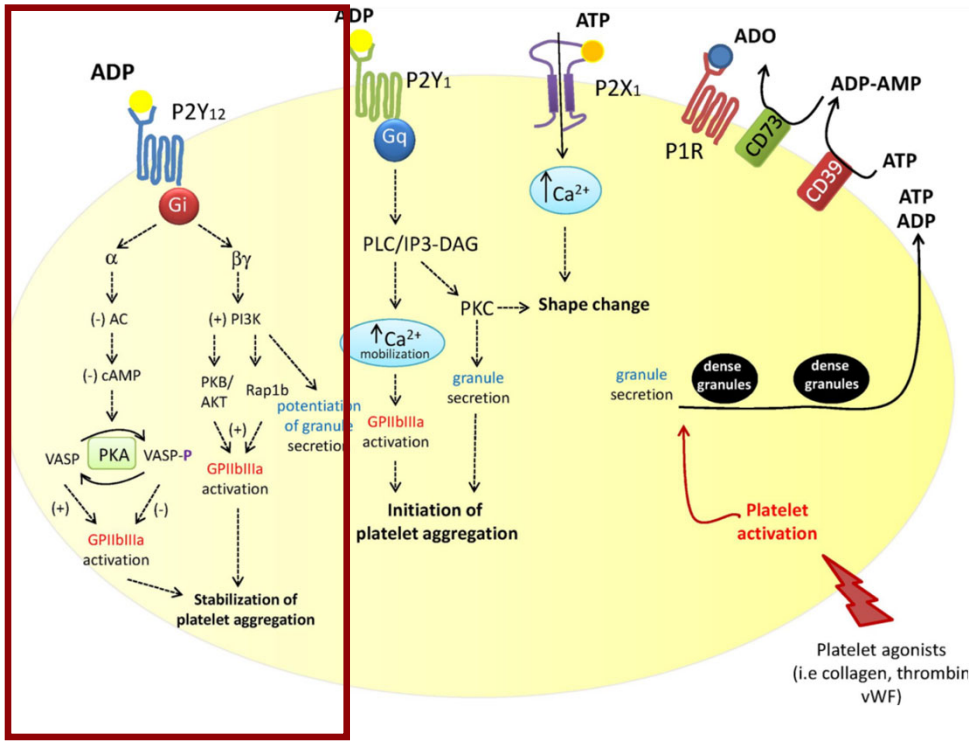
2.

3.

Secondary Prevention of CVD: Additional Antiplatelet Drugs

$P2Y_{12}$ Inhibitors

- Thienopyridine
  - Clopidogrel
  - Prasugrel
  - Ticlopidine (not available in US)
- Cyclopentyltriazolo-pyrimidine
  - Ticagrelor
- Non-thienopyridine
  - Cangrelor (IV)



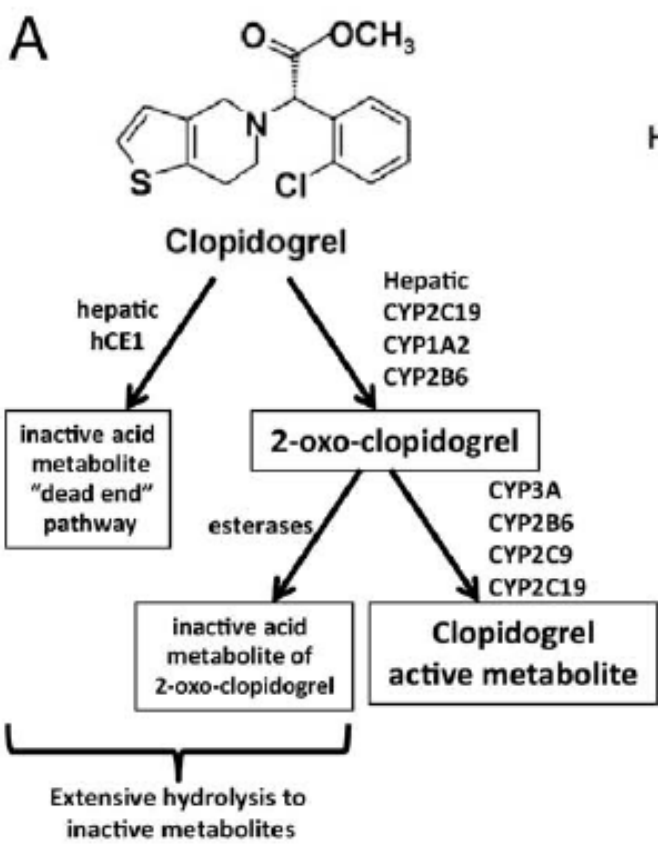
Nature. 2008;451;914-918.

Ticlopidine (Ticlid®)

- MOA: irreversibly blocks the $P2Y_{12}$ component of ADP receptor
- Indications: coronary artery stent placement, thromboembolic stroke
  - Dosing: 250mg po BID
- Adverse effects:
  - Hypercholesterolemia
  - Neutropenia (2.4%)
  - Thrombocytopenia
  - Aplastic anemia
  - Thrombotic thrombocytopenic purpura (TTP)
    - 0.02% risk after stent placement, mortality rate 20%
    - purplish spots on skin/mucous membranes, jaundice, fatigue/weakness
- Monitoring:
  - CBC with differential (baseline, q2wks for 3 months), FLP, LFTs if liver dysfunction suspected
- **No longer available in US; replaced by clopidogrel**

Clopidogrel (Plavix®)

- Selectively and irreversibly blocks the P2Y12 component of ADP receptor
- Activated in liver by a 2-step process (CYP2C19 and CYP3A)
- Clopidogrel and 2-oxo-clopidogrel are substrates and inhibitors of CYP1A2, CYP2B6, and CYP2C19



Clopidogrel (Plavix®)

- FDA approved indications:
  - Recent MI, recent stroke, established peripheral artery disease
  - Established CAD
  - Secondary prevention of cardioembolic stroke (pt not a candidate for oral anticoagulation)
  - ACS
    - UA/NSTEMI
    - STEMI
    - PCI

Clopidogrel (Plavix®)

- Dosing:
  - 300mg or 600mg loading dose
  - 75 mg daily
  - With or without food
- Used alone or with ASA
- Patients should not stop taking without talking with provider
- If instructed, stop at least 5 days prior to surgery

Clopidogrel (Plavix®)

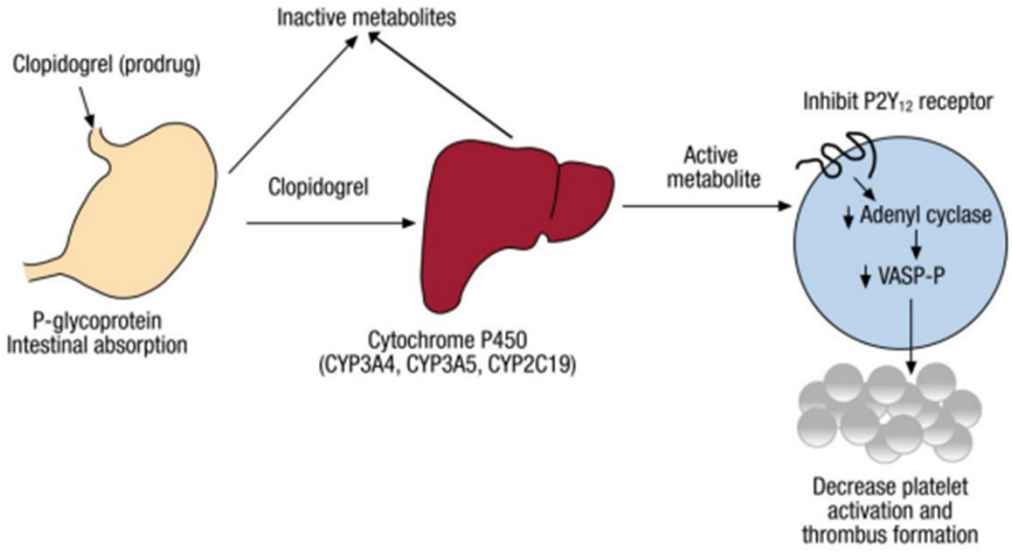
- Adverse effects:
  - Bleeding/bruising
  - Rare TTP
  - Rash (4%)
    - Pruritic, maculopapular
    - Usually occurs around day 3 or 4
    - Can be associated with fever, thrombocytopenia, lymphopenia or increased LFTs
    - Treatment: systemic or topical steroid, antihistamines
    - Options: densensitization protocol, d/c drug

Clopidogrel Drug Interactions

- CYP3A4-metabolized statins (atorvastatin, lovastatin, simvastatin) – inhibits clopidogrel metabolism - ? clinical significance
- PPIs (omeprazole/esomeprazole)
- Calcium channel blockers – may decrease effects of clopidogrel – inhibit CYP3A4
- Ketoconazole – (CYP3A4 inhibitor) – may affect conversion of clopidogrel to active metabolite
- Cimetidine – CYP2C19 inhibitor
- Other agents that increase risk of bleeding
- SSRIs/SNRIs – may increase the risk of bleeding
- Smoking – enhanced platelet inhibition of clopidogrel

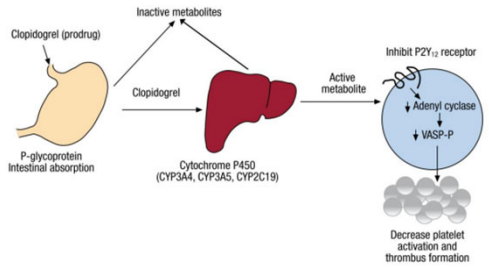
Decreased Clopidogrel Effectiveness

- Reported to occur in 1/3 of patients on clopidogrel
- 1.5- to 5-fold increased risk of thrombosis
- Reason for poor response:
  - Drug interactions
  - Diabetes
  - Genetic variations



Poor Metabolizers of Clopidogrel

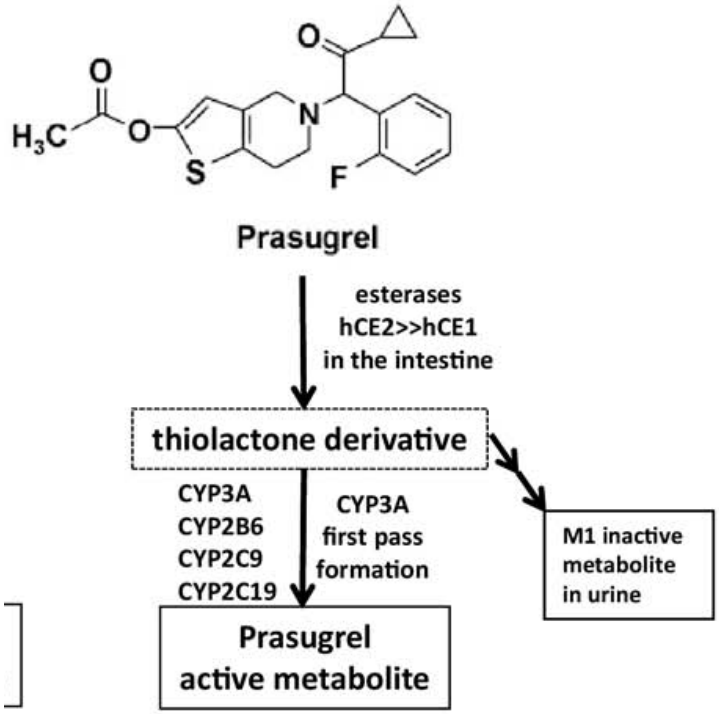
- Boxed warning for clopidogrel
- CYP2C19 mainly responsible for metabolism; different alleles
  - CYP2C19*1 – normal metabolism
  - CYP2C19*2 and *3 – reduced function alleles
    - Account for 85% Caucasian and 99% Asian poor metabolizers
  - CYP2C19*4, *5, *6, *7, *8 – absent or reduced metabolism, less frequent
- Patient must have 2 loss-of-function alleles to be considered a poor metabolizer
  - 2-14% of population considered poor metabolizers



http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm203888.htm

Prasugrel (Effient®)

- Irreversibly blocks the $P2Y_{12}$ component of the ADP receptor
- Activated by CYP3A isoforms, CYP2B6, CYP2C9, and CYP2C19
- CYP2C19 alleles not clinically important
- Faster onset of action than clopidogrel; more complete and consistent inhibition
  - Single step



Prasugrel (Effient®)

- FDA Approved Indications:
  - ACS with PCI and after stent placement
- Dosing
  - 60mg loading dose
  - 10mg daily maintenance dose
    - With ASA 81-325mg/day (81mg/day recommended)
    - Consider 5mg/day in pts < 60kg
  - With or without food
- Boxed warnings for bleeding risk:
  - Significant or fatal bleeding
  - Not recommended in patients ≥ 75 except in patients with DM or prior MI
  - Do not use in patients having urgent CABG surgery
    - D/C ≥7 days prior to any surgery – if ok
  - Contraindications: h/o TIA or stroke and active bleeding

Prasugrel Adverse Effects

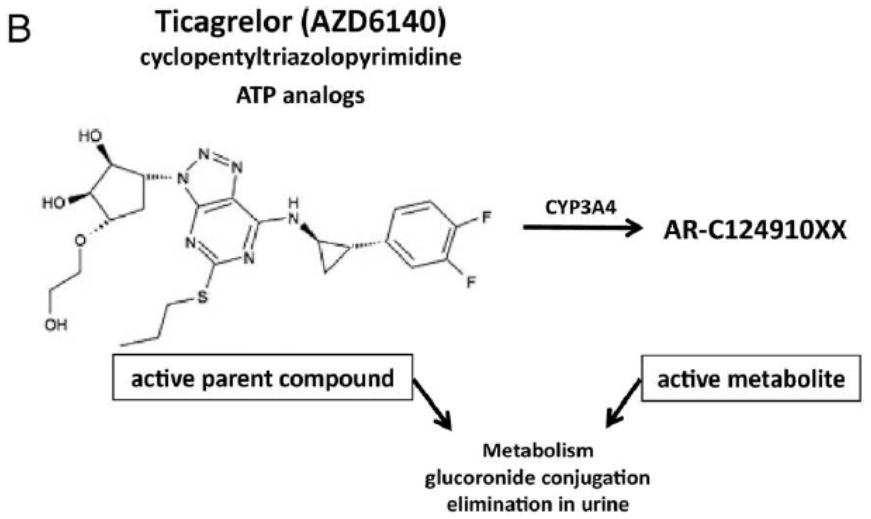
- Bleeding
  - Additional risk factors:
    - Age ≥ 75 years, propensity to bleed, wt < 60kg, CABG or other surgery, concomitant meds that increase risk of bleeding
- HTN (8%)
- Hyperlipidemia (7%)
- HA (6%)
- Backache (5%)
- Rash (3%)
- Rare TTP and hypersensitivity

Prasugrel

- Drug Interactions:
  - CYP3A4 strong inhibitors – may decrease effectiveness of prasugrel
  - Does not appear to interact with other CYP-metabolized drugs (2C19, 2B6, 2C9)
- Patients should not stop taking without talking with provider

Ticagrelor (Brilinta®)

- Reversibly and noncompetitively binds to the P2Y12 component of the ADP receptor
- Active compound
- Metabolized by CYP3A4 to active metabolite
- Genetic variations in CYP isoenzymes do not affect metabolism



Ticagrelor (Brilinta®)

- FDA Approved Indications:
  - ACS (NSTEMI, STEMI), PCI
- Dosing:
  - 180mg loading dose (with ASA 325mg)
  - 90mg BID maintenance dose (started 12 hrs after loading dose) for 12 months
    - With ASA 75-100 mg/day
  - 60mg BID after 12 months
- Boxed warnings:
  - Increased risk of significant or fatal bleeding
  - Aspirin doses > 100mg/day should be avoided
  - Contraindications: severe hepatic impairment, hypersensitivity, active bleeding, h/o ICH
  - Do not use in patients having urgent CABG surgery
    - D/C at least 5 days prior to any surgery – if ok

Ticagrelor Adverse Effects

- Bleeding
  - Additional risk factors:
    - Propensity to bleed, CABG or other surgery, concomitant meds that increase bleeding risk, advanced age
- Dyspnea (≤14%)
  - Resolution within 1 week in 1/3 of patients
- HA (7%)
- Increase SCr (7%)
- Bradyarrhythmias
- Warning about hyperuricemia – use with caution in gout patients (<1%)

Ticagrelor

- Drug interactions
  - Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin) and inhibitors (ketoconazole, ritonavir) – avoid use
  - Avoid lovastatin > 40mg, simvastatin > 40mg (increased statin concentration)
  - Can increase digoxin levels
- Patients should not stop taking without talking with provider

Cangrelor (Kengreal®)

- MOA: selectively and reversibly blocks $P2Y_{12}$ component of the ADP receptor to inhibit platelet aggregation
- Use: PCI pts not previously loaded with an oral $P2Y_{12}$ receptor blocker
- Dosing:
  - Loading: 30 mcg/kg bolus prior to PCI
  - Maintenance: infusion of 4 mcg/kg/minute immediately following bolus continued for at least 2 hours or for the duration of the PCI, whichever is longer
- Onset: 2 minutes
- No antiplatelet effect observed 1 hour after discontinuation
- Adverse Effects: bleeding, renal insufficiency, dyspnea, hypersensitivity
- Transitioning to oral therapy
  - Clopidogrel/prasugrel vs. ticagrelor

Glycoprotein IIb/IIIa Inhibitors

- MOA: Binds to glycoprotein IIb/IIIa receptor which inhibits platelet aggregation
- Adverse effects: thrombocytopenia, bleeding, hypotension

	Abciximab (ReoPro®)	Tirofiban (Aggrastat®)	Eptifibatide (Integrilin®)
Indication	PCI, UA/NSTEMI not responsive to medical therapy & planned PCI w/in 24 hrs	ACS, PCI w/ or w/o stenting	UA/NSTEMI
Reversibility	Slow	Rapid	Rapid
Drug t ½	10-30 min	2 hr	2.5 hr
Excretion	Unknown	40-70% renal	50% renal

Question

- Which of the following statements is CORRECT about $P2Y_{12}$ inhibitors?
  a) Ticagrelor maintenance doses should be given with full dose (325mg) of aspirin.
  b) Cangrelor continues to have an antiplatelet effect for a long time after discontinuation.
  c) Prasugrel is not recommended in patients ≥ 75, except in patients with diabetes or prior MI.
  d) Clopidogrel poor metabolizers have an increase in drug concentrations, resulting in more bleeding.

Overall Bleeding Rates

Medication Class/Dose	# of trials	# of patients	% Rate (95% CI)
ASA < 100 mg	4	12,639	3.6 (3.3-3.9)
ASA 100-325 mg	6	22,745	9.1 (8.7-9.4)
ASA > 325 mg	1	1,540	9.9 (8.4-11.4)
Dipyridamole	2	3,304	6.7 (5.8-7.5)
Clopidogrel	7	19,191	8.5 (8.1-8.8)

Meta-analysis of 338,191 patients in 50 RCTs

Am J Hematol. 2004;75:40-47.

GI Bleeding and Antiplatelets

- Risk factors for GI bleeding:
  - Previous GI bleed or PUD
  - Advanced age
  - Use of anticoagulants, steroids, or NSAIDs
  - H. pylori infection
- Prevention of upper GI bleeding:
  - PPIs or H_2RAs reduce risk of bleeding
    - PPIs > H_2RAs
  - PPIs recommended to reduce bleeding in patients with h/o upper GI bleeding
  - PPIs appropriate if multiple risk factors
- PPIs or H_2RAs not recommended for low-risk patients
- Yosprala (aspirin/omeprazole) approved 2016

JACC. 2010;56(24):2051-2066. ACCF/ACG/AHA Consensus Document.

Interruption of Antiplatelets – CHEST Guidelines

- Secondary prevention of CVD
  - Minor dental or dermatologic procedure, cataract surgery
    - Continue ASA around time of procedure (G2C)
- Noncardiac surgery
  - Moderate-high risk for CV events
    - Continue ASA around time of surgery (G2C)
  - Low risk for CV events
    - Stop ASA 7-10 days before surgery (G2C)
- CABG surgery
  - Continue ASA around time of surgery (G2C)
  - For patients on dual antiplatelets:
    - Continue ASA around time of surgery and stop clopidogrel/prasugrel 5 days before surgery (G2C)

CHEST. 2012. 141(2 Suppl):e327-328S.

Interruption of Antiplatelets – CHEST Guidelines

- Patients with coronary stent, on dual antiplatelet therapy
  - Defer surgery:
    - Defer surgery for 6 weeks after BMS placed (G1C)
    - Defer surgery for 6 months after DES placed (G1C)
  - Surgery necessary before above time frames:
    - Dual antiplatelet therapy recommended around time of surgery

CHEST. 2012. 141(2 Suppl):e327-328S.

Main Points

1.

2.

3.