DEFINITIONS

- **Acute myocardial infarction**
  - Detection of a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile

  *BIDMC Lab manual:* “Troponin-T values as high as 0.10 ng/mL are frequently seen in hospitalized, cardiac patients WITHOUT acute myocardial infarction. In general, though, values >0.10 ng/mL are consistent with acute myocardial infarction. In other words, values between 0.01 and 0.10 are not normal but are not necessarily associated with acute myocardial infarction and represent a gray zone.”

  WITH at least one of the following
  - Symptoms of ischemia
  - New or presumed new significant ST TW changes or new LBBB
  - Development of pathological Q waves on ECG
  - Imaging evidence of new loss of viable myocardium or new RWMA
  - Identification of an intracoronary thrombus by angiography or autopsy

- **Unstable angina:** Angina (at rest, new onset with minimal exertion, or crescendo angina) without elevation in cardiac biomarkers

ACUTE CORONARY SYNDROMES: A SPECTRUM OF DISEASE

<table>
<thead>
<tr>
<th>Unstable angina</th>
<th>NSTEMI</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td>• Ischemic symptoms</td>
<td>• Ischemic symptoms</td>
</tr>
<tr>
<td></td>
<td>• ECG +/- changes</td>
<td>• ECG +/- changes</td>
</tr>
<tr>
<td></td>
<td>• Negative biomarkers</td>
<td>• Positive biomarkers</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>• Medical therapy: ASA + another</td>
<td>Same as unstable angina!</td>
</tr>
<tr>
<td></td>
<td>• Antiplatelet agent, heparin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Risk stratification for possible cath</td>
<td></td>
</tr>
</tbody>
</table>

PATHOPHYSIOLOGY

- Classic teaching is atherosclerotic plaque rupture and thrombus formation
  - White, platelet-rich plaque in UA/NSTEMI
  - Red, fibrin-rich plaque in STEMI
- In NSTEMI, likely from embolization and endothelial dysfunction rather than epicardial occlusion (vs. STEMI)
  - Single culprit lesion identified just 49% of the time. Complete occlusion in just 36%.
  - Even in absence of occlusion, cath shows impaired tissue perfusion (↓ blush), which predicts ↑ TnT
- Location of stable coronary artery disease is a poor predictor of future location of plaque rupture/occlusion
  - Reviewed 29 patients with MIs who had angiography ~1 month prior
    - 66% of patients had occlusion of an artery that was <50% stenotic 1 month prior
    - 97% of patients had occlusion of an artery that was <70% stenotic 1 month prior
    - No correlation between severity of initial stenosis and culprit lesion ($r^2=0.0005, p=NS$)

NATURAL HISTORY

- **STEMI:** 5.5% in-hospital mortality, 11% major bleeding, 11% 30-day case fatality rate, 8% 1-year CFR
- **NSTEMI:** 3.9% in-hospital mortality, 9% major bleeding, 14% 30-day case fatality rate, 18% 1-year CFR
  - ↑ risk of long-term mortality vs. STEMI may be related to ↑ burden of CAD

CHARACTERISTICS OF CARDIAC BIOMARKERS

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Peak</th>
<th>Return to normal</th>
<th>Sensitivity in NSTEMI at &gt; 6 hours after onset presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB</td>
<td>24 h</td>
<td>48-72 h</td>
<td>53%</td>
</tr>
<tr>
<td>TnT</td>
<td>12-48 h</td>
<td>5-14 d</td>
<td>51%</td>
</tr>
<tr>
<td>TnI</td>
<td>24 h</td>
<td>5-10 d</td>
<td>79%</td>
</tr>
<tr>
<td>hsTnI</td>
<td>24 h</td>
<td>5-10 d</td>
<td>82%</td>
</tr>
</tbody>
</table>
CLASSIFICATION

- **Type I:** Spontaneous MI
  - Atherosclerotic coronary artery disease
    - Reduced myocardial perfusion from coronary artery narrowing caused by a nonocclusive thrombus formed on a disrupted atherosclerotic plaque; release of injury markers is thought to result from microembolization of thrombus/plaque debris and blockage of distal blood vessels (most common).
    - Fixed severe narrowing from progressive atherosclerosis or stent restenosis
  - Inflammatory or infectious process causing arterial narrowing, plaque rupture, and/or thrombogenesis
  - Dynamic obstruction, such as focal coronary artery spasm as seen in Prinzmetal's angina or other causes of vasoconstriction

- **Type II:** "Demand ischemia": Oxygen supply/demand mismatch where a condition other than coronary artery disease contributes
  - Increased myocardial \(O_2\) requirement: Fever, tachycardia, sepsis
  - Reduced coronary blood flow: Hypotension, hypertrophic cardiomyopathy, aortic stenosis
  - Reduced myocardial \(O_2\) delivery: Anemia, hypoxemia

- **Type III:** Sudden cardiac death with suggestive symptoms with presumed new ECG changes but no time to check for biomarker elevation

- **Type IV:** Associated with percutaneous coronary intervention (PCI)
  - Challenging to diagnose since patients undergoing PCI often have elevated biomarkers prior to procedure
  - If normal biomarkers prior to procedure, a type IV MI is suggested if biomarkers rise to >99th %ile
  - If elevated biomarkers prior to procedure, post-procedural elevation > 3x 99th %ile is suggestive

- **Type V:** Associated with CABG

APPROACH TO SUSPECTED CARDIAC CHEST PAIN: ACUTE CORONARY SYNDROME

Unstable angina and NSTEMI are managed identically.

- **Rule-out STEMI:** 12-lead ECGs. Ensure it is not a STEMI, since management/acute is quite different.
  - Repeat at 15-30 min intervals if patient remains symptomatic since NSTEMI can evolve to STEMI

- **Relieve ischemic pain:** Morphine, fentanyl, nitroglycerin as below
  - Nitroglycerin (see below)
  - Morphine: if angina symptoms do not immediately resolve with NGT tablets or spray, or if acute pulmonary congestion is present.
    - Morphine sulfate 1-5 mg prn Q 5-30 mins as tolerated by BP
• **DON'T USE NSAIDS:** Increased risk of cardiovascular events (death, MI, Heart failure, stroke)

- **Decrease myocardial oxygen demand:** reduce tachycardia and hypertension
  - **Beta blocker:** cardioselective is preferred (atenolol or metoprolol)
    - Addresses tachycardia, hypertension, and prevents ventricular arrhythmias
    - Goal of HR 60-70
    - Contraindicated in:
      - Cocaine-induced MI. (Give benzodiazepines instead!) Or labetalol.
      - Hypotension
      - Decompensated heart failure
      - Reactive airway disease
      - AV conduction delay > 0.24 s, or 2nd degree AV block
    - Mortality ↓ 50% both at 30 days and at 6 months in patients who receive β-blockers.

- **Nitroglycerin:** Predominantly venodilator (↓ preload), also arteriodilator (↓ afterload)
  - May cause reflex tachycardia (↑ MVO$_2$) unless concurrent beta-blocker given
  - SL NTG (0.4 mg) every 5 min for a total of 3 doses
  - IV NTG for up to 48 h after UA/NSTEMI for ischemia/ongoing chest pain, heart failure, HTN
    - Start at 10-20 mcg/min, increase by 10-20 mcg/min as needed. (Practical limit is 200-300 mcg/min)
    - Does not decrease mortality. Should not preclude other mortality-reducing therapy.
    - Development of tolerance to NTG gtt after ~24 hr.
  - Contraindicated in:
    - Right-sided infarcts since it can cause hypotension
    - Aortic stenosis since patients are preload-dependent
    - Phosphodiesterase inhibitor (ex. sildenafil) taken within 24 hours

- **Intra-aortic balloon pump (IABP) counterpulsation:** (Class IIb) Indicated for:
  - Severe, recurrent ischemia despite intensive medical therapy
  - Hemodynamic instability before/after PCI
  - Mechanical complications of MI

- **Increase oxygen delivery to myocardium**
  - Supplemental O$_2$ for hypoxemic patients only. Hyperoxia can cause coronary vasospasm
  - Use humidified oxygen where possible to avoid nosebleeds

- **Antithrombotic therapy:** heparin or enoxaparin w/aspirin reduces 7-day mortality or MI by 50%.
  - **Aspirin:** Aspirin 325mg chewed x 1 then 81mg QD in all patients who can tolerate
  - **Second antiplatelet therapy:** An ADP P2Y$_{12}$ inhibitor. Choose one of the options below.
    - Details on how to decide which agent to use are located in the “Pharmacology” section below
    - **Clopidogrel** 300-600mg then 75mg QD regardless of conservative/early-invasive strategy (Ib)
      - AHA guidelines suggest 300mg, but there is good data suggesting 600mg loading dose is superior (significant reduction in death, MI, and need for revascularization at 1 month with 600 mg compared to 300 mg [4% v. 12%])
      - Patients already on clopidogrel: No good data on “re-loading”. Give 300mg x1.
      - Metabolism: Is a pro-drug which needs to be activated by CYP2C19
        - Up to 30% are clopidogrel non-responders due to cytP450 polymorphism
        - Omeprazole inhibits CYP2C19 and attenuates the anti-platelet effect of clopidogrel in vitro, but this does not appear to have a clinically significant effect. Pantoprazole does not inhibit CYP2C19
    - **Prasugrel** 60mg x 1 (per AHA 2012, only if PCI is planned), then 10mg QD
      - CAUTION: BLACK BOX WARNING: Age ≥75 or high likelihood of CABG (Risk of bleed)
      - **Avoid in** Weight < 60 kg, age ≥75, patients with a history of CVA/TIA. ↑ bleeding
    - **Ticagrelor** 180mg loading dose (per AHA 2012 even if PCI is not necessarily planned), then 90mg BID
      - CAUTION: BLACK BOX WARNING: if using Ticagrelor, use ASA < 100 mg daily (potential negative interaction between Ticagrelor and ASA 325 mg daily in PLATO Trial).
      - Contraindicated in active pathological bleeding or presence/history of intracranial bleed. Where possible, manage bleeding without discontinuing ticagrelor as the risk of cardiovascular events is increased upon discontinuation.
Some patients may require urgent CABG, and may bleed excessively if given clopidogrel. On the other hand, withholding anti-platelet therapy may be detrimental in the short term.

- Trials demonstrate anti-ischemic benefits of clopidogrel without an increase in life-threatening bleeding during CABG. Thus everyone should get a P2Y\textsubscript{12} inhibitor\textsuperscript{6}.
- ~10% of patients admitted for ACS/NSTEMI require CABG during the index admission. These patients require a 5-7 day “Plavix washout” before surgery if they are stable.
- ALWAYS check with the interventional fellow before loading P2Y\textsubscript{12} inhibitor.

- Anticoagulant therapy: heparin or enoxaparin w/aspirin reduces 7-day mortality or MI by 50%\textsuperscript{3}
  - Unclear if UFH or LMWH is superior
  - Duration: 2-5 days, but no convincing evidence.
  - Initial conservative strategy: anticoagulation for 48 hours
  - Early invasive strategy: Can likely stop anticoagulation after revascularization
  - Bivalirudin and fondaparinux are also Class I, but have level of evidence B
  - Enoxaparin or fondaparinux are preferred over UFH if initial conservative strategy selected unless CABG is planned.

- Guard against ventricular arrhythmias
  - Beta-blocker as above
  - Correct electrolyte abnormalities, repleting K to 4 and Mg to 2

- Guard against ventricular remodeling/aneurysm formation/rupture
  - Discontinue NSAIDs and COX-2 inhibitors (other than ASA)
  - Start ACE-inhibitor/ARB if pulmonary congestion or LVEF <40% and no hypotension

**RISK STRATIFY**

- Early invasive (PCI within 4-48 hrs) strategy if:
  - Unstable: Refractory pain, hemodynamically unstable, electrically unstable (arrhythmia) (AHA Class I)
  - Initially stable, but with high-risk features (AHA Class I):
    - Recurrent angina or ischemia at rest or with low-level activities despite medical therapy
    - PCI within 6 months
    - Prior CABG
    - High risk score: TIMI ≥ 3, GRACE > 140 (see below)
    - Reduced left ventricular function (LVEF less than 40%)
    - Elevated cardiac biomarkers (TnT or TnI)
    - New or presumably new ST-segment depression
    - Signs or symptoms of HF or new or worsening mitral regurgitation
    - High-risk findings from noninvasive testing

- Risk stratification scoring systems advised by AHA: TIMI, GRACE
  - TIMI score: ARSERBA acronym. Predicts mortality, new/recurrent MI, or revascularization at 14 days
    - Age >= 65 years
    - Risk factors (3+) for CHD: HTN, DM, HLD, smoking, or positive family history of early MI
    - Stenosis of coronaries >= 50%
    - ECG ST segment deviation
    - Recurrent angina (2+ anginal episodes in prior 24 hours)
    - Biomarkers: Elevated serum cardiac biomarkers
    - ASA within 7 days (marker for more severe coronary disease if event occurred despite ASA)
  - GRACE score (Global Registry of Acute Coronary Events). High risk if > 140.
    - Use online calculator: [http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html](http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html)
    - Variables: Age, SBP, HR, Cr, cardiac arrest, CHF class, ST segment deviation, elevated biomarkers

**INITIAL CONSERVATIVE MANAGEMENT STRATEGY:** For low risk patients, as above

- If during the conservative strategy, the patient develops high risk features, they should go to angiography
  - High risk features: recurrent symptoms, heart failure, serious arrhythmias
- Echocardiogram to evaluate LVEF: consider angiography if LVEF is newly <40%
● Stress test: All patients (Class I) without high risk features
  ○ If results not low risk: angiography
  ○ Low risk: can be discharged
● Aspirin: 81mg QD continue indefinitely
● Clopidogrel/prasugrel/ticagrelor: 1-12 months
● Continue UFH for 48 hours or give enoxaparin or fondaparinux for the duration of hospitalization or 8 days.

EARLY INVASIVE MANAGEMENT STRATEGY: For high risk patients, as above, angiography.
● Benefits: ↓ angina, ↓ readmission, ↓ MI risk, ↑ long-term survival in appropriately selected patients.
● Risks: AKI (6-13%), Contrast and atheroemboli. No ↑ risk of HD, bleeding
● Possible scenarios
  ○ Need CABG (3VD)
    ■ Continue ASA
    ■ Continue heparin until 12-24 h prior to CABG
    ■ Discontinue clopidogrel 5-7 days prior to elective CABG
  ○ Percutaneous coronary intervention
    ■ Continue ASA
    ■ Continue clopidogrel/prasugrel/ticagrelor. Give loading dose if not given pre-cath.
    ■ Consider adding GpIIb/IIIa inhibitor: delay to angiography, high-risk features, recurrent pain
      ● Timing unclear. Not in AHA guidelines. Usually just started periprocedural. Some suggest upstream (>1h before cath) use for very high risk patients only, but never >12 h before cath.
      ● Not indicated if bivalrudin is used as anticoagulant
    ■ Discontinue anticoagulation following uncomplicated cases
  ○ Non-obstructive CAD seen
    ■ Continue ASA
    ■ Continue clopidogrel. Give loading dose if not given pre-cath
    ■ Continue heparin for 48 hours
  ○ No significant CAD seen: management at practitioner’s discretion

MANAGE ARRHYTHMIAS
● Atrial arrhythmias: rate control or cardiovert if hemodynamically unstable
● Ventricular arrhythmias
  ○ General principles
    ■ Optimize electrolytes: K > 4, Mg > 2
    ■ Beta blocker
    ■ Lidocaine NOT recommended for NSVT but can be used for sustained VT and triggered VT
  ○ Polymorphic, very rapid VT, pulseless VT
    ■ Unsynchronized cardioversion (defibrillation)
  ○ Sustained monomorphic VT with angina, hypotension, pulmonary edema
    ■ Synchronized cardioversion
  ○ Sustained monomorphic VT without angina, hypotension, pulmonary edema
    ■ Amiodarone 150mg IV x 1
    ■ Alternative: procainamide 20mg/min until termination, hypotension, QRS > 50%
    ■ Third-line: Lidocaine 0.5mg-0.75mg/kg repeat q5-10min (100mg x 1)
  ○ Ventricular fibrillation: Proven higher incidence in hypokalemia (this is why we replete K!)
  ○ VT storm: > 4 VT/VF in one hour

SUBACUTE MANAGEMENT
● Medical management without stent
  ○ ASA 75-162mg indefinitely
  ○ Clopidogrel/prasugrel/ticagrelor for 9-12 months
● Bare metal stent
  ○ ASA 162-325mg x 1 month, then ASA 75-162mg indefinitely
  ○ Clopidogrel/prasugrel/ticagrelor for at least a month and ideally for one year
● Drug-eluting stent
○ ASA 162-325mg x 3-6 month, then ASA 75-162mg indefinitely
○ Clopidogrel/prasugrel/ticagrelor for at least one year

● Long-term antiplatelet therapy
○ Aspirin: indefinitely
○ Clopidogrel/prasugrel/ticagrelor: 9-12 months

● Statins: Atorvastatin 80mg or other high-dose statin (rosuvastatin) is preferred indefinitely regardless of LDL
  ⇒ PROVE-IT TIMI 22\textsuperscript{15}: Randomized 4162 patients with acute MI to pravastatin 40mg versus atorvastatin 80mg
  ○ Primary end-point was death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization
  ○ At 2 years, endpoint occurred in 26.3\% of pravastatin group and 22.4 \% of atorvastatin group (p<0.005)
  ○ Difference emerged at 30 days and was persistent

● Long-term anticoagulation: for AF or ventricular thrombus/apical aneurysm
● ACE-inhibitor/ARB if anterior territory is involved or EF =< 40\% or in heart failure
● Beta blocker: All patients without contraindications
● SSRI: Consider if clinical signs of depression.
  ⇒ SADHEART Trial\textsuperscript{21}: Major depressive disorder (MDD) occurs in 15\% to 23\% of patients with acute coronary syndromes and constitutes an independent risk factor for morbidity and mortality. Sertraline is safe in CAD.

PHARMACOLOGY

ASPIRIN: 325mg chewed x 1 then 81mg QD in all patients who can tolerate
  ⇒ Antiplatelet Trialists’ Collaboration\textsuperscript{8}: ASA meta-analysis
  ● Reduction of risk of vascular mortality and non-fatal MIs/stroke from 14\% to 9\% with aspirin use in UA
  ● Similar efficacy regardless of aspirin dosage, although there were more side effects with higher doses
  ⇒ ISIS-2\textsuperscript{9}: International Studies of Infarct Survival
  ● 23\% reduction of vascular mortality and 50\% reduction in nonfatal recurrent MIs and strokes after the use of ASA 160 mg daily for 1 month following suspected MI.
  ⇒ CURRENT-OASIS 7\textsuperscript{10}: Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes.
  ● High (600 load, 150 QD days 2-7, then 75 QD) vs. low (300 load, then 75 QD) Clopidogrel, high (300-325 QD) vs low (75-100 QD) aspirin
  ● Randomized patients with ACS treated with PCI in a 2 x 2 design (high v. low dose clopidogrel & high vs. low dose ASA). There was no difference in the composite primary outcome of CV death, MI, or CVA at 30 days between the high (300-325 mg) and low dose ASA (75-100 mg) groups
  ● Decreased risk of in-stent thrombosis (1.6\% vs 2.3\%) in high-dose clopidogrel group
  ● More major bleeding in high-dose clopidogrel dose (2.5\% vs 2.0\%)

CHOOSING THE SECOND ANTI-PLATELET AGENT

THIENOOPYRIDINES: Ticlopidine, clopidogrel, prasugrel. Irreversibly inhibit platelet ADP receptor P2Y\textsubscript{12} subunit.

Ticlopidine (Ticlid): First drug in this class. Not used frequently anymore because of risk of neutropenia, TTP

Clopidogrel (Plavix)
  ● Onset of action: Loading dose of 300mg inhibits 80\% of platelet activity in 5 hours. Faster with 600mg
  ● Metabolism: Prodrug. Requires CYP2C19 to be activated.
    ○ Mutation in ABCB1 intestinal transported decrease effectiveness
    ○ Mutation in CYP2C19 reduce activation of prodrug to active form: 3x risk of in stent thrombosis
    ○ CYP2C19*17 polymorphism accelerates activation leading to bleeding
    ○ Some drugs inhibit CYP2C219 and may lead to decreased platelet inhibition (ex. PPIs) in vitro, but the data is conflicting on if this has any in vivo clinical significance\textsuperscript{15}. Likely should continue PPI if the patient has a strong indication for it.
      ⇒ COGENT trial\textsuperscript{19}: No apparent cardiovascular interaction between clopidogrel and omeprazole
  ● Acute MI: ASA alone vs. ASA + clopidogrel in UA/NSTEMI. No difference in overall mortality. (CURE trial)
    ○ 11.4 vs. 9.3\% CV death/non-fatal MI. ↓ HF, revasc w/clopidogrel
    ○ ↑ bleeding, especially if CABG needed. No significant difference in life-threatening bleeds.
      ⇒ CURE trial\textsuperscript{11}: Clopidogrel + ASA vs. ASA alone. Clopidogrel + ASA reduced a combined endpoint of vascular death, MI,
and stroke by ~20% at both 1 and 9 months after presentation compared to ASA alone.

⇒ PCI-CURE trial\textsuperscript{12}: Pretreatment with clopidogrel ↓ rates of CV death, non-fatal MI, urgent revasc in 30 days
  - Patients undergoing PCI benefited from clopidogrel prior to PCI and s/p PCI.

⇒ CREDO trial\textsuperscript{13}: Loading with 300mg versus no-loading + maintenance. 25.9% RRR death, MI, CVA @ 1 year
  - No significant difference in life-threatening bleeds.

**Prasugrel (Effient):** More potent than clopidogrel
- 60mg load, 90% with >50% inhibition within 1 hour, then 10mg QD
- Absolute contraindications: Previous TIA or stroke
- Relative contraindications: 75 or older or < 60 kg
- is rapidly converted to an active metabolite via plasma esterases and a single CYP activation step, thus shortening its time to onset (1 hour)
- Per AHA 2012, can replace clopidogrel in UA/NSTEMI only if PCI is planned

⇒ TRITON-TIMI 38\textsuperscript{17}: Prasugrel vs. clopidogrel in moderate-high risk ACS with planned PCI
  - 13,608 pts with ACS treated with PCI: Prasugrel vs. Clopidogrel
  - Decreased risk of CV death, non-fatal MI, CVA with prasugrel (9.9% versus 12.1%)
  - Increased risk of bleeding with prasugrel (2.4% vs 1.1%) and fatal bleeding (0.4% vs 0.1%)
  - No difference in overall mortality

⇒ TRILOGY ACS\textsuperscript{20}: Prasugrel versus clopidogrel for up to 30 months. Patients with UA/NSTEMI without PCI
  - Non-significant difference in CV death, MI, CVA prasugrel 13.9% versus clopidogrel 16%
  - No significant difference in bleeding

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ticlopidine (Ticlid)</th>
<th>Clopidogrel (Plavix)</th>
<th>Prasugrel (Effient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP PSY\textsubscript{12} Inhibition</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Onset with loading</td>
<td>Loading ↑ neutropenia</td>
<td>3-5 hours</td>
<td>1 hour</td>
</tr>
<tr>
<td>Duration of effect</td>
<td>5-9 days</td>
<td>5-9 days</td>
<td>5-9 days</td>
</tr>
<tr>
<td>Side effects</td>
<td>Neutropenia, TTP</td>
<td>Rash, neutropenia (rare)</td>
<td>None significant</td>
</tr>
<tr>
<td>Clearance</td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
</tr>
</tbody>
</table>

**NON-THIENOPYRIDINE PLATELET ADP-RECEPTOR P2Y\textsubscript{12} ANTAGONISTS**

Ticagrelor (Brilinta): reversible non-thienopyridine P2Y\textsubscript{12} antagonist.
- **Metabolism:** Does not need to be activated, achieving consistent platelet inhibition within 2 hours.
  - When stopped, platelet function returns to baseline within 1 to 2 days. (Limited CABG washout)

⇒ PLATO\textsuperscript{18}: 18,624 ACS patients (UA/NSTEMI and STEMI) compared ticagrelor versus clopidogrel load then daily
  - Decreased risk of vascular death (MI, CVA) with ticagrelor (9.8%) versus clopidogrel (11.7%), regardless of whether PCI was planned
  - All-cause mortality lower with ticagrelor (4.5% versus 5.9%)
  - No significant difference in major bleeding (11.6% vs 11.2%) but more bleeding with CABG
  - More dyspnea with ticagrelor (13.8% vs 7.8%)

Cangrelor: IV reversible P2Y\textsubscript{12} Inhibitor. Effective within minutes and rapidly metabolized when stopped (60min)
- Complete platelet inhibition vs. clopidogrel’s 60% at regular dosing
- CHAMPION-PCI and PLATFORM, phase 3 trials, terminated early due to unlikelihood of reaching end point

⇒ CHAMPION-PCI: Comparable to clopidogrel at 48 hours for the reduction of death, MI, or revascularization (7.5% vs 7.1%; P = .59) and remained comparable at 30 days. Increased major bleeding (3.6% vs 2.9%; P = .06).

⇒ CHAMPION-PHOENIX: Reduced rate of ischemic events, including stent thrombosis

Elinogrel: IV/PO P2Y\textsubscript{12} inhibitor in phase II testing.
- Currently being evaluated for STEMI (ERASE-MI), non-urgent PCI (INNOVATE-PCI)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ticagrelor (Brilinta)</th>
<th>Cangrelor</th>
<th>Elinogrel</th>
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</thead>
<tbody>
<tr>
<td>ADP PSY\textsubscript{12} Inhibition</td>
<td>Reversible</td>
<td>Reversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Mode of administration</td>
<td>PO</td>
<td>IV</td>
<td>PO/IV</td>
</tr>
<tr>
<td>Onset with loading</td>
<td>2 hours</td>
<td>Minutes</td>
<td></td>
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</tbody>
</table>
MANAGEMENT OF UA/NSTEMI

Mark Tuttle, Ara Tachjian, Grace Hsieh 2014, Mark Tuttle 2017

Duration of effect
1-2 days 1 hour 1 day

Side effects
Dyspnea (14%), ↑ uric acid

Clearance
Hepatic (75%), renal (25%)

GLYCOPROTEIN IIb/IIIa INHIBITORS: All are IV. Affect the final common pathway of platelet inhibition

- Indications: ACS
- Timing: Not clear. Not in AHA guidelines. Some suggest upstream use for very high risk patients only.
  ⇒ CRUSADE: upstream (>1h) vs. periprocedural timing. Nonsignificant ↓ mortality w/upstream.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abciximab (ReoPro)</th>
<th>Eptifibatide (Integrillin)</th>
<th>Tirofiban (Aggrestat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma t½</td>
<td>Minutes</td>
<td>2.5 hours</td>
<td>2.0 hours</td>
</tr>
<tr>
<td>Platelet t½</td>
<td>Days</td>
<td>Seconds</td>
<td>Seconds</td>
</tr>
<tr>
<td>Clearance</td>
<td>Hepatic</td>
<td>Renal</td>
<td>Renal</td>
</tr>
</tbody>
</table>

PROTEASE ACTIVATED RECEPTOR INHIBITORS: Inhibits thrombin (II) receptor of platelets

- Theoretical advantage of localizing antplatelet effects to vicinity of active thrombin generation, ↓ bleeding.
- Two formulations being tested in clinical trials:
  - SCH530348: t½ 5-10 days. (TRA-2P-TIMI 50 trial)
  - E5555: (LANCELOT CAD trial)

SOURCES


