Updates in Therapeutics® 2015:
The Pharmacotherapy Preparatory Review & Recertification Course
Cardiology I
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Conflict of Interest Disclosures

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None.
Cardiology I-Agenda

1. ACS
2. ADHF
3. Life-threatening arrhythmias/ACLS
4. Hypertensive Emergencies
5. Pulmonary Artery Hypertension
Acute Coronary Syndromes


ACS Pathophysiology and Characteristics

Acute Coronary Syndrome

Non STE ACS
- Stable Plaque
- Limited Flow; Platelet Rich; Partial Occlusion
- Priority: Control anginal symptoms
- Priority: Prevent total occlusion
- Priority: Prevent total occlusion
- Priority: Restore patency of infarcted artery

Unstable Angina
- Biomarkers
- Priority: Control CP and other symptoms
- Priority: Control CP and other symptoms
- Priority: Limit infarct size
- Priority: Prevent complications such as arrhythmias or death

NSTEMI
- Biomarkers
- Priority: Control CP etc.
- Priority: Control CP etc.
- Priority: Control CP etc.

STEMI
- Biomarkers
- Priority: Prevent total occlusion
- Priority: Prevent total occlusion
- Priority: Prevent total occlusion
- Priority: Prevent total occlusion

Stable Angina
- Total Occlusion

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Steps for Treating ACS

- Initial evaluation
- Diagnosis
- Risk stratify
- Select an initial strategy for management
- Early Hospital Care
- Secondary prevention

Initial evaluation and diagnosis

- 12 lead ECG within 10 minutes
  - Persistent ST elevation ➔ Reperfusion
  - Non ST elevation ➔ Risk stratify
    - Can perform serial ECGs if first is nondiagnostic

- Serial troponins (Troponin I or T)
  - Draw at presentation, and q3-6 hours
    - (+) MI when troponin rises or falls by ≥ 20%
    - CK-MB is Class III for diagnosis
    - Troponins drawn day 3 or 4 to ascertain infarct size (IIb)
    - BNP may be used as an additional prognostic tool (IIb)

- Early hospital care (MONA+ BB)

Selecting an Appropriate Strategy

- **STEMI →** Immediate reperfusion
  - Primary percutaneous coronary intervention (PCI) is preferred to lytic therapy.
    - FMC-to-device < 90 mins (PCI)
  - Fibrinolytic therapy is indicated for patients with STEMI in whom PCI cannot be performed
    - Within 120 min or in someone not agreeable to PCI
    - Door to needle time < 30 min
  - Goal: restore patency and limit infarct size

- **NSTE-ACS →** Risk stratification
  - Useful for selecting site of care, anti-thrombotic therapies, and invasive management
    - TIMI score
    - GRACE score
  - Treated with either an "early invasive strategy" or an “ischemia-guided strategy”
  - Goal: prevent total occlusion and minimize complications

FMC= First Medical Contact
Risk Stratify

- Risk Calculators
  - TIMI risk score
    - www.timi.org
      - TIMI of 3 or more, greater benefit from invasive and anti-coagulant therapies
  - GRACE risk score
    - http://www.outcomesumassmed.org/grace/acs_risk/acs_risk_content.html
      - predicts in-hospital and postdischarge mortality or MI
        - GRACE score >140 can be identified for early invasive strategies.
If non-ischemic initial ECG and normal troponins
- Treadmill, stress myocardial perfusion imaging, or stress echocardiography before discharge (Class IIa)
- CT angiography in those with no history of CAD (IIa)
“Ischemia-guided strategy”

- **Medical therapy**
  - Lower risk (TIMI 0-1 or GRACE <109)
  - No troponin elevation
  - Patient preference in absence of high risk features

“Early invasive strategy”

- **Revascularization**
  - a diagnostic angiography with intent to perform revascularization
  - for those with refractory angina or hemodynamic or electrical instability or those with high risk based on clinical findings
  - Superior to “ischemia-guided strategy” for those with high risk features
Patient Case #1

66-year old woman

- PMH: prior MI, HTN, HLD, DM
- Presents with sudden-onset diaphoresis, N/V, dyspnea, band-like chest pain (8/10), radiating to left arm
- HPI: 1 month prior, typical angina frequency with less exertion
- ECG: ST depressions in leads II, III, AVF, and hyperdynamic T waves
- Cardiac enzymes positive
Patient Case #1

- Home Meds: aspirin 81mg daily
  simvastatin 40 mg every night
  metoprolol 50 mg twice daily
  metformin 1 gm twice daily

- Diagnosis: NSTE-ACS

- TIMI Risk=6
  - 41% risk at 14 days of: all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization.
Patient Case #1

Which is the best treatment strategy for this patient?

A. Aspirin and clopidogrel, UFH + eptifibatide, and diagnostic cath for possible PCI

B. Aspirin, enoxaparin, with an early invasive approach

C. Ischemia guided strategy with abciximab plus enoxaparin, aspirin, & clopidogrel

D. Ischemia guided strategy with aspirin, clopidogrel, UFH
# Early Hospital Care

<table>
<thead>
<tr>
<th>M = Morphine</th>
<th>Morphine 1 to 5 mg IV every 5 to 30 minutes is reasonable if symptoms are not relieved despite maximally tolerated anti-ischemic medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>O = Oxygen</td>
<td>Supplemental Oxygen only if O2 saturation &lt; 90%, respiratory distress, or high-risk features for hypoxemia</td>
</tr>
</tbody>
</table>
| N = Nitroglycerin | NTG spray or SL tablet 0.4 mg x 3 doses every 5 minutes for continuing ischemic pain  
(if pain unrelieved after one dose, call 911)  
NTG IV 5 mcg/min for persistent ischemia, HF, or hypertension; titrate to CP relief or 200 mcg/minute; CI with phosphodiesterase inhibitor; use should not preclude mortality-reducing therapies |
| A = Aspirin* | ASA chew and swallow non-enteric coated 162–325 mg x 1 dose as soon as possible                                                                                                                                 |
| B = Beta blocker* | Oral preferred w/i 24 hours if no Cl#                                                                                                                                                             |

*mortality reducing  
# HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade
Combatting Thrombus Formation

- Antiplatelets: Aspirin, P2Y12 antagonists, and GPIs

- Anticoagulants: UFH, LMWH, Fondaparinux, Bivalirudin
## Guideline recommendations - ASA

<table>
<thead>
<tr>
<th>Guideline Recommendation</th>
<th>Class /Grade</th>
</tr>
</thead>
</table>
| Initiate 162-325 mg of ASA before PCI. After PCI, give ASA indefinitely.  
• **2013 ACCF/AHA guideline for STEMI** | I |
| Initiate 81-325 mg of non-enteric coated ASA before PCI in patients already taking ASA. In patients not on ASA, give 325 before PCI. After PCI, continue ASA indefinitely.  
• **2014 NSTE-ACS guideline**  
• **2011 ACCF/AHA/SCAI guideline for PCI** | I |
| 81 mg of ASA preferred to higher maintenance doses  
• **2014 NSTE-ACS guideline**  
• **2013 ACCF/AHA guideline for STEMI**  
• **2011 ACCF/AHA/SCAI guideline for PCI** | IIa IIa IIa |

Aspirin

- Established first line-therapy in patients with NSTE-ACS
  - Reduces incidence of recurrent MI and death
  - Loading dose 162-325 mg necessary
  - High dose (>160 mg) is associated with more bleeding than lower dose (<160 mg) in the absence of improved outcomes
  - Avoid enteric-coated initially because of its delayed and reduced absorption
# Class I recommendations - P2Y$_{12}$

<table>
<thead>
<tr>
<th>Guideline Recommendation</th>
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</thead>
</table>
| A loading dose of P2Y$_{12}$ receptor inhibitor should be given before PCI. Options include:  
  a. Clopidogrel 600 mg followed by 75 mg daily  
  b. Prasugrel 60 mg followed by 10 mg daily; or  
  c. Ticagrelor 180 mg followed by 90 mg twice daily | I  
  LOE B  
  LOE B  
  LOE B |
| • 2013 ACCF/AHA guideline for STEMI  
• 2014 NSTE-ACS guideline | 

For NSTE-ACS patients treated with an early invasive or ischemia-guided strategy:  
  a. Clopidogrel 600 mg followed by 75 mg daily  
  b. Ticagrelor* 180 mg followed by 90 mg twice daily | I  
  LOE B  
  LOE B |
| • 2014 NSTE-ACS guideline | 

*Ticagrelor given in preference to clopidogrel (Class IIa) in 2014 NSTE-ACS guideline
Class II recommendations - $\text{P}2\text{Y}_{12}$

<table>
<thead>
<tr>
<th>Guideline Recommendation</th>
<th>Class /Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NSTE-ACS patients treated with an early invasive or ischemia-guided strategy:</td>
<td></td>
</tr>
<tr>
<td>• It is reasonable to use <strong>ticagrelor</strong> in preference to clopidogrel</td>
<td>Ila</td>
</tr>
<tr>
<td>• 2014 NSTE-ACS guideline</td>
<td>LOE B</td>
</tr>
<tr>
<td>For NSTE-ACS patients treated with PCI who are not at risk for bleeding complications</td>
<td></td>
</tr>
<tr>
<td>• It is reasonable to choose prasugrel over clopidogrel</td>
<td>Ila</td>
</tr>
<tr>
<td>• 2014 NSTE-ACS guideline</td>
<td>LOE B</td>
</tr>
<tr>
<td>Prasugrel should not be administered to patients with a prior history of TIA or Stroke</td>
<td></td>
</tr>
<tr>
<td>• 2014 NSTE-ACS guideline</td>
<td>Class III</td>
</tr>
<tr>
<td>• 2013 ACCF/AHA guideline for STEMI</td>
<td></td>
</tr>
</tbody>
</table>
### PK differences P2Y$_{12}$ agents

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Indication</strong></td>
<td>ACS managed medically or with PCI</td>
<td>ACS with PCI</td>
<td>ACS managed medically or with PCI</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>LD: 300-600, MD 75 mg daily</td>
<td>LD: 60 mg, MD 10 mg daily</td>
<td>LD: 180 mg, MD 90 mg <strong>twice daily</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg if &lt;60 kg; BBW &gt;75 y</td>
<td></td>
</tr>
<tr>
<td><strong>Peak Platelet Inhb</strong></td>
<td>300 mg load ~ 6 hrs 600 mg load ~2 hrs</td>
<td>60 mg load ~1-1.5 hrs</td>
<td>180 mg load &lt; 1 hr</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Prodrug; converted by 2-step process involving 2C19 and 3A4</td>
<td>Prodrug; converted to active metabolite via multiple P450 pathways</td>
<td>Not prodrug; Reversible, noncompetitive binding; 3A4 (primary), 3A5, Pgp</td>
</tr>
<tr>
<td><strong>T1/2</strong></td>
<td>8 hrs metabolite</td>
<td>3.7 hours metabolite (range 2-15 hours)</td>
<td>7 hours (parent), 9 hours (active metabolite)</td>
</tr>
</tbody>
</table>
# Clinical Considerations P2Y₁₂

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-responders</strong></td>
<td>Exposure to active drug affected by CYP2C19 and CYP3A4 and PGP polymorphisms</td>
<td>No known issues</td>
<td>No known issues</td>
</tr>
<tr>
<td><strong>Drug/Disease Interactions</strong></td>
<td>PPI's inhibit 2C19, (concomitant use with omeprazole is discouraged per PI); enhanced bleeding with NSAIDS, VKA, O3FA, etc</td>
<td>Less prone but data are limited; enhanced bleeding with NSAIDS, VKA, etc</td>
<td>Careful with asthma, bradycardia: enhanced bleeding with NSAIDS, VKA; limit ASA to &lt;100 mg</td>
</tr>
<tr>
<td><strong>Non-emergent Surgery hold time</strong></td>
<td>5 days</td>
<td>7 days</td>
<td>5 days</td>
</tr>
<tr>
<td><strong>Emergency surgery hold time</strong></td>
<td>In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications (LOE B).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Class recommendations – GPIIb/IIIa

<table>
<thead>
<tr>
<th>Guideline Recommendation</th>
<th>Class /Grade</th>
</tr>
</thead>
</table>
| *Useful* in patients with high risk features, particularly in those not adequately pretreated with clopidogrel or ticagrelor  
• 2014 NSTE-ACS guideline                                                             | I LOE B       |
| Reasonable to administer at time of PCI in those with high risk features adequately treated with clopidogrel  
• 2014 NSTE-ACS guideline                                                              | IIa          |
| Preferred options are eptifibatide and tirofiban  
• 2014 NSTE-ACS guideline                                                              | Class IIb     |
GP IIb/IIIa Inhibitors

- Reduce the incidence of composite ischemic events
  - Primarily through a decrease in documented MI, but may increase risk of bleeding
- Most studies combined GP IIb/IIIa inhibitors with UFH
- Upstream administration has not been shown to be superior to delayed administration (given at time of PCI) in recent trials.
  - No significant reduction in the primary composite of death, MI, RIUR, or TBO at 96h
  - Trend toward reduction in death or MI at 30 days, but no difference in 30-day mortality
  - Higher rates of non-life-threatening bleeding and transfusions

## GP IIb/IIIa Inhibitors

<table>
<thead>
<tr>
<th>Pretreated with P2Y&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Not Pretreated with P2Y&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Renal Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abciximab (ReoPro)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>Of uncertain benefit</td>
<td>PCI: 0.25-mg/kg IV bolus; then 0.125 mcg/kg/minute (maximum 10 mcg/kg) for 12 hours&lt;br&gt;ACS without PCI: Not recommended</td>
</tr>
<tr>
<td>Eptifibatide (Integrilin)</td>
<td>Of uncertain benefit</td>
<td>PCI: 180-mcg/kg IV bolus × 2 (10 minutes apart); 2 mcg/kg/minute started after first bolus for 18–24 hours&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;ACS without PCI: Of uncertain benefit in patients adequately pretreated with a P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitor; single bolus used as above</td>
</tr>
<tr>
<td><strong>Tirofiban (Aggrastat)</strong></td>
<td>Of uncertain benefit</td>
<td>PCI: 25-mcg/kg IV bolus over 3 minutes; then 0.15 mcg/kg/minute for 18–24 hours&lt;br&gt;ACS without PCI&lt;sup&gt;d&lt;/sup&gt;: 0.4 mcg/kg/minute for 30 minutes (LD infusion); then 0.1 mcg/kg/minute for 18–72 hours</td>
</tr>
</tbody>
</table>

<sup>b</sup> Of uncertain benefit<br>
<sup>c</sup> If CrCl <30, ↓ infusion 50%<br>
<sup>d</sup> If dialysis, contraindicated
NSTE-ACS Treatment Algorithm

NSTE-ACS: Definite or Likely

Ischemia-Guided Strategy

1. **Initiate DAPT and Anticoagulant Therapy**
   1. ASA (Class I; LOE: A)
   2. P2Y₁₂ inhibitor (in addition to ASA) (Class I; LOE: B):
      - Clopidogrel or
      - Ticagrelor
   3. Anticoagulant:
      - UFH (Class I; LOE: B) or
      - Enoxaparin (Class I; LOE: A) or
      - Fondaparinux† (Class I; LOE: B)

Early Invasive Strategy

1. **Initiate DAPT and Anticoagulant Therapy**
   1. ASA (Class I; LOE: A)
   2. P2Y₁₂ inhibitor (in addition to ASA) (Class I; LOE: B):
      - Clopidogrel or
      - Ticagrelor
   3. Anticoagulant:
      - UFH (Class I; LOE: B) or
      - Enoxaparin (Class I; LOE: A) or
      - Fondaparinux† (Class I; LOE: B) or
      - Bivalirudin (Class I; LOE: B)

Can consider GPI in addition to ASA and P2Y₁₂ inhibitor in high-risk (e.g., troponin positive) pts (Class IIb; LOE: B):
   - Eptifibatide
   - Tirofiban

Medical therapy chosen based on cath findings

Anticoagulant in ACS

An anticoagulant should be administered to all patients with ACS in addition to antiplatelet therapy to reduce the risk of intracoronary and catheter thrombus formation irrespective of initial treatment strategy.

<table>
<thead>
<tr>
<th>Class I Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI PPCI</td>
</tr>
<tr>
<td>STEMI, with fibrinolytic</td>
</tr>
<tr>
<td>NSTE-ACS, Early invasive strategy</td>
</tr>
<tr>
<td>NSTE-ACS; Ischemia-guided strategy</td>
</tr>
</tbody>
</table>

*reasonable to use as monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist (Class IIa) in NSTE ACS patients high at risk for bleeding

#not to be used as the sole anticoagulant in PCI (Class III)
Unfractionated Heparin

- Intravenous UFH is useful in patients with NSTE-ACS undergoing PCI (Class I)

- Intravenous UFH:
  - Initial bolus of 60 units/kg (maximum 4000 units)
  - Initial infusion of 12 units/kg/hour (maximum 1000 units/hour)
  - Adjusted per aPTT to maintain therapeutic anticoagulation according to specific hospital protocol, continued for 48 hours or until PCI is performed

aPTT = activated partial thromboplastin time
LMWH in ACS

- Class I as anticoagulant option for NSTE ACS
- Molecular weight 1/3 of UFH with balanced anti-Xa and anti-IIa activity
- Does not require routine monitoring
  - Requires calculation of CrCl
- Dosing: 1 mg/kg subcutaneously every 12 hours, continued for the duration of hospitalization or until PCI is performed
  - 30 mg intravenous bolus, then 1 mg/kg for STEMI and select NSTE ACS
  - 1 mg/kg subcutaneously once daily for CrCl < than 30 mL/min
LMWH: Dosing surrounding PCI

- Use of enoxaparin during PCI may be reasonable in patients treated with upstream subcutaneous enoxaparin with an ischemia-guided strategy (IIb).
  - Additional dose of 0.3 mg/kg IV at time of PCI to patients who have received fewer than two therapeutic SQ doses or received the last SQ dose 8 to 12 hours before PCI (Class I).
  - Patients who undergo PCI more than 12 hours after last subcutaneous dose are usually treated with full-dose de novo anticoagulation with an established regimen (e.g., full-dose UFH or bivalirudin).
  - In patients who have not received anticoagulant therapy, a 0.5–0.75 mg/kg intravenous loading dose is needed.
Fondaparinux

- Selective inhibitor of activated factor X
- Well absorbed, t1/2 17 hours
- Renally cleared; CI with CrCl < 30 ml/min
- Monitoring Anti-Xa not required
- Significantly less bleeding than enoxaparin with similar ischemic benefit
Fondaparinux: Dosing

- Fondaparinux: 2.5 mg subcutaneously daily, continued for the duration of hospitalization or until PCI is performed

- Fondaparinux should not be used as the sole anticoagulant to support PCI in patients with NSTE-ACS due to an increased risk of catheter thrombosis (Class III)

  - If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time)
Bivalirudin

- Direct thrombin inhibitor
- Useful as an anticoagulant with or without prior treatment with UFH in patients with NSTE-ACS undergoing PCI (Class I)
- In patients with NSTE-ACS undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist (Class IIa)
Bivalirudin: Dosing

- Bivalirudin: 0.1 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients with early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor.

- For patients who have received UFH, wait 30 minutes, then give 0.75 mg/kg intravenous loading dose, then 1.75 mg/kg/hour intravenous infusion.

- For patients already receiving bivalirudin infusion, give additional 0.5 mg/kg loading dose and increase infusion to 1.75 mg/kg/hour during PCI.
 PCI With Stenting
Initiate/continue antiplatelet and anticoagulant therapy
1. ASA (Class I; LOE: B)
2. P2Y12 Inhibitor (in addition to ASA):
   - Clopidogrel (Class I; LOE: B) or
   - Prasugrel (Class I; LOE: B) or
   - Ticagrelor (Class I, LOE: B)
3. GPI (if not treated with bivalirudin at time of PCI)
   - High-risk features, not adequately pretreated with clopidogrel (Class I, LOE: A)
   - High-risk features adequately pretreated with clopidogrel (Class IIa; LOE: B)
4. Anticoagulant:
   - Enoxaparin (Class I; LOE: A) or
   - Bivalirudin (Class I; LOE: B) or
   - Fondaparinux as the sole anticoagulant (Class III; Harm; LOE: B) or
   - UFH (Class I; LOE: B)

CABG
Initiate/continue ASA therapy and discontinue P2Y12 and/or GPI therapy
1. ASA (Class I; LOE: B)
2. Discontinue clopidogrel/ticagrelor 5 d before, and prasugrel at least 7 d before elective CABG
3. Discontinue clopidogrel/ticagrelor up to 24 h before urgent CABG (Class I; LOE: B). May perform urgent CABG <5 d after clopidogrel/ticagrelor and <7 d after prasugrel discontinued
4. Discontinue eptifibatide/tirofiban at least 2-4 h before, and abciximab ≥12 h before CABG (Class I; LOE: B)

Late Hospital/Posthospital Care
1. ASA indefinitely (Class I; LOE: A)
2. P2Y12 inhibitor (clopidogrel or ticagrelor), in addition to ASA, up to 12 mo if medically treated (Class I; LOE: B)
3. P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), in addition to ASA, at least 12 mo if treated with coronary stenting (Class I; LOE: B)

Patient Case #2

A 45 yo received an elective PCI and drug eluting stent in her RCA. Which one of the following best represents how long DAPT therapy should continue?

- A. At least 1 month
- B. At least 3 months
- C. At least 6 months
- D. At least 12 months
Dual Anti-platelet therapy duration

- Aspirin should be continued indefinitely
  - 81 mg daily with ticagrelor
  - 81-325 mg in all other patients
  - Reasonable to use 81 mg in preference to higher doses (Class IIa)

- DAPT duration is 12 months after ACS with or without stent
  - Duration more or less than 12 months should be jointly made by the clinician and the patient
  - Balancing the risks of stent thrombosis and ischemic complications with bleeding

For BMS for non-ACS, DAT recommended for at least 1 month (ideally out to 12 months), unless high bleeding risk (minimum of 2 weeks)
Patient Case #3

52 YOM

- PMH: HTN, hypertriglyceridemia, smoker
- HPI: presents to major university teaching hospital within 3 hours
  - Crushing 10/10 substernal chest pain radiating while eating (at rest)
  - Nausea, diaphoresis, SOB
  - Never experienced CP of this character/intensity
Patient Case #3

- Home Meds: lisinopril, gemfibrozil
- Vitals: HR 68, BP 178/94, wt 100kg
- ECG:
  - 3mm ST Elevation in V_2-V_4, I, aVL
- Labs:
  - Serum chemistry WNL
  - Positive myoglobin
  - Positive cardiac enzymes
    - CK 175, MB 17.4, Troponin T 0.8
- Diagnosis: STEMI
Which of the following should be done for STEMI treatment?

- A. Primary PCI with stent of artery, abciximab, clopidogrel, aspirin, UFH
- B. Reteplase 10 U bolus x2, 30min apart + UFH 60 U/kg bolus & 12 U/kg/hr
- C. Abciximab + enoxaparin 100mg SQ BID + tenecteplase 25mg IVP
- D. Tirofiban + UFH infusion
Class I: Indicated for patients with STEMI in whom PCI cannot be performed *within 120 min*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase (rt-PA, Activase)</td>
<td>15 mg IV, then 0.75 mg/kg over 30 minutes (max 50 mg), then 0.5 mg/kg (max 35 mg) over 60 minutes</td>
</tr>
<tr>
<td>Reteplase (r-PA, Retavase)</td>
<td>10 units IV, repeat 10 units IV in 30 minutes</td>
</tr>
<tr>
<td>Tenecteplase (TNK-tPA, TNKase)</td>
<td>&lt; 60 kg, 30 mg IV; 60–69 kg, 35 mg IV; 70–79 kg, 40 mg IV; 80–89 kg, 45 mg IV; &gt; 90 kg, 50 mg IV (about 0.5 mg/kg)</td>
</tr>
</tbody>
</table>

r-PA = Reteplase; TNK = tenecteplase; rt-PA = alteplase
## Contraindications to Thrombolytics

<table>
<thead>
<tr>
<th>Relative Contraindications</th>
<th>Absolute Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP &gt; 180/110 mm Hg on presentation or history of chronic poorly controlled HTN</td>
<td>ANY prior hemorrhagic stroke</td>
</tr>
<tr>
<td>History of prior ischemic stroke &gt; 3 months prior</td>
<td>Ischemic stroke within 3 months (except in past 4.5 hours)</td>
</tr>
<tr>
<td>Recent major surgery (&lt;3 weeks prior), Traumatic or prolonged CPR (&gt; 10 minutes)</td>
<td>Intracranial neoplasm or arteriovenous malformation</td>
</tr>
<tr>
<td>Recent internal bleeding (within 2–4 weeks)</td>
<td>Active internal bleeding</td>
</tr>
<tr>
<td>Active peptic ulcer</td>
<td>Aortic dissection</td>
</tr>
<tr>
<td>Noncompressible vascular punctures</td>
<td>Considerable facial trauma or closed-head trauma in past 3 months</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Intracranial or intraspinal surgery within 2 months</td>
</tr>
<tr>
<td>Known intracranial pathology (dementia)</td>
<td>Severe uncontrolled hypertension (unresponsive to emergency therapy)</td>
</tr>
<tr>
<td>Oral anticoagulant therapy</td>
<td></td>
</tr>
</tbody>
</table>
In patients undergoing primary PCI, either UFH or bivalirudin is preferred. (Class I STEMI)

When a fibrinolytic agent is given as a reperfusion strategy, UFH, enoxaparin, and fondaparinux are recommended. (Class I STEMI)

- Those given fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hours with IV UFH or IV/SQ enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SQ fondaparinux during hospitalization, up to 8 days.

- Bivalirudin is not recommended in this population.
## Other Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Should be started and continued indefinitely for all patients with LVEF ≤40% and in those with HTN, DM, or stable chronic kidney disease. IV therapy CI because of risk of hypotension.</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Indicated in patients after MI already receiving therapeutic doses of ACE inhibitor and β-blocker and who have LVEF ≤40%, HF, or DM without CI.</td>
</tr>
<tr>
<td>CCBs</td>
<td>CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects.</td>
</tr>
<tr>
<td>Statins</td>
<td>High-intensity statin therapy (atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day) should be initiated or continued in all patients.</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Topical or oral nitrates are acceptable for antianginal effect in those without ongoing refractory ischemia; ensure nitrate free interval.</td>
</tr>
</tbody>
</table>
Late Hospital Care/Secondary Prevention

A
- Aspirin
- Anti-anginals (SL NTG)
- ACEI/ARBs
- Aldosterone antagonists

B
- Beta-blockers
- Blood pressure

C
- Cholesterol
- Cigarettes

D
- Dual Antiplatelet therapy
- Diet
- Diabetes

E
- Education
- Exercise
Beta blockers

- Indicated in all patients unless CI
  - Start w/i 24 hours in patients who do not have CI
  - If not started w/i 24 hours, reevaluate before D/C
  - IV beta blockers is harmful (Class III) in those at risk for shock

- Reasonable to continue in NSTE ACS patients with normal LV function (Class IIa)
  - Continue for at least 3 years with normal EF
  - Continue indefinitely for EF< 40%

- CI (risk factors for shock):
  - 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other CI (PR interval > 0.24 sec, 2nd or 3rd degree heart block without PM, active asthma, or reactive airway disease)
ACEIs/ARBs

- Should be started and continued indefinitely for all patients with LVEF of < 40% (Class I)
  - ACEIs reduce mortality in patients with recent MI, primarily in those with LV dysfunction

- Recommended also in patients with HTN, DM, and chronic stable kidney dz (Class I)
  - Total mortality and MACE reduced in normal LV function (including DM)

- Use cautiously in the first 24 hours
  - Because of risk for hypotension or renal dysfunction
  - Prudent to initially use short acting (enalapril or captopril) in those at increased risk for ADE
ACEs/ARBs

- ACEIs may be reasonable in all other patients with cardiac or vascular disease (Class IIb)
- ARB can be substituted with similar benefits on survival
  - Class I for HF or MI with LVEF ≤ 40%
  - Class IIa in other cardiac or vascular dz
- Stabilize renal function prior to initiating
  - Re-evaluate creatinine after initiation
- Do NOT combine ACEI + ARB
- CI:
  - hypotension
  - pregnancy
  - bilateral renal artery stenosis
Aldosterone blockade after ACS

- Indicated in patients post-MI already receiving ACE inhibitor and β-blocker and who have:
  - LVEF of 40% or less and either symptomatic HF or diabetes, unless contraindicated (Class I)

- CI:
  - hyperkalemia (potassium 5.0 or greater),
  - CrCl less than 30 mL/minute/1.73 m²
  - SCr greater than 2.5 mg/dL in men and greater than 2.0 mg/dL in women.
Statins

- High intensity statins in all patients without CI
  - Reduces the rate of recurrent MI, coronary heart disease mortality, need for revascularization and stroke.
  - High-risk patients derive greatest benefit from high-intensity statins
    - Atorvastatin 40-80 mg and rosuvastatin 20-40 mg

- CI:
  - Pregnancy
  - Note dosing restrictions on 3A4 interacting medications
Acute Decompensated Heart Failure


Common Precipitating Factors

Medication Related
- Nonadherence with meds
- Recent addition of negative inotropic drugs
  - verapamil, diltiazem, beta blockers
- Initiation of meds that increase salt retention
  - Steroids, TZDs, NSAIDs
- Excessive alcohol or illicit drug use

Disease Related
- Nonadherence with Na+ and fluid restriction
- Acute myocardial ischemia
- Uncorrected high BP
- AF and other arrhythmias
- Pulmonary embolus
- Endocrine abnormalities
- Concurrent infections
- Other acute CV disorders

Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis.

Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF.

ADHF Signs and Symptoms

- **Congestion**
  - DOE or at rest
  - Orthopnea, PND
  - Peripheral edema
  - Rales
  - Early satiety, N/V
  - Ascites
  - Jugular venous distension
  - Hepatojugular reflux

- **Hypoperfusion**
  - Fatigue
  - Altered mental status or sleepiness
  - Cool extremities
  - Worsening renal function
  - Narrow pulse pressure
  - Hypotension
  - Hyponatremia
Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>ADHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>4-7</td>
<td>2-4</td>
</tr>
<tr>
<td>CI</td>
<td>2.8-3.6</td>
<td>1.3-2</td>
</tr>
<tr>
<td>PCWP</td>
<td>8-12 (15-18)</td>
<td>18-30</td>
</tr>
<tr>
<td>SVR</td>
<td>800-1200</td>
<td>1500-3000</td>
</tr>
</tbody>
</table>

- BP = CO x SVR
- CO = SV x HR
- Stroke volume depends on several factors
  - inotropy, afterload, preload
Figure 1-2. Frank-Starling curve.
CI = cardiac index; PCWP = pulmonary capillary wedge pressure.
ADHF Quadrants

**Congestion at Rest?**

- **PCWP Normal**
  - **I. Warm & Dry**
    - PCWP normal
    - CI normal
    - (Compensated)
  - **II. Warm & Wet**
    - PCWP elevated
    - CI normal
    - (Compensated)

- **PCWP Elevated**
  - **III. Cold & Dry**
    - PCWP low/normal
    - CI decreased
    - (Hypoperfused)
  - **IV. Cold & Wet**
    - PCWP elevated
    - CI decreased

**Low Perfusion at Rest?**

- **No**
  - **Cl 2.2**
  - No
- **Yes**
  - Yes

**Diuretic Therapy**

- Furosemide
- Bumetanide
- Torsemide

**Vasodilator Therapy**

- Nitroglycerin
- Nitroprusside
- Nesiritide

**Inotropic Therapy**

- Dobutamine
- Milrinone

Page 2-124, Table 13
Chronic Meds in the midst of ADHF

In patients with HFrEF experiencing a symptomatic exacerbation of HF requiring hospitalization during chronic maintenance treatment with GDMT, it is recommended that GDMT be continued in the absence of hemodynamic instability or contraindications.

Initiation of beta-blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents. Beta-blocker therapy should be initiated at a low dose and only in stable patients. Caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course.
Chronic Meds in the midst of ADHF

- Caution with aggressive diuresis and ACEI/ARB/aldosterone antagonists
  - Caution with initiation or uptitration
  - Increases in SCr (~20%) from ACEI do not worsen outcomes
  - Significant worsening of renal function may warrant dose reduction or temporary discontinuation

- Caution with beta blockers
  - Do NOT discontinue BB in patients who are on dose before admission unless the recent initiation or up-titration was responsible for decompensation
  - Do NOT up-titrate or initiate until euvolemic
  - Consider holding if hemodynamically unstable or when receiving dobutamine therapy

- Caution with digoxin
Patient Case #5

72 YOM admitted for ADHF

HPI:
- Dyspnea on exertion (30 ft → 10 ft)
- Orthopnea (2 pillows → 4 pillows)
- Bilateral lower extremity edema (3+)
- Weight gain 13 kg = 30 lbs in 3 weeks
- Dietary nonadherence

PMH:
- IDCM, LVEF 25%
- Paroxysmal atrial fibrillation
- Hyperlipidemia
Patient Case #5

- **Pertinent Labs:**
  - BNP 2300 (0-50), K⁺ 4.9
  - BUN 32, SCr 2 (baseline 1.9 mg/dL)
  - AST 40, ALT 42, INR 1.3, PTT 42
- **BP 108/62 mmHg, HR 82 BPM, O₂ sat 95%**
- **Home Medications:**
  - carvedilol 12.5 mg 2 times/day
  - lisinopril 40 mg/day
  - furosemide 80 mg two times/day
  - spironolactone 25 mg/day
  - digoxin 0.125 mg/day
ADHF Patient Case #5

Which of the following is the best option for treating his ADHF?

A. Carvedilol 25 mg BID
B. Nesiritide 2 mcg/kg IVB, 0.01 mcg/kg/min
C. Furosemide 120 mg IV BID
D. Milrinone 0.5 mcg/kg/min
### ADHF Quadrants and Treatment

#### Congestion at Rest?

<table>
<thead>
<tr>
<th>Low Perfusion at Rest?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>I. Warm &amp; Dry</td>
<td>II. Warm &amp; Wet</td>
</tr>
<tr>
<td>CI 2.2</td>
<td>PCWP normal CI normal (compensated)</td>
<td>PCWP elevated CI normal</td>
</tr>
<tr>
<td>Yes</td>
<td>III. Cold &amp; Dry</td>
<td>IV. Cold &amp; Wet</td>
</tr>
<tr>
<td>PCWP low/normal CI decreased (Hypoperfused)</td>
<td>PCWP elevated CI decreased</td>
<td></td>
</tr>
<tr>
<td>Normal SVRI</td>
<td>High SVRI</td>
<td></td>
</tr>
</tbody>
</table>
# Hemodynamic Classification

<table>
<thead>
<tr>
<th>Subset</th>
<th>Hemodynamic Parameters</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - Warm and Dry (Normal)</td>
<td>PCWP 15-18 mmHg CI &gt; 2.2 L/min/m²</td>
<td>Optimize oral medications</td>
</tr>
<tr>
<td>II - Warm and Wet (Congestion)</td>
<td>PCWP &gt; 18 mmHg CI &gt; 2.2 L/min/m²</td>
<td>IV diuretics + IV vasodilators (venous)</td>
</tr>
<tr>
<td>III - Cold and Dry (Hypoperfusion)</td>
<td>PCWP 15-18 mmHg CI &lt; 2.2 L/min/m²</td>
<td>If PCWP &lt;15, IVF until 15-18 If PCWP ≥15, MAP &lt;50, IV dopamine If PCWP ≥15, MAP &gt;50, IV inotrope - or- IV vasodilator (arterial)*</td>
</tr>
<tr>
<td>IV - Cold and Wet (Congestion and Hypoperfusion)</td>
<td>PCWP &gt; 18 mmHg CI &lt; 2.2 L/min/m²</td>
<td>If MAP &lt;50, IV dopamine If MAP ≥50, IV inotrope -or- IV vasodilator (venous/arterial)*</td>
</tr>
</tbody>
</table>

*Compelling reason for inotrope = SBP < 90, symptomatic hypotension, or worsening renal function.
Diuretics in Hospitalized Patients

Patients with HF admitted with evidence of significant fluid overload should be promptly treated with intravenous loop diuretics to reduce morbidity.

If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose and should be given as either intermittent boluses or continuous infusion.

When diuresis is inadequate to relieve symptoms, it is reasonable to intensify the diuretic regimen using either:

a. higher doses of intravenous loop diuretics.

b. addition of a second (e.g., thiazide) diuretic.

**ADHF Guidelines: Diuretic Therapy**

- **Recommended** as an IV loop diuretic for patient admitted with fluid overload

- When response to diuretics is minimal, the following should be considered:
  - Fluid & sodium restriction,
  - Initiation of increased doses or continuous infusion of loop diuretic,
  - Addition of a second type of diuretic (metolazone or chlorothiazide), or
  - Ultrafiltration
Diuretic Therapy

- Furosemide 40 mg PO = furosemide 20 mg IV = bumetanide 1 mg IV/PO = torsemide 20 mg IV/PO
- Increase dose before increasing frequency of loop diuretic
  - Ceiling effect at ≈160–200 mg IV furosemide
- Add a second diuretic with a different mechanism of action
  - PO: HCTZ 12.5–25 mg/day, metolazone 2.5–5 mg/day
  - IV: CTZ 250–500 mg/day
    - gastrointestinal edema
    - expensive generic - reserve for NPO or refractory to PO
- Continuous infusion loop diuretic
  - Furosemide 0.1 mg/kg/hour IV doubled every 4–8 hours, maximum 0.4 mg/kg/hour
Patient Case #6

The patient is started on IV loop diuretics with minimal urine output (SCr 2.7, K+ 5.4). He is transferred to the CICU for diuretic-refractory ADHF.

- O₂ sat 87% on 4-L NC
- BP 110/75, HR 75 beats/min
- Plan is to give a 1 time dose of IV Chlorothiazide
Patient Case # 6
In addition to a one-time dose of IV CTZ, how else should DD’s ADHF be treated?

A. Nitroglycerin 20 mcg/minute
B. Sodium nitroprusside 0.3 mcg/kg/minute
C. Dobutamine 5 mcg/kg/minute
D. Milrinone 0.5 mcg/kg/minute
ADHF Quadrants and Treatment

Congestion at Rest?

PCWP

I. Warm & Dry
PCWP normal
CI normal
(compensated)
Optimize oral medications

II. Warm & Wet
PCWP elevated
CI normal
DIURETICS +/-
V Vasodilators (venous)

III. Cold & Dry
PCWP low/normal
CI decreased
(Hypoperfused)

IV. Cold & Wet
PCWP elevated
CI decreased

Normal SVRI
High SVRI

Yes

No

Low Perfusion at Rest?

CI

1.8

2.2

No

Yes

Inotropic Drugs
Dobutamine
Milrinone

Natriuretic Peptides
Nesiritide

or

Vasodilators
Nitroprusside
Nitroglycerin
If symptomatic hypotension is absent, intravenous nitroglycerin, nitroprusside or nesiritide may be considered an adjuvant to diuretic therapy for relief of dyspnea in patients admitted with acutely decompensated HF.
ADHF Guidelines: *Vasodilator Therapy*

In patients without symptomatic hypotension:

- **May be considered** in addition to IV loop diuretics to rapidly improve symptoms
- **May be considered** if persistent symptoms despite maximal loop diuretics and oral drug therapy

*When adjunctive therapy is required, IV vasodilators should be considered over inotropic drugs* (HFSA 2010)

- Administration of IV vasodilators in HFpEF should be done *with caution* because these patients are typically more volume sensitive (ACCF/AHA 2013)
# Vasodilator Therapy

<table>
<thead>
<tr>
<th>Clinical effects</th>
<th>NTP</th>
<th>Nesiritide</th>
<th>NTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilator (venous and arterial)</td>
<td>Vasodilator (venous and arterial)</td>
<td>Vasodilator (venous &gt; arterial)</td>
<td></td>
</tr>
<tr>
<td>Warm &amp; wet, Cold &amp; wet alternate to inotropes, HTN Crises</td>
<td>Warm &amp; wet, Cold &amp; wet alternate to inotropes</td>
<td>Warm &amp; wet, ACS, HTN Crises</td>
<td></td>
</tr>
<tr>
<td>&lt; 10 minutes</td>
<td>20 minutes</td>
<td>1-4 minutes</td>
<td></td>
</tr>
<tr>
<td>Cyanide (hepatic), thiocyanate (renal)</td>
<td>NP receptor C (no renal/hepatic adjustment)</td>
<td>Inactive metabolites in urine</td>
<td></td>
</tr>
</tbody>
</table>

Page 2-128, Table 17.
Patient Case #7

The patient initially responds with 2 liters of urine output overnight and weight decreased by 1 kg next day.

However, by day 5:

- UOP diminished
- Serum creatinine has risen to 4.3 mg/dL
- Drowsy & confused mental status
- Cool, cyanotic extremities
- BP 89/58, HR 98
ADHF Guidelines: Invasive Monitoring

- Routine use of hemodynamic monitoring with invasive IV lines (e.g. pulmonary artery catheter) is not recommended
- Should be considered:
  - Unclear volume status
  - Hypotension (SBP<80)
  - Worsening renal function during therapy
  - Refractory to initial treatment
Patient Case #7

A Swan-Ganz hemodynamic catheter is placed:

- **Pulmonary capillary wedge pressure (PCWP)**
  - 30 (8-12 mmHg, 15-18 mmHg in HF)
- **Cardiac index (CI)**
  - 1.5 (2.8-3.6 L/min/m²)
- **Systemic vascular resistance (SVR)**
  - 2650 (800-1200 dynes/sec/cm⁻⁵)
Patient Case # 7

Which one of the following is the most appropriate medication now?

A. Milrinone 0.2 mcg/kg/min
B. Dobutamine 5 mcg/kg/min
C. Nitroglycerin 20 mcg/min
D. Phenylephrine 20 mcg/min
ADHF Quadrants and Treatment

Congestion at Rest?

Low Perfusion at Rest?

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
</table>
| No | I. Warm & Dry  
PCWP normal  
Cl normal  
(compensated)  
Optimize oral medications |
| Yes | II. Warm & Wet  
PCWP elevated  
Cl normal  
Diuretics +/-  
IV Vasodilators (venous) |
| No | III. Cold & Dry  
PCWP low/normal  
Cl decreased  
(Hypoperfused)  
Inotropic Drugs  
Dobutamine  
Milrinone |
| Yes | IV. Cold & Wet  
PCWP elevated  
Cl decreased  
Normal SVRI  
High SVRI  
Vasodilators  
Natriuretic Peptides  
Nesiritide  
or  
Vasodilators  
Nitroprusside  
Nitroglycerin |
## Hemodynamic Classification

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<td>IV - Cold and Wet (Congestion and Hypoperfusion)</td>
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</tr>
</tbody>
</table>

*Compelling reason for inotrope = SBP < 90, symptomatic hypotension, or worsening renal function.
**ADHF Guidelines: Inotropic Therapy**

- **May be considered** in patients with *diminished peripheral perfusion or end-organ dysfunction*, particularly if:
  - Marginal systolic blood pressure (< 90 mmHg),
  - Symptomatic hypotension exists despite adequate filling pressures, or
  - Unresponsive to, or intolerant of, IV vasodilators

- **May be considered** in similar patients with fluid overload if they respond poorly to IV diuretics or have worsening renal function.
# Inotropic Therapy

<table>
<thead>
<tr>
<th></th>
<th>Dobutamine</th>
<th>Milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>β-agonist, slight peripheral vasodilation</td>
<td>PDE inhibitor, moderate peripheral vasodilation, <strong>inodilator</strong></td>
</tr>
<tr>
<td>Typical dose</td>
<td>5 mcg/kg/min</td>
<td>No bolus, 0.1-0.375 mcg/kg/min</td>
</tr>
<tr>
<td>Indication</td>
<td>ADHF Cold &amp; Wet –or- Cold &amp; Dry (if PCWP &gt; 15)</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>2 minutes</td>
<td>1 hour, 2-3 hours if HF or CrCl &lt; 50 ml/min</td>
</tr>
<tr>
<td>Other comments</td>
<td>Consider if hypotensive.</td>
<td>Consider if receiving a β-blocker.</td>
</tr>
</tbody>
</table>

Page 2-127, Table 16
## Inotropic Support in Refractory HF

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Until definitive therapy (Revascularization, MCS, heart transplantation) patients with cardiogenic shock should receive temporary inotropic support to maintain systemic perfusion and preserve organ function</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Continuous inotropic support is reasonable as “bridge therapy” in patients refractory to GDMT and device therapy who are eligible and waiting for MSC or transplant.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Short term, continuous inotropic support may be reasonable in those with severe systolic dysfunction who present with low BP and significantly depressed cardiac output to maintain systemic perfusion</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Long term, continuous inotropic support may be considered as palliative therapy for symptom control in select patients who are not eligible for MCS or transplant</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Long term or intermittent use of inotropes in patients without severe systolic dysfunction, low output, or impaired output is potentially harmful</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>

Vasopressin Antagonists

- For managing hyponatremia
  - Corrects euvolemic or hypervolemic sodium
  - No status improvement (clinical, mortality, etc.)
  - Hyponatremia resolves after therapy

- Tolvaptan
  - 15 mg PO daily; titrated to 30-60 mg as needed
  - Binds to $V_2$ receptor, in the renal tubule (water reabsorption regulation)
  - Initiate in hospital
  - CI with CYP 3A4 inhibitors

- Role in long term HF management is unclear

### Antiarrhythmic Drug Classes

| Class I Na\(^+\) channel blockers | IA: Quinidine, procainamide, disopyramide |  | Ia: A & V  
|                                  | IB: Lidocaine, mexiletine                  |  | Ib: V  
|                                  | IC: Propafenone, flecainide, morizicine    |  | Ic: SVT & VT |
| Class II β-blockers              | Metoprolol, esmolol, atenolol              |  | A & V  |
| Class III K\(^+\) channel blockers | Amiodarone, sotalol, dofetilide, ibutilide |  | A & V  |
| Class IV Ca\(^{2+}\) channel blockers | Diltiazem, verapamil                      |  | A & V  |
Increased mortality in post MI survivors

- Quinidine
  - N/V/D (30%), TdP
  - DI with warfarin, digoxin
  - Use with AV nodal blocking agent

- Procainamide
  - Lupus-like syndrome, TdP, ADHF
  - Adjust dose in renal/hepatic dysfunction

- Disopyramide
  - Useful in vagally mediated PSVTs
  - Anticholinergic effects, TdP, ADHF
Class IB Antiarrhythmics
Ventricular Arrhythmias

- Lidocaine
  - IV only
  - Used second line to amiodarone for VT
  - Dose reduce in hepatic and renal dysfunction

- Mexilitine
  - CNS Side effects: tremor, dizziness, ataxia, nystagmus
Class IC Antiarrhythmics
Supraventricular Arrhythmias (Mainly)

- Only use if no structural heart disease
  - Increased mortality in HF, CAD, LVH, valvular disease

- Propafenone
  - ADHF, bronchospasm (beta-blocking properties)
  - Digoxin ↑ 70%, warfarin ↑ 50%

- Flecainide
  - ADHF
  - Digoxin ↑ 25%
Class III Antiarrhythmics
Atrial and Ventricular Arrhythmias

- **Sotalol**
  - AF and VT maintenance alone (not conversion)
  - CI in ClCr < 40ml/min (AF), QTc > 440 msec, LVEF <40%

- **Dofetilide**
  - AF conversion and maintenance (not VT)
  - CI in ClCr<20 ml/min, QTc >440 msec
  - Metabolized by 3A4, secreted by kidney

- **Amiodarone**
  - AF and VT conversion and maintenance
  - Multiple AEs - PFTs, TFTs, LFTs, skin, eyes
  - Multiple DIs - warfarin, digoxin, statins (CYP3A4)

* Hospitalization required. QTc 2-3 hrs after 1st 5 doses. Discontinue if QTc> 500 msec.
Class III Antiarrhythmics
Atrial and Ventricular Arrhythmias

- Ibutilide
  - AF conversion only
  - CI QTc > 440 msec, LVEF <30%
  - Metabolized by 3A4

- Dronedarone
  - AF (not permanent AF) maintenance
  - CI QT >500 msec, severe hepatic disease, AVB or HF <50, NYHA Class IV or NYHA Class II-III with recent hospitalization for HF decompensation, QTc >500 msec
  - Metabolized by 3A4, P-gp inhibitor
## ACLS - VF or Pulseless VT

### Algorithm for Pulseless Ventricular Tachycardia or Fibrillation

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.</td>
<td>DEFIBRILLATION (Shock #1)</td>
</tr>
</tbody>
</table>
| 4.   | CPR 2 minutes  
Establish IV/IO access |
| 5.   | Reassess rhythm – **Shock if appropriate and proceed**  
If no sign of ROSC, go to Asystole/PEA algorithm  
If ROSC, initiate **post-cardiac arrest care** |
| 6.   | DEFIBRILLATION (Shock #2) |
| 7.   | CPR 2 minutes  
**Epinephrine** 1 mg IV/IO every 3–5 minutes  
**Vasopressin** 40 units IV/IO × 1 (replaces first or second epinephrine dose)  
Consider advanced airway, capnography |
| 8.   | Reassess rhythm – **Shock if appropriate and proceed**  
If no sign of ROSC, go to Asystole/PEA algorithm  
If ROSC, initiate post-cardiac arrest care |
| 9.   | DEFIBRILLATION (Shock #3) |
| 10.  | CPR 2 minutes  
**Amiodarone**b 300 mg IV/IO × 1; may repeat at 150-mg bolus x 1  
**Reversible causes** of the event should be identified and correctedc |
### Algorithm for Asystole or PEA

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
</table>
| 11. | **CPR 2 minutes**  
IV/IO access  
**Epinephrine** 1 mg IV/IO every 3–5 minutes  
**Vasopressin** 40 units IV/IO × 1 (replaces first or second epinephrine dose)  
Consider advanced airway, capnography |
| 12. | Reassess rhythm – **Shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF**  
If no sign of ROSC, proceed |
| 13. | **CPR 2 minutes**  
Treat reversible causes^b^ |
| 14. | Reassess rhythm – **Shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF**  
If no sign of ROSC, continue steps 11–14  
If ROSC, initiate **post-cardiac arrest care** |

^a^Hypovolemia, hypoxia, hydrogen ion (acidosis), hypo-/hyperkalemia, hypothermia, tension pneumothorax, tamponade (cardiac), toxins, thrombosis (pulmonary), thrombosis (coronary).
Therapeutic Hypothermia

- Post Cardiac Care Algorithm
- Hypothermia is the only intervention shown to improve neurological recovery
- Studies show good outcomes for patients whose bodies were cooled to 32° to 34° C for 12 - 24 hours
- 20 to 50% had good neurological function one year later
ACLS- Symptomatic Bradycardia

- If stable, observe
- If **unstable**, atropine
  - 0.5 mg q 3-5 minutes
  - Max dose 3 mg
- If atropine fails-
  - Transcutaneous pacing
  - Dopamine 2-10 mcg/kg/min
  - Epinephrine 2-10 mcg/min
ACLS-Symptomatic Tachycardia

If rhythm is Regular (Narrow Complex) ➔ SVT

- If unstable, synchronized cardioversion
- If stable, QRS wide or narrow?
- If narrow, use vagal maneuvers +/- adenosine
  - Rapid IV push followed by 20 ml saline flush
  - Elevate extremity
  - Larger doses in theophylline, caffeine, or theobromine
  - Limit to 3 mg in those taking dipyridamole or carbamazepine and in heart transplant or central line
  - Use caution in severe CAD
  - Do not give in asthma
  - Do not give in unstable or irregular wide polymorphic
- CCBs and BBs – caution in WPW
ACLS- Symptomatic Tachycardia

If rhythm is Irregular (narrow complex) \( \Rightarrow \) AF

- Focus on control of ventricular rate
  - Verapamil, diltiazem, BB, +/- dig
  - Rate acceptable if asymptomatic and < 110 bpm

- If unstable, synchronize cardioversion
  - If > 48 hours and stable, do not cardiovert unless TEE shows absence of left atrial clot
  - Risk of thromboembolic event is greatest within the first 10 days (ANTICOAGULATION is imperative)
Pharmacologic Cardioversion

- Drugs used to cardiovert (for up to 7 days):
  - Proven efficacy: *DIP-AF
    - flecainide, dofetilide, propafenone, ibutilide, or amiodarone
  - Less effective: disopyramide, quinidine, and procainamide
  - NOT effective (harmful): digoxin, sotalol

- Drugs used to cardiovert (>7 days):
  - Proven efficacy: dofetilide, amiodarone, ibutilide
Ventricular Arrhythmias (VT):

**Nonsustained VT (NSVT)**
- Three or more consecutive PVCs
- Last <30 seconds
- Terminates spontaneously
  - Asymptomatic: Usually no treatment required
  - Symptomatic: Beta blocker or amiodarone (esp. if EF < 40%)

**Sustained VT**
- Three or more consecutive PVCs
- Lasts > 30 seconds
- Or < 30 sec, but, requires termination because of hemodynamic compromise
  - Implantable Cardioverter defibrillator (ICD)
  - If VT reoccurs after placement or if ICD N/A
    - Ablation, Sotalol, Beta blocker plus amiodarone, amiodarone, correct underlying cause
ACLS- Stable Wide Complex Tach (QRS > 120 msec) ➔ VT or TdP

- Consider adenosine if regular and monomorphic
  - Adenosine can slow rhythm for diagnosis
  - If SVT with aberrancy, can convert
- IV amiodarone (or sotalol), procainamide
  - Lidocaine is second line
  - Avoid procainamide and sotalol if QT prolonged
Torsades de pointes

- Primarily when QTc > 500 msec
- Withdrawal of QT-prolonging medications and correction of low Mg$^{2+}$ and K$^+$
  - Class I (IA and IC) and III agents
  - Assess for drug interactions
  - Assess for QT prolonging drugs
- If unstable, DCC
- If stable, IV magnesium
Chronic Ventricular Arrhythmias

- The risk of cardiac events is often dictated by the underlying heart disease rather than the arrhythmia itself

No SHD
- Asymptomatic
  - Reassurance
- Symptomatic
  - BB
  - Non-DHP CCB
  - Class IC drugs/AADs
  - Catheter ablation
  - ICD for LVEF < 40%

With SHD
- SVT= ↑mortality when EF ≤40%
  - Assess LV function 40-90 days after MI/PCI
- ICD placement
  - Mortality benefit > AADs
  - ↑ICD shocks=↑mortality
  - Catheter ablation/ AADs to reduce shocks

Implantable Cardioverter Defibrillator

- **Primary prevention of SCD**
  - Previous MI, at least 40 d prior and EF \( \leq 35\% \)
  - Nonischemic dilated cardiomyopathy and EF \( \leq 35\% \)
  - Syncope with heart disease and inducible VT/VF
  - High risk for VT/VF; congenital long QT, torsades
e
  - Must have > 1 yr survival expectation

- **Secondary prevention of SCD**
  - Previous resuscitated VF/VT, sustained VT with CHD
  - Must be on optimal chronic meds (BB, ACEI)
  - Must have >1 yr survival expectation
**General AAD Considerations with ICD**

- **β-Blockers**
  - Considered mainstay
  - Effective in suppressing ventricular ectopic beats and reducing SCD across a broad spectrum
  - DOC in LQTS and CPVT

- **Amiodarone**
  - No better than ICD in reducing SCD as a lone agent; no mortality benefit but at least safe in HFrEF
  - Can be used to treat symptomatic NSVT if β-blockers not effective when ICD not indicated
  - Can be used in combination with β-blockers to decrease ICD firing

- **Sotalol**
  - No mortality advantage
  - Can suppress VT and be used to decrease ICD firing
  - Greater proarrhythmic potential; avoid in low EF; renal dosing required
Patient Case #8

68 YOM admitted for syncope

- HPI: presyncopal syndrome
  - Seeing black spots & dizziness, passing out
- In hospital on telemetry:
  - Sustained ventricular tachycardia (VT)
- Vital signs: BP 120/75, HR 80 BPM
- Labs: BUN 30 mg/dl, SCr 2.2 mg/dl (~ ClCr 30 mL/min)
Patient Case #8

Past Medical History
- HF NYHA class III
  - LVEF 30%
- MI x2
- HTN x20 yrs
  - Left ventricular hypertrophy
- Diabetes
  - Nephropathy

Medications
- Lisinopril 5 mg QD
- Furosemide 20 mg BID
- Metoprolol 25 mg BID
- Digoxin 0.125 mg QD
- Glyburide 5 mg QD
- Aspirin 81 mg QD
Patient Case #8

Which is the best drug therapy to initiate for treatment of sustained VT?

A. Amiodarone 150mg IV over 10min, 1mg/min x 6 hrs, then 0.5mg/min
B. Sotalol 80mg BID, titrated to QTc ~ 450 msec
C. Dofetilide 500mcg BID, titrated to QTc ~ 450 msec
D. Procainamide 20mg/min, max 17mg/kg
Heart Failure (HFrEF)
- Avoid IA and IC agents
- Atrial arrhythmias – amiodarone, dofetilide
- Ventricular arrhythmias - amiodarone

Acute MI
- Avoid IA and IC agents
- Dofetilide – neutral effect on mortality in LV dysfunction post-MI
Drug Induced Arrhythmias

- Drug-induced QT prolongation
  - Ensure proper renal/hepatic dosing adjustments.
  - Review electrolyte abnormalities and thyroid function tests.
  - Ensure that all electrolytes are maintained at critical levels: $K^+$ greater than 4 mmol/L and less than 5 mmol/L, $Mg^{++}$ greater than 2 mg/dL.
  - Ensure that all ECG parameters are within normal limits (e.g., QT interval less than 500 milliseconds).

- Bradycardia or atrioventricular block
  - β-Blocker, calcium channel blocker, digoxin
  - Administer antidote if appropriate (e.g., calcium for calcium channel blocker toxicity).

- Review for drug interactions
  - Antiarrhythmic agents have drug-drug interactions that may cause significant outcomes.
Hypertensive Crises


Hypertensive Crises

Emergency

- Severe elevations in blood pressure (e.g. > 180/120 mmHg) with the presence of acute or ongoing target organ damage (TOD)
- Requires immediate blood pressure lowering to prevent or limit further TOD

Urgency

- Accelerated, malignant, or perioperative hypertension in the absence of symptoms or new or progressive target-organ damage
- Short term risk not as high, so requires BP reduction over several days to weeks
Crisis Considerations

- It is the presence of acute TOD that distinguishes an emergency from urgency and determines the treatment approach.
  - NOT the elevation of the blood pressure
  - The relative risk and rate of increase in blood pressure is more important than the actual blood pressure.

- There is no “typical” presentation;
  - Emergent HTN can present with symptoms ranging from HA, visual disturbances, confusion, weakness, and seizures, to chest pain and SOB.

- Acute target-organ damage
  - hypertensive encephalopathy, intracranial hemorrhage, or other acute neurologic deficit; UA or acute MI; acute HF; pulmonary edema; aortic dissection; retinopathy or papilledema; decreased urine output or acute renal failure; eclampsia
Treatment Goals

Emergency
- Lower MAP by no more than 20-25% (within 30 minutes to 1 hour, then toward 160/100-110 mm Hg within 2-6 hours)
- 10-15% ↓ DBP is thought by some to be an approach
- BP should be monitored every 5-10 minutes until goal MAP is reached and life-threatening TOD resolves
- Failure to lower BP (>10 mm Hg) within ~60 minutes, rethink strategy
- IV medications

Urgency
- Lower arterial pressure to goal or near goal within 24 hours or longer
- Oral medications can be used
Patient Case #11

68-year old man

- PMH: ESRD on HD, HTN, CAD s/p MI, moderately depressed LVEF, GERD
- Presents with acute-onset SOB and CP
- After HD, had large BBQ meal with salt & smoked cocaine-laced marijuana
- Medication noncompliance for 2 days and 2 kg weight gain within 24hrs
- Worsening orthopnea, acute chest tightness, nausea, pain 7/10
Patient Case #11

Presents to the emergency dept.

- BP: 250/120mmHg
- PE: crackles ½ way up lungs
- CXR: bilateral fluffy infiltrates, cephalization
- ECG: sinus tachycardia, HR 122, ST depressions in leads II, III, AVF
- Labs: BUN 48, SCr 11.4; BNP 2350, Trop 1.5,
- Admitted for hypertensive emergency
Patient Case #11

Which one of the following is the best medication to manage this crisis?

A. IV NTG 5mcg/min, titrated to 25% reduction in MAP
B. Labetolol 2mcg/min, titrated to 50% reduction in MAP
C. Sodium nitroprusside 0.25mcg/kg/min, titrated to 25% reduction in MAP
D. Clonidine 0.1mg PO every 2 hrs PRN, titrated to 50% reduction in MAP
<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Preferred Intravenous Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute aortic dissection</td>
<td>Labetalol, esmolol alone or in combination with nicardipine, clevidipine, or nitroprusside (β-Blocker must precede other agents) (Avoid hydralazine)</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>Nitroprusside, nitroglycerin, nesiritide, or ACE inhibitors in combination with diuretics if pulmonary edema (Note: Avoid β-blockers)</td>
</tr>
<tr>
<td>Acute intracerebral hemorrhage/acute ischemic stroke</td>
<td>Labetalol, nicardipine</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>β-Blocker in combination with nitroglycerin If heart rate &lt; 70 beats/minute, consider nicardipine or clevidipine</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Nesiritide, nitroglycerin, nitroprusside</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Fenoldopam, nicardipine, clevidipine</td>
</tr>
<tr>
<td>Eclampsia or preeclampsia</td>
<td>Hydralazine, labetalol, nicardipine</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>Nitroprusside, labetalol, fenoldopam, nicardipine</td>
</tr>
<tr>
<td>Perioperative hypertension</td>
<td>Clevidipine, esmolol, nicardipine, nitroglycerin, nitroprusside (Note: Avoid unopposed β-blockade)</td>
</tr>
<tr>
<td>Sympathetic crisis</td>
<td>Nicardipine, fenoldopam, clevidipine, phentolamine (Note: Avoid unopposed β-blockade)</td>
</tr>
</tbody>
</table>
# Hypertensive Emergency

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside*</td>
<td>Cyanide/thiocyante toxicity Cl: Renal/hepatic failure</td>
</tr>
<tr>
<td>Esmolol and Labetalol</td>
<td>Bronchospasm, HF exacerbation, bradycardia/heart block</td>
</tr>
<tr>
<td>Nicardipine*</td>
<td>Reflex tachycardia, N/V Caution: Angina/MI, acute HF, ↑ ICP</td>
</tr>
<tr>
<td>Nitroglycerin*</td>
<td>Headache, nausea, tachyphylaxis</td>
</tr>
<tr>
<td>Hydralazine*</td>
<td>Reflex tachycardia, HA, variable duration</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>Renal insufficiency/failure, hyperkalemia Cl: Pregnancy, renal artery stenosis</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Headache, flushing, cerebral ischemia</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>Renal/hepatic failure, geriatrics not studied, Caution: HF, β-blocker use, etc.</td>
</tr>
</tbody>
</table>

*Caution: ↑ ICP

Page 2-144, Table 24.
Questions?

It will all be worth it in the end.