Pharmacotherapy for Post-Myocardial Infarction Patient

Manouchkathe Cassagnol, Pharm.D., CGP, BCPS
Assistant Clinical Professor of Clinical Pharmacy Practice
College of Pharmacy and Allied Health Professions
St. John’s University
Clinical Coordinator of Internal Medicine Pharmacotherapy
Long Island Jewish Medical Center
cassagnm@stjohns.edu
718-990-5374

Presentation Objectives

Pharmacist Educational Objectives
- Describe the post myocardial infarction (MI) patient and their treatment options
- List pharmacotherapy used in the treatment of the post-MI patient

Pharmacy Technician Educational Objectives
- Describe the treatment options for the post-MI patients
- List the drug products used in the treatment of post-MI patient
What is Acute Coronary Syndrome (ACS)

Atherosclerosis of the epicardial vessels

- Chronic Stable Exertional Angina Pectoris
- Coronary Artery Vasospasm

Unstable Angina Acute Coronary Syndrome (ACS)

- non-ST-segment elevation myocardial infarction (NSTEMI)
- ST-segment elevation myocardial infarction (STEMI)

Myocardial infarction diagnosed by biomarkers only
Definition of ACS

**UNSTABLE ANGINA**
Non occlusive thrombus, Non specific ECG changes, Normal cardiac enzymes

**NSTEMI**
Occluding thrombus causes damage, ST depression ± T wave inversion, Elevated cardiac enzymes

**STEMI**
Complete thrombus occlusion, ST elevation or new LBBB, Elevated cardiac enzymes

---

Acute Coronary Syndromes (ACS)

![Diagram showing the relationship between different types of ACS](image-url)
Build-up of Plaque in Arterial Walls

- Hardening of the arteries
  - Result of plaque that has built up along inside of artery walls
- Can occur in any artery in body
  - Coronary arteries: Coronary artery disease (CAD)
- Can lead to:
  - Myocardial infarction
  - Transient ischemic attack or stroke
  - Pain in area of body deprived of oxygen-rich blood

Risk Factors for ACS

<table>
<thead>
<tr>
<th>Causative Risk factors</th>
<th>Conditional Risk Factors</th>
<th>Predisposing Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>High triglycerides</td>
<td>Obesity/overweight</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Small LDL particles</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>High total and LDL cholesterol</td>
<td>Lipoprotein (a)</td>
<td>Male gender</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>Elevated homocysteine</td>
<td>Family history of CAD</td>
</tr>
<tr>
<td>Type 1 and 2 DM</td>
<td>C-reactive protein</td>
<td>Socioeconomic factors</td>
</tr>
<tr>
<td></td>
<td>Plasminogen activator</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>inhibitor-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated fibrinogen</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac Interventions

Clinical Presentation to Acute Care Setting

Percutaneous Coronary Intervention

Fibrinolysis

Overview of Stent Technology

Bare Metal Stents
- No Medicine
- \(\downarrow\) Stenosis & thrombosis

Drug Eluting Stents
- Antiproliferative agent
- \(\downarrow\) Stenosis and early thrombosis; \(\uparrow\) late thrombosis
Risk of Rehospitalization in MI

- Median risk-standardized 30-day readmission rate for acute MI ~20%
- Transition of care services present opportunity to improve rate
- Acute care settings are expected to initiate these services
- Patient Protection and Affordable Care Act will financially penalize institutions

www.ahrq.gov

Long term Pharmacotherapeutic Treatment Options for Post-MI patients

<table>
<thead>
<tr>
<th>Therapeutic Category</th>
<th>Drug/Drug Class</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>Aspirin</td>
<td>Ø cyclooxygenase and synthesis of platelet thromboxane $A_2$</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Selective, irreversible inhibition of adenosine diphosphate (ADP) binding to platelet receptor (P2Y$_{AC}$ ADP receptor)</td>
</tr>
<tr>
<td></td>
<td>Prasugrel</td>
<td>ADP receptor</td>
</tr>
<tr>
<td></td>
<td>Ticagrelor</td>
<td>Direct inhibition of P2Y12 ADP receptor</td>
</tr>
</tbody>
</table>
Features of Clopidogrel

- **LD**: 300-600mg; **MD**: 75mg/day
- **Indication**: reduction of atherothrombotic events as follows: recent MI, recent stroke, PAD, ACS
- **Contraindications**: Active Bleed
- **Drug Interactions**: atorvastatin (theoretical), proton pump inhibitors
- **Adverse Drug Reactions**: bleeding, TTP, hepatic function impairment.

Clopidogrel: Metabolism Specifics

- **Prodrug** → **2-oxo-clopidogrel** → hydrolysis
- Inhibition reaches steady state 3 – 7 days
- Average steady state inhibition level 40 – 60%
- Platelet aggregation and bleeding return to baseline in 5 days

Prescribing Information. Plavix® Bristol-Myers Squibb 2005
Thrombotic Thrombocytopenic Purpura (TTP)

- Disorder of blood coagulation system
- Signs and symptoms
  - Neurologic symptoms (bizarre behavior, AMS, HA, stroke) 65%
  - Kidney failure 46%
  - Fever 33%
  - Thrombocytopenia
  - Microangiopathic hemolytic anemia
- Hemolysis, end-organ damage
  → plasmapheresis

Contribution CYP450 3A4 Activity to Clopidogrel Resistance

- Interindividual variation in platelet inhibition
- Low responders or nonresponders
- Possible mechanistic explanations
  - Drug-drug interactions
  - Platelet reactivity before clopidogrel dosing
  - Platelet $P2Y_{AC}$ receptor genetic polymorphism
  - Defects in signaling pathways
  - Low baseline 3A4 activity

Atorvastatin Reduces the Ability of Clopidogrel to Inhibit Platelet Aggregation


- Clopidogrel is an inactive prodrug
  - 85% hydrolyzed to an inactive metabolite
  - 15% via CYP 3A4 to active metabolite
- Atorvastatin is a CYP 3A4 substrate
- Observed that clopidogrel less effective with coadministration of atorvastatin

FDA Advisory Statement on Proton Pump Inhibitors

- Many proton inhibitors undergo 2C19 metabolism
- Competitive inhibition
- Most studies site omeprazole with greatest risk
- Least risk may be with pantoprazole
- May use in patient with increased risk of gastrointestinal bleed

Limitations of Clopidogrel

- Delayed onset
- Modest antiplatelet effect
- Variability in response

CLARITY-TIMI 28

- N=3491 STEMI patients
- Clopidogrel 300 mg then 75 mg + aspirin 75 -162 mg
- Primary composite endpoint: occluded infarct-related artery on angiography or death or recurrent MI before angiography
- 31% reduction in primary endpoint additional benefit in patient undergoing PCI

Sabatine et al. NEJM.2005;352:1179
**CURE**

- N=12,562 NSTEMI
- Clopidogrel 300mg then 75mg daily + aspirin
- Primary composite outcome: CV death, nonfatal MI or stroke
- 18.4% relative risk reduction in treatment group

Yusuf et al. NEJM.2001;345:494

---

**CREDO**

- N=2,116 ACS undergoing PCI
- Clopidogrel 300mg then 75mg daily + aspirin
- Primary composite outcome: CV death, nonfatal MI or stroke
- 26.9% relative reduction of death and 3% absolute risk reduction (NNT= 33)

Yusuf et al. NEJM.2001;345:494
CURRENT-OASIS 7

- N= 25,000 ACS patients
- Clopidogrel (600mg day1, 150mg 6d, 75 mg vs. clopidogrel 300 then 75mg/d)
- Aspirin low dose vs. high dose
- Primary Outcome: reduction in CV death, MI, or stroke at 30 days
- 13% RRR in primary outcome and 46% RRR stent thrombosis

Mehta S. NEJM 2010;363:930-42

Features of Prasugrel

- LD: 60mg; MD: 10mg or 5 mg
- **Indication**: reduction of atherothrombotic events in patients ACS undergoing PCI
- **Caution**: < 60kg, >75 y/
- **Adverse Drug Reactions**: Fatal and non fatal bleeding
Prasugrel: Metabolism Specifics

- Prodrug (thienopyridine)
- CYP2B6, 2C9, 2C19
- Single step metabolism
- Active metabolite half life 7 hours

Prescribing Information. Prasugrel® Eli-Lilly 2011

TRITON-TIMI 38

- N=13,608 ACS patients
- 60 mg prasugrel then 10 mg/d vs. clopidogrel 300mg then 75mg
- Primary composite endpoint: CV death, non fatal MI, or nonfatal stroke
- 19% lower incidence in primary outcome in study group
- Lower incidence of MI, urgent target vessel revascularization, and stent thrombosis

Wiviott S. NEJM 2007;357:2001
Features of Ticagrelor

- **LD**: 180mg; **MD**: 90mg twice daily
- **Indication**: reduction of atherothrombotic events in ACS patients undergoing PCI
- **Drug interaction**: simvastatin or lovastatin >40mg, digoxin
- **Contraindication**: >aspirin 100mg
- **Adverse Drug Reactions**: Fatal and non fatal bleeding

Ticagrelor: Metabolism Specifics

- Cyclopentyltriazolopyrimidine
- Does not need hepatic activation
- **CYP3A4/5**: inhibits Pgp, CYP 3A4, 2C9
- Active metabolite half life 7-9 hours
PLATO

- N=18,624 ACS patients ± STE
- 180 mg ticagrelor then 90 mg/bid vs. clopidogrel 300-600 mg then 75mg
- Primary composite endpoint: CV death, non fatal MI, or nonfatal stroke
- 16% lower incidence in primary outcome in study group (NNT=52.6)
- Lower incidence of MI, urgent target vessel revascularization, and stent thrombosis

Wiviott S. NEJM 2009;361:1045

Dual Antiplatelet Therapy

- Use aspirin up to 325mg orally
- Use with P2Y12 receptor antagonist
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
- Reduce risk of late stent thrombosis (DES)

ACC/AHA 2009 Guideline Update for the Management of Patients with UA/STEMI/NSTEMI/PCI available at www.americanheart.org
Clinical Predictors of DES Thrombosis

- Advanced age
- ACS
- Diabetes
- Low ejection fraction
- Prior brachytherapy
- Renal failure

Factors Related to Premature Discontinuation

- Cost of P2Y12 antagonist
- Older age
- Lower socioeconomic status
- Lower education level
- Not receiving proper education prior to discharge
- Going home from hospital
Prevention of Premature Discontinuation

- Assess need for DES placement
- Provide continuous and comprehensive education
- Do not stop antiplatelet minor procedures
- Delay procedures
- Continue aspirin through procedures
- Bridging not indicated

AHA/ACC/SCAI/ACS/ADA Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients with Coronary Artery Stents www.americanheart.org

Patient Assistance Program

- Uninsured
- Low income
- Medicare D

- 90 days clopidogrel for 1 year www.bmspaf.org
- 120 days prasugrel for 1 year www.lillytruassist.com
- Ticagrelor at no cost for 1 year www.azandme.com
ACCF/AHA Recommendations for Antiplatelet Therapy UA/NSTEMI

- Aspirin for all patients
- Invasive strategy (PCI)
  - Clopidogrel 300-600 mg LD then 75 mg for 1 year OR
  - Clopidogrel 600 mg then 150mg for 6 days followed by 75 mg/daily (Class IIb)
  - Prasugrel 60mg LD then 10 mg for 1 year
- Low risk aspirin + clopidogrel for at least 1 month
- CABG d/c clopidogrel 5 days; prasugrel 7 days prior

ACCF/AHA 2011 Guideline Update for the Management of Patients with UA/NSTEMI available at www.americanheart.org

ACCF/AHA Recommendations for Antiplatelet Therapy STEMI/PCI

- Aspirin for all patients (81-325mg)
- non-ACS
  - Clopidogrel 600 mg LD then
  - 75 mg daily ≥ 1 yr DES and ≥1 month BMS (2 wks bleed)
- ACS (BMS or DES) for ≥ 1 year
  - Clopidogrel 600 mg LD then 75mg
  - Prasugrel 60mg LD then 10 mg
  - Ticagrelor 180 mg LD then 90 mg twice daily
- DAPT > 12 month in DES

### Pharmacotherapeutic Treatment Options for Post-MI patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug(s)/Drug Class</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihyperlipidemic</td>
<td>Statins</td>
<td>Competitive inhibitor of HMG-CoA reductase → last regulated step in synthesis of cholesterol; Up-regulating LDL-receptor activity; Reduce entry LDL into circulation</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Angiotensin-converting Enzyme Inhibitors (ACEI) &amp; Angiotensin receptor Blockers (ARB)</td>
<td>Directly Ø ACE → Ø conversion of ATI to ATII → vasoconstriction &amp; aldosterone secretion → ↓ BP Directly Ø ATII receptors → vasoconstriction &amp; aldosterone secretion → ↓ BP</td>
</tr>
<tr>
<td>Antianginal/Anti-Ischemic Therapy</td>
<td>Beta-blockers (BB)</td>
<td>Ø β-receptors → ↓ inotropic state, sinus rate, AV conduction, blood pressure → ↓ MVO2 demand &amp; LV perfusion</td>
</tr>
</tbody>
</table>

ATI = angiotensin I; ATII = angiotensin II; cGMP = cyclic guanosine monophosphate; AV = atrioventricular; MVO2 = myocardial oxygen demand; LV = left ventricular;
Features of HMG CoA-Reductase Inhibitors

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hyperlipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contra-indication</td>
<td>Active liver disease or unexplained persistent elevated LETs; pregnancy (stop if LETs 3X ULN)</td>
</tr>
<tr>
<td>Adverse Effect</td>
<td>HA, insomnia, paresthesia, peripheral neuropathy, abnormal dreams, pancreatitis, hepatitis, flatulence, gynecomastia, myopathy, rhabdomyolysis</td>
</tr>
<tr>
<td>Drug/Food Interactions</td>
<td>ETOH,azole antifungals, cyclosporin, erythromycin, fibric acid derivatives, niacin, oral contraceptives, warfarin, grapefruit juice</td>
</tr>
</tbody>
</table>

Statin & 6’,7’ Dihydroxybergamottin
Food-Drug Interaction

- Seville oranges and grapefruit
- Inhibits CYP450 3A4
- Sustained effect of up to 7 days
- SEPERATING DOSING BY A COUPLE OF HOURS DOES NOT WORK!!!
Pharmacologic & Pharmacokinetic Properties of Statins

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin</th>
<th>Simvastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Pitavastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL ↓ (%)</td>
<td>38 – 54</td>
<td>28 – 48</td>
<td>19 – 40</td>
<td>52 – 63</td>
<td>30–45%</td>
</tr>
<tr>
<td>Metabolite</td>
<td>Active</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>15 – 30</td>
<td>2 – 3</td>
<td>1.3 – 2.8</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Food</td>
<td>None</td>
<td>None</td>
<td>↓Abs</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Solubility</td>
<td>Lipophillic</td>
<td>Lipophillic</td>
<td>Hydrophillic</td>
<td>Lipophillic</td>
<td>Hydrophillic</td>
</tr>
<tr>
<td>CYP 450</td>
<td>3A4</td>
<td>3A4/5</td>
<td>Sulfation</td>
<td>2C9</td>
<td>2C9</td>
</tr>
<tr>
<td>Equipotent</td>
<td>10</td>
<td>20</td>
<td>40</td>
<td>5</td>
<td>1-2</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Randomized Endpoint Trials With Statins: Acute Coronary Syndrome Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>LDL-C mg/dL</th>
<th>LDL-C (%Δ)</th>
<th>Placebo CHD Rate (%)</th>
<th>CHDEvent ↓ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACL¹</td>
<td>Atorvastatin 80 mg vs. Placebo</td>
<td>124 (72)</td>
<td>↓42</td>
<td>-</td>
<td>↓26</td>
</tr>
<tr>
<td>AVERT²</td>
<td>Atorvastatin 80 mg vs. PCI</td>
<td>145 (77)</td>
<td>↓42</td>
<td>-</td>
<td>↓36</td>
</tr>
<tr>
<td>PROVE IT³</td>
<td>Atorvastatin 80 mg Pravastatin 40 mg</td>
<td>106 (62)</td>
<td>↓51</td>
<td>-</td>
<td>↓16</td>
</tr>
</tbody>
</table>

FDA Advisory for Simvastatin

- 80mg should not be initiated in statin naïve patients
- Statin tolerant patients can be continued
- Increased risk of myopathy
- New starting dose 40 mg

www.fda.gov

Everyone can get atorvastatin

- Generic available late 2011
- Lipitor $4 dollar copay
- Maximum 600 dollars per calendar year
- DAW must be on prescription

www.pfizer.com
ACCF/AHA Recommendations for Antiplatelet Therapy ACS

- Initiate therapeutic lifestyle changes
- Use omega 3 fatty acids (at least 1 gram)
- Lipid lowering medication should be initiated prior to discharge
- Target LDL-C < 100 mg/dL (Class Ia) <70 mg/dL (Class IIb)
- Triglyceride<200mg/dL HDL-C >40mg/dL

ACCF/AHA 2007 Guideline Update for the Management of Patients with STEMI available at www.americanheart.org

Pharmacotherapeutic Treatment Options for Post-MI patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug(s)/Drug Class</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihyperlipidemic</td>
<td>Statins</td>
<td>Competitive inhibitor of HMG-CoA reductase → last regulated step in synthesis of cholesterol; Up-regulating LDL-receptor activity; Reduce entry LDL into circulation</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Angiotensin-converting Enzyme Inhibitors (ACEI) &amp;</td>
<td>Directly Ø ACE → Ø conversion of ATI to ATII → vasoconstriction &amp; aldosterone secretion → ↓ BP</td>
</tr>
<tr>
<td></td>
<td>Angiotensin receptor Blockers (ARB)</td>
<td>Directly Ø ATII receptors → vasoconstriction &amp; aldosterone secretion → ↓ BP</td>
</tr>
<tr>
<td>Antianginal/Anti-Ischemic Therapy</td>
<td>Beta-blockers (BB)</td>
<td>Ø β-receptors → ↓ inotropic state, sinus rate, AV conduction, blood pressure → ↓ MVO2 demand &amp; LV perfusion</td>
</tr>
</tbody>
</table>

ATI = angiotensin I; ATII = angiotensin II; cGMP = cyclic guanosine monophosphate; AV = atrioventricular; MVO2 = myocardial oxygen demand; LV = left ventricular;
## Pharmacologic Features and Dosing Parameters for ACEI

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>$t_{1/2}$ (h)</th>
<th>Excretion</th>
<th>Dose (mg)</th>
<th>Equi-potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Capoten®</td>
<td>2</td>
<td>Renal</td>
<td>6.25 – 150</td>
<td>12.5 mg</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vasotec®</td>
<td>1.3</td>
<td>Renal</td>
<td>2.5 – 40</td>
<td>5 mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Prinivil®</td>
<td>12</td>
<td>Renal</td>
<td>5 – 40</td>
<td>10 mg</td>
</tr>
<tr>
<td>Benazepril</td>
<td>Lotensin®</td>
<td>10 – 11</td>
<td>Renal/Bile</td>
<td>5 – 80</td>
<td>10 mg</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Altace®</td>
<td>2 – 50*</td>
<td>Renal</td>
<td>1.25 – 20</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Accupril®</td>
<td>2 – 25</td>
<td>Renal</td>
<td>5 - 80</td>
<td>10 mg</td>
</tr>
<tr>
<td>Moexipril</td>
<td>Univasc®</td>
<td>2 – 12</td>
<td>Renal</td>
<td>7.5 – 30</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Aceon®</td>
<td>3 - 120</td>
<td>Renal</td>
<td>2 - 16</td>
<td>2 mg</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Mavik®</td>
<td>~ 10</td>
<td>Renal</td>
<td>1 – 8</td>
<td>1 mg</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril®</td>
<td>~1 1.5</td>
<td>Renal/Bile</td>
<td>10 - 80</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

## Pharmacologic Features and Dosing Parameters for ARBs

<table>
<thead>
<tr>
<th></th>
<th>Candesartan (Atacand®)</th>
<th>Irbesartan (Avapro®)</th>
<th>Losartan (Cozaar®)</th>
<th>Olmesartan (Benicar®)</th>
<th>Telmisartan (Micardis®)</th>
<th>Valsartan (Diovan®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing (mg/day)</td>
<td>8 - 32</td>
<td>150 – 300</td>
<td>50 – 100</td>
<td>20 – 40</td>
<td>20 – 80</td>
<td>80 - 320</td>
</tr>
<tr>
<td>Frequency</td>
<td>QD –BID</td>
<td>QD</td>
<td>QD – BID</td>
<td>QD</td>
<td>QD</td>
<td>QD</td>
</tr>
<tr>
<td>Food effects</td>
<td>No effect</td>
<td>No effect</td>
<td>↓ &lt; 14%</td>
<td>No effect</td>
<td>↓ &lt; 20%</td>
<td>↓ 50%</td>
</tr>
<tr>
<td>Vd</td>
<td>0.13 L/kg</td>
<td>53 – 93 L</td>
<td>~ 34 L</td>
<td>~ 17 L</td>
<td>~ 500 L</td>
<td>17 L</td>
</tr>
<tr>
<td>Half-life</td>
<td>~ 9 hr</td>
<td>~ 11 – 15 hr</td>
<td>~ 6 – 9 hr</td>
<td>~ 13 hr</td>
<td>~ 24 hr</td>
<td>~ 6 hr</td>
</tr>
<tr>
<td>Excretion urine</td>
<td>~ 33%</td>
<td>~ 20%</td>
<td>~ 45%</td>
<td>~ 35 – 45%</td>
<td>~ 0.49%</td>
<td>~ 13%</td>
</tr>
<tr>
<td>Excretion feces</td>
<td>~ 67%</td>
<td>~ 80%</td>
<td>~ 50%</td>
<td>50 – 60%</td>
<td>&gt; 97%</td>
<td>~ 83%</td>
</tr>
</tbody>
</table>
Biological Effects of Angiotensin II in Vascular Endothelium

ACEI and ARB-induced Angioedema

Localized, non-inflammatory, nonpruritic swelling of skin caused fluid build-up in interstitial tissue → ASPHYXIATION

ACEI-induced Angioedema incidence 2 to 10 per 1000

Cross-reactivity <10%

Angioedema

Genetic Predisposition: α-1 antitrypsin deficiency & C₁ esterase inhibitor protein deficiency

Features of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

| Indication                                      | HTN, HF, MI, LV dysfunction, Diabetic nephropathy |
| Contraindication                               | Angioedema related to ACEI, Category D (2nd trimester) |
| Adverse Effect                                 | Angioedema, cough, hyperkalemia, acute renal failure, skin rash, dysgeusia (captopril), hepatotoxicity, neutropenia, agranulocytosis |
| Drug Interactions                              | Antacids, allopurinol (captopril), capsaicin (ACEI), NSAIDs, lithium, digoxin, potassium-sparing diuretics, K supplement. |
Studies of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Clinical Effect (HOPE)

Ramipril 10 mg/daily reduced rates of death from CV causes by 26% (p <0.001), MI by 20% (p<0.001), stroke by 32% (p<0.001), death from any cause by 16% (p=0.005), revascularization procedures by 15% (p=0.002), cardiac arrest by 37% (p=0.03), HF by 23% (p<0.001); only ↓ BP 2 – 3 mmHg (NEJM 2000;342:145-53)

OPTIMAAL

Captopril 50 mg tid vs. losartan 50 mg
No difference in primary outcome of all cause mortality
Trend toward better outcome with captopril (he Lancet, Volume 360, Issue 9348, Pages 1884 - 1885.)

VALIANT

Captopril 50 mg tid vs. valsartan 80 mg
Post MI patients withLV dysvfunction
No difference in outcome measures (Eur J Heart Fail. 2003 Aug;5(4):537-44.)

ACCF/AHA Recommendations for ACE/ARB Therapy ACS

- ACEI for all patients
- Avoid in hypotension
- Start short-acting captopril then switch to longer acting once stable
- Can use valsartan 160mg/d in ACEI intolerance
- Can use valsartan monotherapy
- Most benefit seen in anterior wall MI, LV dysfunction, DM

ACCF/AHA 2011 Guideline Update for the Management of Patients with UA/NSTEMI available at www.americanheart.org
Pharmacotherapeutic Treatment Options for Post-MI patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug(s)/Drug Class</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihyperlipidemic</td>
<td>Statins</td>
<td>Competitive inhibitor of HMG-CoA reductase $\rightarrow$ last regulated step in synthesis of cholesterol; Up-regulating LDL-receptor activity; Reduce entry LDL into circulation</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Angiotensin-converting Enzyme Inhibitors (ACEI)</td>
<td>Directly $\emptyset$ ACE $\rightarrow$ $\emptyset$ conversion of ATI to ATII $\rightarrow$ vasoconstriction &amp; aldosterone secretion $\rightarrow$ ↓ BP</td>
</tr>
<tr>
<td></td>
<td>Angiotensin receptor Blockers (ARB)</td>
<td>Directly $\emptyset$ ATII receptors $\rightarrow$ vasoconstriction &amp; aldosterone secretion $\rightarrow$ ↓ BP</td>
</tr>
<tr>
<td>Antianginal/Anti-Ischemic Therapy</td>
<td>Beta-blockers (BB)</td>
<td>$\emptyset$ $\beta$-receptors $\rightarrow$ ↓ inotropic state, sinus rate, AV conduction, blood pressure $\rightarrow$ ↓ MVO$_2$ demand &amp; LV perfusion</td>
</tr>
</tbody>
</table>

ATI = angiotensin I; ATII = angiotensin II; cGMP = cyclic guanosine monophosphate; AV = atrioventricular; MVO$_2$ = myocardial oxygen demand; LV = left ventricular;

Properties of Beta Adrenergic Blockers

<table>
<thead>
<tr>
<th>Indication</th>
<th>Stable and unstable angina, heart failure (compensated), AMI, Migraine Supraventricular and Ventricular arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindication</td>
<td>Severe bradycardia, pre-existing high degree AV block, sick sinus syndrome, unstable LV failure. Relative: asthma, bronchospastic disease, severe depression, peripheral vascular disease</td>
</tr>
<tr>
<td>Adverse Effect</td>
<td>Fatigue, exercise intolerance, lethargy, insomnia, nightmares, worsening claudication, impotence</td>
</tr>
</tbody>
</table>

Titrate to HR 55 – 60 bpm
Pharmacologic and Dosing Features of Beta Blockers in Clinical Use

<table>
<thead>
<tr>
<th>Drugs</th>
<th>B₁</th>
<th>ISA</th>
<th>Half-Life (h)</th>
<th>Lipid Solubility</th>
<th>Dose for Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol (Tenormin®)*</td>
<td>++</td>
<td>-</td>
<td>6 – 7</td>
<td>Low</td>
<td>50 – 200 mg/day</td>
</tr>
<tr>
<td>Acebutolol (Sectral®)</td>
<td>++</td>
<td>+</td>
<td>3 – 4</td>
<td>Moderate</td>
<td>200 – 600 mg BID</td>
</tr>
<tr>
<td>Betaxolol (Kerlone®)</td>
<td>++</td>
<td>-</td>
<td>14 – 22</td>
<td>Low</td>
<td>10 – 20 mg/day</td>
</tr>
<tr>
<td>Bisoprolol (Zebeta®)</td>
<td>++</td>
<td>-</td>
<td>9 – 12</td>
<td>Low</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Esmolol (IV) (Brevibloc®)</td>
<td>++</td>
<td>-</td>
<td>0.15</td>
<td>None - Low</td>
<td>50 – 300 mcg/kg/min</td>
</tr>
<tr>
<td>Labetalol (Trandate®)*c</td>
<td>-</td>
<td>N/A</td>
<td>8 - 12</td>
<td>Moderate</td>
<td>200 – 600 mg BID</td>
</tr>
<tr>
<td>Metoprolol (Lopressor®)*b</td>
<td>++</td>
<td>-</td>
<td>3 – 7</td>
<td>Mod – high</td>
<td>50 – 200 mg BID</td>
</tr>
<tr>
<td>Nadolol (Corgard®)*</td>
<td>-</td>
<td>-</td>
<td>20 – 24</td>
<td>Low</td>
<td>40 – 80 mg/day</td>
</tr>
<tr>
<td>Pindolol (Visken®)</td>
<td>-</td>
<td>+++</td>
<td>3 – 4</td>
<td>Moderate</td>
<td>2.5 – 7.5 mg TID</td>
</tr>
<tr>
<td>Propranolol (Inderal®)*b</td>
<td>-</td>
<td>-</td>
<td>3 – 5</td>
<td>High</td>
<td>20 – 80 mg BID</td>
</tr>
<tr>
<td>Timolol (Blocadren®)</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>Low - mod</td>
<td>10 mg BID</td>
</tr>
</tbody>
</table>

“-” = none; “+” = low; “++” = moderate; “+++) = high
*FDA approved for Angina; a intrinsic sympathomimetic activity; b long-acting formulation available; c α₁-blockade and non-selective β-blockade

ACCF/AHA Recommendations for Antiplatelet Therapy UA/NSTEMI

- Beta blockers for all patients
- Beta blockers should be continued long-term
- Tritrate to effect
- Metoprolol extensively studied
- Carvedilol can be used (hypotension)