TREATMENT OF ACUTE CORONARY SYNDROMES

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Libin Cardiovascular Institute of Alberta
Disclosures

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  - Grants/Research Support: NIH
  - Speakers Bureau/Honoraria: Pfizer, Servier
Prevalence of CVD in adults by age and sex (NHANES: 2005-2008) – USA


Three types of Acute Coronary Syndromes:

1. Unstable angina (UA)
2. Non ST-elevation myocardial infarction (NSTEMI)
3. ST-elevation myocardial infarction (STEMI)
Acute Coronary Syndrome

Electrocardiogram

- ST Elevation
- No ST Elevation

Cardiac Markers

- Negative
- Positive

Myocardial Infarction

- Current of Injury
- Unstable angina

- STEMI
  - Q-wave MI
- NSTEMI
  - Non-Q wave MI
Why are the clinical presentations so different?

Stable or unstable angina

Unstable angina or NSTEMI

STEMI
Why do we care what kind of ACS it is?

- Patients with ACS are at risk of major adverse cardiac events (MI, CHF, dysrhythmias, CVA, death)
- Risk of adverse outcome is not equal – STEMI > NSTEMI > UA
- Management depends on the type of ACS
  - Triage and disposition
  - Decision and timing of invasive vs. non-invasive testing
  - Choice of medical therapy including thrombolytics
Acute coronary syndromes

- All three are *usually* caused by atherosclerosis with (more common) or without (less common) an **unstable coronary plaque**
- Less common causes:
  - vasospasm
  - arterial thrombus
  - coronary dissection
Clinical classification of different types of myocardial infarction

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Spontaneous myocardial infarction related to ischemia due to a <strong>primary coronary event</strong> such as plaque erosion and/or rupture, fissuring, or dissection</td>
</tr>
<tr>
<td>Type 2</td>
<td>Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension</td>
</tr>
<tr>
<td>Type 3</td>
<td><strong>Sudden unexpected cardiac death</strong>, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood</td>
</tr>
<tr>
<td>Type 4a</td>
<td>Myocardial infarction associated with <strong>PCI</strong></td>
</tr>
<tr>
<td>Type 4b</td>
<td>Myocardial infarction associated with <strong>stent thrombosis</strong> as documented by angiography or at autopsy</td>
</tr>
<tr>
<td>Type 5</td>
<td>Myocardial infarction associated with <strong>CABG</strong></td>
</tr>
</tbody>
</table>
Approach to the management of UA/NSTEMI
Early invasive strategy

- **Definition:** Diagnostic angiography with intent to perform revascularization within 24hrs

- **Indicated in UA/NSTEMI patients who have:**
  - refractory angina
  - hemodynamic or electrical instability
  - heart failure or LVEF <40%
  - elevated risk for clinical events (Class I)
Highest Risk: **Immediate**
Cath/Intervention (Class 1B)

- Pts with NSTEMI and:
  - Hemodynamic instability or cardiogenic shock
  - Severe left ventricular dysfunction or heart failure
  - Recurrent or persistent rest angina despite intensive medical therapy
  - New or worsening mitral regurgitation or new ventricular septal defect
  - Sustained ventricular arrhythmias
Clinical Predictors of Risk

Background Risk
- Age/gender
- Diabetes
- Extracardiac vascular disease
- Heart failure
- Renal dysfunction
- Aspirin resistance
- Genetic markers

Clinical Presentation
- Severity of symptoms
- Acute ECG changes
  - ST depression
  - ST elevation
  - Marked T inversion
- Elevated cardiac markers
### Medical History

<table>
<thead>
<tr>
<th>Points</th>
<th>Age in Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>=20</td>
</tr>
<tr>
<td>0</td>
<td>30-39</td>
</tr>
<tr>
<td>18</td>
<td>40-49</td>
</tr>
<tr>
<td>36</td>
<td>50-59</td>
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<tr>
<td>55</td>
<td>60-69</td>
</tr>
<tr>
<td>73</td>
<td>70-79</td>
</tr>
<tr>
<td>91</td>
<td>80-89</td>
</tr>
<tr>
<td>100</td>
<td>≥90</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>History of Congestive Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>History of Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

### Findings at Initial Hospital Presentation

<table>
<thead>
<tr>
<th>Points</th>
<th>Resting Heart Rate, beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≤49.9</td>
</tr>
<tr>
<td>3</td>
<td>50-69.9</td>
</tr>
<tr>
<td>9</td>
<td>70-89.9</td>
</tr>
<tr>
<td>14</td>
<td>90-109.9</td>
</tr>
<tr>
<td>23</td>
<td>110-149.9</td>
</tr>
<tr>
<td>35</td>
<td>150-199.9</td>
</tr>
<tr>
<td>43</td>
<td>≥200</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Systolic Blood Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>≤79.9</td>
</tr>
<tr>
<td>22</td>
<td>80-89.9</td>
</tr>
<tr>
<td>18</td>
<td>100-119.9</td>
</tr>
<tr>
<td>14</td>
<td>120-139.9</td>
</tr>
<tr>
<td>10</td>
<td>140-159.9</td>
</tr>
<tr>
<td>4</td>
<td>160-199.9</td>
</tr>
<tr>
<td>0</td>
<td>≥200</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>ST-Segment Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

### Findings During Hospitalization

<table>
<thead>
<tr>
<th>Points</th>
<th>Initial Serum Creatinine, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-0.39</td>
</tr>
<tr>
<td>3</td>
<td>0.4-0.79</td>
</tr>
<tr>
<td>5</td>
<td>0.8-1.19</td>
</tr>
<tr>
<td>7</td>
<td>1.2-1.59</td>
</tr>
<tr>
<td>9</td>
<td>1.6-1.99</td>
</tr>
<tr>
<td>15</td>
<td>2-3.99</td>
</tr>
<tr>
<td>20</td>
<td>≥4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Elevated Cardiac Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>No In-Hospital Percutaneous Coronary Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

#### Risk Categories
- **Low risk**: < 108
- **Med risk**: 109-140
- **High risk**: >140

Based on data from Arch Int Med 2003; 163:2345-53.
# TIMI Risk score for UA/NSTEMI

<table>
<thead>
<tr>
<th>HISTORICAL</th>
<th>POINTS</th>
<th>RISK OF CARDIAC EVENTS (%) BY 14 DAYS IN TIMI IIIB*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $\geq 65$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>$\geq 3$ CAD risk factors (FHx, HTN, ↑ chol, DM, active smoker)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Known CAD (stenosis $\geq 50%$)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ASA use in past 7 days</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PRESENTATION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent ($\leq 24$H) severe angina</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>↑ cardiac markers</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ST deviation $\geq 0.5$ mm</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**RISK SCORE = Total Points (0 - 7)**

*Entry criteria: UA or NSTEMI defined as ischemic pain at rest within past 24H, with evidence of CAD (ST segment rise)*

Antman et al *JAMA 2000; 284*: 835 - 842

For more info go to www.timi.org
# TIMI RISK SCORE for STEMI

<table>
<thead>
<tr>
<th>HISTORICAL</th>
<th>POINTS</th>
<th>RISK SCORE</th>
<th>30-DAY MORTALITY IN InTIME II(%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75</td>
<td>3</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>65-74</td>
<td>2</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>DM or HTN or angina</td>
<td>1</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>EXAM</td>
<td></td>
<td>2</td>
<td>4.4</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>3</td>
<td>4</td>
<td>7.3</td>
</tr>
<tr>
<td>HR &gt;100 bpm</td>
<td>2</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Killip II-IV</td>
<td>2</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Weight &lt; 67 kg (150 lb)</td>
<td>1</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>PRESENTATION</td>
<td></td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Anterior STE or LBBB</td>
<td>1</td>
<td>&gt;8</td>
<td>36</td>
</tr>
<tr>
<td>Time to Rx &gt; 4 hrs</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RISK SCORE = Total points (0-14)

*Entry criteria: CP > 30 min, ST ↑, sx onset < 6hrs, fibrinolytic-eligible

For more info go to www.timi.org

Prognosis based on STEMI TIMI score

**InTIME-2:** n=14114, mean 30 day mortality 6.7%

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65-74 / ≥ 75</td>
<td>2/3</td>
</tr>
<tr>
<td>Systolic Blood Pressure &lt; 100</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt; 100</td>
<td>2</td>
</tr>
<tr>
<td>Killip II-IV</td>
<td>2</td>
</tr>
<tr>
<td>Anterior STE or LBBB</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes, h/o HTN, or h/o angina</td>
<td>1</td>
</tr>
<tr>
<td>Weight &lt; 67 kg</td>
<td>1</td>
</tr>
<tr>
<td>Time to treatment &gt; 4 hours</td>
<td>1</td>
</tr>
</tbody>
</table>

**Risk Score:** 0 - 14 possible points

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Mortality at 30 Days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>4.4</td>
</tr>
<tr>
<td>4</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>12.4</td>
</tr>
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<td>6</td>
<td>16.1</td>
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<tr>
<td>7</td>
<td>23.4</td>
</tr>
<tr>
<td>8</td>
<td>26.8</td>
</tr>
<tr>
<td>&gt;8</td>
<td>35.9</td>
</tr>
</tbody>
</table>

**% at risk:**
- 0: 12%
- 1: 22%
- 2: 16%
- 3: 16%
- 4: 14%
- 5: 9%
- 6: 6%
- 7: 3%
- 8: 2%
- >8: 1%

Morrow et al. Circ 2000;102:2031
ACC/AHA guidelines for UA/NSTEMI

Early invasive strategy in patients with any of the following high-risk indicators

- Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy
- Elevated TnT or TnI
- New or presumably new ST-segment depression
- Recurrent angina/ischemia with CHF symptoms, an $S_3$ gallop, pulmonary edema, worsening rales, or new or worsening MR
- High-risk findings on noninvasive stress testing
- Depressed LV systolic function (eg, EF less than 0.40 on noninvasive study)
- Hemodynamic instability
- Sustained ventricular tachycardia
- PCI within 6 months
- Prior CABG

Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf
Benefits/Evidence Early Invasive

- ↓ myocardial infarction\(^1,3,4\)
- ↓ recurrent angina/readmission for angina\(^1,3,4\)
- ↓ death (1 yr)\(^1\)
- Sustained benefits for ischemic outcomes to 6mo\(^1,3\)/ 1yr\(^1,4\) /5yrs\(^1,4\)

**Meta-analyses\(^5\):**
- ↓ death/non-fatal Mi post d/c to 1 yr IF (+) troponin
- ↓ angina class/repeat hospitalization

(2) TIMI IIIB  Circulation. 1994;89(4):1545
(4) RITA 3  Lancet. 2002;360(9335):743
(5) JAMA. 2005;293(23):2908;  JACC. 2006;48(7):1319
TIMACS Trial: Early (<24hrs) vs. delayed (>36hrs) intervention in ACS without ST elevation

Death/MI/RI at 180 days

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Delayed</th>
<th>Early</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1438</td>
<td>1593</td>
</tr>
<tr>
<td>30</td>
<td>1303</td>
<td>1485</td>
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<td>60</td>
<td>1243</td>
<td>1417</td>
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<td>90</td>
<td>1230</td>
<td>1402</td>
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<td>120</td>
<td>1209</td>
<td>1394</td>
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<tr>
<td>150</td>
<td>1205</td>
<td>1386</td>
</tr>
<tr>
<td>180</td>
<td>1187</td>
<td>1366</td>
</tr>
</tbody>
</table>

Cumulative Hazard

- Delayed
- Early

HR 0.72
95% CI 0.58-0.79
P=0.002

When not to use early invasive approach

- Low risk patients
- Patients with extensive comorbidities (e.g., liver or pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization
- Patients who will not consent to revascularization regardless of the findings
In-hospital diagnostic testing

- All patients with ACS need to have:
  1. Assessment of coronary arteries (invasive vs. noninvasive)
  2. Assessment of LV function (LV gram at cath vs. echo)
  3. Assessment of exercise tolerance on medications (stress test vs. mobilizing on ward)
Non-invasive testing

- Exercise stress test
- Myocardial perfusion imaging (MPI)
- Stress echocardiogram
- CT coronary angiogram
- Stress cardiac MRI

- Each test has advantages and disadvantages
- Need to think about information obtained, risk, sensitivity/specificity, cost, availability, etc.
Summary: Approach to UA/NSTEMI

- **Low risk**
  - Noninvasive risk stratification
    - Symptoms controlled and low risk non-invasive test
    - Medical management and secondary prevention

- **Intermediate risk**
  - Recurrent symptoms or high risk non-invasive test

- **High risk**
  - Invasive risk stratification (cardiac cath)
Treatment of ACS
Initial management in ACS

- ABCs
- Cardiac monitor, O₂, iv access
- Antiischemic therapy – β blockers, NTG, calcium channel blockers
- Antiplatelet/anticoagulant therapy – ASA, heparin/fondaparinux, clopidogrel/ticagrelor, +/- Gllb/Illa inhibitors
- Determine whether urgent revascularization is required
Revascularization

- **STEMI:**
  - PCI (percutaneous coronary intervention) or thrombolysis essential to restore blood flow to myocardium

- **NSTEMI:**
  - Medical therapy will usually resolve ischemia
  - PCI if persistent ischemic symptoms despite maximal medical management
  - Thrombolysis contraindicated
Thrombolytic therapy

- Many types – most popular are plasminogen activators that act on clot-bound fibrin (tPA, rPA, TNK)
- Indicated within first 12 hours (the earlier the better) of chest pain with STEMI
- Successful ~70% of the time
- Major risk is bleeding – 1% risk of IC bleeding which increases with age
- Expensive
Indications for thrombolytics

- **Class I:**
  - \( ST^\uparrow \geq 1 \text{mm} \) in 2 or more contiguous leads + time to therapy <12hrs
  - New LBBB with Hx suggestive of acute MI + time to therapy <12hrs

- **Class IIa:**
  - True posterior STEMI + time to therapy <12hrs
  - \( ST^\uparrow \geq 1 \text{mm} \) in 2 or more contiguous leads + time to therapy 12-24hrs + ongoing symptoms

- **Class III (ie. Don’t do it):**
  - \( ST^\uparrow \) + time to therapy >24hrs + symptoms resolved
  - ST depression only
Absolute and relative contraindications to the use of thrombolytic therapy in patients with acute ST elevation myocardial infarction*

### Absolute contraindications

- History of any intracranial hemorrhage
- History of ischemic stroke within the preceding three months, with the important exception of acute ischemic stroke seen within three hours which may be treated with thrombolytic therapy
- Presence of a cerebral vascular malformation or a primary or metastatic intracranial malignancy
- Symptoms or signs suggestive of an aortic dissection
- A bleeding diathesis or active bleeding, with the exception of menses; thrombolytic therapy may increase the risk of moderate bleeding, which is offset by the benefits of thrombolysis
- Significant closed-head or facial trauma within the preceding three months

### Relative contraindications

- History of chronic, severe, poorly controlled hypertension or uncontrolled hypertension at presentation (blood pressure >160 mmHg systolic and/or >110 mmHg diastolic; severe hypertension at presentation can be an absolute contraindication in patients at low risk)
- History of ischemic stroke more than three months previously
- Dementia
- Any known intracranial disease that is not an absolute contraindication
- Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
- Major surgery within the preceding three weeks
- Internal bleeding within the preceding two to four weeks or an active peptic ulcer
- Noncompressible vascular punctures
- Pregnancy
- Current warfarin therapy - the risk of bleeding increases as the INR increases
- For streptokinase or anistreplase - a prior exposure (more than five days previously) or allergic reaction to these drugs

* May not be all-inclusive or definitive.

When is PCI preferred?

- Skilled PCI lab is available within 90 min with surgical backup
- High risk from STEMI – cardiogenic shock, large territory at risk/infarcted
- Contraindication to fibrinolysis
- Late presentation (>3hrs)
- Diagnosis of STEMI is in doubt
Triage and Transfer for PCI: STEMI

- Those presenting to a non-PCI-capable facility should be triaged to fibrinolytic therapy or immediate transfer for PCI

- **Decision depends on:**
  - mortality risk of the STEMI
  - risk of fibrinolytic therapy
  - duration of the symptoms when first seen
  - time required for transport to a PCI-capable facility
**FOR THE CURRENT MAJORITY OF HOSPITALS FIBRINOLYSIS WILL BE THE PREFERRED OPTION**

**CCS WORKING GROUP ALGORITHM**

*Assumes the diagnosis of STEMI is not in doubt and PCI facility is expert and provides 24/7 capability.*

**Evaluate:**
- Time since onset of symptoms
- MI risk (patient & ECG)
- Risk of fibrinolysis
- Time to fibrinolysis or PCI

**Reperfusion indicated?**

**Contraindication to fibrinolysis?**

**Does the patient have Killip class 3/4 or other high-risk AMI features?**

**Is PCI reliably available within 60 minutes of time to fibrinolysis?**

**Transfer to PCI center and/or perform PCI**

**Give fibrinolysis and appropriate cardiopulmonary support and transfer to tertiary cardiac center**

**PCI or fibrinolysis**

**Give fibrinolysis**
Importance of Time to Treatment

*Pivotal factor in successful reperfusion therapy*

**Fibrinolysis**

- > 100 trials
- > 50,000 patients

**Primary PCI**

<table>
<thead>
<tr>
<th>Symptom onset to randomization (hours)</th>
<th>30-day death, re-MI, stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>4.7</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>7.6</td>
</tr>
<tr>
<td>2.5-4</td>
<td>8.8</td>
</tr>
<tr>
<td>&gt; 4-12</td>
<td>12.2</td>
</tr>
</tbody>
</table>

n = 790

Short-Term Outcomes (4-6 Weeks)

- **Primary PCI 3872**
- **Fibrinolysis 3867**

<table>
<thead>
<tr>
<th>Event</th>
<th>% of Patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10</td>
<td>p=0.0002</td>
</tr>
<tr>
<td>Death, excludes SHOCK trial</td>
<td>5</td>
<td>p=0.0003</td>
</tr>
<tr>
<td>Non-Fatal MI</td>
<td>3</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>25</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Total stroke</td>
<td>5</td>
<td>p=0.0004</td>
</tr>
<tr>
<td>ICH</td>
<td>2</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Major bleed</td>
<td>7</td>
<td>p=0.032</td>
</tr>
<tr>
<td>Death, MI, or stroke</td>
<td>15</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

A few words on PCI...
Percutaneous coronary intervention (PCI)

- **POBA:** plain old balloon angioplasty
  - Restenosis rate of ~30%
  - Still used in bifurcation lesions or when dual antiplatelet contraindicated

- “PCI” often used to mean stent implantation, although by definition means any percutaneous coronary intervention
Early Stents
Later Stents
Types of coronary stents

- **Bare metal stents**
  - Endothelialize within several weeks
  - Require plavix for minimum of 1 month
  - Risk of in-stent stenosis <10%

- **Drug eluting stents**
  - Endothelialization requires months ➔ plavix for 1 yr
  - Risk of in-stent stenosis in ~1%
  - Risk of in-stent thrombosis <1% when plavix d/c’d
  - Reserved for diabetics, small arteries, prior in-stent stenosis
Revascularization in STEMI

- Whatever you do, do it quickly
- “Time is muscle”
- If thrombolysis employed, will need further risk stratification prior to discharge
  - Invasive vs. non-invasive strategy depending on patient risk
Medical therapy in ACS
ACS: medical therapy

- Proven secondary prevention measures:
- “asa-beta-stati-pril-ogrel”
  - ASA
  - Beta-blockers
  - Statins – Lipid lowering
  - ACE-inhibition
  - Thienopyridines – eg. clopidogrel (12 months)
ASA

- **Class I indication**
- Cyclooxygenase inhibitor
  - inhibits formation of thromboxane A2
- Reduces the relative risk of subsequent vascular events (nonfatal MI, nonfatal stroke, and vascular death) by approximately 22%
- No difference in outcomes between daily doses of 81, 160 and 325 mg
Clopidogrel (Plavix)

- Blocks ADP mediated platelet activation
- Should be considered in most patients with ACS
- Decreases events by 25%
- Expensive and generally well tolerated
- Used in ASA allergy
- Major risk is excessive bleeding especially if CABG surgery to be performed within 5 days of last dose
Other Thienopyridines

- **Ticlopidine**
  - 46%↓ nonfatal MI and combined endpoint of vascular death or nonfatal MI at six months in patients not on ASA
  - More hematological side effects than plavix

- **Prasugrel**
  - ↓combined endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke compared to plavix
  - More bleeding and more expensive than plavix

- **Ticagrelor**
  - ↓death, increased bleeding compared to plavix
Heparin

- Binds to AT-III and inhibits thrombin, and inhibits Factor Xa
- LMWH has higher Factor Xa activity and can be given without monitoring of PTT
- Should be considered in all patients with UA/NSTEMI
- Decreases events by 25%
- Major risks: bleeding, HIT
Heparin (unfractionated or low-molecular weight) plus aspirin vs aspirin alone in unstable ACS

### Endpoint of death / MI

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Timing of endpoint</th>
<th>Heparin + ASA</th>
<th>Aspirin</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Théroux</td>
<td>1988</td>
<td>243</td>
<td>5 days</td>
<td>1.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>RISK</td>
<td>1990</td>
<td>399</td>
<td>5 days</td>
<td>1.4%</td>
<td>3.7%</td>
</tr>
<tr>
<td>ATACS</td>
<td>1994</td>
<td>214</td>
<td>5 days</td>
<td>3.8%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Gurfinkel</td>
<td>1995</td>
<td>284</td>
<td>5 days</td>
<td>2.9%</td>
<td>9.6%</td>
</tr>
<tr>
<td>FRISC</td>
<td>1996</td>
<td>1506</td>
<td>6 days</td>
<td>1.8%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Total</td>
<td>2646</td>
<td></td>
<td></td>
<td>4.6%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>
ESSENCE: Primary outcome
Death, MI, recurrent angina

19% risk reduction
\( P = 0.016 \)

Fondaparinux

- Binds to antithrombin, inactivating factor Xa
- Does not interact with platelets or platelet factor 4 ➔ no thrombocytopenia
- Compared to heparin:
  - Similar rates for recurrent ischemia, MI
  - Lower rates for death and major bleeding with fondaparinux
  - Small increased risk of catheter-related thrombi
GIIb/IIIa inhibitors

- Block final common pathway of platelet aggregation
- Should be considered in high risk patients only
- Usually used in conjunction with invasive approach (catheterization)
- Very, very expensive
- iv use in CCU setting
GIIb/IIIa inhibitors

- Risks are:
  - Bleeding, although intracranial bleeding not increased
  - Thrombocytopenia (need to monitor platelet count closely)
HMG Co-A reductase inhibitors

- Effectively reduce cholesterol (LDL decreases by up to 50%) by blocking enzyme involved in cholesterol synthesis
- Indicated to decrease mortality in all patients with atherosclerosis including those post-MI
- Safe and generally well tolerated
- Watch for myositis (<1%)
## Comparison of statins

<table>
<thead>
<tr>
<th>Product characteristics</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Cerivastatin</th>
<th>Rosuvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum LDL cholesterol change (%)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>-34</td>
<td>-34</td>
<td>-41</td>
<td>-50</td>
<td>-24</td>
<td>-28</td>
<td>-63 (ref. 23)</td>
</tr>
<tr>
<td>Serum triglyceride change (%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>-16</td>
<td>-24</td>
<td>-18</td>
<td>-29</td>
<td>-10</td>
<td>-13</td>
<td>-28 (ref. 23)</td>
</tr>
<tr>
<td>Serum HDL cholesterol change (%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>+9</td>
<td>+12</td>
<td>+12</td>
<td>+6</td>
<td>+8</td>
<td>+10</td>
<td>+10 (ref. 23)</td>
</tr>
<tr>
<td>HMG-CoA reductase IC50 (nM)</td>
<td>NA</td>
<td>55.1</td>
<td>18.1</td>
<td>15.2</td>
<td>17.9</td>
<td>13.1</td>
<td>11.8 (ref. 24)</td>
</tr>
<tr>
<td>Plasma half-life (hours)</td>
<td>2</td>
<td>1–2</td>
<td>1–2</td>
<td>14</td>
<td>1.2</td>
<td>2–3</td>
<td>18-20 (ref. 25)</td>
</tr>
<tr>
<td>Effect of food on drug absorption</td>
<td>Increased absorption</td>
<td>Decreased absorption</td>
<td>None</td>
<td>None</td>
<td>Negligible</td>
<td>None</td>
<td>None (ref. 26)</td>
</tr>
<tr>
<td>Optimal time of administration</td>
<td>With meals (morning and evening)</td>
<td>Bedtime</td>
<td>Evening</td>
<td>Evening</td>
<td>Bedtime</td>
<td>Evening</td>
<td>Anytime (ref. 25)</td>
</tr>
<tr>
<td>Penetration into the central nervous system</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No (ref. 27)</td>
</tr>
<tr>
<td>Renal excretion of absorbed dose (%)</td>
<td>10</td>
<td>20</td>
<td>13</td>
<td>2</td>
<td>&lt; 6</td>
<td>33</td>
<td>10 (ref. 28)</td>
</tr>
<tr>
<td>Mechanism of hepatic metabolism</td>
<td>Cytochrome P450 3A4</td>
<td>Sulfation</td>
<td>Cytochrome P450 3A4</td>
<td>Cytochrome P450 3A4</td>
<td>Cytochrome P450 2C9</td>
<td>Cytochrome P450 3A4, 2C8</td>
<td>Cytochrome P450 2C9 and 2C19 (ref. 26)</td>
</tr>
</tbody>
</table>

**Key:** LDL = low density lipoprotein; HDL = high density lipoprotein; † note that all figures are comparative changes at 40 mg/d of lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, rosvuastatin and 0.3 mg cerivastatin
Cholesterol Lowering - Non-lipid lowering effects

- Improvement in endothelium-dependent vasodilation
- Direct release of NO (caveolin)
- Upregulation and stabilization of eNOS
- Decreases caveolin-1 expression and interaction with eNOS
- Upregulation of SOD
- Reduction of NAD(P)H oxidase mRNA expression
- Decrease superoxide formation
- Anti-inflammatory properties (↓CRP, attenuate leukocyte adhesion molecules)
- Plaque stabilization (↓MMP-2, ↑collagen, ↓macrophages)
ACE Inhibitors

- Class I indication if LVEF <40% or CHF, otherwise Class IIa
- Pharmacology: block angiotensin converting enzyme, block bradykinin breakdown
- Decrease mortality in patients with decreased LV function post MI and those with CHF
- Decrease CV events in subjects with atherosclerosis or diabetes
Angiotensin receptor blockers

- Pharmacology: block angiotensin receptors (AT1 receptor)
- Generally second line drugs for CHF, LV dysfunction in patients intolerant of ACE-Is
- Don’t block bradykinin breakdown
- Growing mortality reduction data is now available as it is for ACE-inhibitors, but usually used for ACE-intolerant patients
Early hospital care in MI

- CCU care with bedrest for 12-24 hours
- Progressive ambulation on ward for 3-7 days depending on risk status
- Risk stratification if treated medically or with thrombolytic therapy
- Education about risk factors
Post-hospital care of MI

- Cardiac rehabilitation
- Smoking cessation
- Dietary modification
- Off work for 2-6 weeks
- No driving for 4 weeks if LV dysfunction
- Restart daily activities within first few days and increase to full activity by 4 weeks
Conclusions

- Majority of ACS are caused by plaque rupture
- Decision for early invasive vs. noninvasive strategy depends on patient risk
- For STEMI, revascularization is key
- In general, PCI is preferred to thrombolytic
- ASA-beta-stati-pril-ogrel
- Aggressive risk factor modification is essential