Acute Coronary Syndrome
Unstable Angina & Non-STEMI

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Cardiovascular Medicine
Disclosures

- Member, Clinical Working Group, AHA Get With The Guidelines-Resuscitation
- Member, Cath PCI and CART-CL R&P Committee
- Liaison for the Interventional Cardiology Section, ACC
- Guest Editor, JAHA and Circ Outcomes
Myocardial necrosis caused by an unstable ischemic syndrome most often due to plaque rupture, most often accompanied by typical chest discomfort, EKG changes, and a rise/fall in biomarkers.
ACS: Pathogenesis

- Plaque rupture or erosion of vulnerable fibrous cap
- Platelet activation/thrombin
- Intracoronary thrombosis
- Cell necrosis, cardiac enzyme release
Platelets & Coagulation

Franchi et al. Nature Reviews Cardiology 2017
What is an MI in 2020?

Cardiac Injury?

Acute
Rise and/or fall in cTn

Ischemic Mechanism?
History, ECG, echo, etc

yes

Picture c/w plaque rupture?

Type I MI

Precipitant?
Anemia, HTN urgency, arrhythmia, etc

Type II MI

no

Chronic
Flat but elevated cTn

Think structural heart disease, renal disease

Non ischemic acute injury
PE, CHF

Adapted from ACC SAP - James De Lemos
Epidemiology of Acute MI

Figure 1. Age- and sex-adjusted incidence rates of acute MI, 1999 to 2008. I bars represent 95% confidence intervals. MI indicates myocardial infarction; STEMI, ST-elevation myocardial infarction. Reprinted with permission from Yeh et al. (14).
MINOCA

- Spontaneous coronary artery dissection
- Coronary vasospasm
  - Prinzmetal’s angina
  - Cocaine
- Takotsubo cardiomyopathy
- Myocarditis
- Coronary embolism
Coronary embolism
RISK STRATIFICATION

1. What is the likelihood that symptoms are due to plaque rupture?

2. What is the likelihood of a bad outcome?
Short term risk of death

- Accelerating symptoms
- Hemodynamic instability
- Dynamic ST-segment deviation (not TWI)
- + cardiac biomarkers
- Ventricular arrhythmias
**Risk Scores**

**TIMI**
1) age ≥65 years 2) ≥3 risk factors 3) known coronary stenosis of ≥50% 4) ST-segment deviation 5) ≥2 anginal events in 24 hours 6) use of aspirin in prior 7 days 7) elevated troponin
Early Invasive v. Conservative
High Risk ACS

Death, MI, Rehosp for ACS at 6 Months

O.R 0.78
95% CI (0.62, 0.97)
p=0.025

Cannon NEJM 2001
Early invasive vs. conservative

<table>
<thead>
<tr>
<th>Biomarker Status</th>
<th>No. of Individuals</th>
<th>Death, MI, or Rehospitalization With ACS Events, No.</th>
<th>Odds Ratio (95% CI)</th>
<th>Favors Invasive Strategy</th>
<th>Favors Conservative Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Invasive Strategy</td>
<td>Conservative Strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Woman</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker Positive</td>
<td>550</td>
<td>550</td>
<td>118</td>
<td>156</td>
<td>0.67 (0.50-0.88)</td>
</tr>
<tr>
<td>Biomarker Negative</td>
<td>743</td>
<td>743</td>
<td>152</td>
<td>163</td>
<td>0.94 (0.61-1.44)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker Positive</td>
<td>1392</td>
<td>1353</td>
<td>260</td>
<td>382</td>
<td>0.56 (0.46-0.67)</td>
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<tr>
<td>Biomarker Negative</td>
<td>1126</td>
<td>1168</td>
<td>229</td>
<td>300</td>
<td>0.72 (0.51-1.01)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker Positive</td>
<td>1942</td>
<td>1903</td>
<td>378</td>
<td>538</td>
<td>0.59 (0.51-0.69)</td>
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<tr>
<td>Biomarker Negative</td>
<td>1869</td>
<td>1911</td>
<td>381</td>
<td>463</td>
<td>0.79 (0.58-1.06)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>ST-Segment Deviation</th>
<th>Favors Invasive Strategy</th>
<th>Favors Conservative Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Woman</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST deviation present</td>
<td>671</td>
<td>667</td>
</tr>
<tr>
<td>ST deviation absent</td>
<td>859</td>
<td>864</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST deviation present</td>
<td>1561</td>
<td>1559</td>
</tr>
<tr>
<td>ST deviation absent</td>
<td>1938</td>
<td>1932</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST deviation present</td>
<td>2232</td>
<td>2226</td>
</tr>
<tr>
<td>ST deviation absent</td>
<td>2797</td>
<td>2796</td>
</tr>
</tbody>
</table>
Risk Stratification

Unstable angina or NSTEMI diagnosis

- Very high risk: Clinical instability*
  - Immediate invasive <2 h
- High risk: GRACE >140, TIMI ≥4
  - Early invasive 2–24 h
- Intermediate risk: GRACE 109–140, TIMI 2–3
  - Delayed invasive 25–72 h
- Low risk: GRACE <109, TIMI ≤1
  - Medical/non-invasive strategy

If at non-PCI-capable hospital
- Very high risk: immediate transfer to PCI-capable hospital
- High risk: same-day transfer
- Intermediate risk: transfer for PCI within 72 h
- Low risk: transfer if pursuing invasive treatment

Clinical instability*, rise in cTn, or ECG changes
- Invasive evaluation + Non-invasive ischaemic testing

Reed et al Lancet 2017
Medical Management
Platelets & Coagulation

Franchi et al Nature Reviews Cardiology 2017
Aspirin

**Class I therapy**

- 162-325mg

- Rapidly inhibits thromboxane A<sub>2</sub> production

- ~50% reduction in death or MI in ACS

- Aspirin allergic- use clopidogrel

- Low dose vs. high dose for long-term prevention??
AHA/ACC Class I- All patients with NSTE-ACS without contraindications who are treated with either an early invasive or ischemia-guided strategy

<table>
<thead>
<tr>
<th>P2Y12 inhibitors</th>
<th>Load</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>300 mg/ 600 mg</td>
<td>75 mg daily</td>
</tr>
<tr>
<td>Prasugrel*</td>
<td>60 mg</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>180 mg</td>
<td>90 mg BID</td>
</tr>
</tbody>
</table>
Clopidogrel – CURE trial

Cardiac Death, Nonfatal MI, or Stroke at 1-year

- Benefit seen
  - Medical mx
  - PCI
  - CABG subset
- 20% reduction ischemic outcomes
- Major bleed increased: 2.7% vs. 3.7%

13,608 patients with high-risk ACS (STEMI, NSTEMI)

Prasugrel 60 mg LD, 10 mg daily vs. clopidogrel 300 mg LD, 75 mg daily

Randomization was performed after coronary anatomy was defined

1-year efficacy: death from CV cause, MI or stroke

Hazard ratio: 0.81; 95% CI: 0.73–0.90; *P* < 0.001; NNT 46

Cardiovascular death/non-fatal myocardial infarction/non-fatal stroke

Hazard ratio: 1.32; 95% CI: 1.03–1.68; *P* = 0.03; NNH 167

Major non-CABG bleeds

Wiviott et al NEJM 2007
## History of Stroke or TIA

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HISTORY OF TIA/STROKE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>19.1</td>
<td>14.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5.0</td>
<td>2.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Net</td>
<td>23.0</td>
<td>16.0</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>NO HISTORY OF TIA/STROKE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>9.5</td>
<td>12.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2.3</td>
<td>1.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Net</td>
<td>11.8</td>
<td>13.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Age ≥ 75, Weight &lt; 60 kg, or History of TIA/stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>16.1</td>
<td>16.0</td>
<td>0.83</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4.3</td>
<td>3.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Net</td>
<td>20.2</td>
<td>19.0</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Wiviott et al NEJM 2007
Prasugrel in medically managed ACS

TRILOGY ACS
9326 patients

ACS: + troponin or ST depression

Medically managed ACS within 10 days of the index event

Prasugrel 30 mg LD and 10 mg daily*
Clopidogrel 300 mg LD and 75 mg daily
Randomization was performed after coronary anatomy was known.

No benefit of upstream initiation of prasugrel in NSTEMI (ACCOAST trial).
ACS: STEMI and non-STEMI

- Ticagrelor 180 mg LD 90 mg bid
- Clopidogrel 300 mg LD 75 mg

- 1^e efficacy: death from vascular case, MI or stroke at 1-year
  - MI alone
  - All-cause death and vascular death
  - No increase in primary bleeding
  - Increase in non-CABG bleeding, and fatal ICH

Wallentin L et al. NEJM 2009
Ticagrelor

- Only drug to demonstrate a reduction in all-cause mortality
- Benefit of ticagrelor seen in patients treated medically and with PCI
- Patients were pre-treated with ticagrelor prior to arrival to the cath lab
- Interaction with dose of aspirin – higher dose of aspirin was associated with reduced efficacy of ticagrelor
Metabolism of P2Y12 inhibitors
Clopidogrel Dose Response Variability

Cellular factors:
- Increased platelet turnover
- Decreased metabolic activity
- Up-regulation of P2Y_{12} or P2Y_{1}
- Up-regulation of P2Y-independent pathways

Genetic Factors:
- CYP polymorphisms
- GPIa polymorphisms
- PY2_{12} polymorphisms
- GPIIIa polymorphisms

Clinical factors:
- Age
- Compliance
- Under-dosing
- Poor absorption
- Drug interactions
- ACS
- Diabetes
- BMI

Reduced response to clopidogrel
CLOPIDOGREL VS. PRASUGREL

Response to Prasugrel

Response to Clopidogrel

Clopidogrel Responder

Clopidogrel Non-responder

*Responder = ≥25% IPA at 4 and 24 h

Brandt JT et al Am Heart J. 2007
Popular GENETICS trial

- 2488 STEMI patients undergoing Primary PCI
- **Standard therapy** (ticagrelor or prasugrel)
- **Genotype-guided therapy** (ticagrelor or prasugrel for carriers, clopidogrel for non-carriers)
- $1^0$ efficacy: death, MI, stroke, stent thrombosis, major bleeding
- $1^0$ bleeding: PLATO major or minor bleeding

Classens et al NEJM 2019
**ISAR-REACT 5**

**Ticagrelor vs. Prasugrel**

- 4018 patients with ACS
- Ticagrelor 180 mg LD and 90 mg bid
- Prasugrel 60 mg LD and 10 mg daily*
- No pre-treatment with prasugrel for UA/NSTEMI
- Funded by German Center of CV Research

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**Death, MI or stroke – Primary efficacy endpoint**

**Bleeding – Primary Safety Endpoint**

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Hazard ratio, 1.12 (95% CI, 0.83–1.51)  
\( P=0.46 \)

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1989</td>
<td>1773</td>
</tr>
<tr>
<td>2</td>
<td>1441</td>
<td>1465</td>
</tr>
<tr>
<td>4</td>
<td>1399</td>
<td>1427</td>
</tr>
<tr>
<td>6</td>
<td>1356</td>
<td>1397</td>
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<tr>
<td>8</td>
<td>1319</td>
<td>1357</td>
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<tr>
<td>10</td>
<td>1296</td>
<td>1333</td>
</tr>
<tr>
<td>12</td>
<td>1266</td>
<td>1307</td>
</tr>
</tbody>
</table>

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Schupke et al NEJM 2019
Cangrelor

- Intravenous
- Onset of action: 2 min
- $T_{1/2}$: 3-5 min
- Completely reversible within 1 hour

CHAMPION-PHOENIX study
- ACS, stable angina undergoing PCI
- Compared 2 hour cangrelor vs. oral therapy
- Significant reduction in ischemic events and stent thrombosis

Role in patients with surgical disease where interruption of P2Y12 inhibitor may be considered harmful

Bhatt et al. NEJM 2013
Glycoprotein IIb/IIIa

**Abciximab (RheoPro)**
- Monoclonal antibody
- High affinity, rapid onset of action
- Effect reversed within 12-24 hours
- Bleeding, thrombocytopenia
- Platelet transfusion

**Eptifibatide (Integrellin) & Tirofiban (Aggrastat)**
- Small molecule inhibitors
- Bolus dose followed by infusion
- Renally cleared, contraindicated in dialysis
- Effect lasts 2-4 hours

**High clot burden**
**Patients not pre-treated with P2Y12 inhibitors**
Anti-thrombotic therapy

Class I: Anti-coagulation recommended for all patients

Heparin

- UFH- unfractionated heparin
- LMWH- enoxaparin
  - Ok to use, but ACT may not be reliable. Repeat dosing if last dose was >8 hours ago

Alternative agents- (lower risk of bleeding)

- Fondaparinux (anti-Xa)
  - Not used often for invasively managed patients due to concerns for guide catheter thrombosis

- Bivalirudin (anti-IIa)
Bivalirudin

- Direct thrombin inhibitor (not dependent on ATIII)

- HORIZONS-AMI (STEMI) and ACUITY (NSTEMI)
  - compared bivalirudin to combination of heparin + GPI (era of lower pre-treatment with P2Y12)
  - predominant benefit was reduction in bleeding

- Heat PPCI (STEMI Patients)
  - Predominantly radial access
  - No routine use of GPI
  - Heparin was more effective in reducing MACE (5.7% vs. 8.7%), and had similar bleeding
  - 3x fold increased risk of acute stent thrombosis with bival
# ACS Medical Management

<table>
<thead>
<tr>
<th>Oxygen</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>For O2 saturation &lt;90%, respiratory distress, or hypoxemia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nitrates</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual every 5 min × 3 for continuing pain</td>
<td></td>
</tr>
<tr>
<td>IV for persistent ischemia, heart failure, or uncontrolled hypertension</td>
<td></td>
</tr>
<tr>
<td>Nitrates are contraindicated with recent use of a PDE5 inhibitors</td>
<td>III</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analgesic Therapy</th>
<th>IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Morphine may be reasonable for continued chest pain despite maximally tolerated anti-ischemic medications</td>
<td></td>
</tr>
<tr>
<td>NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization</td>
<td>III</td>
</tr>
</tbody>
</table>
## Beta-adrenergic blockers

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate within the first 24 h (in the absence of CHF, low-output state, risk for shock, heart block, active asthma)</td>
<td>I</td>
</tr>
<tr>
<td>Sustained-release Metoprolol Succinate, Carvedilol, or Bisoprolol is recommended with concomitant NSTE-ACS, <em>stabilized</em> HF, and reduced systolic function</td>
<td>I</td>
</tr>
<tr>
<td>Continue in patients with normal LV function with NSTE-ACS</td>
<td>IIa</td>
</tr>
<tr>
<td>IV beta blockers are potentially harmful when risk factors for shock are present</td>
<td>III</td>
</tr>
</tbody>
</table>
IV followed by Oral Metoprolol in STEMI

**COMMIT (N = 45,852)**

- **Death**
  - Placebo: 1797 deaths (7.8%)
  - Metoprolol: 1774 deaths (7.7%)
  - 1% (SE 3) proportional risk reduction (p=0.7)

- **ReMI**
  - Placebo: 8% (SE 1%)
  - Metoprolol: 7% (SE 1%)
  - P=0.002

**Totality of Evidence (N = 52,411)**

- **Death (any cause)**
  - 26 small trials
  - MIAMI
  - ISIS-1
  - COMMIT (low-risk only)
  - Total
  - Death 13% (P=0.0006)

- **ReMI**
  - 22% (P=0.0002)

- **VF**
  - 15% (P=0.002)

**Risk factors for cardiogenic shock**
- Heart failure
- Age > 70
- Systolic blood pressure < 120
- Sinus tachycardia > 110 or heart rate < 60
- Increased time since onset of STEMI symptoms

*Lancet. 2005;366:1622*
Renin-Angiotensin System Inhibitor

- **Class I**
  - ACEI within 24 hours- acute MI, CHF, EF<40%
  - ARB for ACEI intolerance
  - Aldosterone antagonist- AMI patients on ACEI/BB and EF <40% with symptomatic CHF or DM

- **Class II**
  - ACEI reasonable for all patients without contraindications
ACE Inhibitors in AMI

**SAVE** - EF ≤40% (captopril)
**AIRE** - clinical CHF (ramipril)
**TRACE** - EF ≤35% (trandolapril)

Cumulative Mortality

- **Placebo:** 866/2971 (29.1%)
- **ACE-I:** 702/2995 (23.4%)
- **OR:** 0.74 (0.66–0.83)

<table>
<thead>
<tr>
<th>Years</th>
<th>ACE-I</th>
<th>Placebo</th>
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<tr>
<td>0</td>
<td>2995</td>
<td>2971</td>
</tr>
<tr>
<td>1</td>
<td>2250</td>
<td>2184</td>
</tr>
<tr>
<td>2</td>
<td>161</td>
<td>1521</td>
</tr>
<tr>
<td>3</td>
<td>892</td>
<td>853</td>
</tr>
<tr>
<td>4</td>
<td>223</td>
<td>138</td>
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</table>
Aldosterone Blockade Post-MI

Randomized 3-14 d. post MI:
Eplerenone (titrated 50mg daily) vs. placebo
Cholesterol management

<table>
<thead>
<tr>
<th>Action</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate or continue high-intensity statin therapy in patients with no contraindications</td>
<td>I</td>
</tr>
<tr>
<td>Obtain a fasting lipid profile, preferably within 24 h</td>
<td>IIa</td>
</tr>
</tbody>
</table>

Statin therapy

**Age <75 (high intensity):**
- Atorvastatin 40-80 mg daily
- Rosuvastatin 20-40 mg daily

**Age >75 (moderate intensity):**
- Atorvastatin 10-20 mg daily
- Rosuvastatin 5-10 mg daily
- Simvastatin 20-40 mg daily
- Pravastatin 40-80 mg
~10,000 patients (40% ACS); completed 1-year of DAPT after coronary DES
Extended DAPT with extended dual antiplatelet therapy for 12 months

Mauri et al. NEJM 2014

**Table 3. Bleeding End Point during Month 12 to Month 30.**

<table>
<thead>
<tr>
<th>Bleeding Complications</th>
<th>Continued Thienopyridine (N=4710)</th>
<th>Placebo (N=4649)</th>
<th>Difference</th>
<th>Two-Sided P Value for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
<td>percentage points (95% CI)</td>
<td></td>
</tr>
<tr>
<td>GUSTO severe or moderate†</td>
<td>119 (2.5)</td>
<td>73 (1.6)</td>
<td>1.0 (0.4 to 1.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>38 (0.8)</td>
<td>26 (0.6)</td>
<td>0.2 (-0.1 to 0.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Moderate</td>
<td>81 (1.7)</td>
<td>48 (1.0)</td>
<td>0.7 (0.2 to 1.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>BARC type 2, 3, or 5</td>
<td>263 (5.6)</td>
<td>137 (2.9)</td>
<td>2.6 (1.8 to 3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 2</td>
<td>145 (3.1)</td>
<td>72 (1.5)</td>
<td>1.5 (0.9 to 2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 3</td>
<td>122 (2.6)</td>
<td>68 (1.5)</td>
<td>1.1 (0.6 to 1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 5</td>
<td>7 (0.1)</td>
<td>4 (0.1)</td>
<td>0.1 (-0.1 to 0.2)</td>
<td>0.38</td>
</tr>
</tbody>
</table>
DAPT Score

Clinical Prediction Variable

Age, y
- ≥75
- 65-<75
- <65

Cigarette smoking
Diabetes mellitus
MI at presentation
Prior PCI or prior MI
Paclitaxel-eluting stent
Stent diameter <3 mm
CHF or LVEF <30%
Vein graft stent
Total score range

Yeh et al JAMA 2015
Triple therapy

- Concomitant indication for long-term anticoagulation
- Triple therapy is associated with a markedly high risk of bleeding and should be minimized as much as possible

Considerations
- Use of bare metal stents
- Discontinuing anticoagulation until DAPT can be completed
- P2Y12 + warfarin (WOEST)
- P2Y12 + 15 mg daily rivaroxaban (PIioneer-AF)
- P2Y12 + apixaban/dabigatran

- Triple therapy for shortest duration
  - Avoid ticagrelor or prasugrel
Summary

- UA/NSTEMI patients represent a heterogeneous group with varying risk of adverse outcomes

- Early risk stratification can be used to tailor treatment intensity with the likelihood of benefit and risk

- Antithrombotics and antiplatelet agents are critical in the management

- Long-term treatment with beta blockers, RAAS blockers, statins and risk factor modification is key
Thank You