**Evidence-Based Management of Acute Coronary Syndromes**

*Update in Hospital Medicine*

*September 30, 2020*

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**Disclosures**

Research Grant Support through BWH: Agen; Anthos Therapeutics, Inc.; AstraZeneca; Daiichi-Sankyo; Eisai; Intarcia; Medicines Company; MedImmune; Merck; Novartis; Pfizer

Scientific Advisory Boards & Consulting: Athera; Agen; Anthos Therapeutics; AstraZeneca; Bristol-Myers Squibb; DaiCor; Dr. Reddy's Laboratories; Intarcia; Merck

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**ECG**

- **What to look for**
  - STE or LBBB not known to be old
  - ST depression ≥0.5 mm; TWI >1 mm
  - Coronary distribution

- **What else to look for**
  - Q waves or poor R-wave progression (PRWP)

- **How to look for it**
  - 12-lead ECG w/in 10 mins of presentation
  - Compare to prior ECGs
  - Obtain serial ECGs (initial ⊕ in <50% ACS Pts)

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**Where is the Lesion?**

- Acute Coronary Syndromes
  - Non-ST elevation ACS
  - ST elevation ACS

  - CK-MB
  - Tn

  - UA
  - NSTEMI
  - STEMI

  - UA
  - NQwMI
  - QwMI

---

**Where is the Lesion?**

- Acute Coronary Syndromes
  - STEMI
  - NSTEMI
  - UA

- Acute Coronary Syndromes
  - QwMI
  - Non-ST elevation ACS
  - ST elevation ACS

- Acute Coronary Syndromes
  - UA
  - NQwMI
  - QwMI

- Acute Coronary Syndromes
  - STEMI
  - NSTEMI
  - UA

---

Investigational, unlabeled and/or unapproved uses of drugs or devices will be discussed in this presentation.
**ECG Special Placement**

Right-sided leads (V_{4R})  
Posterior leads (V_{7-V_{9}})

To diagnose RV infarct in setting of inferior STEMI (due to proximal RCA occlusion)

To diagnose posterior MI (due to LCx occlusion) in setting of concerning sx and either ant. ST depressions or normal ECG

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**Ruling In & Ruling Out MI**

*Case #1*

75 yo M p/w chest pain x 15 minutes that started 3 hours ago, now resolved.

ECG without abnormalities.

Your biomarker testing strategy is:

A. Check troponin now; if undetectable, discharge to home
B. Check troponin now and in 1 hour; if both <99\%ile and no change over time, discharge to home
C. Check troponin now and 3-6 hours after sx onset; if both <99\%ile, discharge to home

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---

**ACS: Biomarkers**

<table>
<thead>
<tr>
<th>Era</th>
<th>Assay</th>
<th>Measure at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancient History (1980s)</td>
<td>CK-MB</td>
<td>q8 hrs × 3</td>
</tr>
<tr>
<td>Dawn of modern cardiac markers (1990s)</td>
<td>Troponin</td>
<td>q8 hrs × 3</td>
</tr>
<tr>
<td>Recent past</td>
<td>Troponin</td>
<td>3-6 hrs after sx onset</td>
</tr>
<tr>
<td>Now</td>
<td>hs-Troponin</td>
<td>± 1-3 hrs later (depending on time from sx onset to presentation)</td>
</tr>
</tbody>
</table>

---

**Partners Pathway**

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**4th Universal Definition of MI**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Injury</td>
<td>Tn &gt;99%ile (acute if rise and/or fall)</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>Acute myocardial injury + clinical evidence of acute myocardial ischemia (eg, sx, ECG, imaging)</td>
</tr>
<tr>
<td>Type 1</td>
<td>Atherothrombosis (plaque rupture or erosion)</td>
</tr>
<tr>
<td>Type 2</td>
<td>Imbalance between myocardial O&lt;sub&gt;2&lt;/sub&gt; supply &amp; demand unrelated to acute atherothrombosis</td>
</tr>
<tr>
<td>Type 3</td>
<td>Cardiac death w/ sx + ECG w/ Tn available</td>
</tr>
<tr>
<td>Type 4</td>
<td>PCI-related (clinical + Tn &gt;10× 99%ile)</td>
</tr>
<tr>
<td>Type 5</td>
<td>CABG-related (clinical + Tn &gt;10× 99%ile)</td>
</tr>
</tbody>
</table>
**Type 2 MI & Myocardial Injury**

- **Type 2 MI** ≠ MI not due to ACS
  - ↓ myocardial perfusion
  - Coronary artery spasm, embolism, dissection
  - HTN, profound sustained bradycardia, severe anemia
  - ↑ myocardial demand
  - Profound sustained tachycardia; HTN
- **Myocardial Injury** = ↑ Tn w/o clinical s/s ischemia
  - Heart failure, myocarditis, CMP, Takotsubo
  - Cardiac ablation, defibrillation, cardiac confusion
  - PE, PHT
  - Stroke, SAH, critical illness

---

**Revascularization in STEMI**

*Case #2*

65 yo M p/w STEMI, w/ inferior ST segment elevations. Brought for immediate coronary angiography and found to have occluded RCA, which is successfully stented and Pt doing well. Also noted to have 80% mid LAD lesion and a 50% LCx lesion.

A. Low level stress test before discharge
B. Stent the LAD lesion during this hospitalization or w/in 6 wks
C. Stent the LAD & LCx lesions now

---

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**ACS Likelihood**

<table>
<thead>
<tr>
<th>Feature</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Chest or L arm pain or discomfort as chief ex or prior decienga</td>
<td>Chest or L arm pain or discomfort as chief ex</td>
<td>Prob ischemic as w/o internal/Extraneous characteristics or Recent cocaine use</td>
</tr>
<tr>
<td>Age ≥ 70 y</td>
<td>Male sex</td>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Exam</td>
<td>Transient MI murmur, HTN</td>
<td>Transient vascular disease</td>
<td>Chest discomfort reproduced by palp</td>
</tr>
<tr>
<td>ECG</td>
<td>New, or presumably new, transient ST elevation (≥1 mm) or T wave inversion (≥0.1 mV) in multiple precordial leads</td>
<td>PT elevation ≤ 0.5 mm or T wave inversion ≤ 0.1 mm in leads w/ dominant R axis</td>
<td>Transient or inversion ≤ 0.1 mV in leads w/ dominant R axis</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Elevated</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>


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**Preventive PCI in STEMI**

**COMPLETE: 2016 Pts w/ STEMI + MVD**

Revasc of all sign/l lesions (≥70% or 50-69% w/ FFR ≤ 0.80) w/in 45 days vs. culprit only

- Hazard ratio, 0.74 (95% CI, 0.60-0.91)
- P=0.004

- Complete revascularization
**Immediate PCI of all other lesions >70% (incl CTO) vs. Culprit only, with option for staged PCI**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Culprit Only</th>
<th>Multivessel PCI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast (ml)</td>
<td>190</td>
<td>250</td>
<td>0.001</td>
</tr>
<tr>
<td>Death or RRT (%)</td>
<td>45.9</td>
<td>55.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Death</td>
<td>43.3</td>
<td>51.6</td>
<td></td>
</tr>
<tr>
<td>RRT</td>
<td>11.6</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>1.2</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>16.6</td>
<td>22.0</td>
<td></td>
</tr>
</tbody>
</table>

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**What To do after Fibrinolysis?**

- If it fails [persistent STE (<50% resolution) or sx, development of shock, evidence of infarct-related artery reocclusion]: rescue PCI
- If it succeeds:
  - Non-invasive ischemia testing (ie, stress test), OR
  - Transfer high-risk pts w/in 3-24 hrs for elective PCI (high-risk = anterior MI, inferior MI w/ low EF or RV infarct, extensive STE or LBBB, HF, hypotension or tachycardia)

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**Which NSTEACS Go to the Cath Lab?**

*Case #3*
72 yo F w/ chest pain that started 3 hours ago.
ECG shows inferior ST segment depressions. Troponin elevated.
Now chest pain free and ECG normalized.

A. Stress test in 48 hours
B. Cath immediately
C. Cath within 24 hours
D. Cath within 72 hours

---

**Management Strategy in NSTEACS**

**INVASIVE**
(ie, angiography for all in ~48 hrs)

- Initial Med Rx
- PCI / CABG
- Long-term Med Rx

**CONSERVATIVE**
(ie, selective angiography)

---

**Benefit of INV vs CONS Strategy**

INV Strategy reduces cardiac complications by ~20%, particularly recurrent ACS

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**NSTEACS**
Initial Med Rx ➔ PCI / CABG ➔ Long-term Med Rx

**CONT'd Med Rx**

---

**Go to the Cath Lab?**

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Now chest pain free and ECG normalized.

A. Stress test in 48 hours
B. Cath immediately
C. Cath within 24 hours
D. Cath within 72 hours
Troponin Treatment Interaction

\[ \text{Cons} \quad \text{INV} \]

**Interaction**

\[ P<0.001 \]

\[ \text{OR}=1.60 \]

\[ (0.83-3.0) \]

\[ N=734 \]

\[ \text{N}=181 \]

\[ \text{N}=213 \]

\[ \text{N}=693 \]

**2014 ACC/AHA NSTEACS Guidelines:**

- **Immediate (w/in 2 h)**
  - Refractory angina
  - Signs or symptoms of HF or new or worsening MI
  - Recurrent angina or ischemia at rest or with low-level activity despite intensive med Rx
- **Early Invasive (w/in 24 h)**
  - TIMI Risk Score 22
  - GRACE score >180
  - Diabetics
  - GFR <60 mL/min/1.73m²
  - EF <40
  - Early postinfarction angina
  - PCI w/in 6 mo
  - Prior CABG
- **Delayed Invasive (w/in 25-72 h)**
  - TIMI Risk Score ≥2
  - New ST depression
  - Early Invasive
  - Prior CABG
  - PCI w/in 6 mo
  - GFR <60
  - GRACE score >109
  - TIMI Risk Score ≥2

**Anti-Ischemic Therapy**

- **Nitrites**
  - Sx relief; no mort benefit (GISSI-3 & ISIS-4)
- **Beta-blockers**
  - ↓ Ischemia, ↓ D/MI (in AMI trials)
  - PO (not IV) and only if not in HF or at risk for shock
- **Calcium channel blockers**
  - If ischemia despite max βB or βB contra.
- **Morphine**
  - Pain, CHF, agitation; don’t mask angina
- **Oxygen**

**Antithrombotic Therapy**

**Case #4**

65 yo M p/w chest pain that started 2 hours ago.

ECG shows anterior ST segment depressions. Troponin elevated.

Has received aspirin.

- A. Add an oral P2Y₁₂ inhibitor: clopidogrel
- B. Add an oral P2Y₁₂ inhibitor: prasugrel
- C. Add an oral P2Y₁₂ inhibitor: ticagrelor
- D. Add an intravenous P2Y₁₂ inhibitor: cangrelor
- E. Add an intravenous GP IIb/IIIa inhibitor: epifibatide
**Antithrombotic Therapy Acutely**

- **Start with COX Inhibitor** (e.g., aspirin)
- **Almost always add**: P2Y<sub>12</sub> Inhibitor (e.g., ticagrelor or prasugrel preferred over clopidogrel)
- **Sometimes also add** (typically in cath lab): glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban)

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**Primary efficacy endpoint: CV death, MI or stroke**

18,624 Patients w/in 24 hrs of onset of ACS

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Days after randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>9,333</td>
</tr>
<tr>
<td></td>
<td>6,628</td>
</tr>
<tr>
<td></td>
<td>6,460</td>
</tr>
<tr>
<td></td>
<td>6,219</td>
</tr>
<tr>
<td></td>
<td>6,743</td>
</tr>
<tr>
<td></td>
<td>5,161</td>
</tr>
<tr>
<td></td>
<td>4,147</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>9,291</td>
</tr>
<tr>
<td></td>
<td>8,521</td>
</tr>
<tr>
<td></td>
<td>8,362</td>
</tr>
<tr>
<td></td>
<td>8,124</td>
</tr>
<tr>
<td></td>
<td>7,643</td>
</tr>
<tr>
<td></td>
<td>5,086</td>
</tr>
<tr>
<td></td>
<td>4,047</td>
</tr>
</tbody>
</table>

- HR 0.94 (95% CI 0.77-0.92) P=0.0003

Cardiovascular Death: 4.4% vs. 5.1%, HR 0.79 (0.69-0.89), P=0.001

- All cause Mortality: 4.5% vs. 5.9%, HR 0.78 (0.69-0.89), P<0.001

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**Prasugrel vs. Ticagrelor**

ISAR-REACT 5: 4018 Pts w/ ACS

- Hazard ratio 1.36 [1.09-1.70]; P=0.002

---

**ACCOAST design**

- NSTE-ACS + Troponin ≥ 1.1 times ULN local lab value
- Clopidogrel 300 mg loading (before angiography)
- PCI within 24 hrs
- Prasugrel 30 mg loading (before angiography)
- PCI within 24 hrs
- Medical management before PCI
- Prasugrel 10 mg or 5 mg based on weight and age for 30 days

---

**1<sup>st</sup> Efficacy End Point (All Patients)**
Cangrelor: Intravenous P2Y12 Inhibitor

CHAMPION PHOENIX:
N = 10,900 patients with stable angina or ACS
Cangrelor (2-4 hrs, then clopidogrel) vs. clopidogrel. Start at time of PCI

<table>
<thead>
<tr>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, ischemic-driven</td>
<td>4.7%</td>
<td>5.9%</td>
<td>0.70 (0.66,0.93)</td>
</tr>
<tr>
<td>Revasc, Stent Thrombosis</td>
<td>4.9%</td>
<td>5.9%</td>
<td>1.56 (0.83,2.93)</td>
</tr>
</tbody>
</table>

Anticoagulants in NSTEMI

- INVASIVE STRATEGY
  - UFH
  - Bivalirudin
  - Enoxaparin (LMWH)
  - Discontinue after uncomplicated PCI

- CONSERVATIVE STRATEGY
  - UFH (Rx for 48 hrs)
  - Enoxaparin (LMWH) (Rx until end of hosp, up to 8 days)

Long-Term Antithrombotic Therapy

Case #5
64 yo M p/w NSTEMI. Drug-eluting stent placed in LAD. In addition to lifelong aspirin, you would also recommend:

A. P2Y₁₂ inhibitor for 30 days
B. P2Y₁₂ inhibitor for 1 year
C. P2Y₁₂ inhibitor for as long as tolerated if high ischemic risk and low bleeding risk
D. Adding low-dose rivaroxaban

Ticagrelor in Patients w/ Prior MI

21,162 Patients w/ MI 1-3 years prior
All on low-dose ASA
Median follow-up 33 months

Ticagrelor 90 mg
HR 0.88 (95% CI 0.75 – 0.96)
P=0.008

Ticagrelor 60 mg
HR 0.84 (95% CI 0.74 – 0.95)
P=0.004

Drop Aspirin after 1-3 Months (ie, P2Y₁₂ MonoRx)?

O'Donoghue ML, Murphy SA, and Sabatine MS. Circulation 2020; epub ahead of print
**Triple Therapy**

*C. Warfarin (INR 2-3), aspirin and ticagrelor
B. Full dose NOAC, aspirin, and clopidogrel
C. Full dose NOAC and clopidogrel
D. Reduced dose NOAC and clopidogrel

**Data from RCTs of Triple Rx**

- *Control arm:* warfarin + ASA + P2Y12 inhibitor
  
- *Exptal arms:* full or reduced-dose DOAC
  
  - Eliminating ASA (↓ dose of DOAC) ↓ bleeding vs. triple Rx w/ warfarin
  
  - Some regimens w/o ASA had numerically ↑ rates of MI vs. regimens w/ ASA
  
  - Stent thrombosis is rare (<1%)
  
  - Regimens w/ reduced-dose DOACs had numerically ↑ rates of ischemic stroke vs. regimens w/ warfarin

**AUGUSTUS: Safety**

4614 Pts w/ AF + either:

- ACS+PCI (37%), ACS w/o PCI (24%), Elective PCI (39%)

- Median time from ACS to randomization 6 (IQR 3-10) days

- Drug-eluting stent placed in LAD. 50% lesions in RCA and LCx.

**Lipid-Lowering Therapy**

*C. Warfarin (INR 2-3), aspirin and ticagrelor
B. Full dose NOAC, aspirin, and clopidogrel
C. Full dose NOAC and clopidogrel
D. Reduced dose NOAC and clopidogrel

**AUGUSTUS: Efficacy**

- Median time from ACS to randomization 6 (IQR 3-10) days

- Drug-eluting stent placed in LAD. 50% lesions in RCA and LCx.

- LDL-C on admission (not on any lipid-lowering Rx) was 180 mg/dL. Started on atorva 80 mg. What else would you recommend?

  - A. Target LDL-C reduction of 50%
  
  - B. Target LDL-C of 70 mg/dL
  
  - C. Add ezetimibe
  
  - D. Add PCSK9 inhibitor
  
  - E. Add ezetimibe and/or PCSK9 to get LDL-C <70 (eg, ≤40 mg/dL)
Lipid-Lowering Therapy

Case #7
64 yo M w/ h/o NSTEMI 2 years ago now p/w NSTEMI.
Drug-eluting stent placed in LAD. 50% lesions in RCA and LCx.
LDL-C on admission (not on any lipid-lowering Rx) was 180 mg/dL.
Started on atorv 80 mg. What else would you recommend?

A. Target LDL-C reduction of 50%
B. Target LDL-C of 70 mg/dL
C. Add ezetimibe
D. Add PCSK9 inhibitor
E. Add ezetimibe and/or PCSK9i to get LDL-C <70 (eg, ≤40 mg/dL)

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

Hazard ratio 0.80 (99% CI: 0.73-0.88)
P = 0.0001

Clinical Outcomes by Baseline LDL-C

CVD, MI, stroke, UA, or car revasc

HR (95% CI)  
P interaction

All Patients  
0.85 (0.79-0.92)  
0.65
Baseline LDL-C <70 mg/dL  
0.80 (0.60-1.07)  

Baseline LDL-C ≥70 mg/dL  
0.86 (0.79-0.92)  

CVD, MI, or stroke

All Patients  
0.80 (0.73-0.88)  

Baseline LDL-C <70 mg/dL  
0.70 (0.48-1.01)  

Baseline LDL-C ≥70 mg/dL  
0.81 (0.73-0.89)  

CV Death, MI, Stroke

Hazard ratio 0.80 (99% CI: 0.73-0.88)
P = 0.0001

LDL-C at 4 weeks

PROVE IT – TIMI 22

4162 patients hospitalized w/in prior 10 d for ACS

Atorvastatin 80 mg
(avg achieved LDL = 62 mg/dl)

Evolocumab (anti-PCSK9 mAb)

Hazard ratio 0.89 (99% CI: 0.82-0.97)
P = 0.0001

EVOLO study results

All Patients

0.89 (0.82-0.97)  
P = 0.0001

EVOLO study results

All Patients

0.89 (0.82-0.97)  
P = 0.0001
β-blockers, ACEI/ARB, MRA

- Beta-blockers
- Oral BB initiated w/in 1-24 hrs if w/o:
  - signs of HF, evidence of low-output state, or 1 risk of cardiogenic shock
  - other contraindication (PR >0.24 sec, 2/3º heart block w/o PPM, active asthma, reactive airway disease)
- ACEI (or ARB if cannot tolerate ACEI)
- LVEF <40%, or
- HTN, diabetes, or stable CKD
- MRA
  - If not ACEI/ARB & BB; and
  - Cr ≤2.5, K ≤5, and
  - LVEF <40%, diabetes, or HF

Summary

- Diagnose ACS using H&P, 12-lead ECG, troponin
- Anti-ischemic Rx: beta-blocker, nitrates
- For STEMI: select Primary PCI vs Lytic
- For UA/NSTEMI: select Invasive vs. Conservative Strategy
  - Tend to use INV strategy for higher risk patients (eg, Tn positive)
- Select Antiplatelet Regimen
  - ASA
  - P2Y12 Inhibitor: ticagrelor or prasugrel (or clopidogrel)
  - GP IIb/IIIa inhibitor (typically at time of PCI)
- Select Anticoagulant: UFH, LMWH, bivalirudin, or fondaparinux
- Long-term therapy
  - ASA, P2Y12 inhib (? indefinitely if tolerated), BB, statin (± EZE = PCSK9)
  - 7 ACEI, 7 Aldo inhib

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