Evidence-Based Management of Acute Coronary Syndromes

Update in Hospital Medicine

October 2021

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Disclosures

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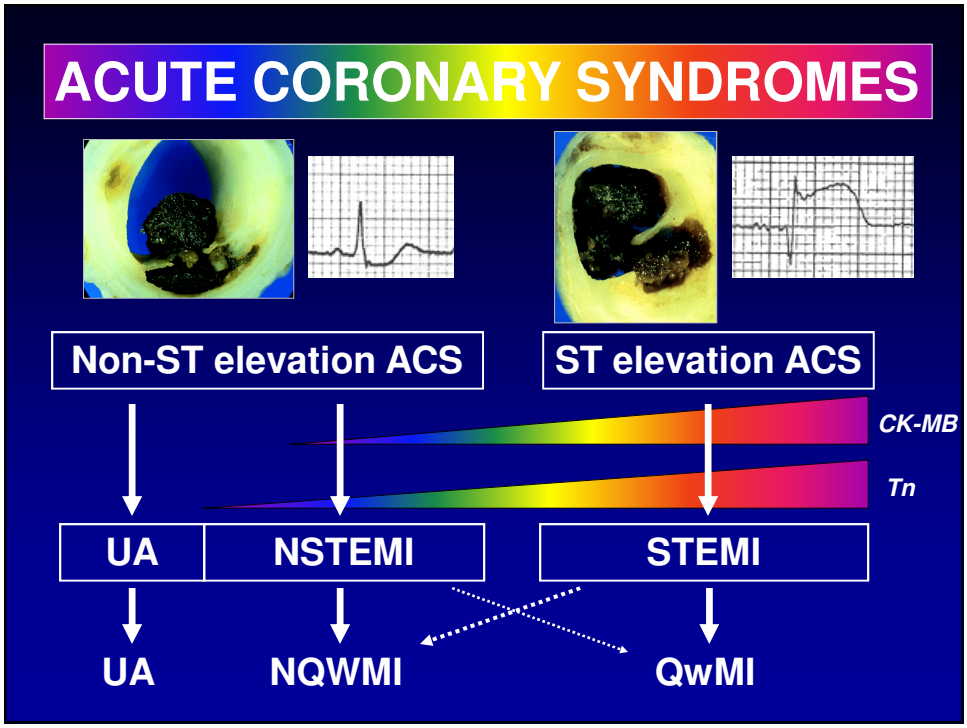
Investigational, unlabeled and/or unapproved uses of drugs or devices will be discussed in this presentation.



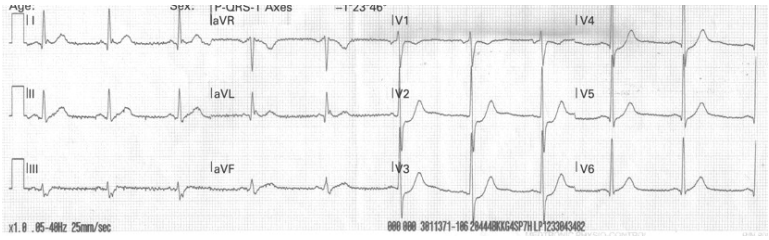
H&P

- **History**
  - Cardinal sx of angina
    1. Substernal chest discomfort w/ characteristic quality (pressure) & duration (minutes)
    2. Provoked by physical exertion or emotional stress
    3. Relieved by rest of NTG
  - Typical angina: All 3 features
  - Atypical angina: 2 of 3 features
  - Noncardiac chest pain: 0 or 1 feature
- **Physical exam**
  - Pain not reproducible
  - Signs of vascular disease
  - Signs of HF

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)

Where is the Lesion?



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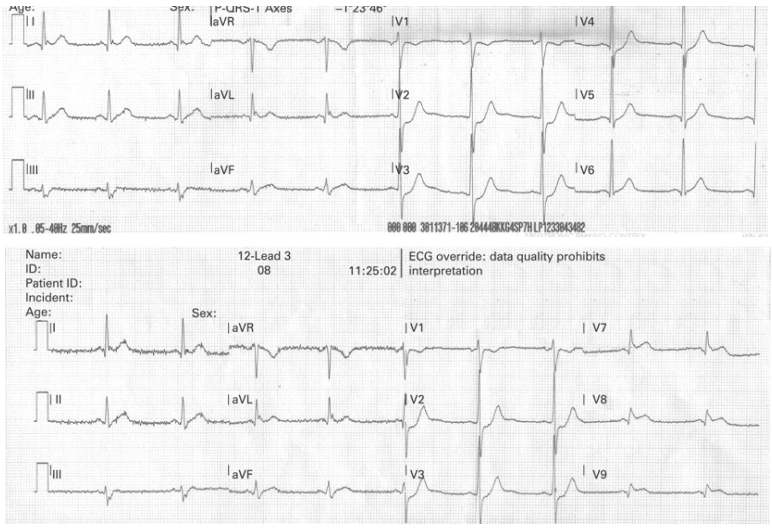
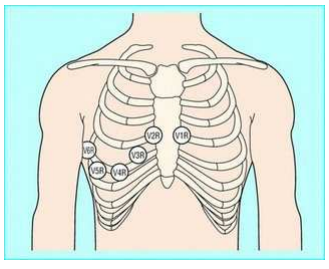
Where is the Lesion?



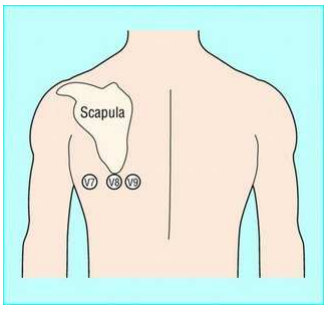
ECG Special Placement

Right-sided leads (V_{4R})



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

Posterior leads (V_7-V_9)



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

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 high-sensitivity troponin testing strategy is:

A. Check now; if undetectable, discharge to home

B. Check now and in 1 hour; if both <99th %ile and no change over time, discharge to home

C. Check now and 3-6 hours after sx onset; if both <99th %ile, discharge to home

Ruling In & Ruling Out MI

Case #1

75 yo M p/w chest pain x 15 minutes that started 4 hours ago, now resolved.

ECG without abnormalities.

Your high-sensitivity troponin testing strategy is:

A. Check now; if undetectable, discharge to home

B. **Check now and in 1 hour; if both <99th %ile and no change over time, discharge to home**

C. Check now and 3-6 hours after sx onset; if both <99th %ile, discharge to home

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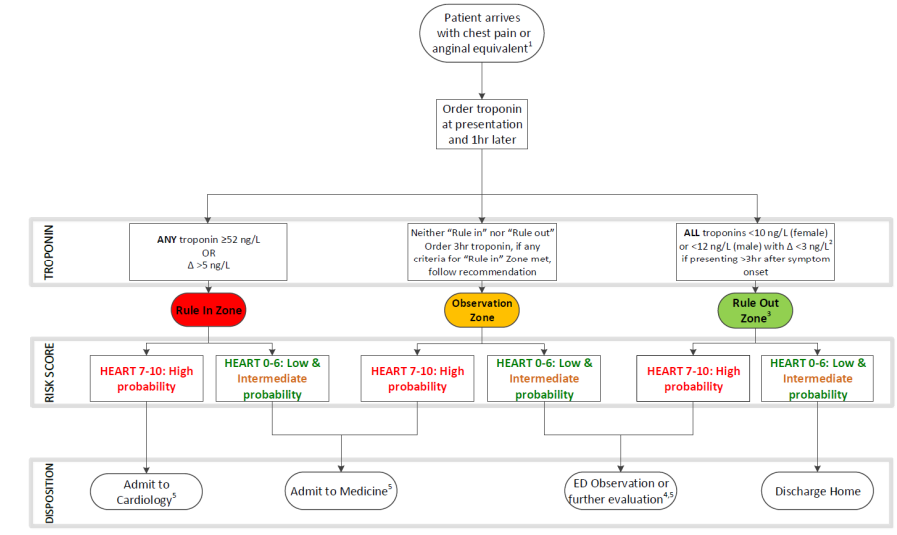
ACS: Biomarkers

Era	Assay	Measure at presentation + …
Ancient History (1980s)	CK-MB	q8 hrs × 3
Dawn of modern cardiac markers (1990s)	**Troponin**	q8 hrs × 3
Recent past	Troponin	**3-6 hrs after sx onset**
Now	**hs-Troponin**	**± 1-3 hrs later** (depending on time from sx onset to presentation) **Examine absolute and Δ**

Partners Pathway



4th Universal Definition of MI

Definition	Criteria
Myocardial **Injury**	Tn >99th %ile (acute if rise and/or fall)
Acute Myocardial **Infarction**	Acute myocardial injury + clinical evidence of acute myocardial ischemia (eg, sx, ECG, imaging)
Type 1	**Atherothrombosis** (plaque rupture or erosion)
Type 2	Imbalance between myocardial O_2 supply & demand **unrelated** to acute atherothrombosis
Type 3	**Cardiac death** w/ sx + ECG Δs before Tn available
Type 4	**PCI-related** (clinical + Tn >5× 99th %ile)
Type 5	**CABG-related** (clinical + Tn >10× 99th %ile)

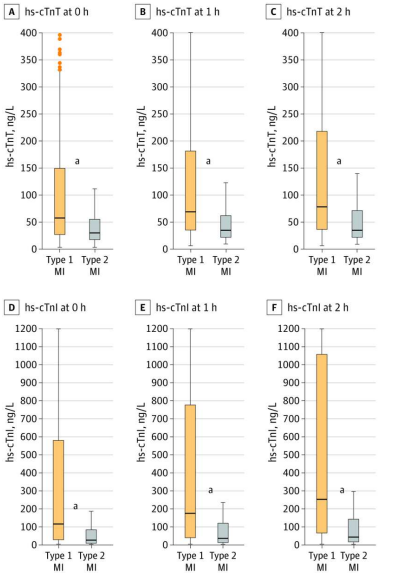
JACC 2018

Type 2 MI & Myocardial Injury

- **Type 2 MI = MI not due to ACS**
  - ↓ myocardial perfusion
    - Coronary artery spasm, embolism, dissection
    - HoTN, 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 contusion
  - PE, PHT
  - Stroke, SAH, critical illness

Type 1 vs. 2 MI

- **Largely a clinical diagnosis …**



JAMA Cardiol. Published online April 21, 2021

ACS Likelihood

Feature	High	Intermediate	Low
History	• Chest or L arm pain or discomfort as chief sx ≈ prior doc angina • Known h/o CAD	• Chest or L arm pain or discomfort as chief sx • Age >70 y • Male sex • Diabetes mellitus	• Prob ischemic sx w/o intermed-likelihood characteristics • Recent cocaine use
Exam	• Transient MR murmur, HoTN, diaphoresis, pulm edema, or rales	• Extracardiac vascular disease	• Chest discomfort reproduced by palp
ECG	• New, or presumably new, transient ST deviation (≥1 mm) or TWI (≥2 mm) in multiple precordial leads	• Fixed Q waves • ST depression 0.5-1 mm or TWI >1 mm	• Tw flattening or inversion <0.1 mV in leads w/ dominant R waves • Normal ECG
Biomarkers	• Elevated	• Normal	• Normal

ACC/AHA 2007 UA/NSTEMI Guidelines. *Circulation* 2007;116:e148

Low probability ACS Pts

- **Who?**
  - Resolution of sx (and no hemodynamic or electrical instability)
  - Normal serial ECGs
  - Normal serial cardiac troponins
- **Reasonable next steps**
  - Noninvasive functional or imaging test
  - Timing
    - Before d/c or
    - W/in 72 hrs after d/c (if very low risk Pt - TIMI Risk Score 0); ASA, NTG
  - If can exercise & interpretable ECG: exercise ECG stress test
  - Vasodilator if cannot exercise
  - Imaging if ECG uninterpretable
  - Coronary CT angiography also reasonable

Not low-probability ACS

- **Who?**
  - Concerning history
  - Persistent sx
  - Hemodynamic or electrical instability
  - Ischemic ECG
  - Elevated cardiac troponin
- **Next steps**
  - Consult cardiology
  - Anti-ischemic therapy
  - Invasive (ie, coronary angiography) or conservative (stress test) strategy
  - Antithrombotic therapy
  - Risk factor modification

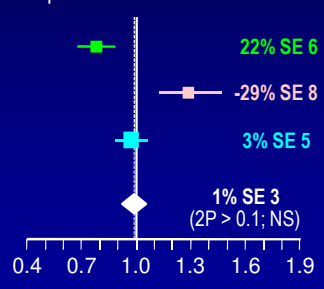
Anti-Ischemic Therapy

- **Nitrates**
  - 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**

COMMIT: Effects of METOPROLOL on Death

45,852 Patients p/w AMI w/in 24 hrs; ASA; lytic therapy (~1/2)
Randomized to metoprolol (5 mg IV q 5 min x 3,
50 mg PO q 6 hr x 4, then 200 mg XL qd) or placebo

Cause(s)	Metoprolol (22,929)	Placebo (22,923)
Arrhythmia	388 (1.7%)	498 (2.2%)
Shock	496 (2.2%)	384 (1.7%)
Other causes	890 (3.9%)	915 (4.0%)
ANY DEATH	1774 (7.7%)	1797 (7.8%)



COMMIT Collaborative Group. *Lancet.* 2005;366:1622.

Beta-Blockers in ACS

Class I

Oral βB should be initiated in the first 24 hrs if w/o any of following:
1) heart failure,
2) low output state,
3) ↑ risk for cardiogenic shock, or
4) other relative contraindications (PR >0.24 sec, 2° or 3° AVB, active asthma, or reactive airways disease)

Class III Harm

IV βB at time of presentation if risk factors for shock

Risk factors for cardiogenic shock (the greater the number of risk factors present, higher the risk) are:
age >70 yrs, SBP <120 mm Hg, HR >110 bpm or <60 bpm, and ↑ time since onset of symptoms.

Circ 2013;127:e362

Which NSTEACS Go to the Cath Lab?

Case #2

72 yo F p/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 now
B. Stress test in 48 hours
C. Cath immediately
D. Cath within 24 hours
E. Cath within 72 hours

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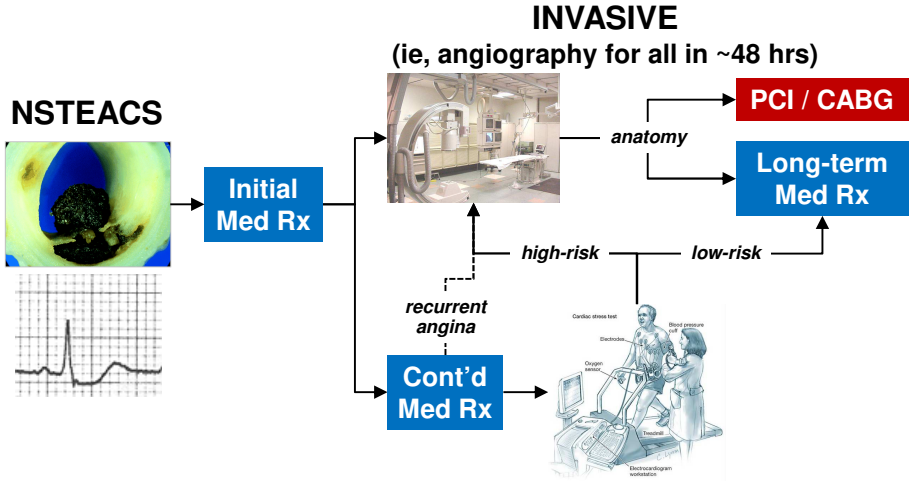
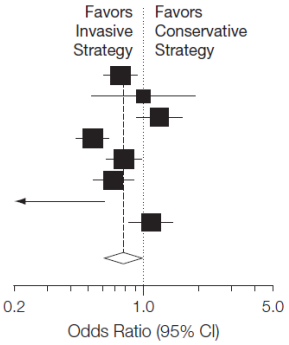
Management Strategy in NSTEACS



Benefit of INV vs CONS Strategy

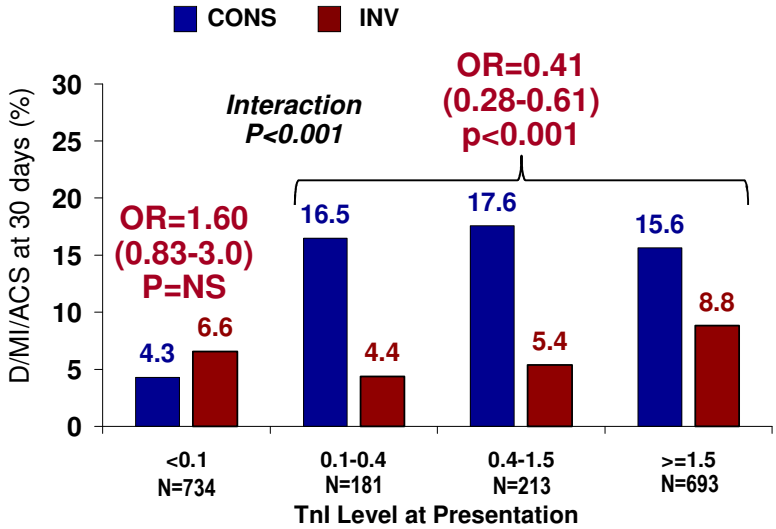
All Patients	Rates of Death, MI, or Rehospitalization With ACS, No./Total No. (%)		Odds Ratio (95% CI)
	Invasive Strategy	Conservative Strategy	
TIMI IIIB[10]	122/895 (13.6)	171/915 (18.7)	0.75 (0.61-0.93)
MATE[11]	27/111 (24.3)	22/90 (24.4)	0.99 (0.52-1.90)
VANQWISH[18]	148/462 (32.0)	124/458 (27.7)	1.22 (0.92-1.61)
FRISC II[1]	196/1093 (17.9)	322/1102 (29.2)	0.53 (0.43-0.65)
TACTICS-TIMI 18[7]	177/1114 (15.9)	215/1106 (19.4)	0.78 (0.63-0.97)
RITA 3[2]	122/895 (13.6)	171/915 (18.7)	0.69 (0.53-0.88)
VINO[20]	5/64 (7.8)	19/67 (28.4)	0.21 (0.07-0.62)
ICTUS[8]	137/604 (22.7)	126/596 (21.1)	1.09 (0.83-1.44)
Overall	1075/5083 (21.1)	1313/5067 (25.9)	0.78 (0.61-0.98)



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

O'Donoghue M, et al. *JAMA* 2008;300:71-80

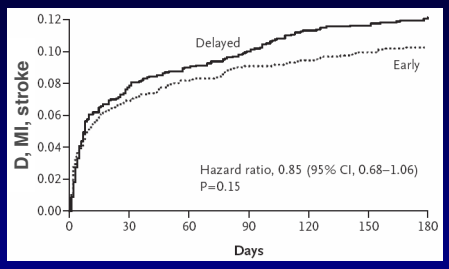
Troponin Treatment Interaction

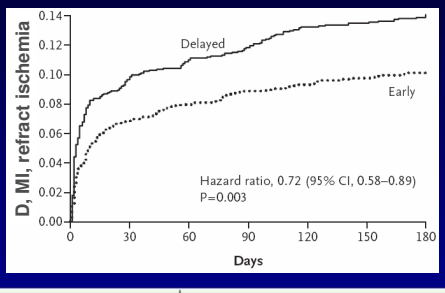


Cannon CP et al. *NEJM* 2001;344:1879

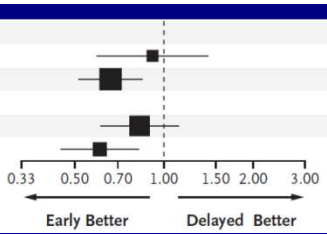
TIMACS

3031 Patients with NSTEACS
Cath w/in 24 h (median 14 h) or >36 h (median 50 h)





Elevated cardiac marker				
No	666	11.8	12.9	0.92 (0.59–1.41)
Yes	2365	8.8	13.0	0.67 (0.52–0.85)
GRACE score				
0–140	2049	7.5	8.8	0.83 (0.61–1.12)
≥141	982	13.7	21.6	0.62 (0.45–0.83)



Mehta SR et al. *NEJM* 2009;360:2165-75

2014 ACC/AHA NSTEACS Guidelines: Early Invasive

Immediate (w/in 2 h)	Early Invasive (w/in 24 h)	Delayed Invasive (w/in 25-72 h)	Ischemia-Guided
• Refractory angina • Signs or symptoms of HF or new or worsening MR • Recurrent angina or ischemia at rest or with low-level activity despite intensive med Rx	• GRACE score >140 • Temporal Δ in Tn • New or presumably new ST depression	• TIMI Risk Score ≥2 • GRACE score >109-140 • Diabetes • GFR <60 mL/min/1.73m^2 • EF <0.40 • Early postinfarction angina • PCI w/in 6 mo • Prior CABG	• TIMI Risk Score 0-1 • GRACE score <109 • Low-risk Tn-neg female patient • Patient or clinician preference in absence of high-risk features

Circulation 2014;130:2354-94

Noninvasive Testing Options

- **Pt needs to be free of ischemia for 12-24 hours**
- **Testing options**
  - If can exercise & interpretable ECG: exercise ECG stress test
  - Vasodilator if cannot exercise
  - Imaging if ECG uninterpretable or cannot exercise [also reasonable in all given intermediate-to-high risk of CAD]
  - Coronary CT angiography

Antithrombotic Therapy

Case #3

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 $P2Y_{12}$ inhibitor: clopidogrel
B. Add an oral $P2Y_{12}$ inhibitor: prasugrel
C. Add an oral $P2Y_{12}$ inhibitor: ticagrelor
D. Add an intravenous $P2Y_{12}$ inhibitor: cangrelor
E. Add an intravenous GP IIb/IIIa inhibitor: eptifibatide

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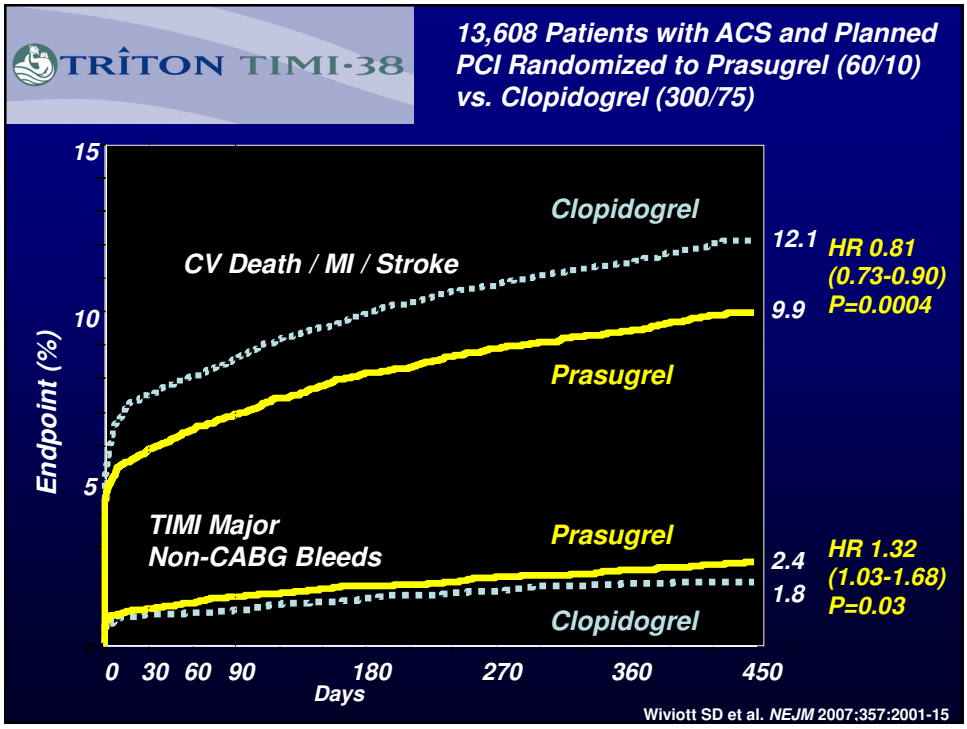
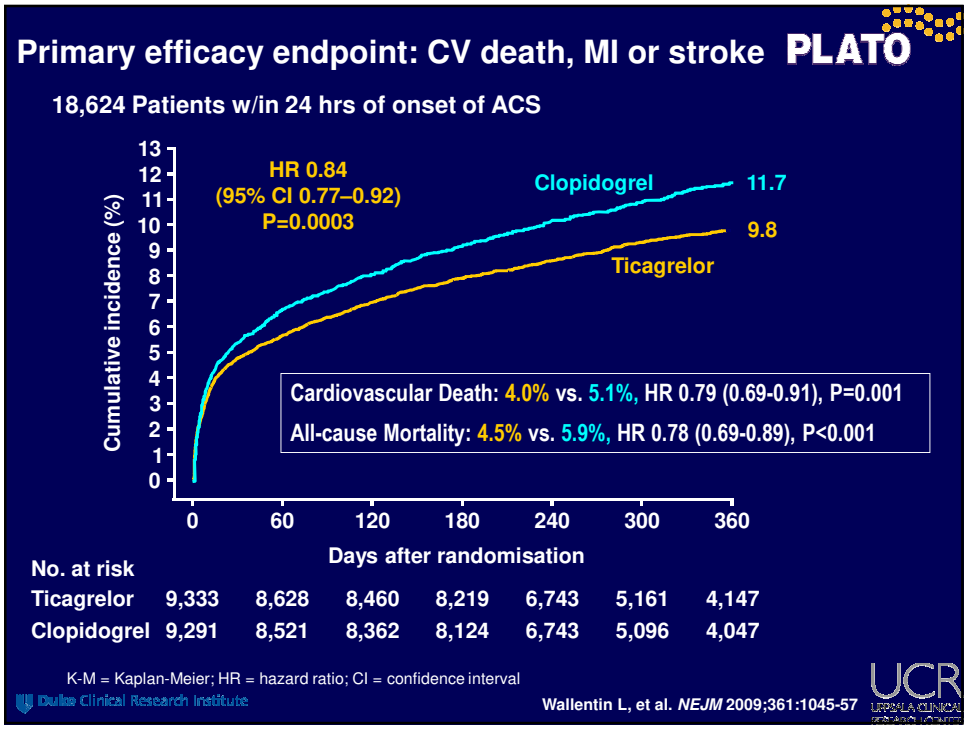
Antiplatelet Therapy Acutely

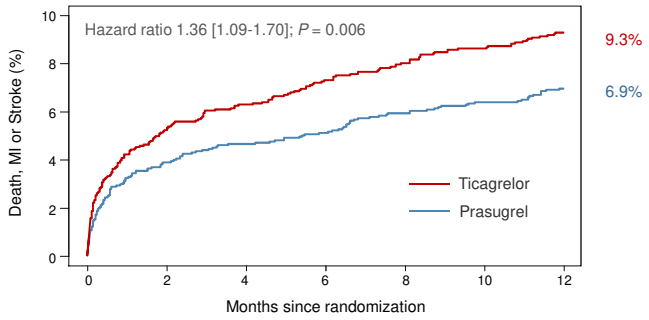
- ***Start with*** **COX Inhibitor (ie, aspirin)**
- ***Almost always add:*** **$P2Y_{12}$ Inhibitr (eg, ticagrelor or prasugrel preferred over clopidgrel)**
- ***Sometimes also add (typically in cath lab)*: glycoprotein IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban)**


TRITON TIMI-38
13,608 Patients with ACS and Planned PCI Randomized to Prasugrel (60/10) vs. Clopidogrel (300/75)
Endpoint (%)
15
10
5
0
CV Death / MI / Stroke
Clopidogrel
Prasugrel
12.1
9.9
HR 0.81
(0.73-0.90)
P=0.0004
TIMI Major
Non-CABG Bleeds
Prasugrel
Clopidogrel
2.4
1.8
HR 1.32
(1.03-1.68)
P=0.03
0 30 60 90 180 270 360 450
Days
Wiviott SD et al. NEJM 2007:357:2001-15


Primary efficacy endpoint: CV death, MI or stroke
PLATO
18,624 Patients w/in 24 hrs of onset of ACS
Cumulative incidence (%)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
HR 0.84
(95% CI 0.77–0.92)
P=0.0003
Clopidogrel
11.7
9.8
Ticagrelor
Cardiovascular Death: 4.0% vs. 5.1%, HR 0.79 (0.69-0.91), P=0.001
All-cause Mortality: 4.5% vs. 5.9%, HR 0.78 (0.69-0.89), P<0.001
0 60 120 180 240 300 360
Days after randomisation
No. at risk
Ticagrelor 9,333 8,628 8,460 8,219 6,743 5,161 4,147
Clopidogrel 9,291 8,521 8,362 8,124 6,743 5,096 4,047
K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval
Duke Clinical Research Institute
Wallentin L, et al. NEJM 2009;361:1045-57
UCR

Prasugrel vs. Ticagrelor

ISAR-REACT 5: 4018 Pts w/ ACS



NEJM 2019;epub

$P2Y_{12}$ Inhibitor Pretreament?
(ie, before angiography)

PROS

- How clopidogrel & ticagrelor (but not prasugrel) were studied
- Earlier platelet inhibition *should* ↓ risk of further ischemic events
- Ensures dual antiplatelet therapy fully in effect during PCI

CONS

- RCTs of preRx have not shown clinical benefit
- PreRx does ↑ risk of bleeding
- If anatomy warrants CABG, could delay surgery
- Ticagrelor & prasugrel fairly fast acting (onset 30 mins)
- IV $P2Y_{12}$ inhib available

Anticoagulants in NSTEACS

- **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)*

ST-Elevation MI (STEMI)

- **Consider immediate reperfusion therapy**
- **In whom?**
  - Within 12 hrs of sx onset, or
  - 12-24 hrs after sx onset if clinical or ECG evidence of ongoing ischemia
- **How?**
  - **Primary PCI** (including transfer to PCI-capable hosp if door-in to door-out time will be <30 min & 1st med contact to PCI anticipated <120 min)
  - Fibrinolytic (barring contraindications*)

*Absolute: prior ICH; intracranial neoplasm, aneurysm, or AVM; stroke or head trauma w/in 3 mos; active internal bleeding or diathesis; suspected AoD

*Relative: severe HTN; stroke; prolonged CPR; recent bleed, surgery or trauma; noncompressible vasc puncture; pregnancy; current use of anticoagulants

Revascularization in STEMI

Case #4

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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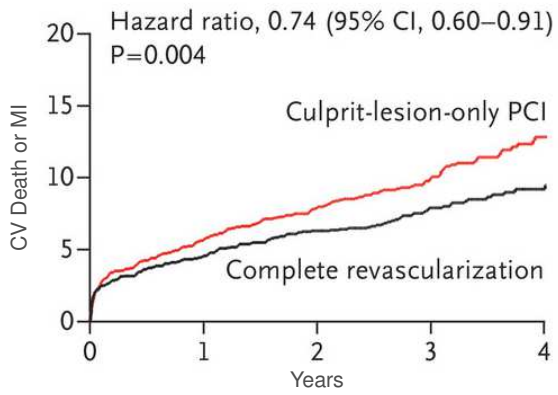
Preventive PCI in STEMI

COMPLETE: 2016 Pts w/ STEMI + MVD

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

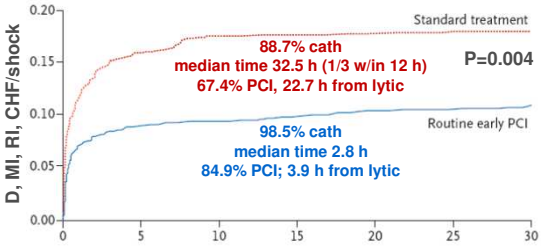


Mehta et al. *NEJM* 2019;epub

What To Do after Fibrinolysis?

- **If it <u>fails</u> (persistent STE [<50% resolution] or sx, development of shock, evidence of infarct-related artery reocclusion): rescue PCI**
- **If it <u>succeeds</u>:**
  - **Non-invasive ischemia testing (ie, stress test), <u>OR</u>**
  - **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)

- ***1059 high-risk STEMI Pts Rx'd with lytic***
- ***Rand. to immed transfer w/ PCI w/in 6 h or rec for cath w/in 2 wks (earlier if needed)***



Transfer-AMI, *NEJM* 2009;360:2705-18

Long-Term Antithrombotic Therapy

Case #5

64 yo M p/w NSTEMI. History of prior MI and diabetes.

Drug-eluting stent placed in LAD.

For his long-term anti-platelet regimen, you would recommend:

A. ASA + $P2Y_{12}$ inhibitor for 30 days
B. ASA + $P2Y_{12}$ inhibitor for 1 year
C. ASA + $P2Y_{12}$ inhibitor for as long as tolerated if high ischemic risk and low bleeding risk
D. ASA + $P2Y_{12}$ inhibitor for 3 months and then $P2Y_{12}$ inhib. monoRx

Long-Term Antithrombotic Therapy

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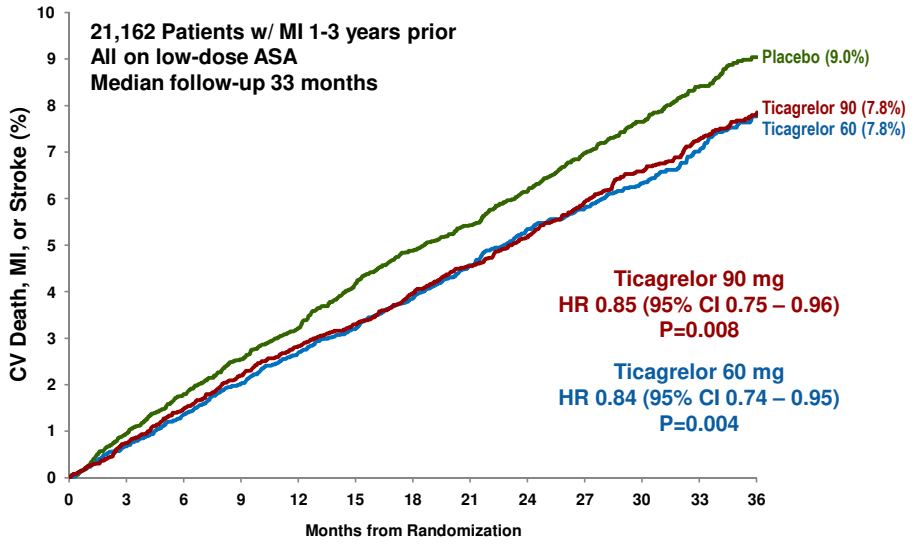
Ticagrelor + ASA Better Than ASA Alone



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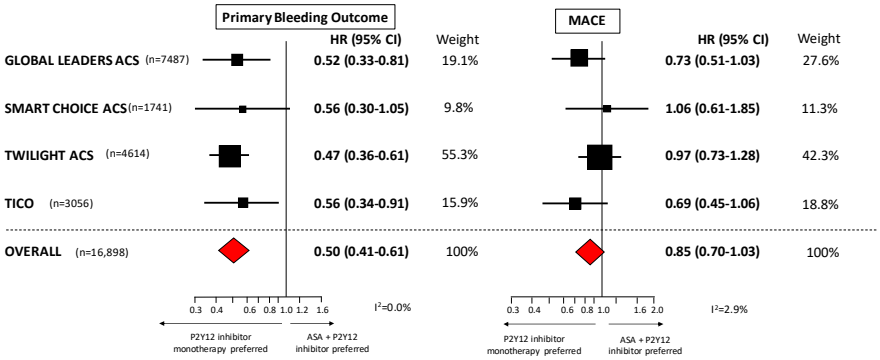
Bonaca MP et al. and Sabatine MS. *NEJM* 2015; 372:179

Drop Aspirin after 1-3 Months (ie, $P2Y_{12}$ MonoRx)?



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

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Duration of P2Y12 Inhibition?

- **$P2Y_{12}$ inhibitor + ASA** compared w/ **ASA alone**
  - ↓↓ MACE over 30 days, 1 year, and 3 years
  - ↑ bleeding
- **$P2Y_{12}$ inhibitor** compared w/ **$P2Y_{12}$ inhibitor + ASA**
  - Drop ASA 1-3 months after ACS
  - = MACE over 1 year; ↓↓ bleeding
- **Therefore:**
  - Reasonable to start with DAPT
  - After 3 months, transition to $P2Y_{12}$ inhibitor monotherapy (ideally ticagrelor) longterm
  - Temper decision based on ischemic and bleeding risk
    - High ischemic risk: prior MI, multivessel CAD, polyvasc disease, DM, CKD
    - High bleeding risk: ICH, h/o bleeding, anemia, cirrhosis, malignancy

Triple Therapy

Case #6

72 yo F w/ HTN, DM, prior stroke p/w NSTEMI.

2 drug-eluting stents placed in proximal LAD.

On aspirin and ticagrelor.

Develops AF next day.

What regimen do you discharge her on:

A. 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

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Data from RCTs of Triple Rx

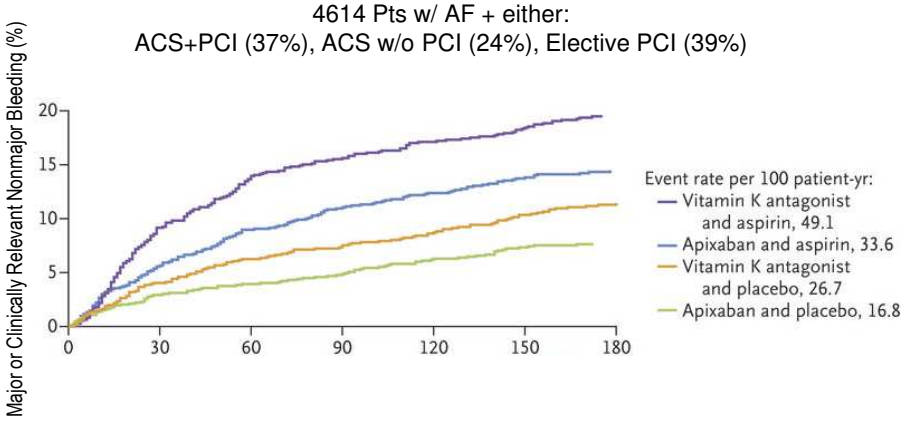
Control arm:* *warfarin + ASA + P2Y12 inhibitor
Exp'tal arms:* *full or reduced-dose DOAC with or without ASA

- **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**

Lancet 2013;381:1107; *NEJM* 2016;375:2423 & 2017:377:1513; & 2019;380:1509

AUGUSTUS: Safety

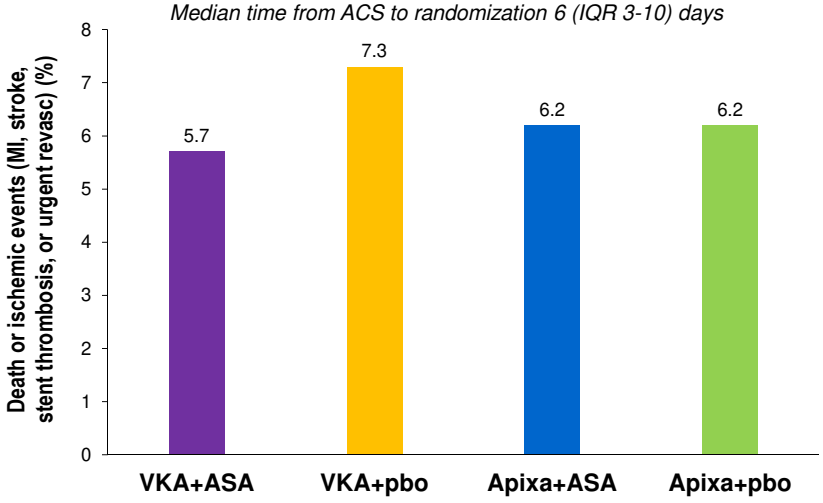
4614 Pts w/ AF + either:
ACS+PCI (37%), ACS w/o PCI (24%), Elective PCI (39%)



NEJM 2019;380:1509

AUGUSTUS: Efficacy

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



NEJM 2019;380:1509-1524

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 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 PCSK9i to get LDL-C <70 (eg, ≤40 mg/dL)

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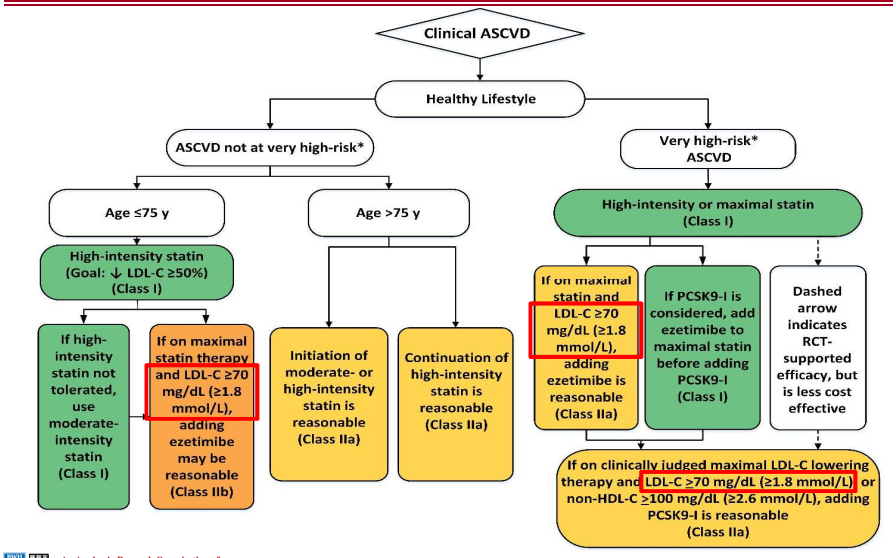
2018 AHA/ACC Guideline Secondary Prevention Recommendations



2019 ESC Dyslipidemia Guidelines

Recommendations	Class[a]	Level[b]
In secondary prevention patients at very high risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) are recommended.[33-35, 119, 120]	I	A

[c]Prior ACS, stable angina, coronary revascularization, stroke, TIA, PAD

For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal < 1.0 mmol/L (< 40 mg/dL) may be considered.[119, 120]

β-blockers, ACEI/ARB, MRA

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

Circulation 2014;130:2354-94

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
  - + $P2Y_{12}$ 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, $P2Y_{12}$ inhib (? indefinitely if tolerated), βB, statin (± EZE ± PCSK9i)
  - ? ACEI, ? Aldo inhib

Disclosures

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Scientific Advisory Boards & Consulting:

Amgen; AstraZeneca; Fibrogen; Intarcia; Merck; Moderna; Novo Nordisk

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