Evidence-Based Management of Acute Coronary Syndromes

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Disclosures

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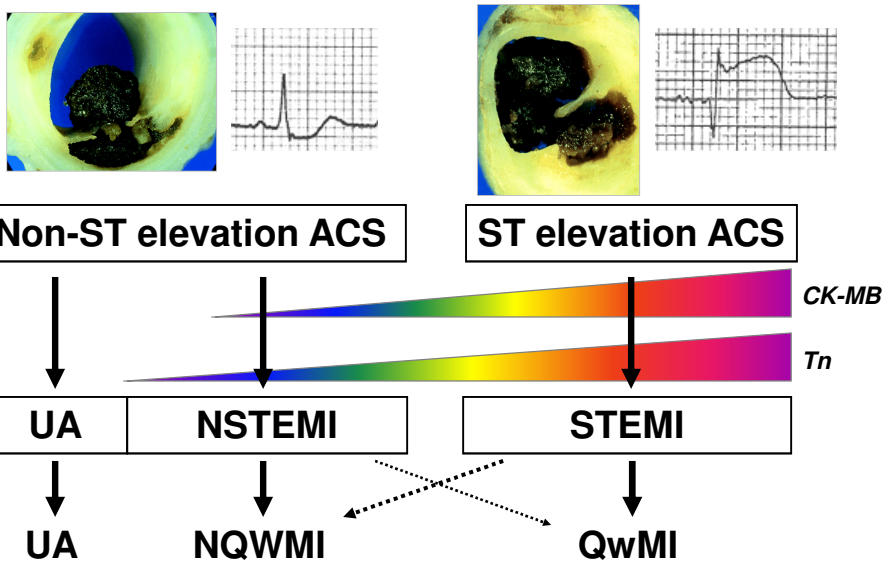
Investigational, unlabeled and/or unapproved uses of drugs or devices may be discussed in this presentation.

ACUTE CORONARY SYNDROMES



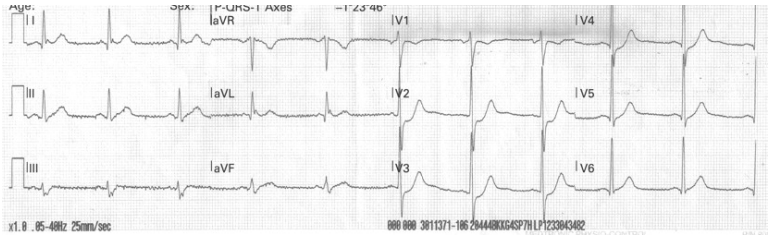
H&P

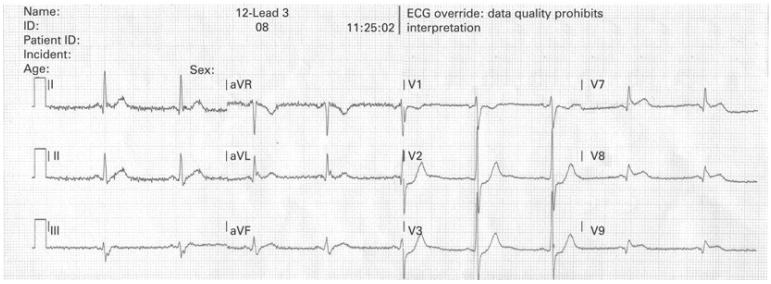
- **History**
  - Cardinal sx of angina
    1. Substernal chest discomfort w/ characteristic quality (pressure) & duration (minutes)
    2. Provoked by physical exertion or emotional stress
    3. Relieved by rest of NTG
  - Cardiac (“typical angina”): All 3 features
  - Possibly cardiac (“atypical angina”):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

ACS: ECG

- **What to look for**
  - STE or LBBB not known to be old
  - ST depression ≥0.5 mm; TWI ≥2 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; obtain serial ECGs (initial ⊕ in <50% ACS Pts)
  - R-sided leads if inferior STE; posterior leads if persistent anterior ST depressions or concerning hx and nl ECG

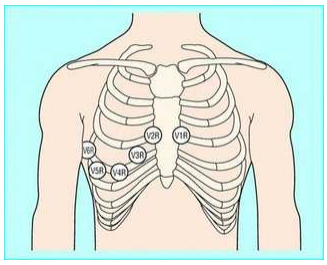
Where is the Lesion?





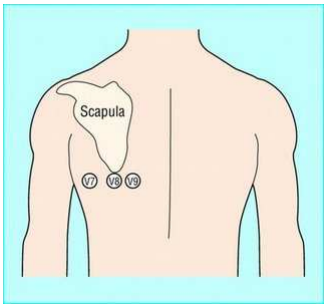
ECG Special Placement

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 4 hours ago, now resolved.

ECG without abnormalities.

Your high-sensitivity troponin testing strategy is:

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

Ruling In & Ruling Out MI

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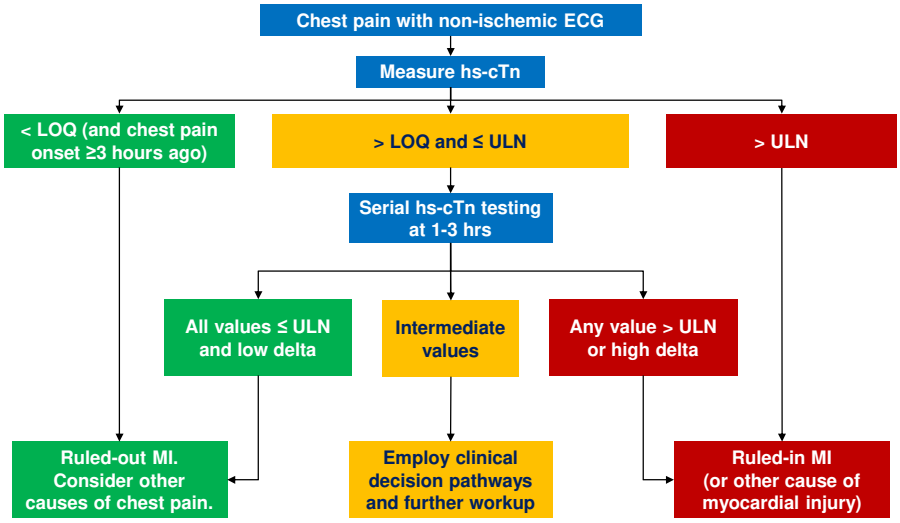
C. Check troponin now and 3-6 hours after sx onset; if both <99th %ile, discharge to home

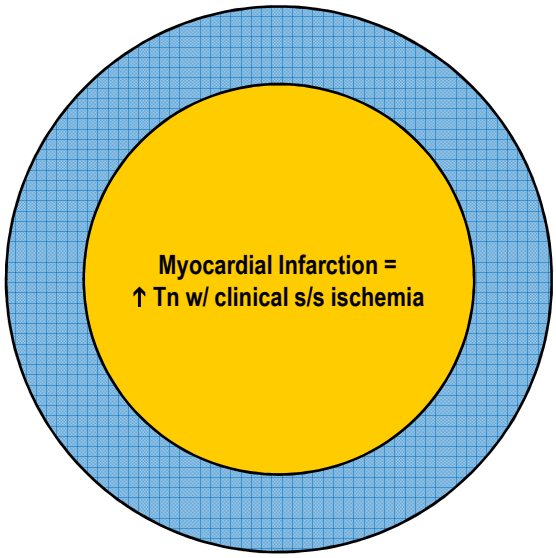
ACS: Biomarkers

Era	Assay	Measure at presentation + …
Ancient History (1950s)	AST & LDH	q12 hrs x 4
Middle Ages (1960s)	CK	q12 hrs x 2
Renaissance (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**

Troponin Testing Algorithm



Myocardial Injury vs. Infarction



Myocardial Injury (and not MI)
= ↑ Tn w/o clinical s/s ischemia

- Decompensated HF, myocarditis, Takotsubo
- Cardiac ablation, defibrillation, cardiac contusion
- PE, PHT
- Stroke, SAH, critical illness

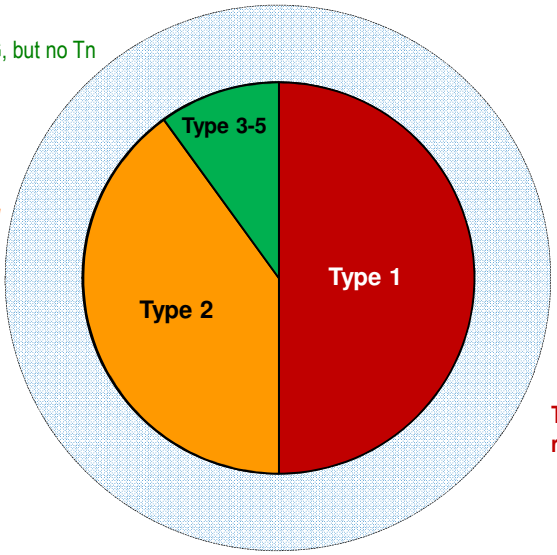
Type 1 vs. Type 2 MI

Types 3-5 MI:
Cardiac death w/ sx & ECG, but no Tn
PCI-related
CABG-related

Type 2 MI = myocardial O_2 supply/demand imbalance *unrelated* to acute atherothrombosis

↓ myocardial perfusion
- Coronary artery spasm, embolism, dissection
- HoTN, profound sustained bradycardia, severe anemia

↑ myocardial demand
- Profound sustained tachycardia
- Extreme HTN



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- Decompensated HF, myocarditis, Takotsubo
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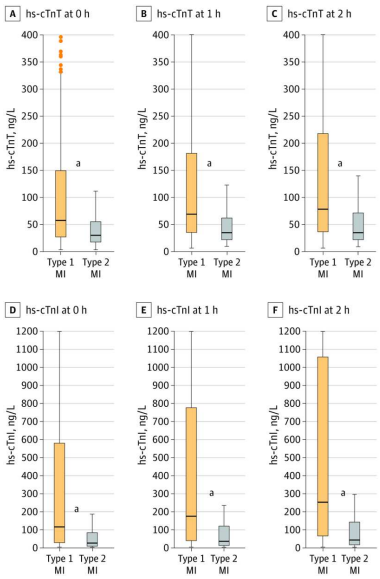
Type 1 MI = Due to ACS (plaque rupture or erosion)

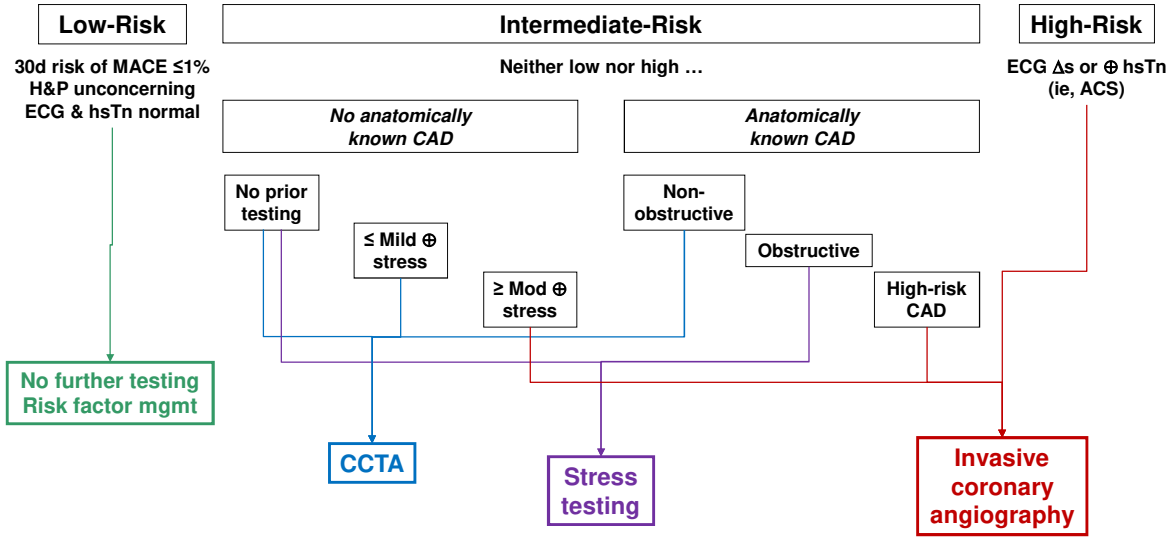
Type 1 vs. 2 MI

- **Largely a clinical diagnosis …**



JAMA Cardiol. 2021;6:771-780

Acute Chest Pain



JACC 2021;78:e187

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
- **Supplemental oxygen (if hypoxemic)**

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 #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 45% 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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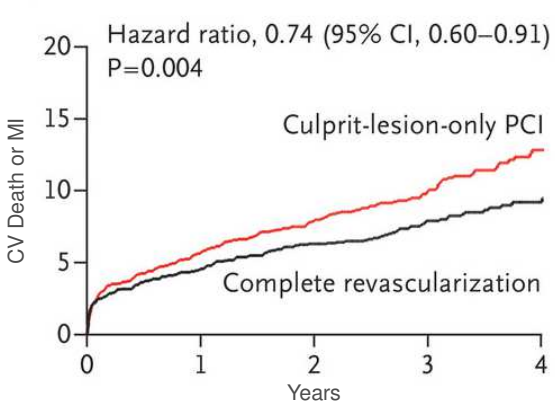
Preventive PCI in STEMI

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;381:1411

Cardiogenic Shock in STEMI

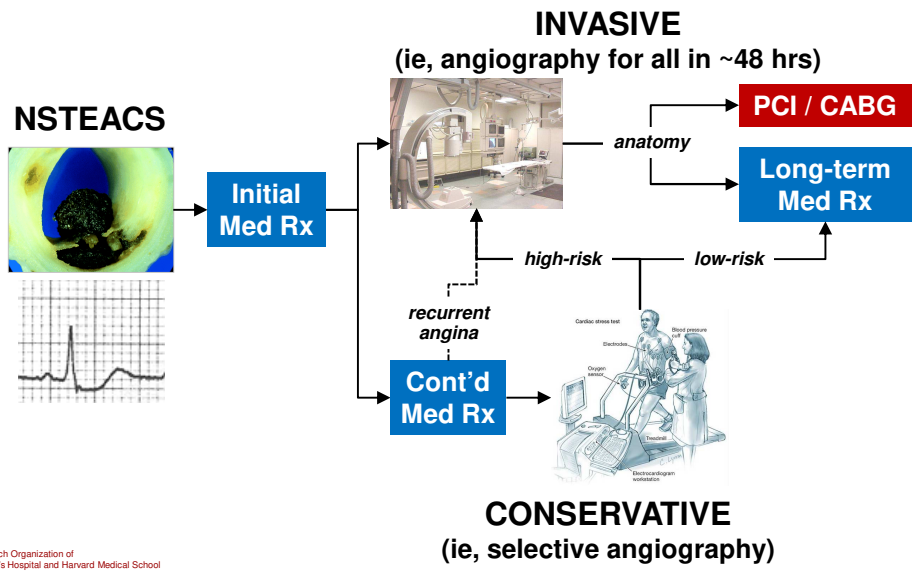
DanGer Shock: 360 (non-comatose) Pts w/ STEMI & Cardiogenic Shock

Table 3. End Points and Adverse Events in the Intention-to-Treat Population.*

Event	Microaxial Flow Pump plus Standard Care (N = 179)	Standard Care Alone (N = 176)	Effect Size (95% CI)†
Primary end point: death from any cause at 180 days — no. (%)	82 (45.8)	103 (58.5)	0.74 (0.55 to 0.99)‡
Secondary end point			
Composite cardiac end point — no. (%)§	94 (52.5)	112 (63.6)	0.72 (0.55 to 0.95)
No. of days alive and out of the hospital (range)¶	82 (0 to 177)	73 (0 to 179)	8 (−8 to 25)
Adverse events			
Composite safety end point — no. (%)‖	43 (24.0)	11 (6.2)	4.74 (2.36 to 9.55)
Moderate or severe bleeding — no. (%)**	39 (21.8)	21 (11.9)	2.06 (1.15 to 3.66)
Limb ischemia — no. (%)	10 (5.6)	2 (1.1)	5.15 (1.11 to 23.84)
Renal-replacement therapy — no. (%)	75 (41.9)	47 (26.7)	1.98 (1.27 to 3.09)
Stroke — no. (%)	7 (3.9)	4 (2.3)	1.75 (0.50 to 6.01)
Cardioversion after ventricular tachycardia or fibrillation — no. (%)	59 (33.0)	52 (29.5)	1.17 (0.75 to 1.83)
Sepsis with positive blood culture†† — no. (%)	21 (11.7)	8 (4.5)	2.79 (1.20 to 6.48)

NEJM 20124;390:1382-93

Management Strategy in NSTEACS



Which NSTEACS Go to the Cath Lab?

Case #3

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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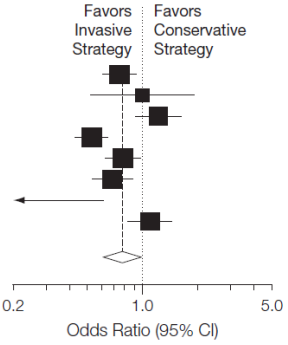
Benefit of INV vs CONS Strategy

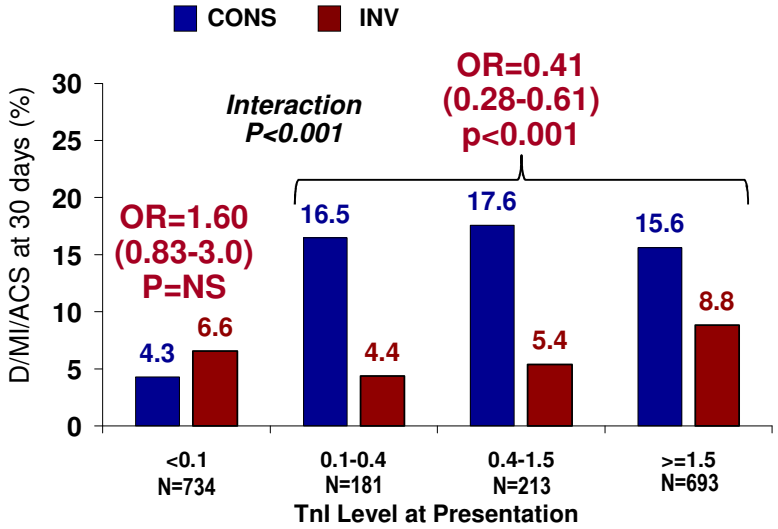
All Patients	Rates of Death, MI, or Rehospitalization With ACS, No./Total No. (%) Invasive Strategy	Conservative Strategy	Odds Ratio (95% CI)
TIMI IIIB[10]	122/895 (13.6)	171/915 (18.7)	0.75 (0.61-0.93)
MATE[11]	27/111 (24.3)	22/90 (24.4)	0.99 (0.52-1.90)
VANQWISH[18]	148/462 (32.0)	124/458 (27.7)	1.22 (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

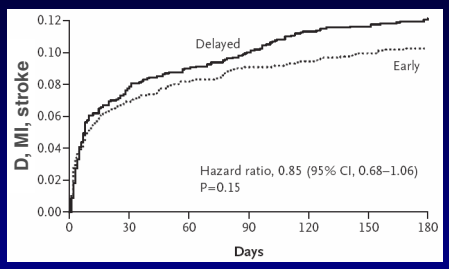
Troponin Treatment Interaction

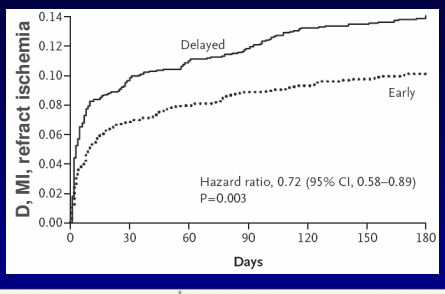


Cannon CP et al. *NEJM* 2001;344:1879

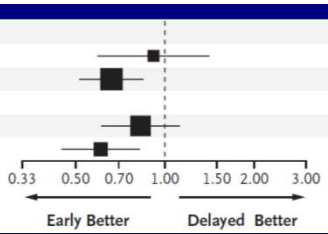
TIMACS

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

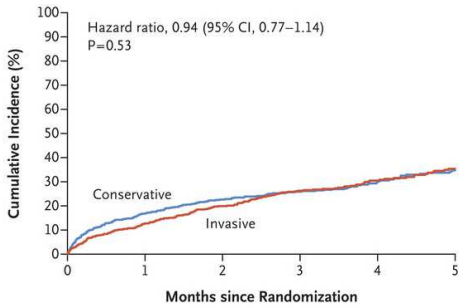
2014 ACC/AHA NSTEACS Guidelines: Early Invasive

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

INV vs CONS in Elderly

SENIOR-RITA: INV vs. CONS in 1518 Pts ≥75 yrs (mean 82 yrs) w/ NSTEMI



Kunadian V et al. *NEJM* 2024;epub ahead of print

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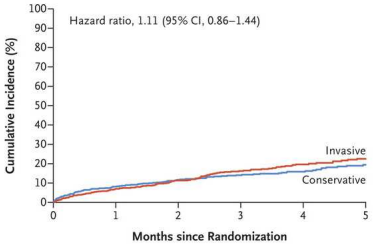
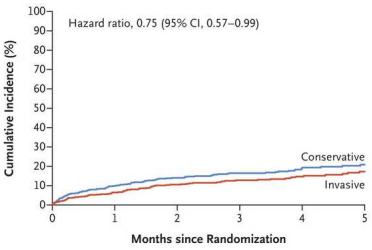
SENIOR-RITA: INV vs. CONS in 1518 Pts ≥75 yrs (mean 82 yrs) w/ NSTEMI

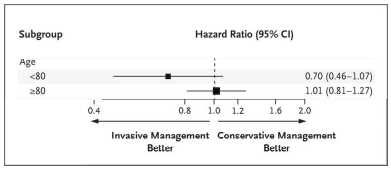
Revasc in 50% of INV arm (60-75% in other trials)

CV Death



MI





Procedural complications in <1%

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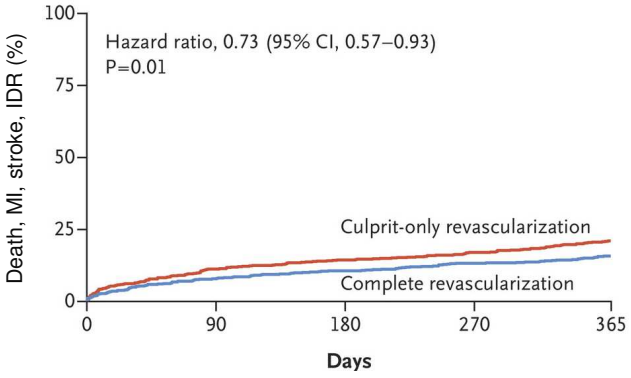
Kunadian V et al. *NEJM* 2024;epub ahead of print

Complete Revasc in All MI

FIRE: 1445 Older Pts w/ MI (65% NSTEMI) + MVD

Physiology-guided complete revasc vs. culprit-only



End Point	Complete	Culprit-Only	HR (95% CI)
Primary EP	15.7	21.0	0.73 (0.57-0.93)
Death	9.2	12.8	0.70 (0.51-0.96)
MI	4.4	7.0	0.62 (0.40-0.97)
Stroke	1.7	1.0	1.73 (0.68-4.40)
IDR	4.3	6.8	0.63 (0.40-0.98)

IDR, ischemia-driven revascularization

Biscaglia et al. *NEJM* 2023;389:889-98

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 #4a

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

ECG shows anterior ST segment depressions. Troponin elevated.

Receives aspirin. Goes for cath and found to have a 90% ulcerated LAD lesion. Plan for PCI.

What other antiplatelet therapy should he get?

A. Clopidogrel
B. Prasugrel
C. Ticagrelor
D. Cangrelor
E. Eptifibatide

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Antithrombotic Therapy

Case #4b

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

ECG shows anterior ST segment depressions. Troponin elevated.

Receives aspirin. Plan is for coronary angiography in next 24 hrs.

What other antiplatelet therapy should he get?

A. Clopidogrel at time of PCI
B. Prasugrel now
C. Ticagrelor now or at time of PCI
D. Cangrelor now
E. Eptifibatide now

Antithrombotic Therapy

Case #4b

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

ECG shows anterior ST segment depressions. Troponin elevated.

Receives aspirin. Plan is for coronary angiography in next 24 hrs.

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E. Eptifibatide now

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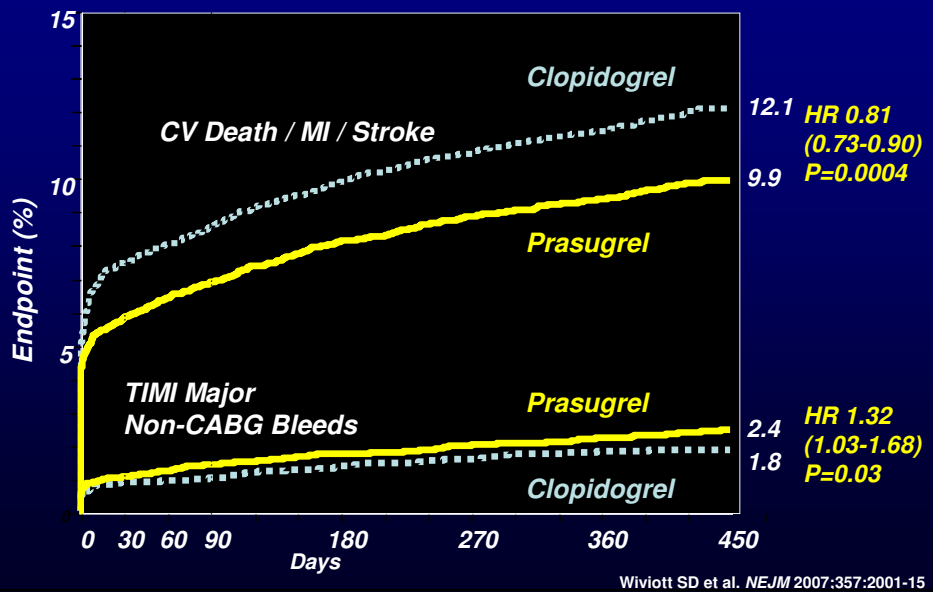
TRÎTON TIMI-38

13,608 Patients with ACS and Planned PCI Randomized to Prasugrel (60/10) vs. Clopidogrel (300/75)

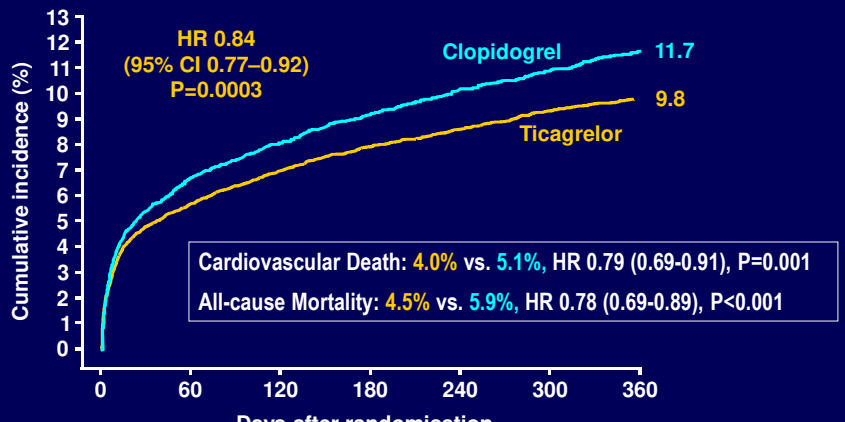


Wiviott SD et al. *NEJM* 2007:357:2001-15

Primary efficacy endpoint: CV death, MI or stroke

PLATO

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



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

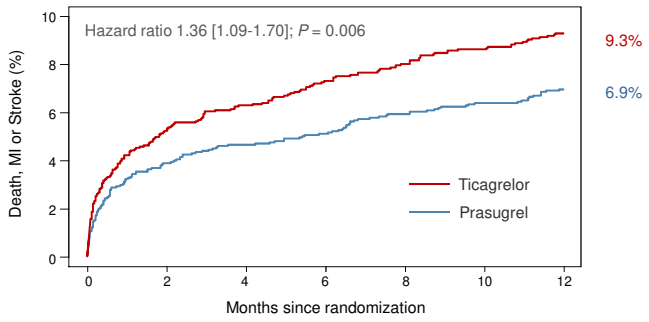
Duke Clinical Research Institute

Wallentin L, et al. *NEJM* 2009;361:1045-57

UCR UPPSALA CLINICAL RESEARCH CENTRE

Prasugrel vs. Ticagrelor

ISAR-REACT 5: 4018 Pts w/ ACS



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NEJM 2019;381:1524-1534

Antiplatelet Therapy Acutely

- ***Start with* aspirin**
- ***Almost always add:* $P2Y_{12}$ inhibitor**
  - Oral agents: ticagrelor & prasugrel more potent and preferred over clopidogrel because reduce risk of ischemic events (but more bleeding)
  - No clear benefit for starting before PCI, and more bleeding
  - IV agent: cangrelor (fast on & off); can give at time of PCI in $P2Y_{12}$-naïve Pts
- ***Sometimes also add (typically in cath lab)*: glycoprotein IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban)**

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Duration of Antiplatelet Therapy

Scenario	Recommendation
Most patients	DAPT for 12 mos
High ischemic risk (& low bleeding risk & tolerated DAPT well to date)	Consider continuing ASA + $P2Y_{12}$ inhibitor beyond 12 mos
Low ischemic risk and/or high bleeding risk	Consider dropping ASA after 1-3 mos and just continue $P2Y_{12}$ inhibitor (ideally ticagrelor; if high bleeding risk, consider checking *CYP2C19* genotype before clopidogrel monoRx)
Need to stop all antiplatelet	Ideally wait ≥1 mo after BMS and ≥3-6 mos after DES. If cannot and high-risk stent, consider bridging with cangrelor or GP IIb/IIIa inhibitor.

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)*

Triple Therapy

Case #5

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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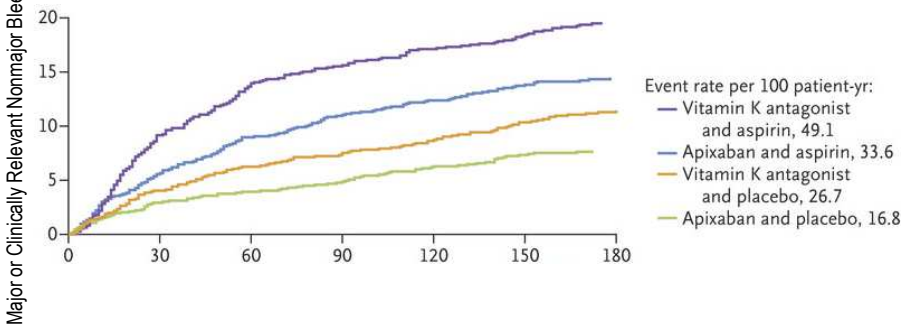
AUGUSTUS: Safety

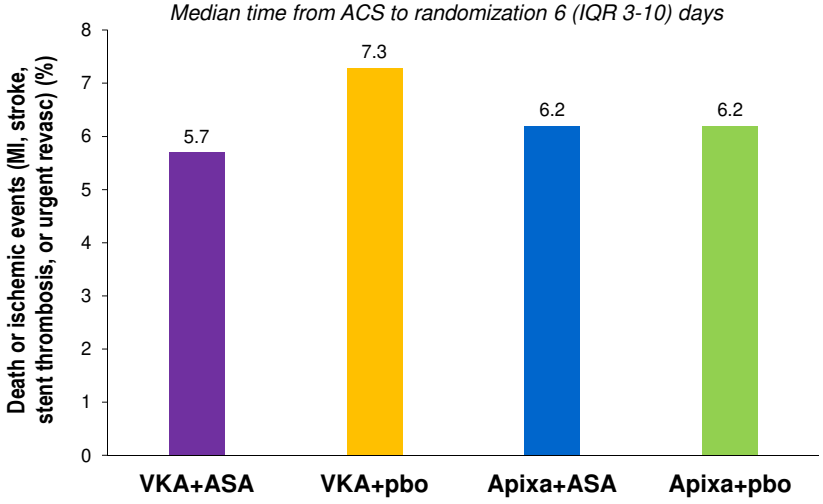
4614 Pts w/ AF + either:
ACS+PCI (37%), ACS w/o PCI (24%), Elective PCI (39%)
All received P2Y12 inhibitor (>90% clopi)



NEJM 2019;380:1509

AUGUSTUS: Efficacy

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



NEJM 2019;380:1509-1524

What if the Pt needs OAC (eg, AF)?

- **High rate of bleeding with triple Rx (ASA + $P2Y_{12}$ + OAC)**
- **DOAC preferred over warfarin because less bleeding (no head-to-head, but apixaban w/ best data vs. VKA)**
- **Would <u>not</u> ↓ DOAC dose b/c may not adequately protect against stroke**
- **In terms of antiplt, start w/ DAPT: ASA + $P2Y_{12}$ inhibitor (clopidogrel)**
- **Drop ASA at hospital d/c or, if high ischemic risk, after 1 month**
- **Consider dropping $P2Y_{12}$ inhib after 6-12 mos, depending on bleeding risk**

Lipid-Lowering Therapy

<u>Case #6</u>

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 <55

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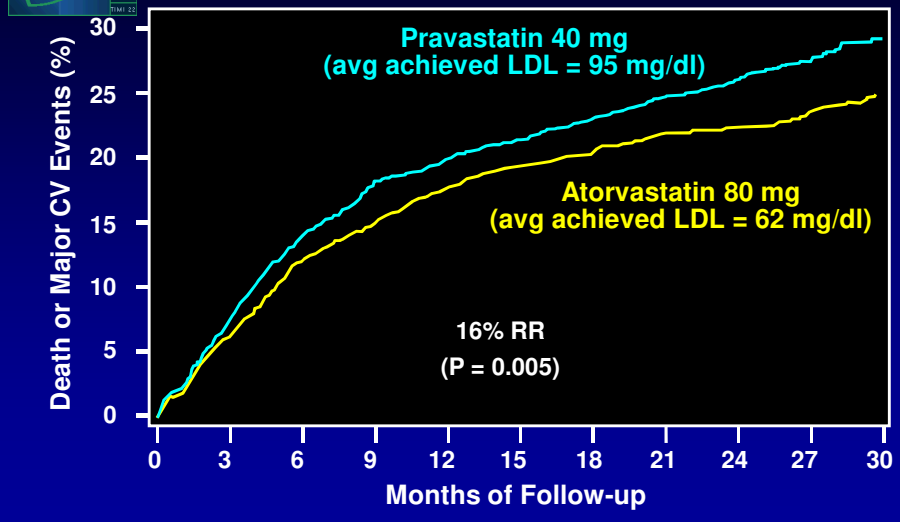
PROVE IT – TIMI 22

4162 patients hospitalized w/in prior 10 d for ACS

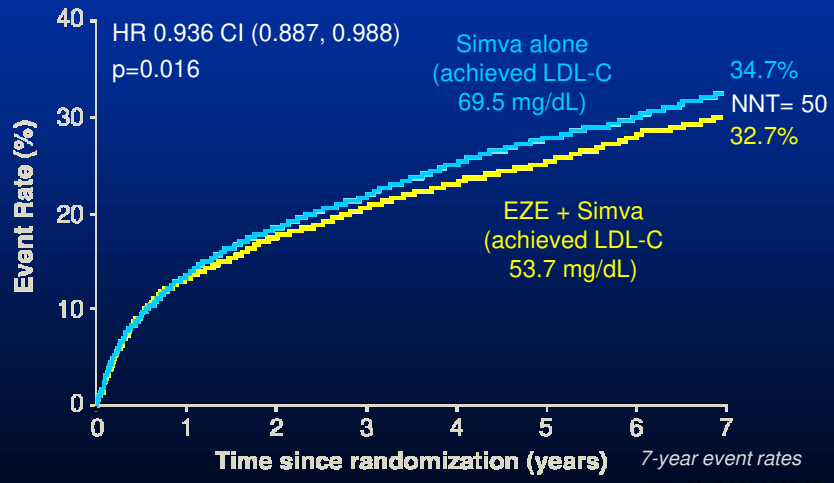


Cannon et al. *NEJM* 2003; 350: 1495

Primary Endpoint — ITT

IMPROVE-IT

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



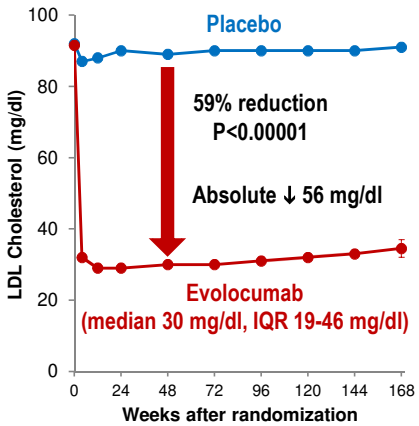
NEJM 2015;372:2387-97

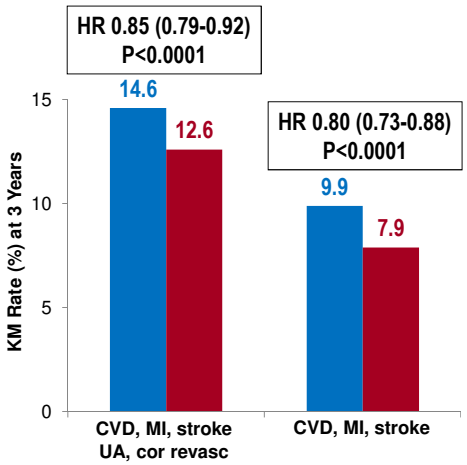
TIMI

Summary of Effects of PCSK9i Evolocumab

fourier

- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





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Sabatine MS et al. *NEJM* 2017;376:1713-22

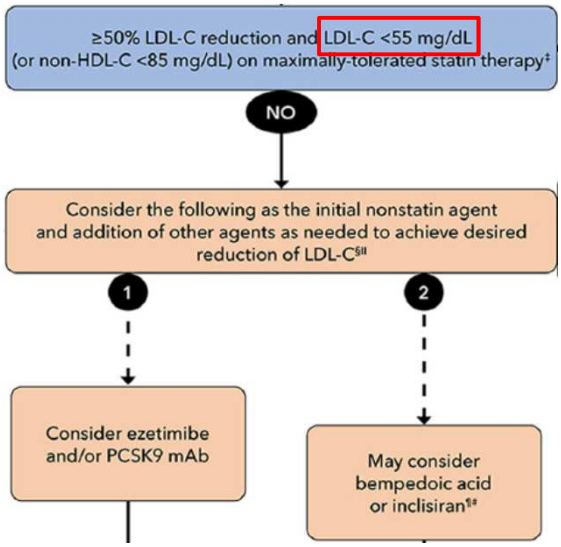
2019 ESC Dyslipidemia Guidelines

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

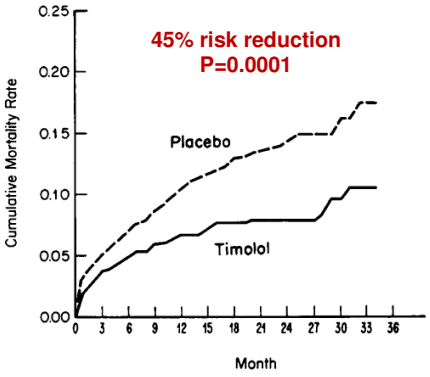
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal < 1.0 mmol/L (< 40 mg/dL) may be considered.[119, 120]

2022 ACC Expert Consensus Decision Pathway



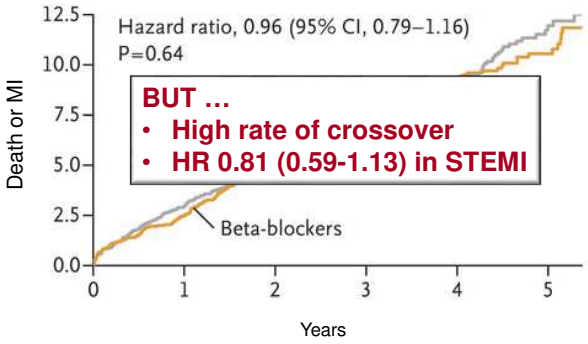
β-blockers

1884 Patients 1-4 weeks after acute MI
Randomized to β-blocker vs. placebo



NEJM 1981;304:801

5020 Patients 1-7 days after acute MI w/ nl LVEF
Randomized to β-blocker vs. placebo



NEJM 2024;390:1372

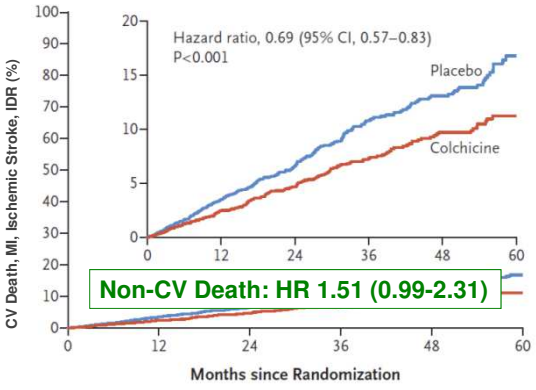
ACEI/ARB, MRA

- **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% and either clinical s/s of HF or diabetes

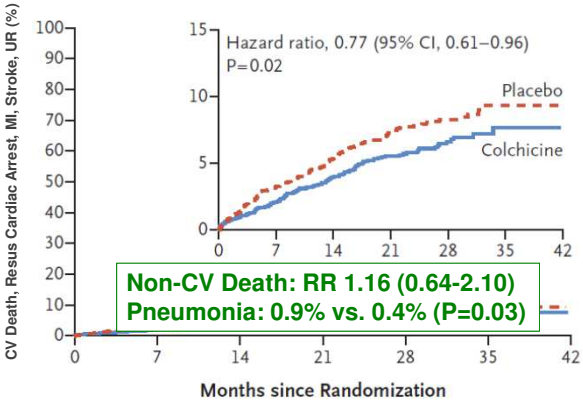
Circulation 2014;130:2354-94

Colchicine

LoDoCo2: 5522 Pts w/ CCD



COLCOT: 4745 Pts w/in 30d of MI



NEJM 2020;383:1838-47 & 2019;381:2497-505

Take Home Points

- **Diagnose ACS using H&P, 12-lead ECG, troponin**
- **For STEMI: select Primary PCI** vs Lytic
- **For NSTE-ACS: select Invasive** (eg, ⊕ Tn) **vs. Conservative Strategy**
- **Anti-ischemic Rx:** beta-blocker, nitrates
- **Select Antiplatelet Regimen**
  - ASA
  - + $P2Y_{12}$ Inhibitor: ticagrelor, prasugrel (or clopidogrel); consider timing
- **Select Anticoagulant:** UFH, LMWH (or bivalirudin)
- **Long-term therapy**
  - ASA (maybe drop after 3 mos), $P2Y_{12}$ inhibitor (at least 12 mos, if not longer)
  - ? β-blocker (if low LVEF or STEMI), statin (+ EZE + PCSK9i)
  - ? ACEI, ? Aldo inhibitor
  - ? Colchicine

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