Acute Coronary Syndromes

HMS/MGH
Internal Medicine Comprehensive Review and Update
June 10, 2022

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Disclosures

Research Grant Support through BWH:

Amgen; Anthos Therapeutics; AstraZeneca; Daiichi-Sankyo; Ionis; Merck; Novartis; Pfizer

Scientific Advisory Boards & Consulting:

Amgen; Anthos Therapeutics; AstraZeneca; Beren Therapeutics; Fibrogen; Merck; Moderna; Novo Nordisk; Silence Therapeutics

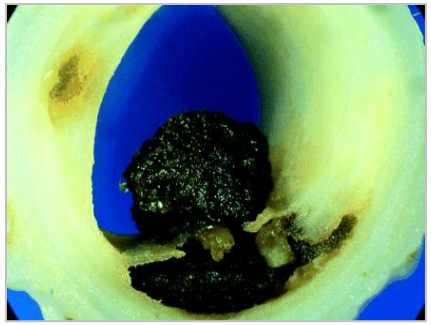
Learning Objectives

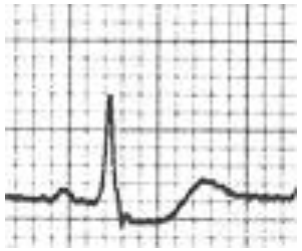
- **Understand the signs and symptoms of ACS**
- **Understand the acute pharmacologic and catheter-based treatment options**
- **Understand the long-term therapy**

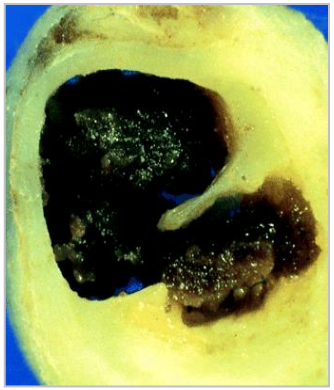
Outline

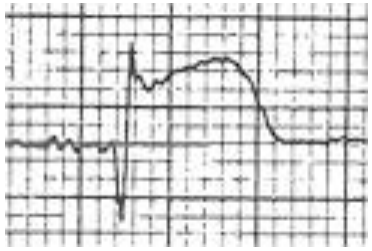
1. Diagnosing ACS
2. Who goes to the cath lab & when
3. Anti-ischemic therapy
4. Antithrombotic therapy
5. Long-term therapy

ACUTE CORONARY SYNDROMES









Non-ST elevation ACS

ST elevation ACS

CK-MB

Tn

UA | **NSTEMI**

STEMI

UA

NQWMI

QwMI

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

Value of H&P for ACS

Factor	LR (95% CI)
Radiation to right arm or shoulder	4.7 (1.9-12)
Radiation to both arms or shoulders	4.1 (2.5-6.5)
Exertional	2.4 (1.5-3.8)
Radiation to left arm	2.3 (1.7-3.1)
Associated with diaphoresis	2.0 (1.9-2.2)
Associated with nausea or vomiting	1.9 (1.7-2.3)
>Previous angina or ≈ previous MI	1.8 (1.6-2.0)
Described as pressure	1.3 (1.2-1.5)
Pleuritic	0.2 (0.1-0.3)
Positional	0.3 (0.2-0.5)
Sharp	0.3 (0.2-0.5)
Reproducible with palpation	0.3 (0.2-0.4)
Inframammary location	0.8 (0.7-0.9)
Nonexertional	0.8 (0.6-0.9)

JAMA 2005;294:2623

ACS: 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)

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

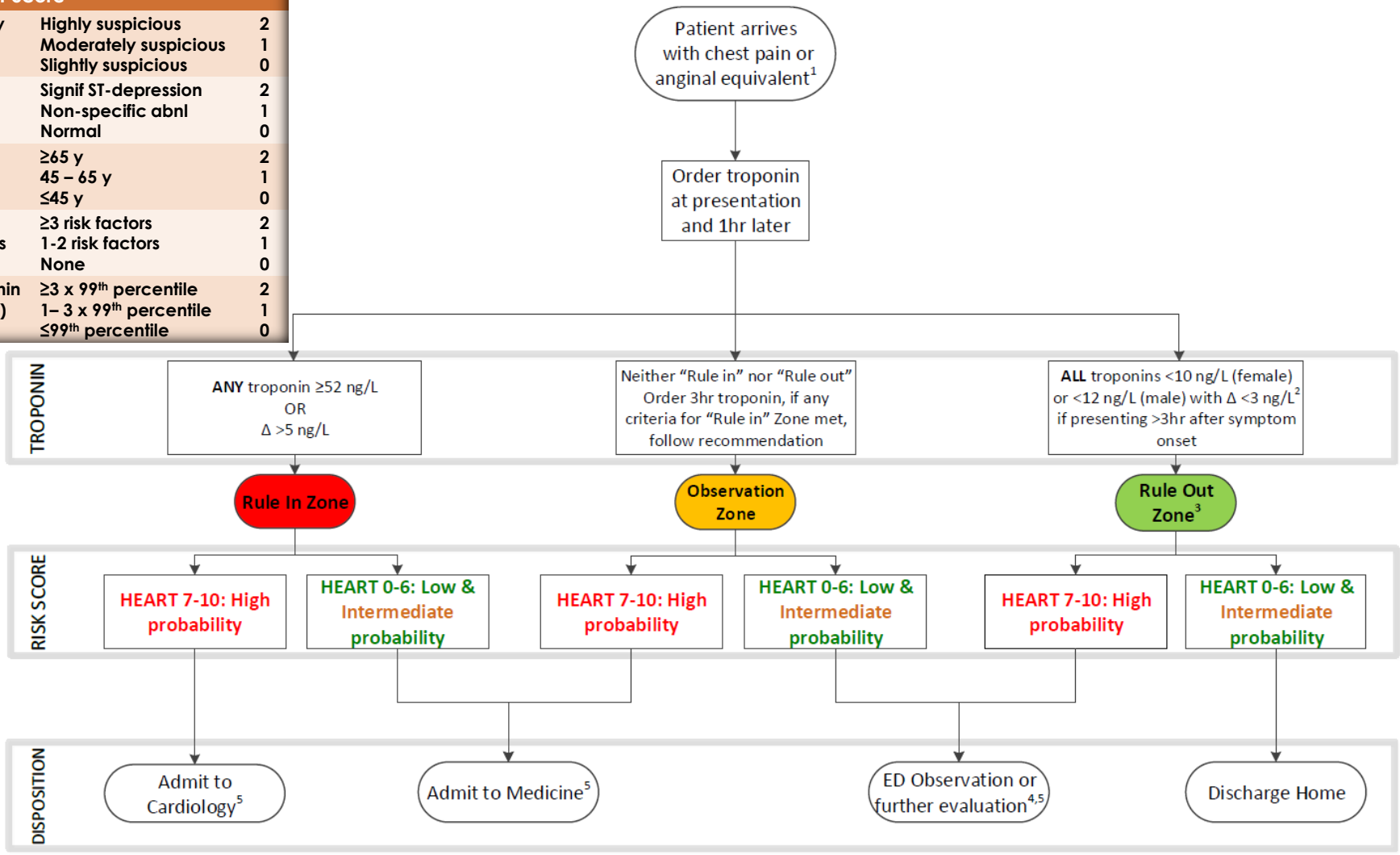
C. Check now and 3-6 hours after sx onset; if both <99th %ile, discharge to home

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**

Partners Pathway

HEART Score		
History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Signif ST-depression	2
	Non-specific abnl	1
	Normal	0
Age	≥65 y	2
	45 – 65 y	1
	≤45 y	0
Risk factors	≥3 risk factors	2
	1-2 risk factors	1
	None	0
Troponin (serial)	≥3 x 99th percentile	2
	1– 3 x 99th percentile	1
	≤99th percentile	0



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)

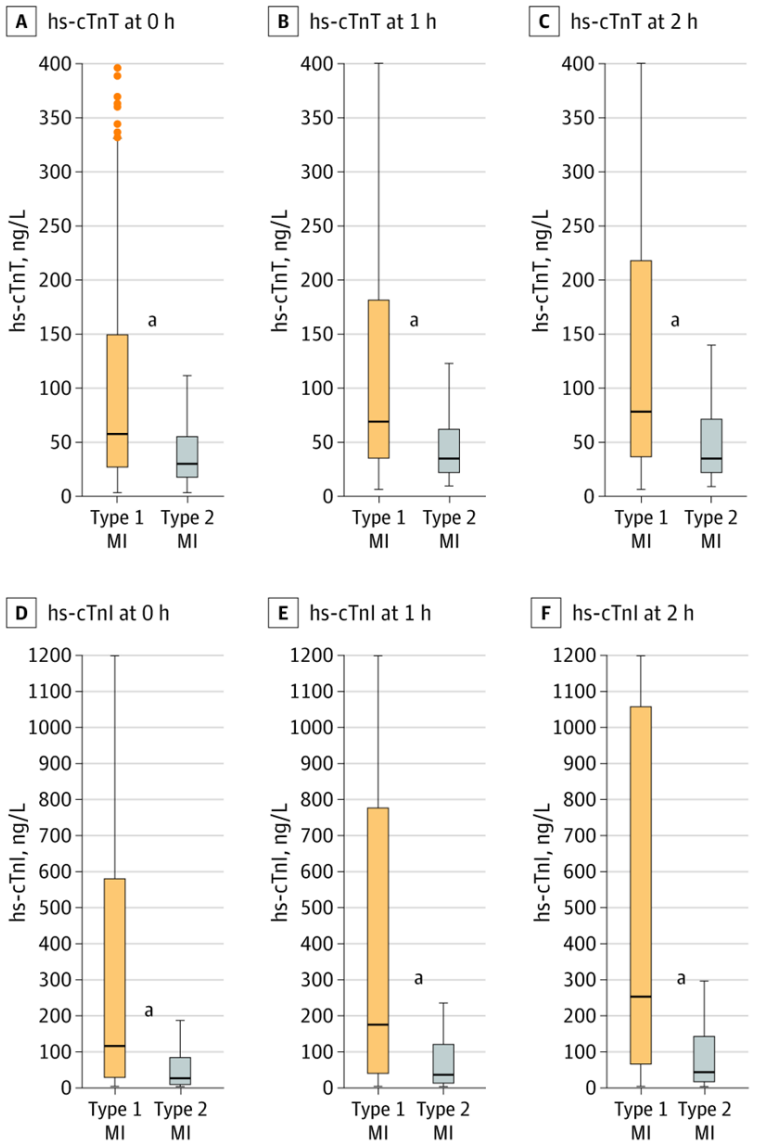
JACC 2018

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

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**

STEMI & Reperfusion

Case #2

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

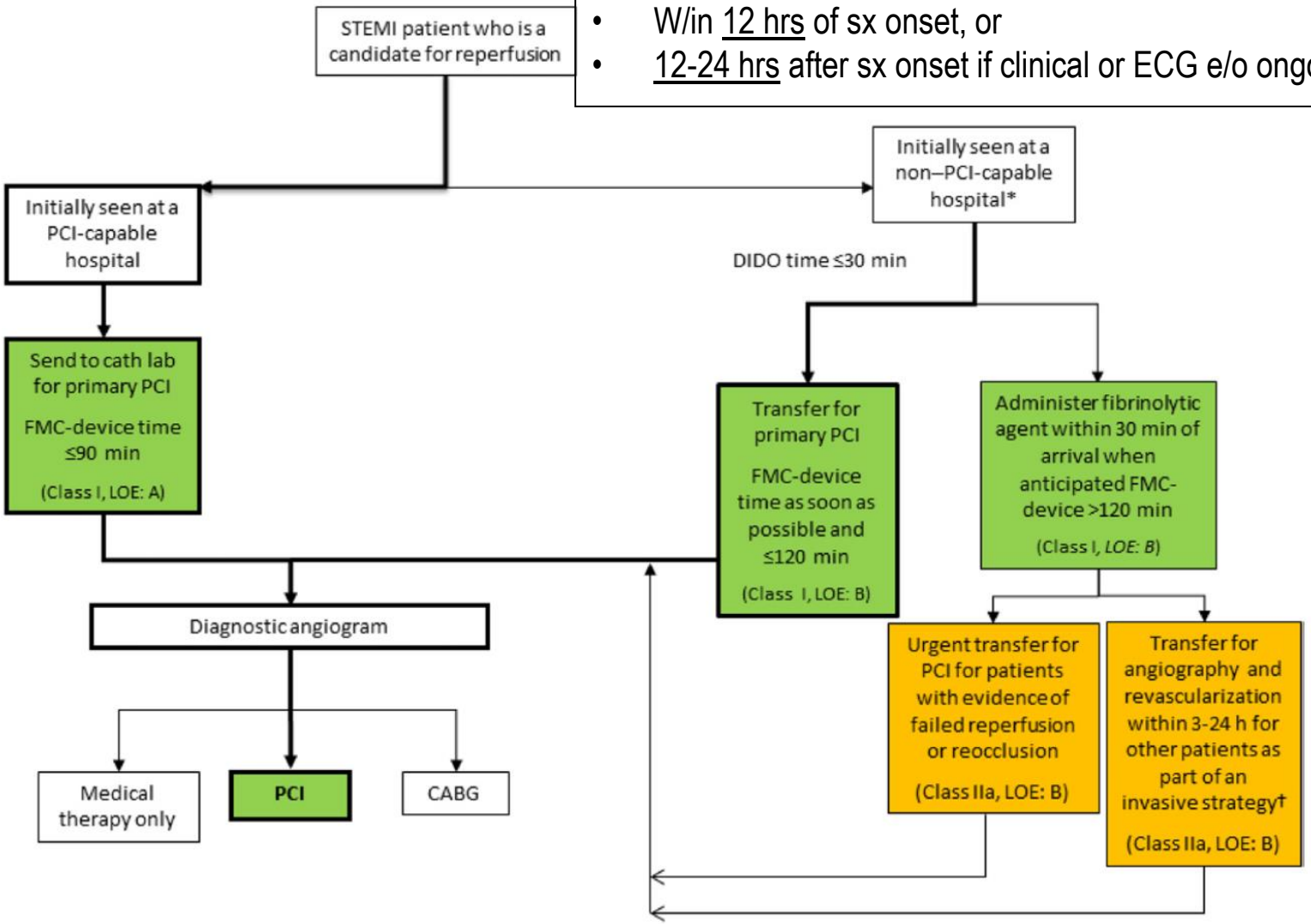
ECG shows anterior ST segment elevations.

Your hospital does not offer primary PCI, but an affiliated hospital 60 mins away does

A. Administer lytic at your hospital and transfer only if recurrent ischemia
B. Administer lytic at your hospital and transfer for angiography
C. Transfer to the other hospital for PCI

STEMI Reperfusion Guidelines

- W/in 12 hrs of sx onset, or
- 12-24 hrs after sx onset if clinical or ECG e/o ongoing ischemia



Revascularization in STEMI

Case #3

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.

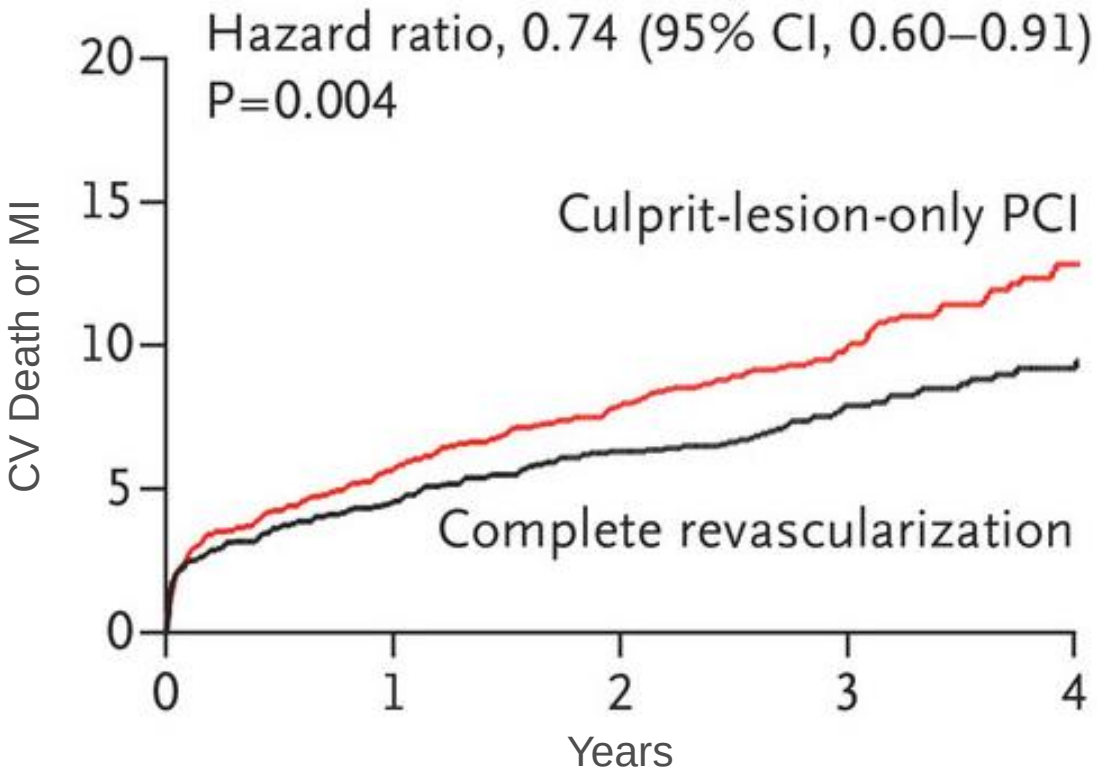
Also noted to have 80% mid LAD lesion and a 45% LCx lesion.

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

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

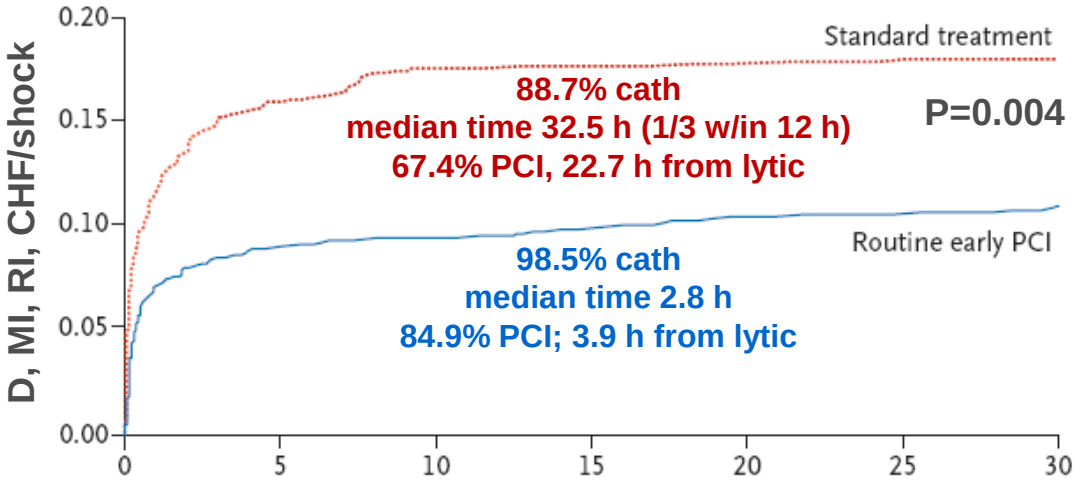


Mehta et al. *NEJM* 2019;epub

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

Which NSTEACS Go to the Cath Lab?

Case #4

72 yo F p/w chest pain that started 3 hours ago.

ECG shows inferior ST segment depressions. Troponin elevated.

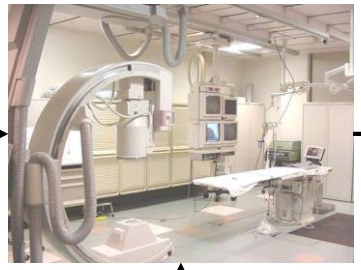
Now chest pain free and ECG normalized.

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

Management Strategy in NSTEACS

INVASIVE

(ie, angiography for all in ~48 hrs)

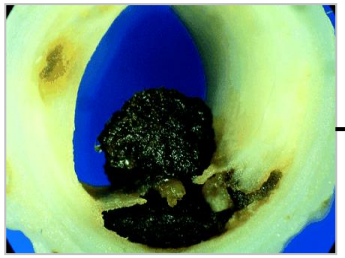


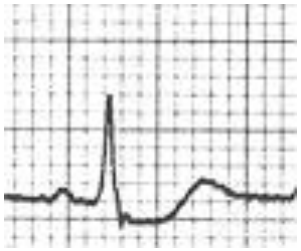
PCI / CABG

anatomy

Long-term Med Rx

NSTEACS





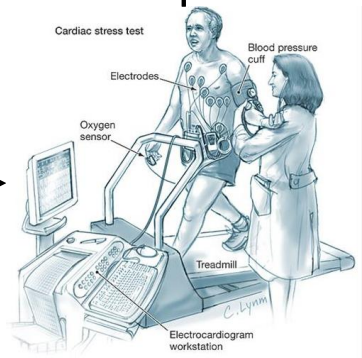
Initial Med Rx

high-risk

low-risk

recurrent angina

Cont'd Med Rx

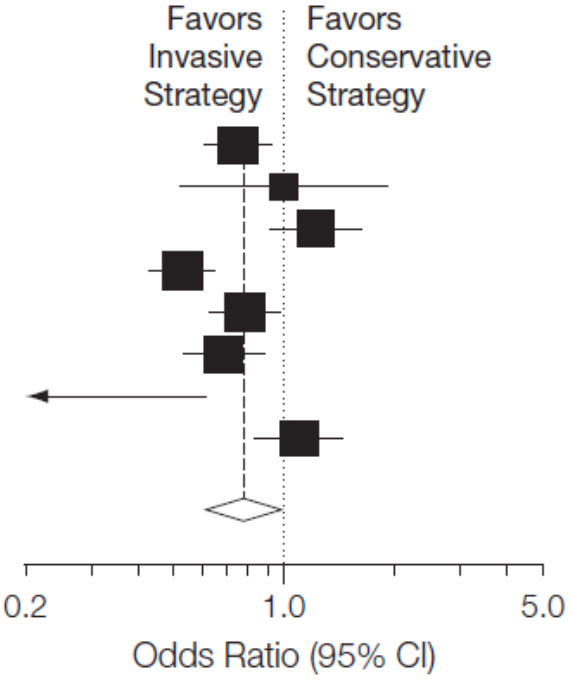


CONSERVATIVE

(ie, selective angiography)

Benefit of INV vs CONS Strategy

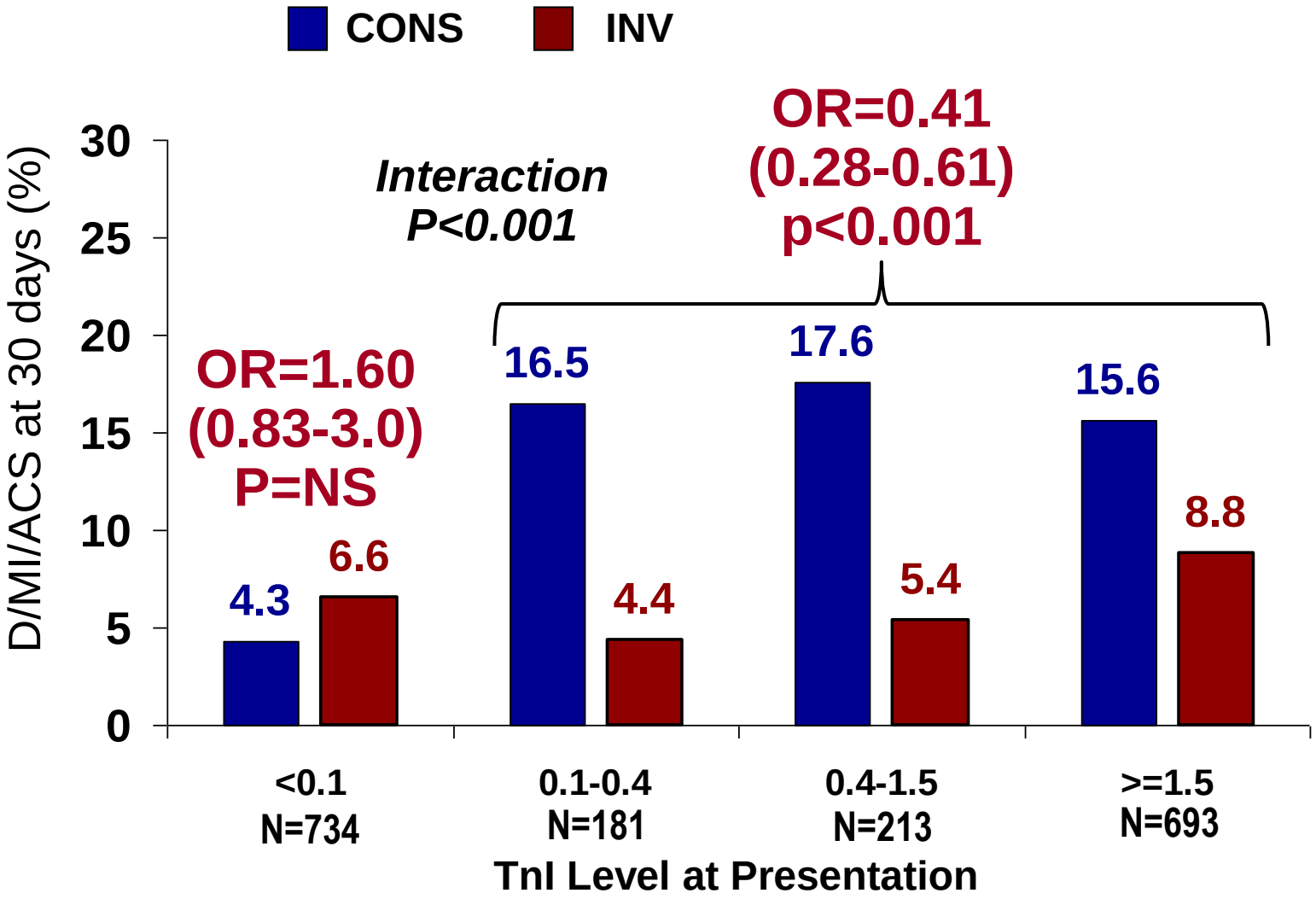
All Patients	Rates of Death, MI, or Rehospitalization With ACS, No./Total No. (%): Invasive Strategy	Rates of Death, MI, or Rehospitalization With ACS, No./Total No. (%): Conservative Strategy	Odds Ratio (95% CI)
TIMI IIIB[10]	122/895 (13.6)	171/915 (18.7)	0.75 (0.61-0.93)
MATE[11]	27/111 (24.3)	22/90 (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

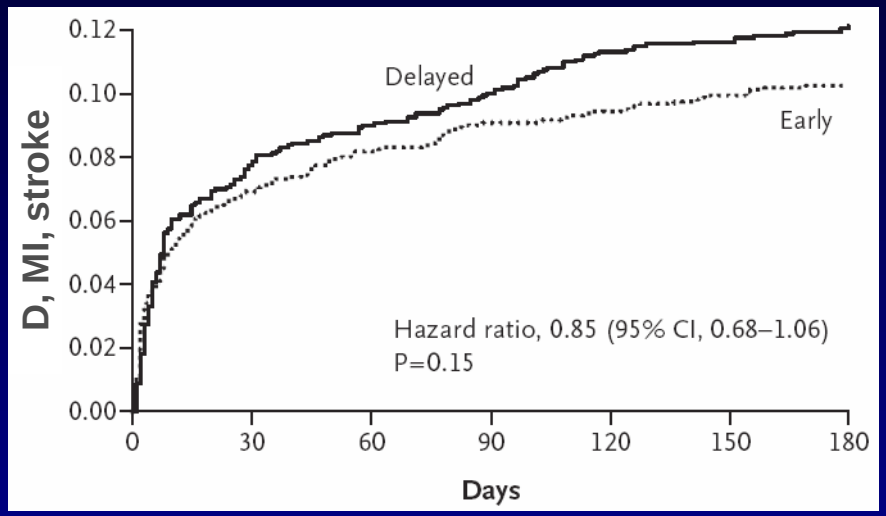
Troponin Treatment Interaction

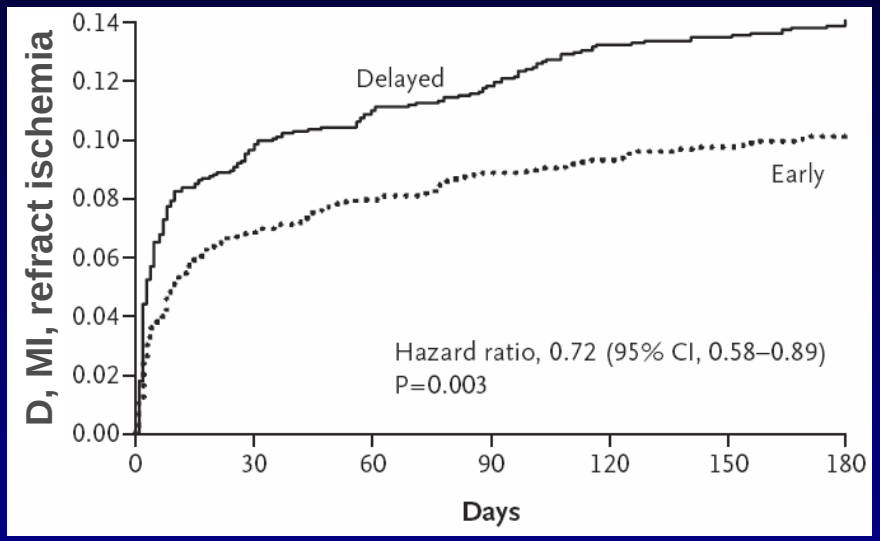


Cannon CP et al. *NEJM* 2001;344:1879

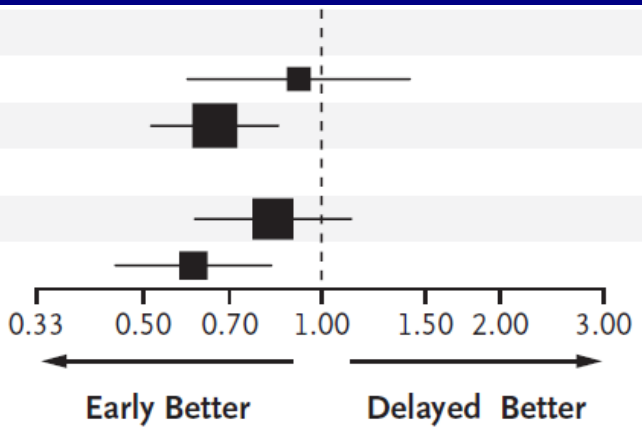
TIMACS

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

Antithrombotic Therapy

Case #5

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

ECG shows anterior ST segment depressions. Troponin elevated.

Has received aspirin.

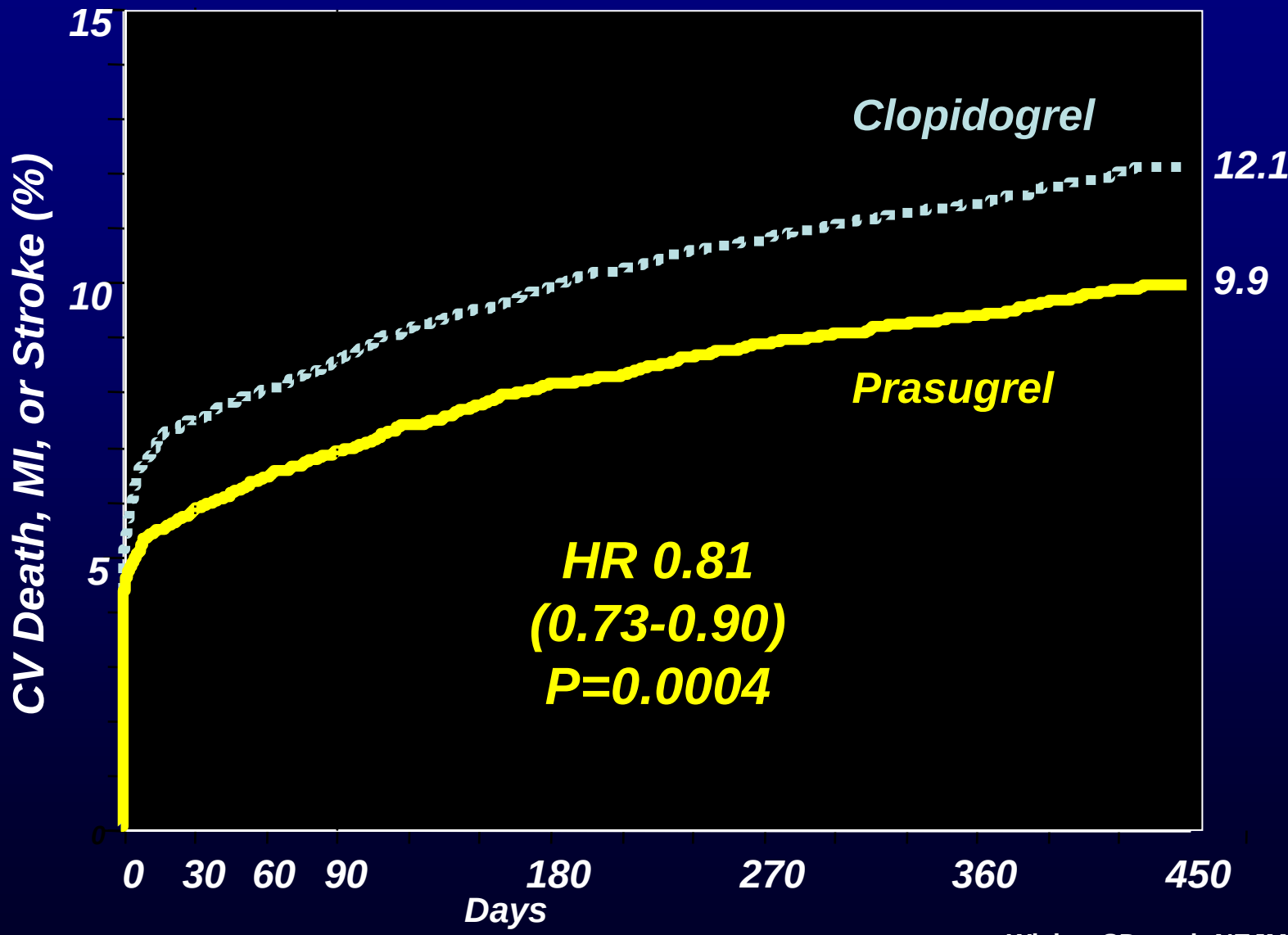
A. Add an oral $P2Y_{12}$ inhibitor: clopidogrel
B. Add an oral $P2Y_{12}$ inhibitor: prasugrel
C. Add an oral $P2Y_{12}$ inhibitor: ticagrelor
D. Add an intravenous $P2Y_{12}$ inhibitor: cangrelor
E. Add an intravenous GP IIb/IIIa inhibitor: eptifibatide

Antiplatelet Therapy Acutely

- ***Start with*** **COX Inhibitor (ie, aspirin)**
- ***Almost always add:*** **$P2Y_{12}$ ADP Receptor Blocker (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. Clopi (300/75)

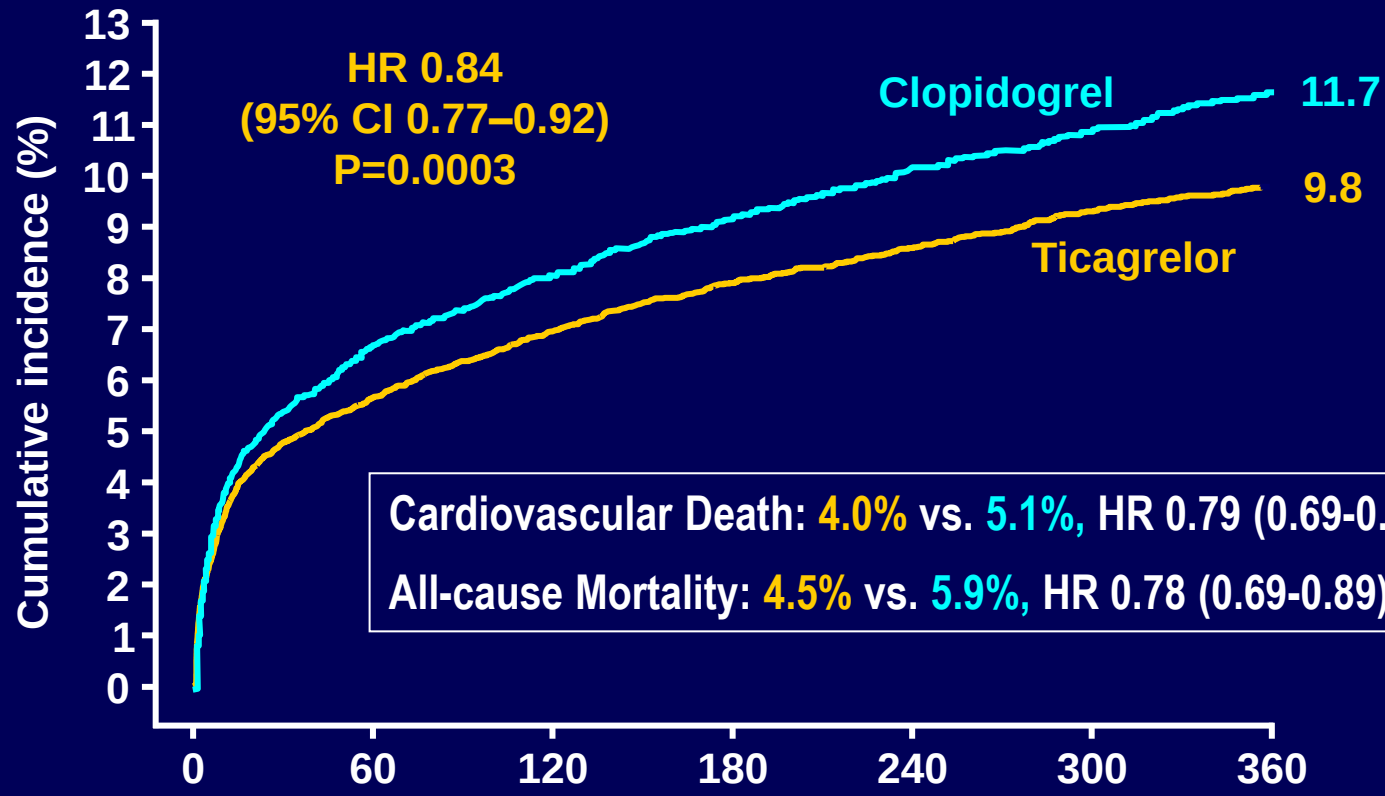


Wiviott SD et al. *NEJM* 2007;357:2001-15

Primary efficacy endpoint: CV death, MI or stroke

PLATO

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



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

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

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

$P2Y_{12}$ 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 <u>not</u> shown clinical benefit
- PreRx <u>does</u> ↑ 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)*

Long-Term Antithrombotic Therapy

Case #6

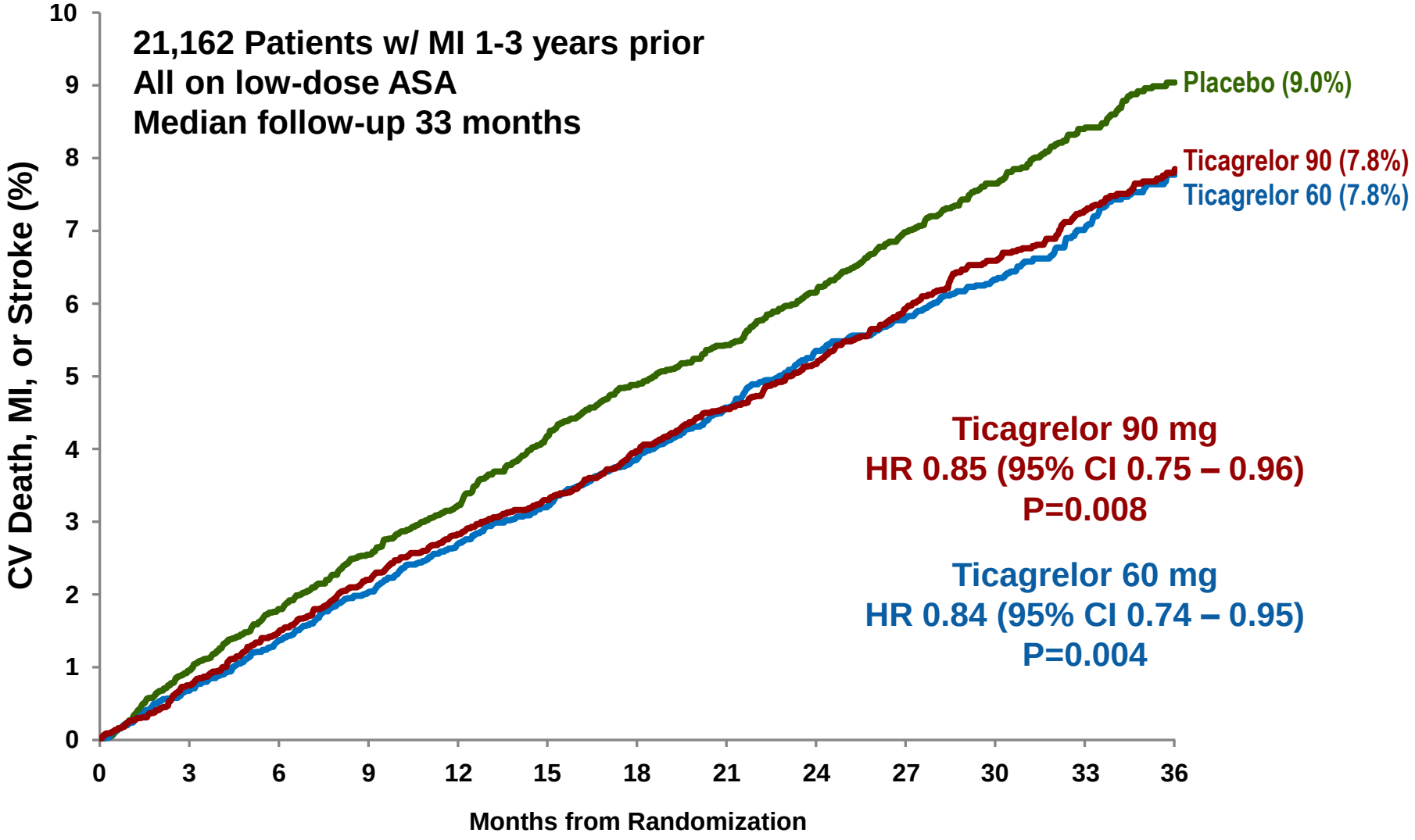
64 yo M p/w NSTEMI. History of prior MI and diabetes.

Drug-eluting stent placed in LAD.

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

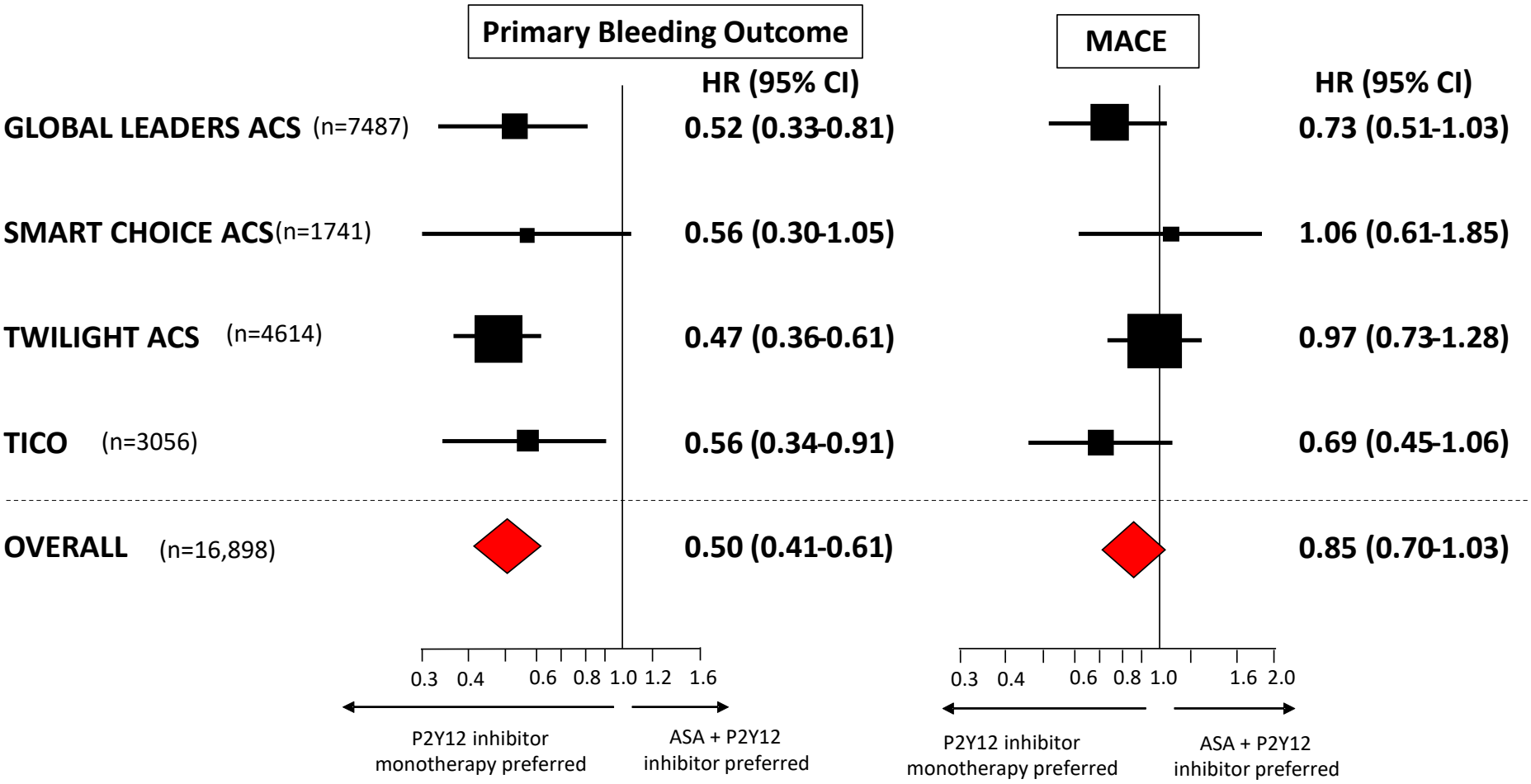
A. ASA + $P2Y_{12}$ inhibitor for 30 days
B. ASA + $P2Y_{12}$ inhibitor for 1 year
C. ASA + $P2Y_{12}$ inhibitor for as long as tolerated if high ischemic risk and low bleeding risk
D. ASA + $P2Y_{12}$ inhibitor for 3 months and then $P2Y_{12}$ inhib. monoRx

Long-Term Dual Antiplt Rx



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

Drop ASA after 1-3 Mos?



O'Donoghue ML, Murphy SA, and Sabatine MS. *Circulation* 2020;142:538-45

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

ACS & AF

Case #7

72 yo F w/ HTN & DM 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 DOAC, aspirin, and clopidogrel
C. Full-dose DOAC and clopidogrel
D. Reduced-dose DOAC and clopidogrel

Data from RCTs of Triple Rx

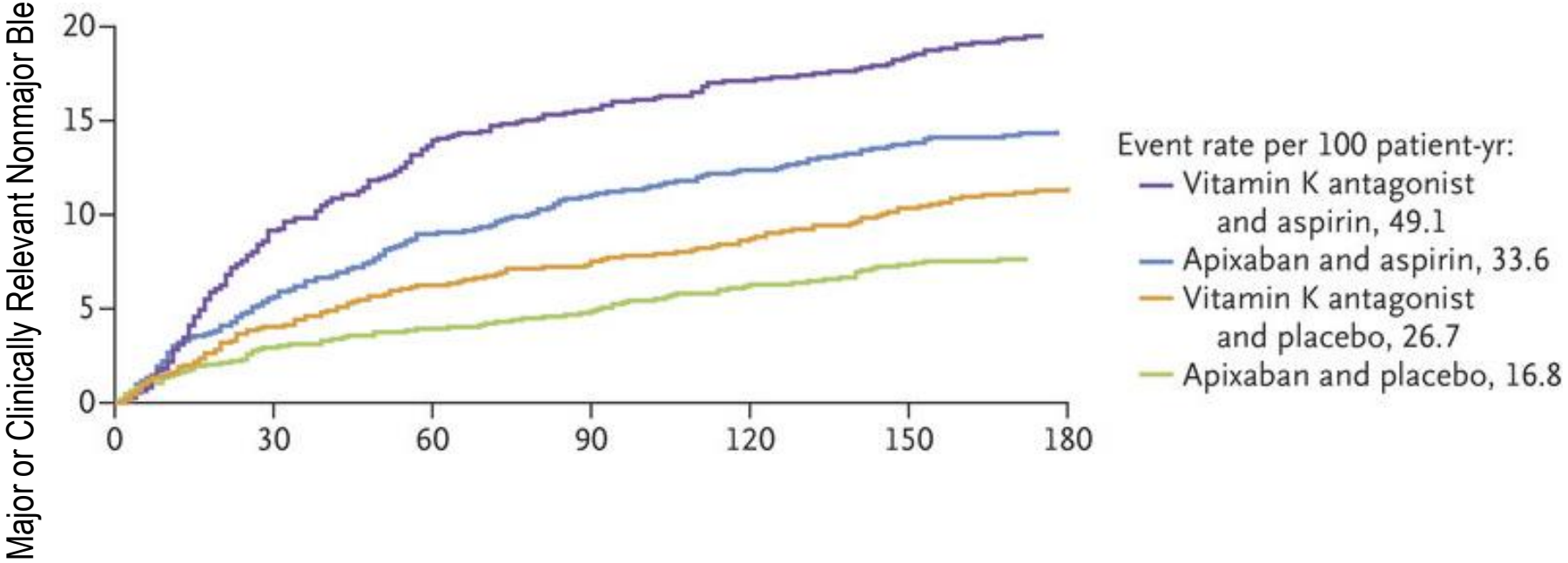
Control arm: ***warfarin + ASA + P2Y12 inhibitor***
Exp'tal arms: ***full or reduced-dose DOAC with or without ASA***

- **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

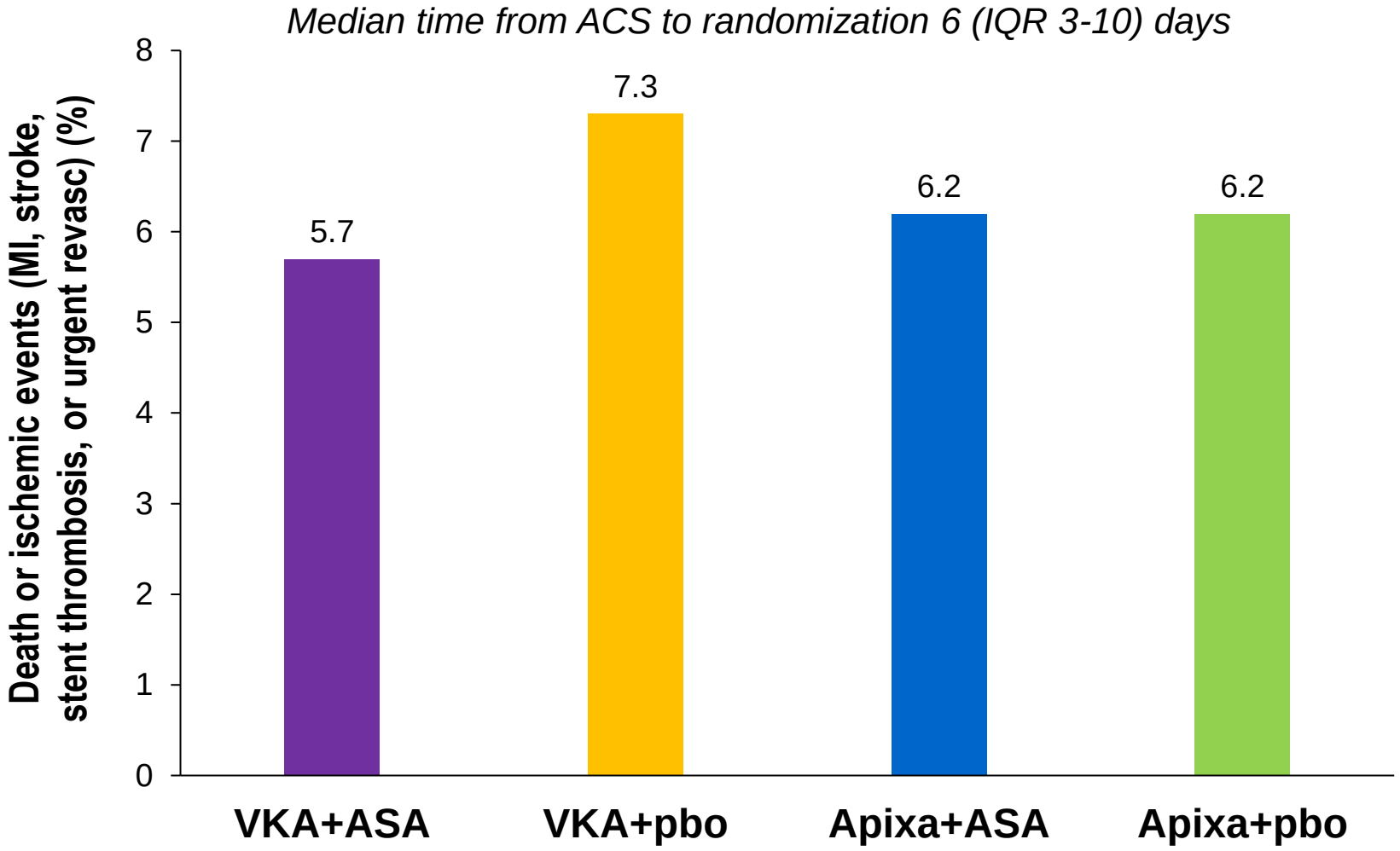
AUGUSTUS: Safety

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



NEJM 2019;380:1509

AUGUSTUS: Efficacy



NEJM 2019;380:1509-1524

Lipid-Lowering Therapy

Case #8

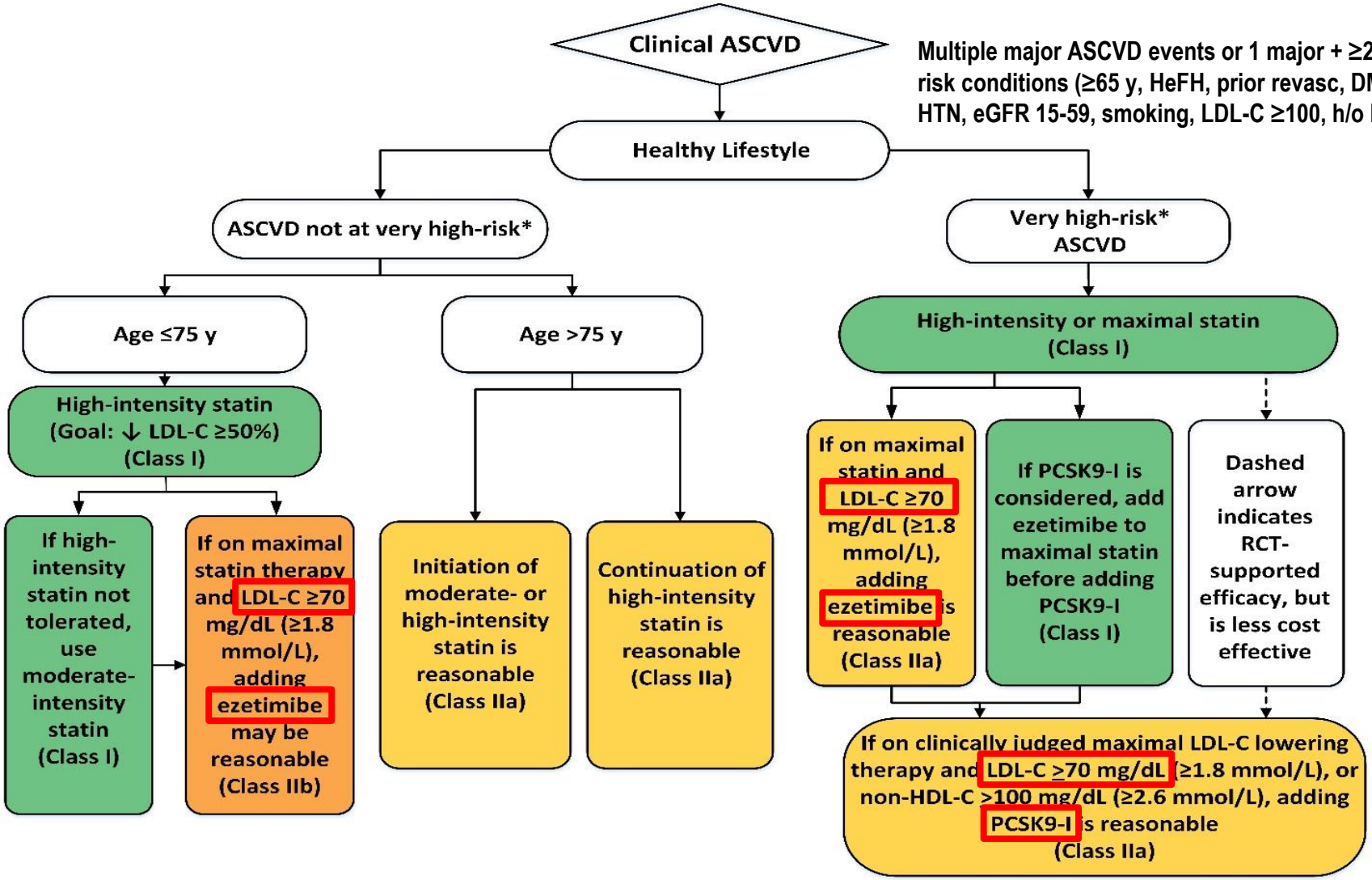
64 yo M w/ h/o NSTEMI 2 years ago now p/w NSTEMI.

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)

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

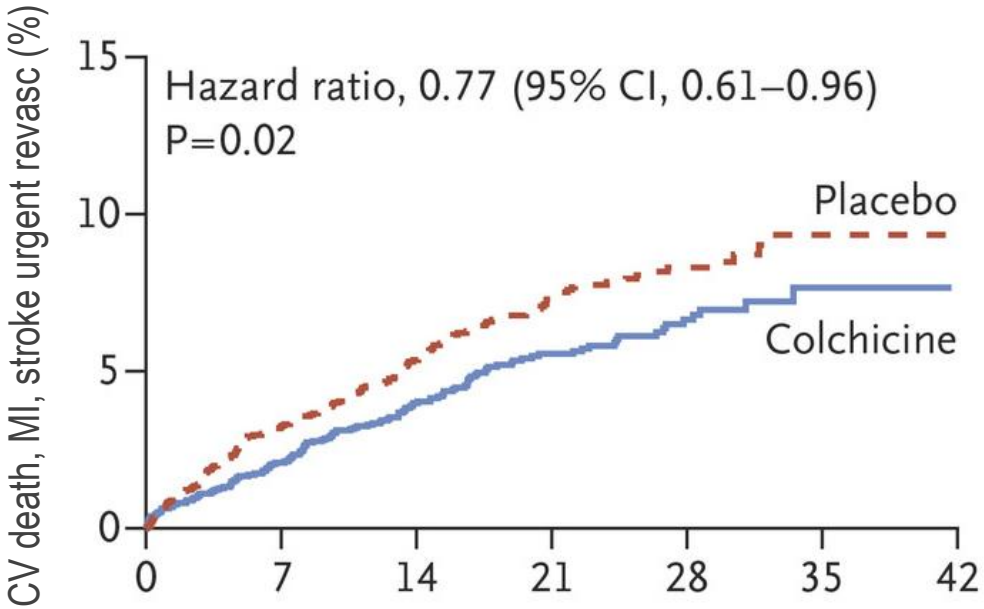
- **Beta-blockers**
  - *Oral* BB initiated w/in 1st 24 hrs if *w/o:*
    - signs of HF; evidence of low-output state; ↑ risk of cardiogenic shock
    - other contraindication (PR >0.24 sec, 2/3º heart block w/o PPM, active asthma, reactive airway disease)
  - If *stabilized* HF, metoprolol succinate, 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

Treating Inflammation?

COLCOT: 4745 Pts within 30d of acute MI

Colchicine 0.5 mg qd vs. placebo



PROS

- **Large relative risk reduction**
- **Benefit of similar magnitude also seen in smaller ACS trial (COPS) trial and in trial of Pts with stable ischemic heart disease (LoDoCo2)**

CONS

- **Rates of non-CV death numerically higher in this trial, COPS, and LoDoCo2 (HR 1.51, 95% CI 0.99-2.31)**

NEJM 2019;381:2497-505

Summary

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