Evidence-Based Management of Acute Coronary Syndromes

Update in Hospital Medicine

October 2023

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TIMI Study Group | BRIGHAM AND WOMEN'S HOSPITAL | HARVARD MEDICAL SCHOOL

Disclosures

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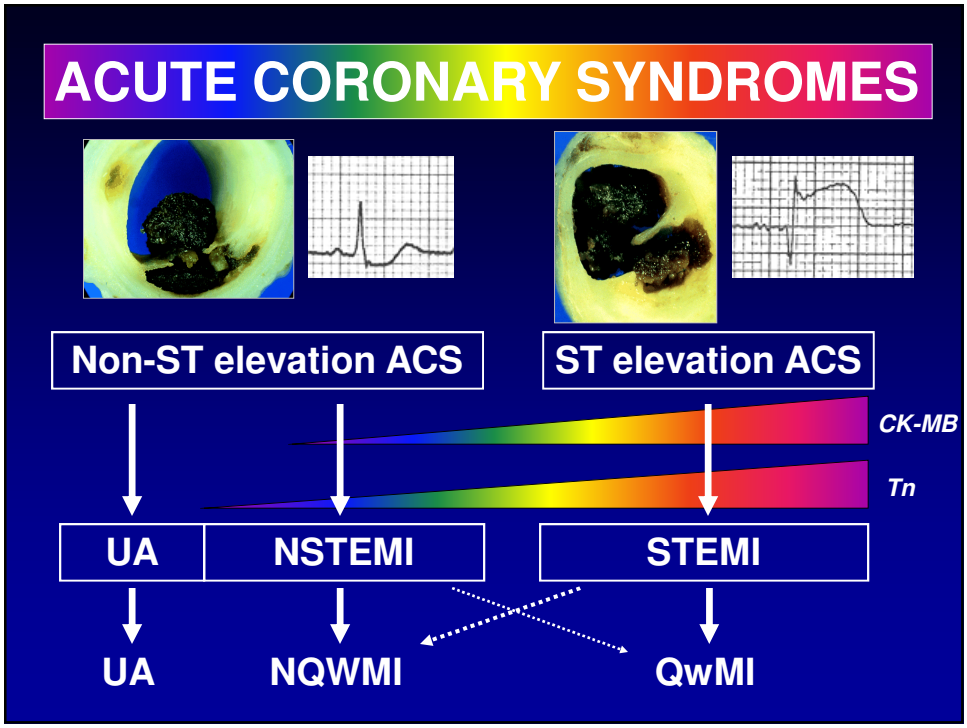
Investigational, unlabeled and/or unapproved uses of drugs or devices will be discussed in this presentation.



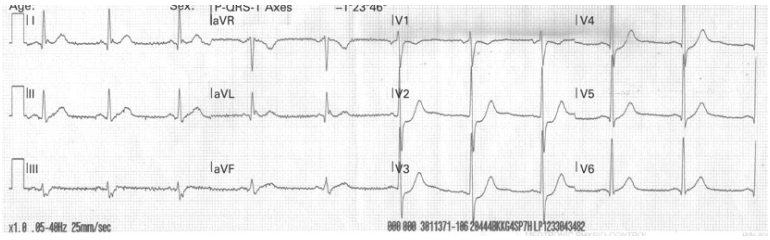
H&P

- **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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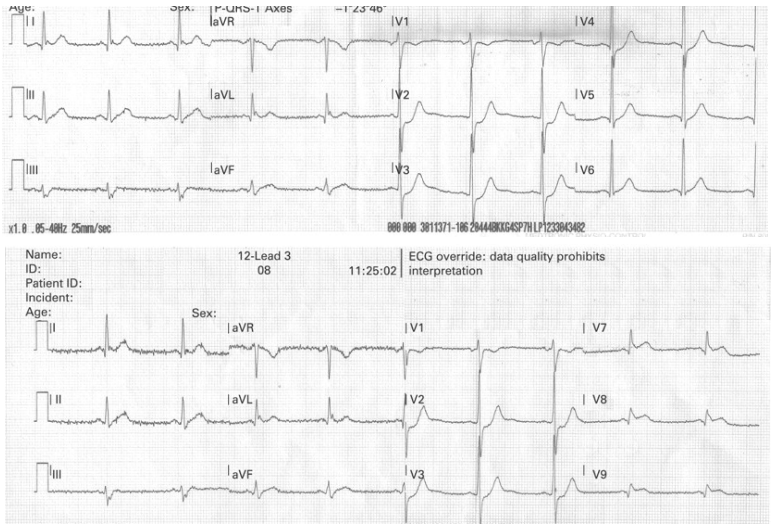
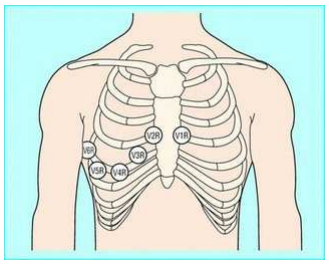


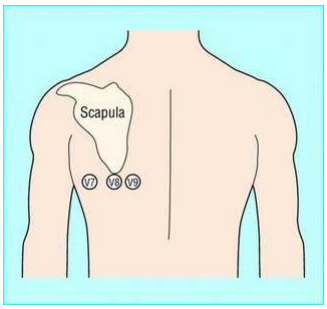
ECG Special Placement

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 occurred 4 hours ago.

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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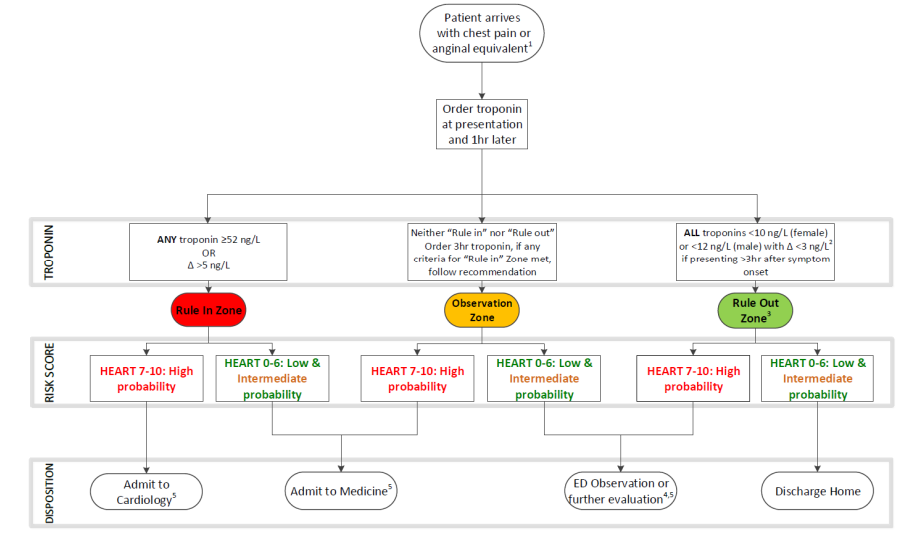
ACS: Biomarkers

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**

MGB 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)

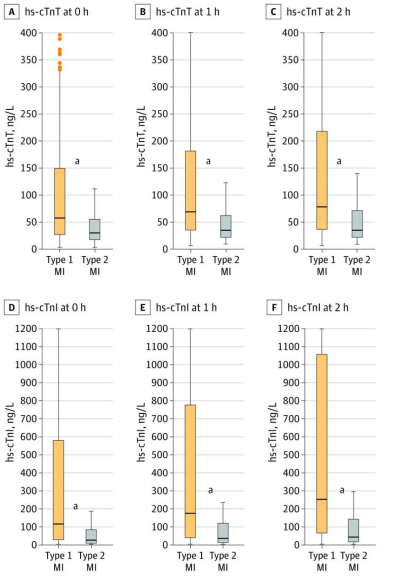
JACC 2018

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 …**



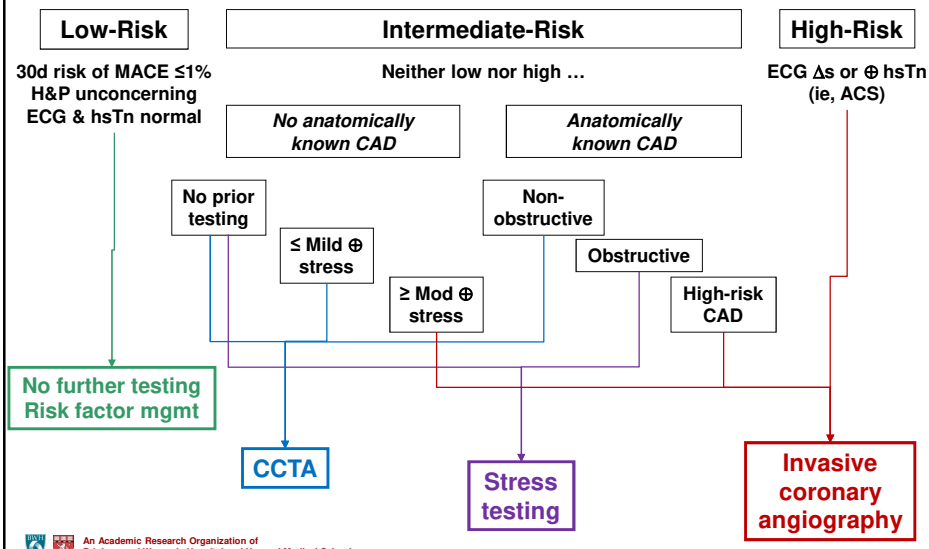
JAMA Cardiol. Published online April 21, 2021

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

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
- **Oxygen**

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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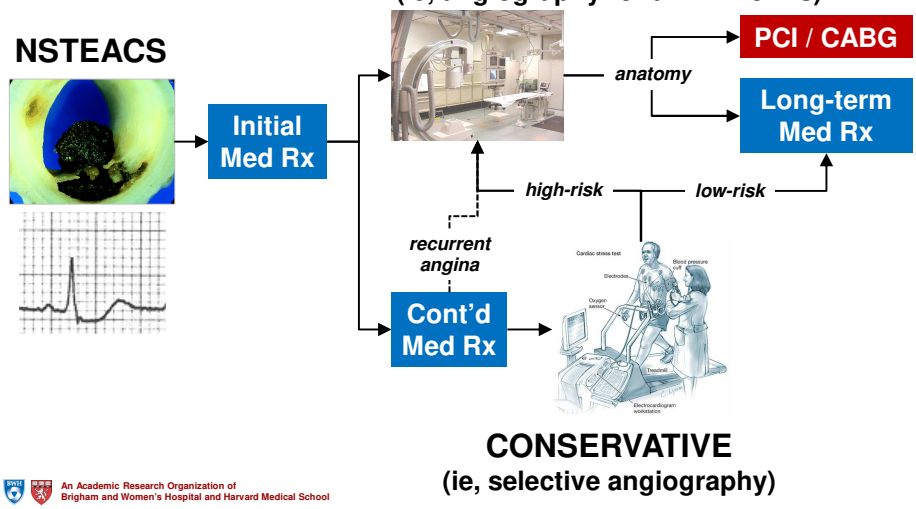
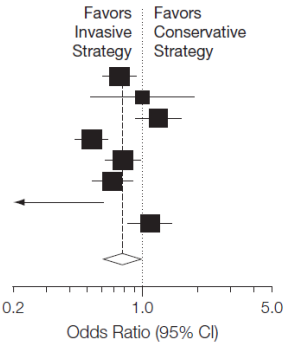
Management Strategy in NSTEACS



Benefit of INV vs CONS Strategy

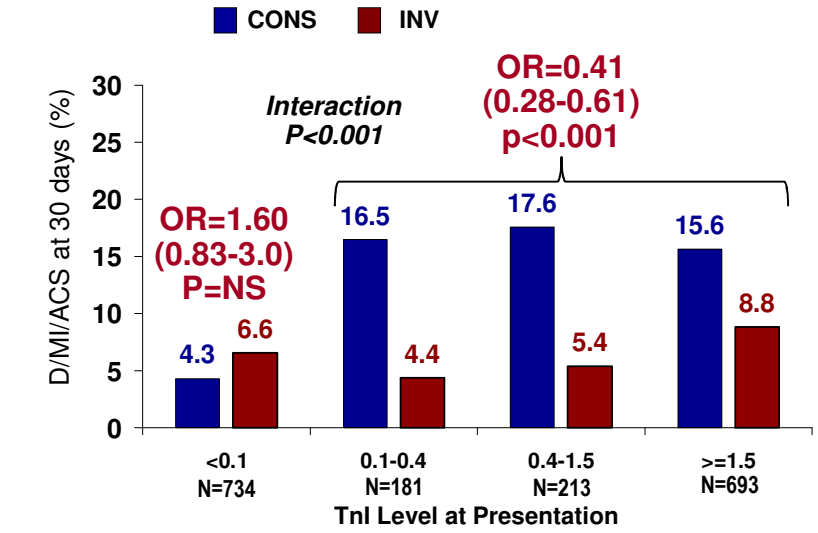
All Patients	Rates of Death, MI, or Rehospitalization With ACS, No./Total No. (%)		Odds Ratio (95% CI)
	Invasive Strategy	Conservative Strategy	
TIMI IIIB[10]	122/895 (13.6)	171/915 (18.7)	0.75 (0.61-0.93)
MATE[11]	27/111 (24.3)	22/90 (24.4)	0.99 (0.52-1.90)
VANQWISH[18]	148/462 (32.0)	124/458 (27.7)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



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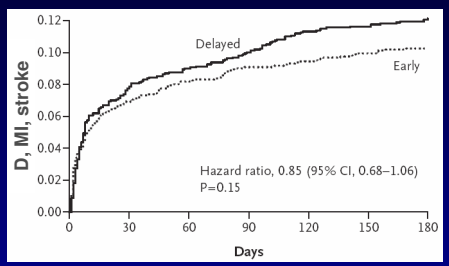
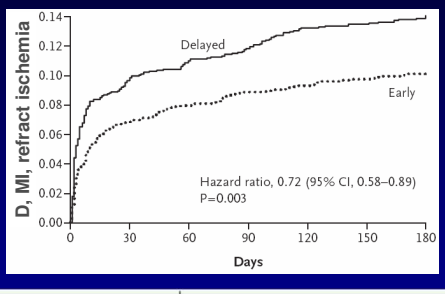
Cannon CP et al. *NEJM* 2001;344:1879

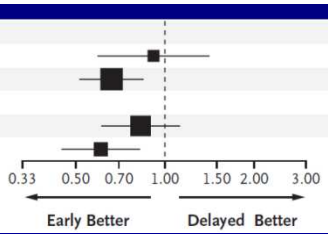
TIMACS

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

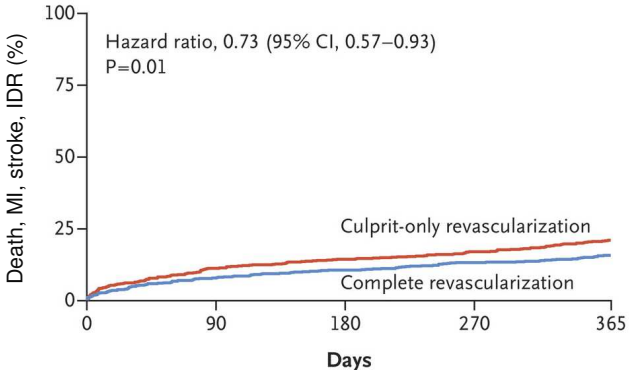
Immediate (w/in 2 h)	Early Invasive (w/in 24 h)	Delayed Invasive (w/in 25-72 h)	Ischemia-Guided
• Refractory angina • Signs or symptoms of HF or new or worsening MR • Recurrent angina or ischemia at rest or with low-level activity despite intensive med Rx	• GRACE score >140 • Temporal Δ in Tn • New or 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

Complete Revasc in All MI

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

Physiology-guided complete revasc vs. culprit-only



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

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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

Antiplatelet Therapy

Case #3

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

ECG shows anterior ST segment depressions. Troponin elevated.

Receives aspirin. Goes to the cath lab and is found to have a 90% ulcerated LAD lesion.

What antiplatelet drug would you add?

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

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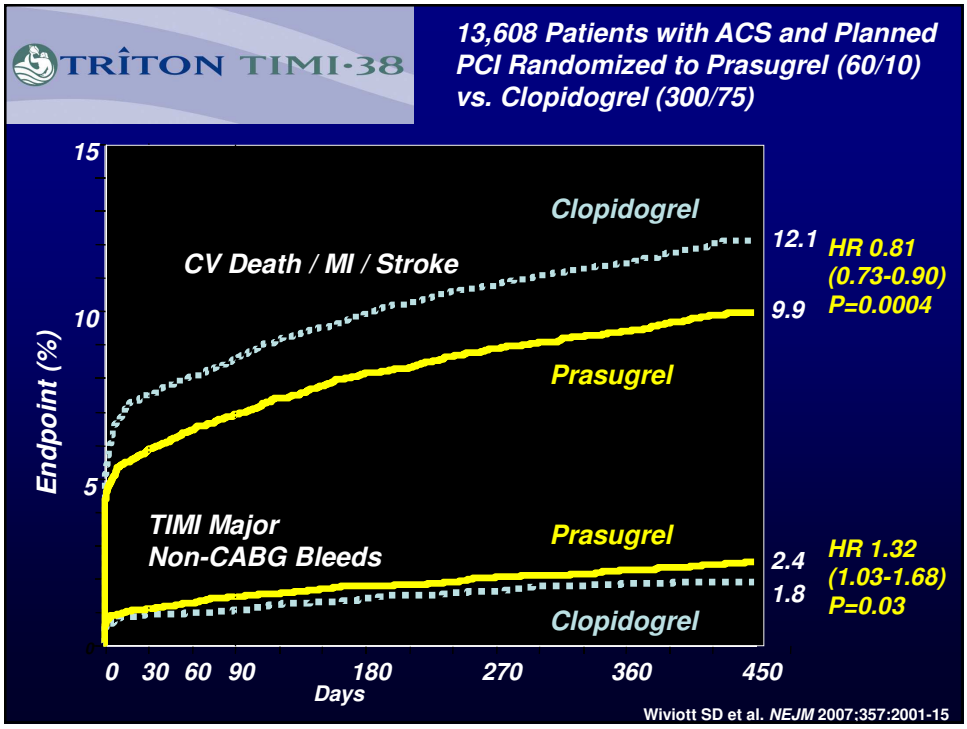
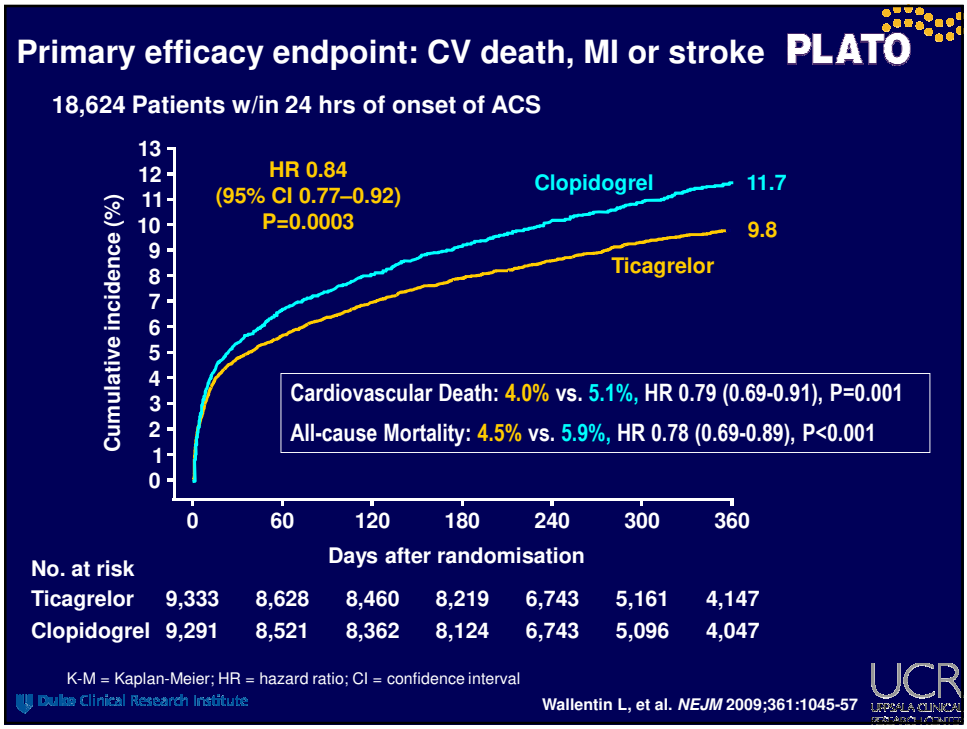

TRITON TIMI-38
13,608 Patients with ACS and Planned PCI Randomized to Prasugrel (60/10) vs. Clopidogrel (300/75)
Endpoint (%)
15
10
5
0
CV Death / MI / Stroke
Clopidogrel
Prasugrel
12.1
9.9
HR 0.81
(0.73-0.90)
P=0.0004
TIMI Major
Non-CABG Bleeds
Prasugrel
Clopidogrel
2.4
1.8
HR 1.32
(1.03-1.68)
P=0.03
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

Antiplatelet Therapy Acutely

- ***Start with*** **COX Inhibitor (ie, aspirin)**
- ***Almost always add:*** **$P2Y_{12}$ Inhibitor**
  - Ticagrelor or prasugrel preferred over clopidogrel
  - Typically give oral $P2Y_{12}$ at time of PCI
  - Cangrelor if worried about oral absorption
- ***Sometimes also add (typically in cath lab)*:**
  glycoprotein IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban)

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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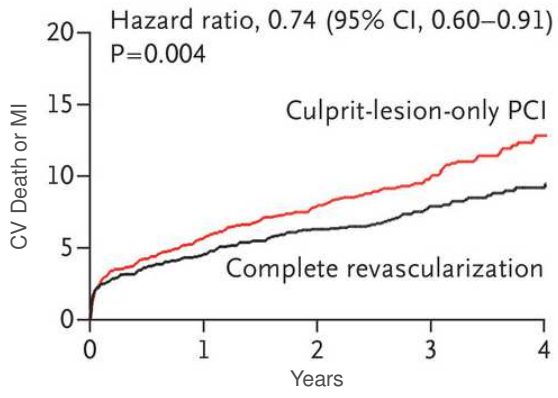
Preventive PCI in STEMI

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

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

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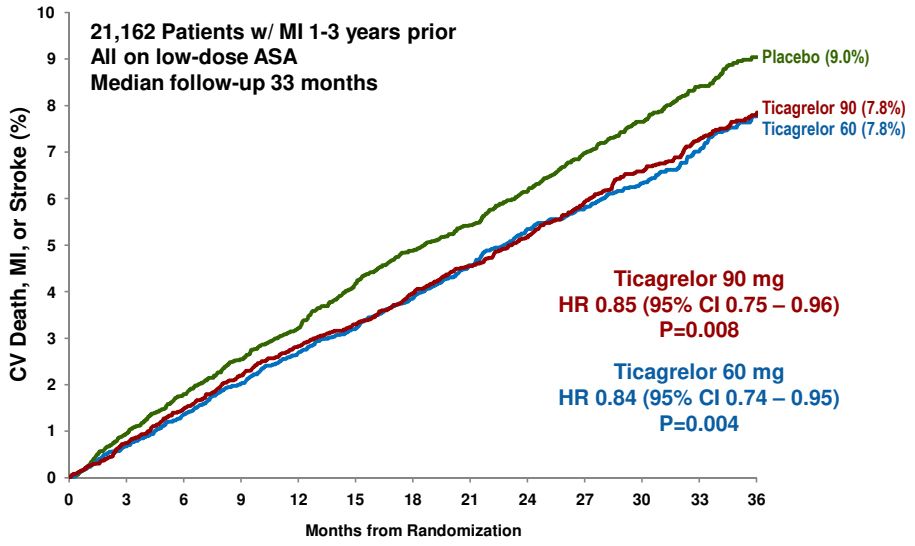
Ticagrelor + ASA Better Than ASA Alone



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

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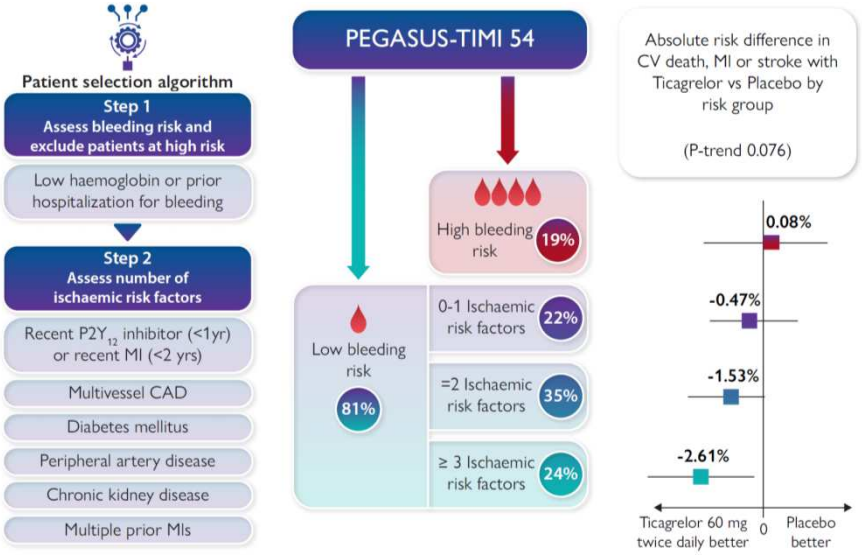

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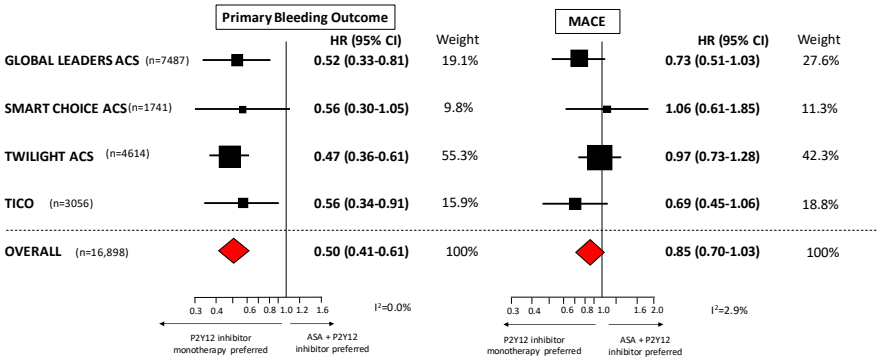
Bonaca MP et al. and Sabatine MS. *EHJ* 2022;in press

Drop Aspirin after 1-3 Months (ie, P2Y$_{12}$ MonoRx)?



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

Duration of P2Y12 Inhibition?

- **Start with DAPT ASA + P2Y$_{12}$ inhibitor (ticag or prasugrel preferred)**
- **For most patients: continue for 12 mos**
- **If high ischemic risk (and low bleeding risk & tolerated DAPT well to date), consider continuing ASA + P2Y$_{12}$ inhibitor beyond 12 mos**
- **Could consider dropping ASA after 3 mos and just continue P2Y$_{12}$ inhib (ideally ticagrelor)**
- **If high bleeding risk, would use clopidogrel over ticag or prasugrel and drop ASA after 3 mos**

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 should be her long-term antithrombotic regimen:

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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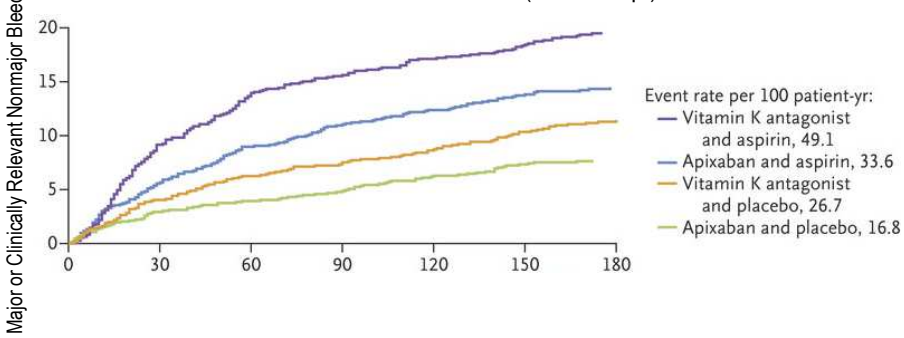
AUGUSTUS: Safety

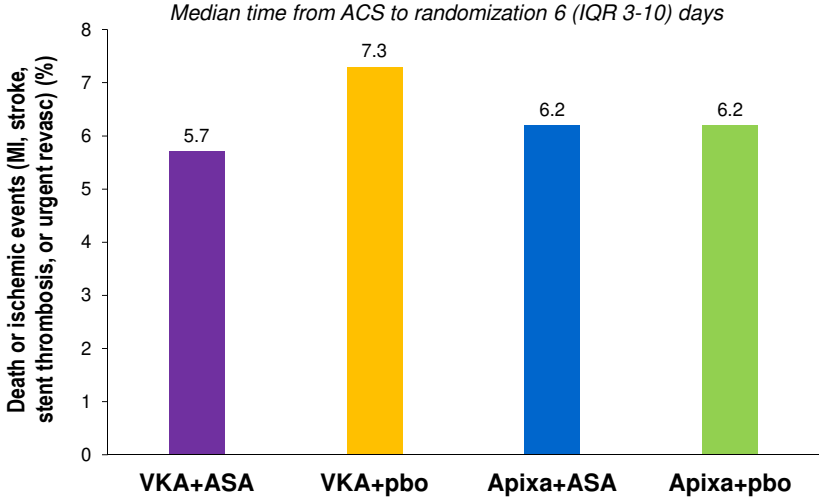
4614 Pts w/ AF + either:
ACS+PCI (37%), ACS w/o PCI (24%), Elective PCI (39%)
All received P2Y12 inhibitor (>90% clopi)



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?

- **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 to reduce bleeding risk)**
- **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 #7</u>

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

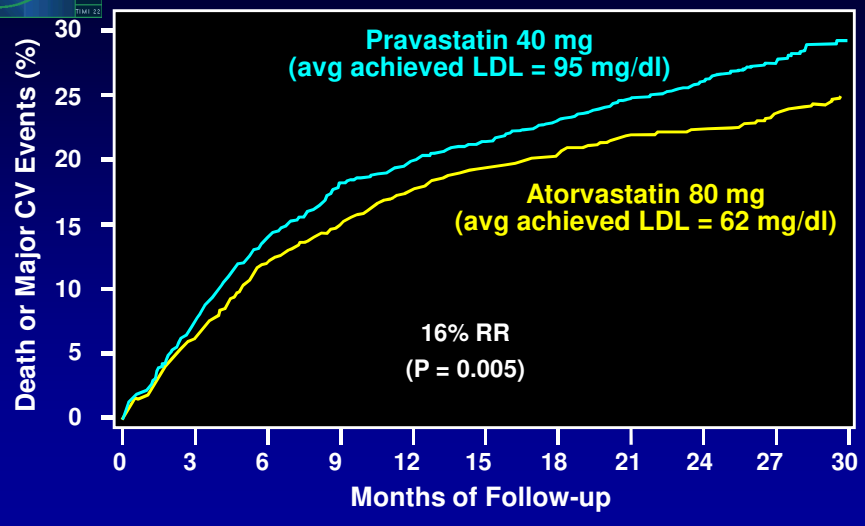
Drug-eluting stent placed in LAD. 50% lesions in RCA and LCx.

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 <70 (eg, ≤40 mg/dL)

PROVE IT – TIMI 22

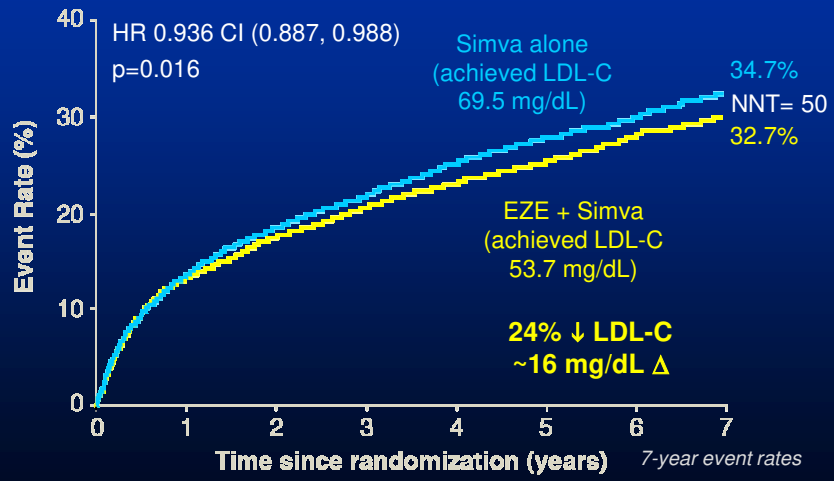
4162 patients hospitalized w/in prior 10 d for ACS



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

Primary Endpoint — ITT

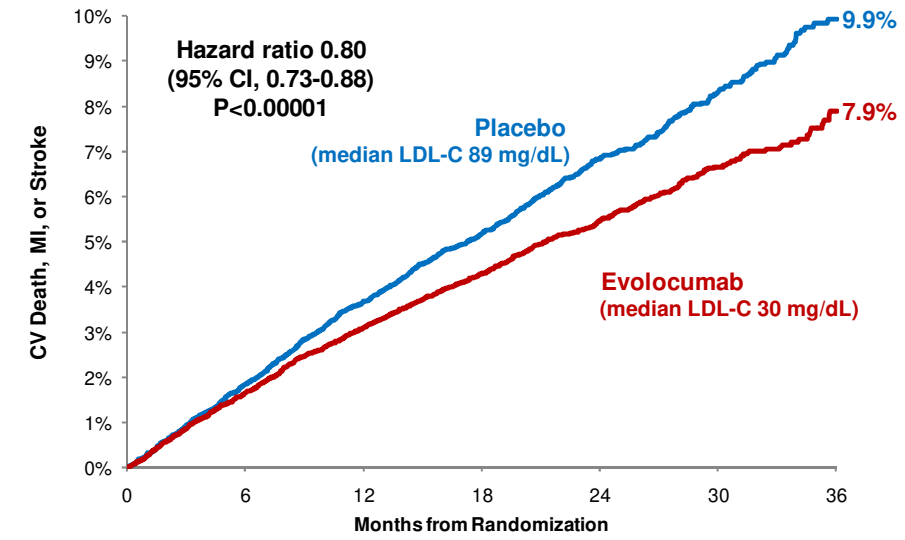
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

NEJM 2015;372:2387-97

Evolocumab (anti-PCSK9 mAb)



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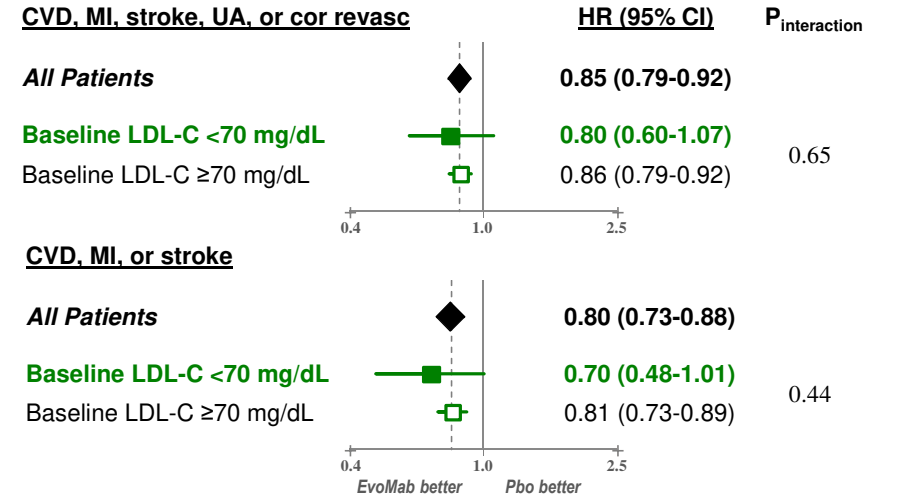
Sabatine MS et al. *NEJM* 2017;376:1713-22

Clinical Outcomes
by Baseline LDL-C



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Giugliano RP et al. and Sabatine MS. *JAMA Cardiol* 2017;2:1385-91

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]

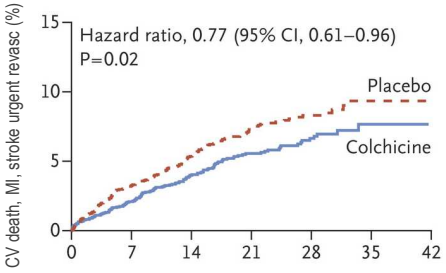
β-blockers, ACEI/ARB, MRA

- **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, nitrates
- **For STEMI:** *select Primary PCI vs Lytic*
- **For NSTEACS:** *select Invasive vs. Conservative Strategy*
  - Tend to use INV strategy for higher risk patients (eg, Tn positive)
- **Select Antiplatelet Regimen**
  - ASA + $P2Y_{12}$ inhib: ticag or prasugrel (or clopidogrel); typically at time of PCI
- **Select Anticoagulant:** UFH, LMWH, bivalirudin, or fondaparinux, typically just through PCI
- **Long-term therapy**
  - ASA + $P2Y_{12}$ inhib (then tailor)
  - βB, statin ± EZE (± PCSK9i)
  - ? ACEI, ? Aldo inhib, ? colchicine

Disclosures

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