Antiplatelet Therapy Selection
A Case-Based Discussion

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Dallas CARDIOVASCULAR INNOVATIONS 2013

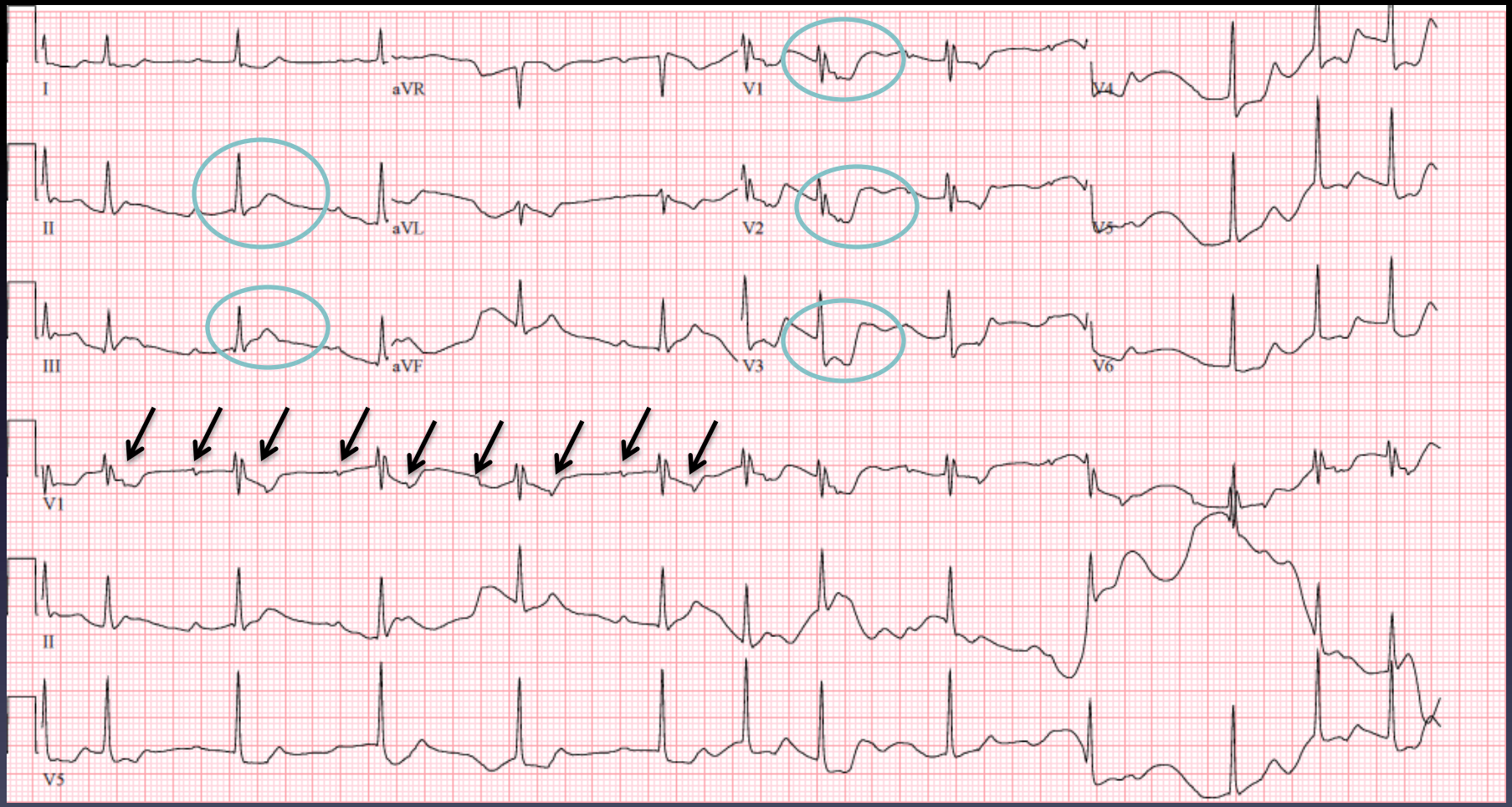
I, Timothy A. Mixon MD, have no financial disclosures

Case #1

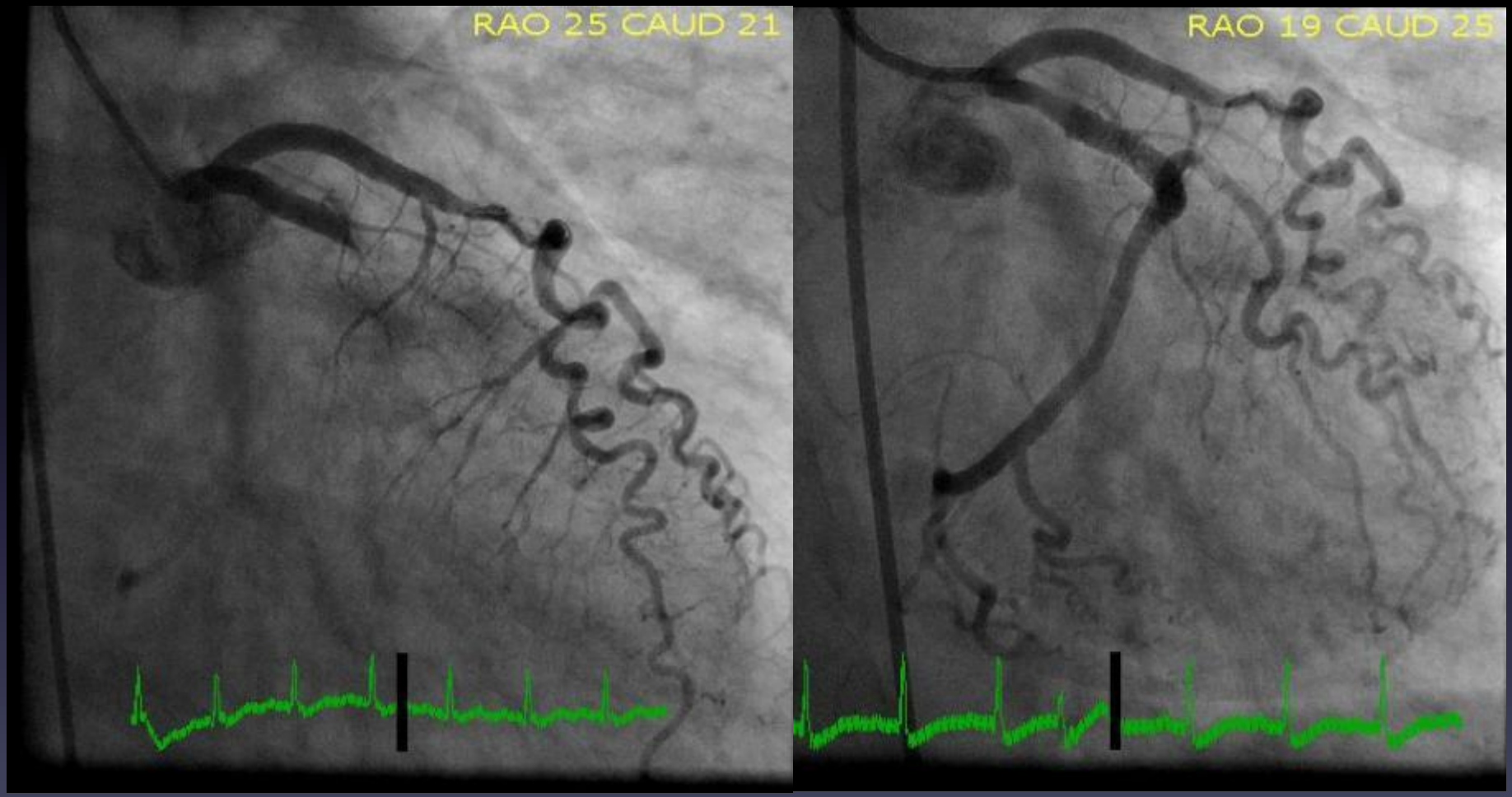
CC: 65 y/o woman transferred due to sudden onset chest pain and syncope.

- En route, symptomatic bradycardia noted
  - 2:1 AV block → transcut pacing (midazolam 15 mg!)
  - Led to intubation
- Direct admit to cath lab
- Left dominant system. Occluded proximal LCx
- Noncritical disease within LAD and nondominant RCA

Inferior-posterior injury pattern
Advanced AV block



Coronary Angiogram



Therapeutic Decision Making

- Received: Aspirin PR, UFH IV (4000 U bolus), Intubated (No NG tube)
- What could we add?
  - UFH
    - UFH alone (Goal ACT ≈ 300 sec)
    - IIb/IIIa receptor antagonist (in cath lab) + UFH (Goal ACT 200-250 sec)
  - Bivalirudin +
    - Prasugrel or ticagrelor via NG tube (when available)
    - IC abciximab
    - ? Cangrelor (not yet available in US)
- Used: IV bivalirudin, + "post PCI" dosing until thienopyridine

Clinical Question #1

How do we manage antiplatelet/anticoagulant therapy when patients cannot take anything by mouth?

Bivalirudin in STEMI

- Reduced NACE (equal MACE, reduced bleeding)
- Reduced 30 day and 1 year mortality
- Increased early ST rare enough not to increase MI /death within bivalirudin group
- Post hoc analysis: Early ST decreased by
  - Preprocedural UFH administration
  - Prolonged bivalirudin infusion

EUROMAX

n=2218

Pre-hospital initiation of…

Bivalirudin vs. UFH + IIb/IIIa antagonist in STEMI

EUROMAX
EUROpean AMbulance ACS AngioX Trial

90% randomized in ambulance
50% clopidogrel use / 50% ticagrelor or prasugrel (90% loaded "before" angiography)
≈ 50/50 radial : femoral

Primary Endpoint: Reduced 30 day Death/bleeding (8.4% vs. 5.1%, p<0.002)

Reduced major bleeding (6.1% vs. 2.7% , p<0.001, RRR 57%)

Similar to Horizons AMI: equal MACE, reduced bleeding = reduced NACE

No statistical difference in death at 30 days

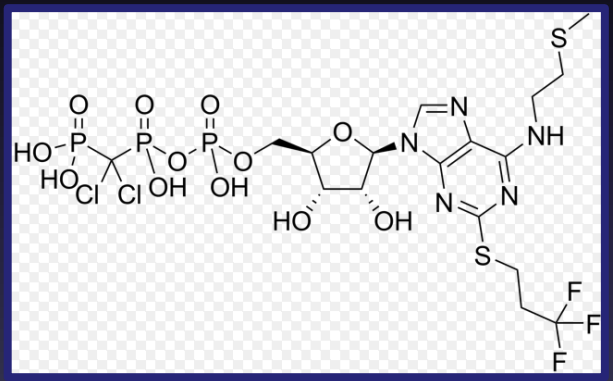
Statistically higher early ST (0.2% vs. 1.1% RR 6.1 p=0.007)

Presented at TCT 2013
Steg et al. NEJM Online October 29, 2013

Cangrelor

CHAMPION-PHOENIX

- Novel direct, P2Y12 receptor antagonist
- Similar to ticagrelor
- Rapid onset / Rapid offset
- Does NOT require bio-activation
- IV formulations only
- n > 11,000 undergoing PCI
- 60% stable angina, 40% ACS
- 80% UFH , 20% bivalirudin

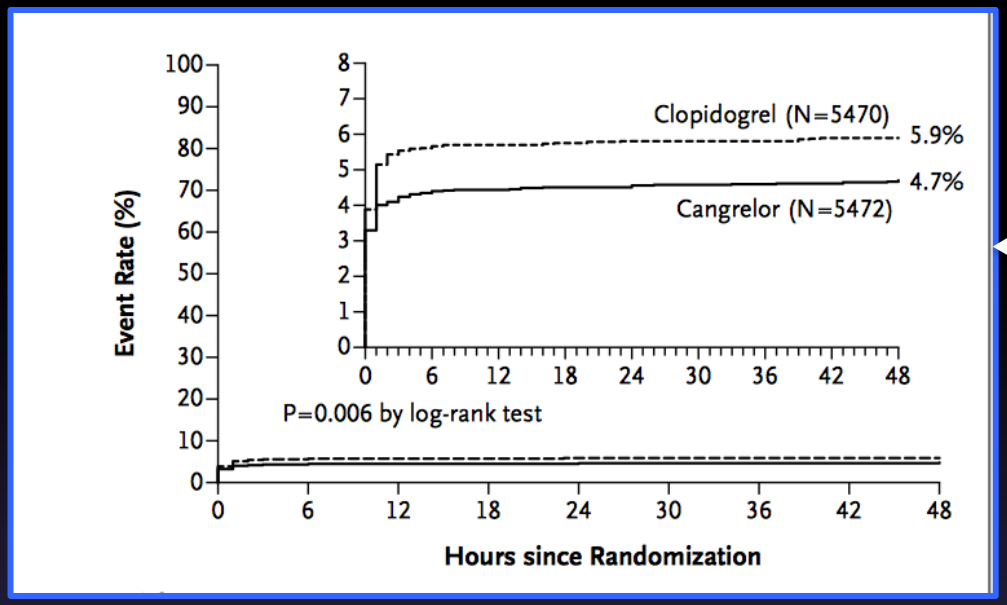


Not currently FDA approved

N Engl J Med. 2013; 368(14):1303-13

Cangrelor

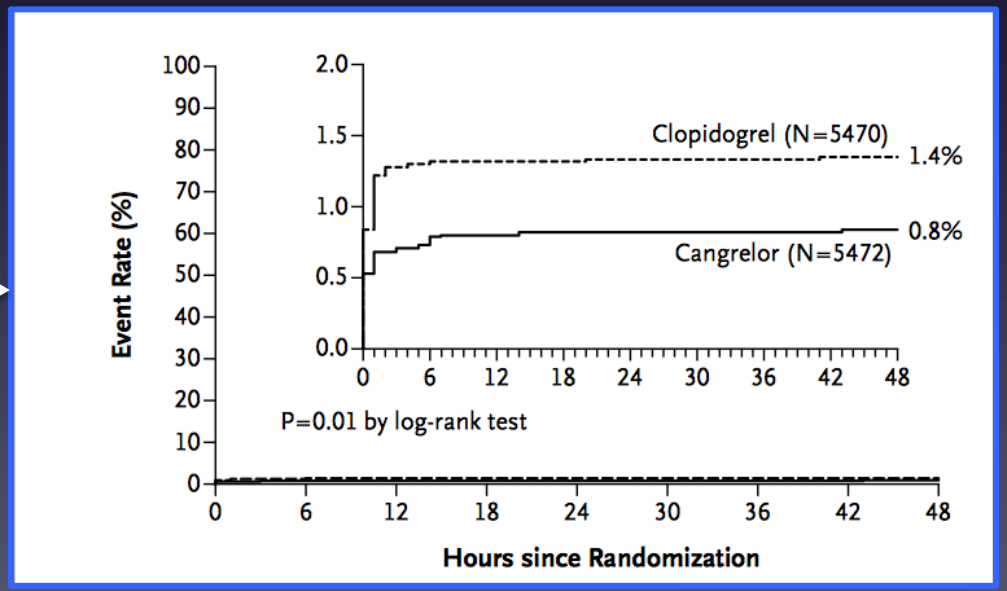
CHAMPION-PHOENIX



Primary End Point, composite of:

1. All cause death,
2. MI,
3. Ischemia driven revascularization,
4. Acute stent thrombosis

Secondary End Point:
Acute stent thrombosis
(within 48 hours)



Not currently FDA approved

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Part 2: Post Cath Lab Course

- Traumatic NG insertion → significant oral-nasal bleeding
  - Hgb 12 → 8.5 after 36 hours
  - Actions:
    - Prasugrel changed to clopidogrel
    - "DVT" prophylaxis UFH stopped
- Day 4: Paroxysmal atrial fibrillation
  - $CHADS_2$ score = 2 (HTN, diabetes)
  - $CHADS_2$-VaSC = 4 (+ age, gender)

Clinical Question #2

How do we manage antiplatelet agents when anticoagulants are needed?

Options

1. Absentmindedly "ignore" the atrial fibrillation, continue DAPT
2. Deem the atrial fib transient and provoked, therefore ignore it
3. Prophylax for atrial fib-induced stroke, + utilize DAPT for ACS/stent implant
   - What INR do you strive for?
   - Would you utilize newer oral anticoagulant?
   - Which platelet $P2Y_{12}$ receptor antagonist?
   - What do you do with aspirin?
4. Use warfarin + either clopidogrel or aspirin


Rock
Hard Place

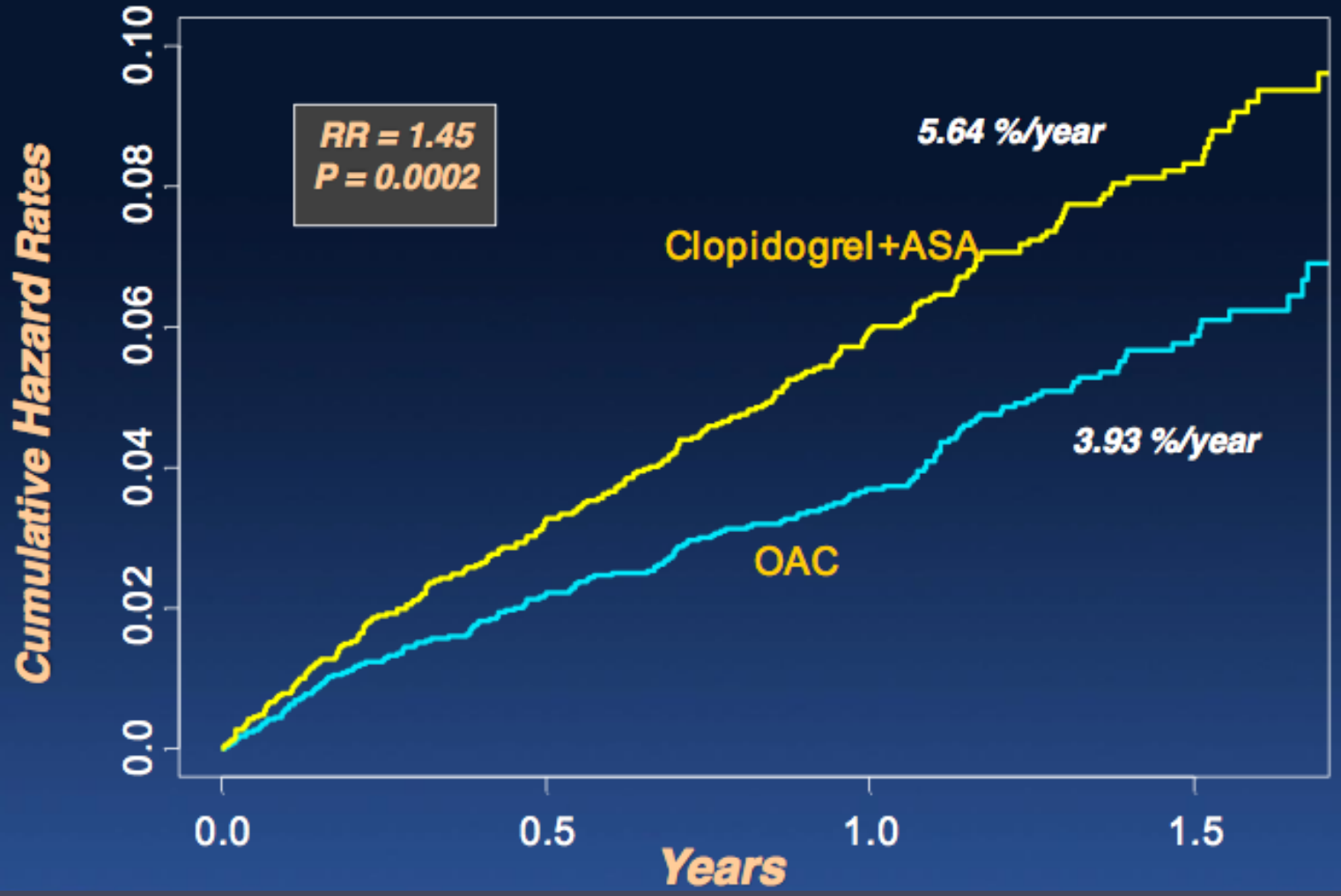
Between a rock and a hard place

Association of bleeding and adverse outcomes

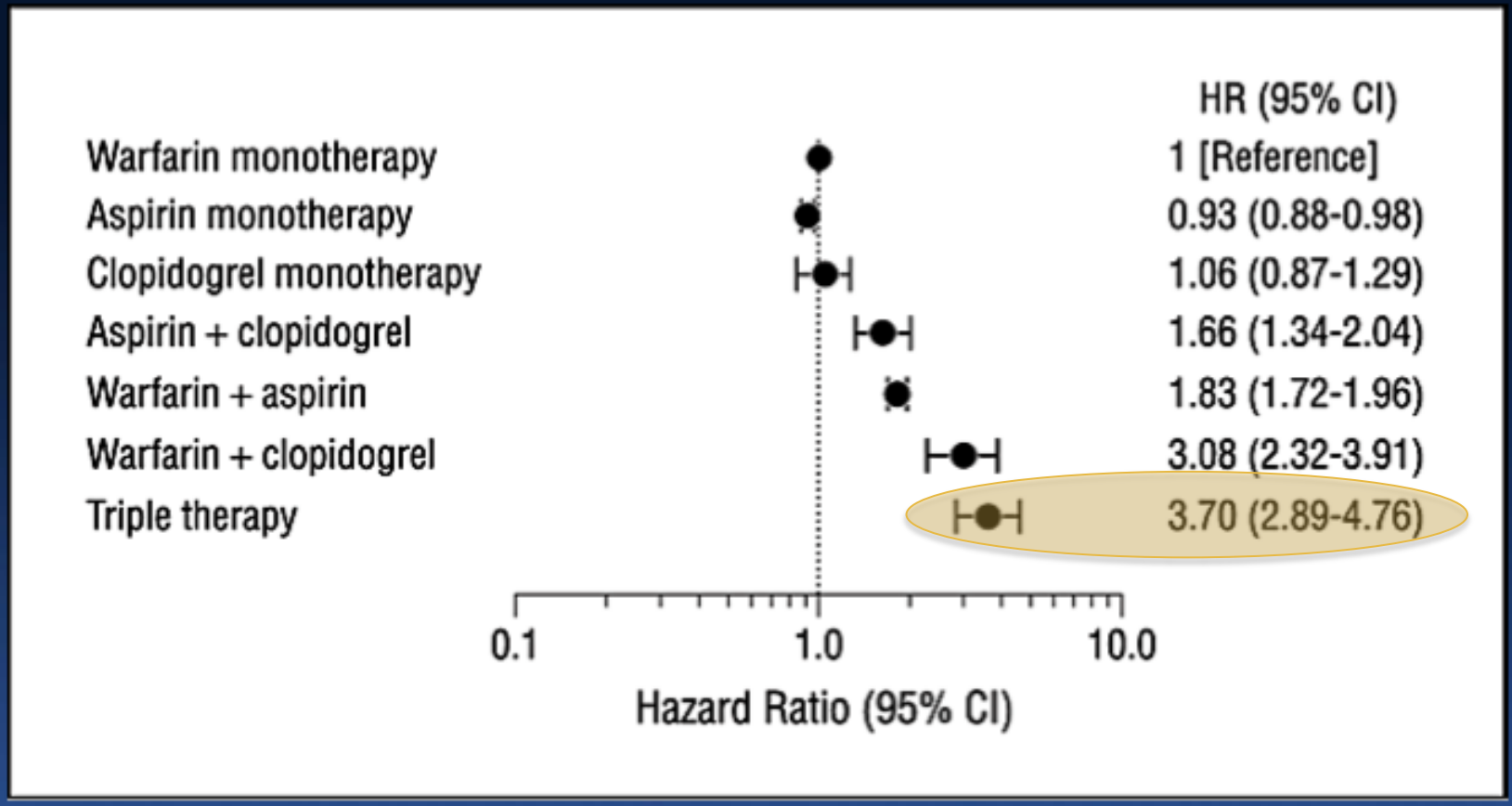
Bleeding associated with increased…

1. Mortality
2. Myocardial infarction
3. Stroke
4. Stent thrombosis

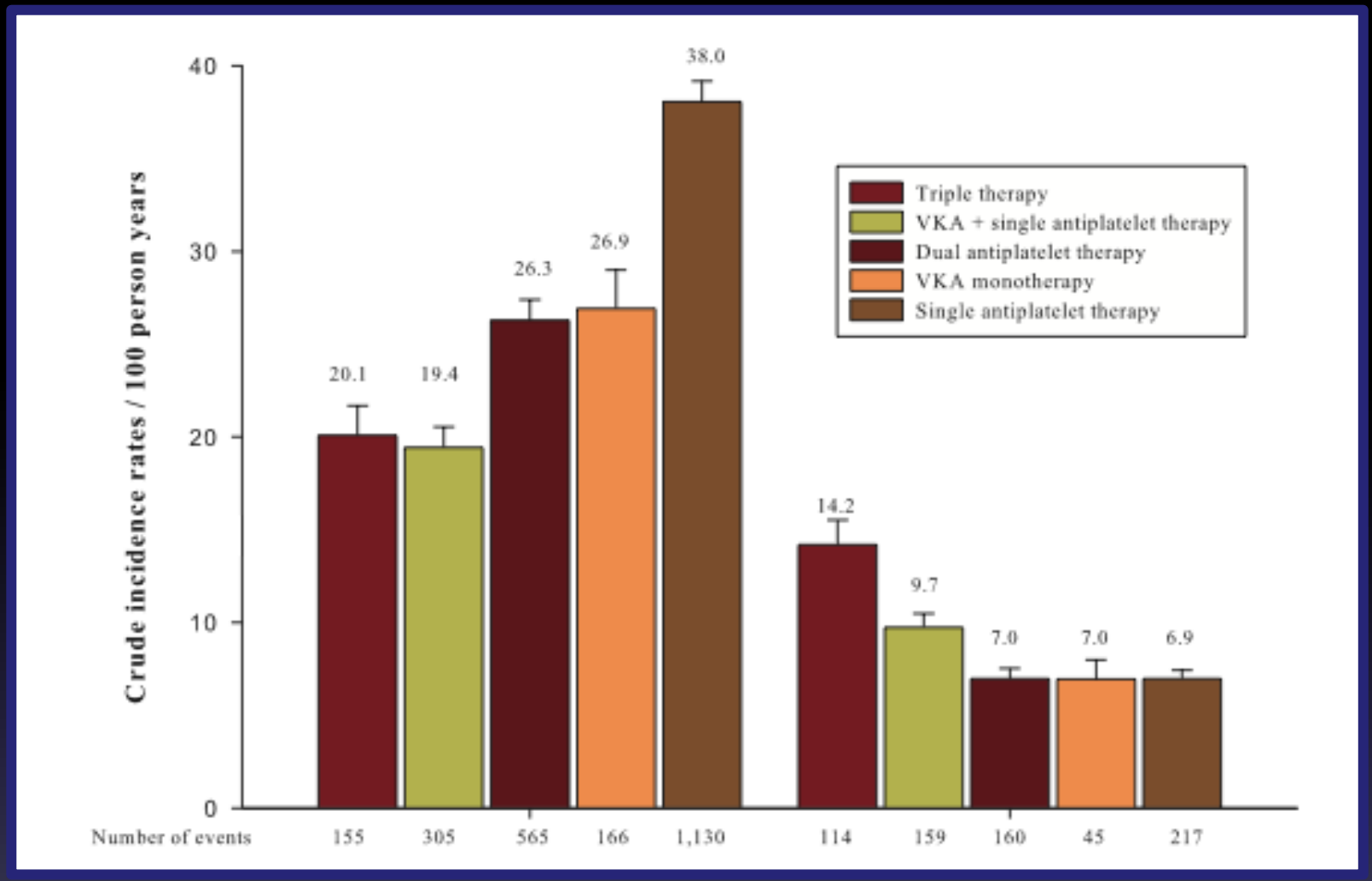
ACTIVE W: Stroke, Non-CNS Systemic Embolism, MI & Vascular Death



Bleeding associated with warfarin, aspirin, clopidogrel in patients with AF n=82,854



Hansen et al, Arch Intern Med 2010; 170: 1433f



CV Death + MI + ischemic stroke

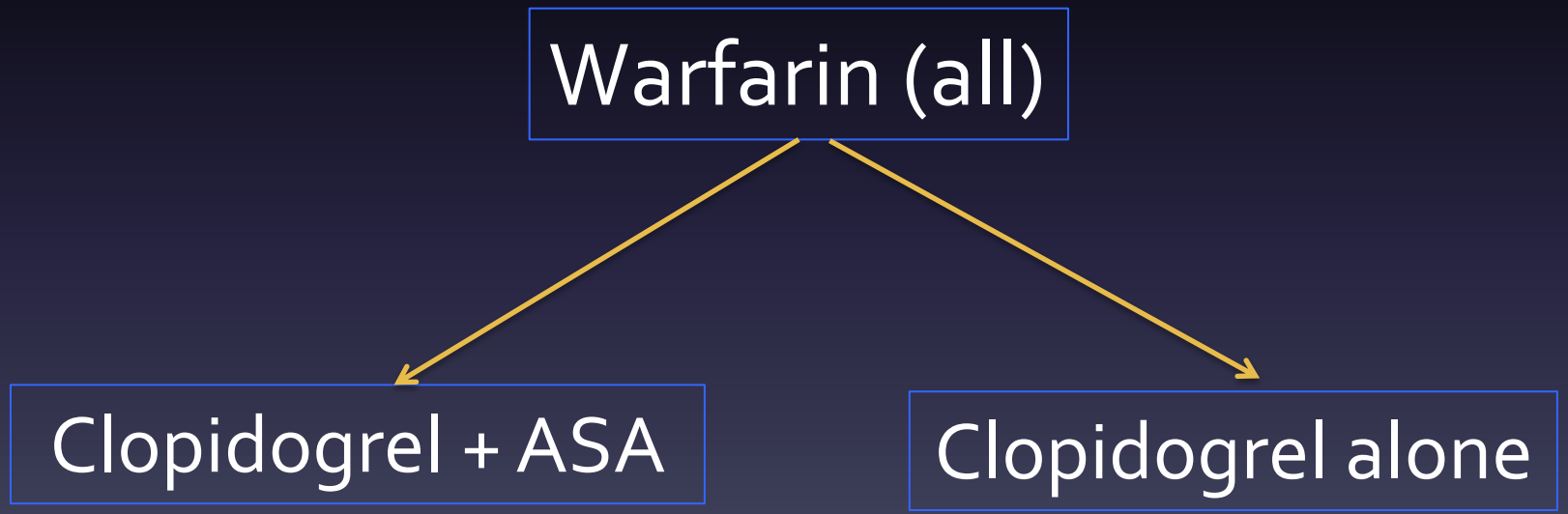
Fatal+ nonfatal bleeding

Danish Registry
Circulation 2012; 126: 1185-1193

Guidance—WOEST Trial

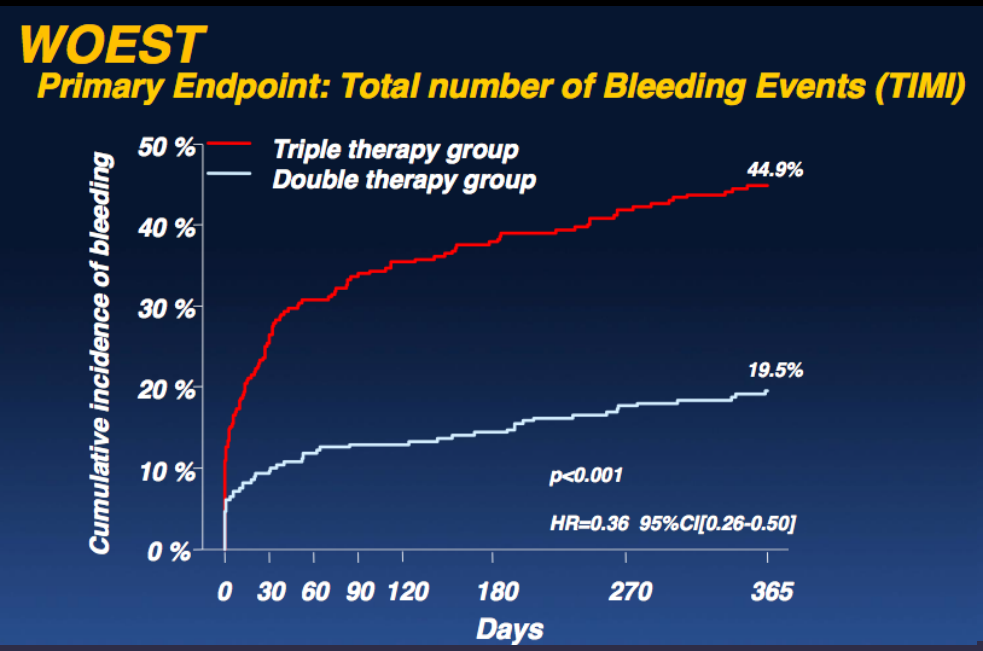
n=573

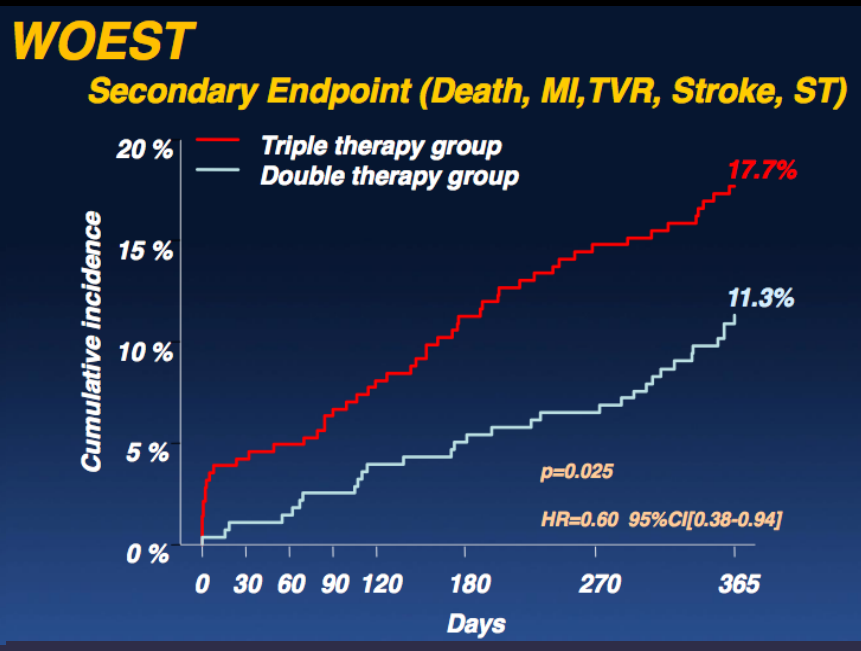
PCI patients in need of anticoagulation



Dewilde et al. *Lancet* 2013; 381: 1107-1115

Results—WOEST Trial





Bleeding ↓ by 64%

Ischemic Events ↓ by 40%

Dewilde et al. *Lancet* 2013; 381: 1107-1115

2013 ACC/AHA STEMI Guidelines

Class 1

- Anticoagulant therapy with a vitamin K antagonist should be provided to patients with STEMI and *atrial fibrillation with CHADS2 score ≥ 2*, (LOE C)
  - 2011 PCI guidelines point out that bleeding is increased, therefore monitoring, esp for GI bleeding, is warranted.
- The duration of triple-antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor *should be minimized* to the extent possible to limit the risk of bleeding. (LOE C)

Class IIb

- Targeting vitamin K antagonist therapy to *a lower INR* (e.g. 2.0-2.5) might be considered in patients with STEMI who are receiving DAPT (LOE C)

ESC Guidelines

- Generally make stronger statements that prasugrel or ticagrelor should be used over clopidogrel in ACS
- 6 months of triple therapy
  - Warfarin 2.0-2.5
  - Low dose aspirin
  - Clopidogrel
- After 6 months: warfarin 2.0-2.5 + ASA or clopidogrel

Future Guidance

Pioneer AF-PCI Trial

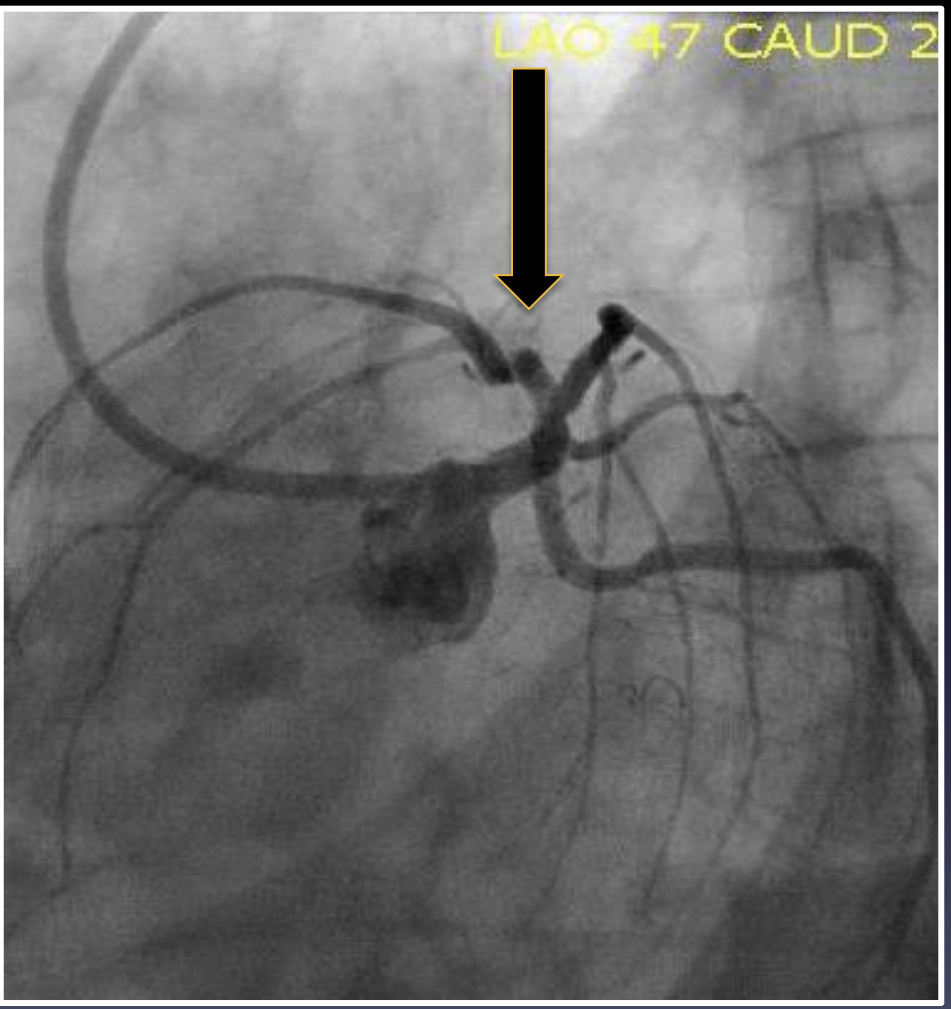
Bleeding endpoints using various combinations of:

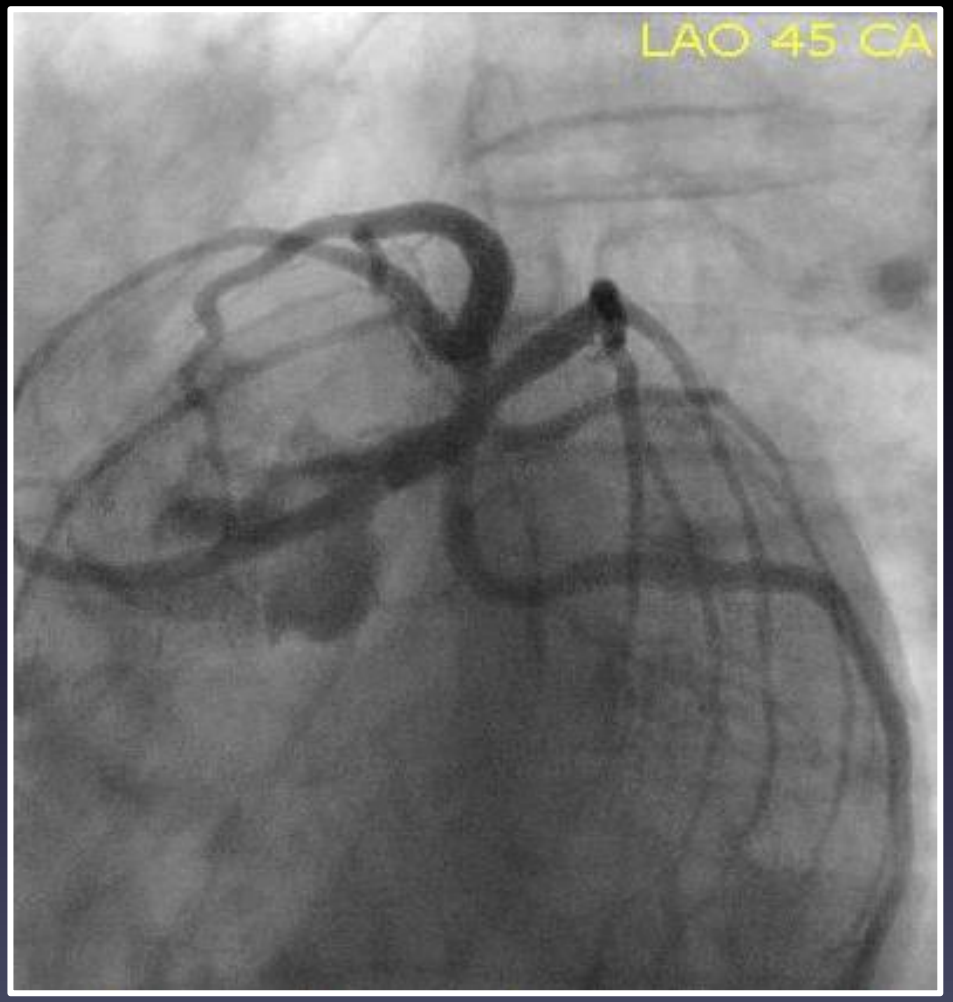
- Rivoraxaban 2.5 – 15 mg BID or warfarin
- Clopidogrel (or newer $P2Y_{12}$ antagonists)
- ASA (low dose of varying duration)

http://clinicaltrials.gov/show/NCT01830543, accessed 10/30/2013

Here we go again…

- 53 y/o man presents with anterior ST elevation
- 2 years ago: inferior MI due to stent thrombosis of RCA (stents in Houston 1 week previously, noncompliant with clopidogrel)
- Interim: received bifurcating stents in LAD/diag (San Antonio)





+ UDS. VerifyNow (after clopidogrel relaoding)…
240 PRUs

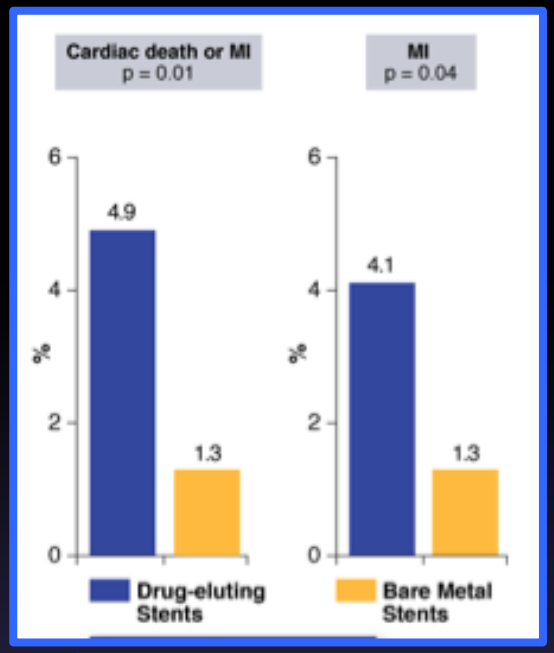
Clinical Question #3

What is associated with stent thrombosis and what is the optimal duration of DAPT?

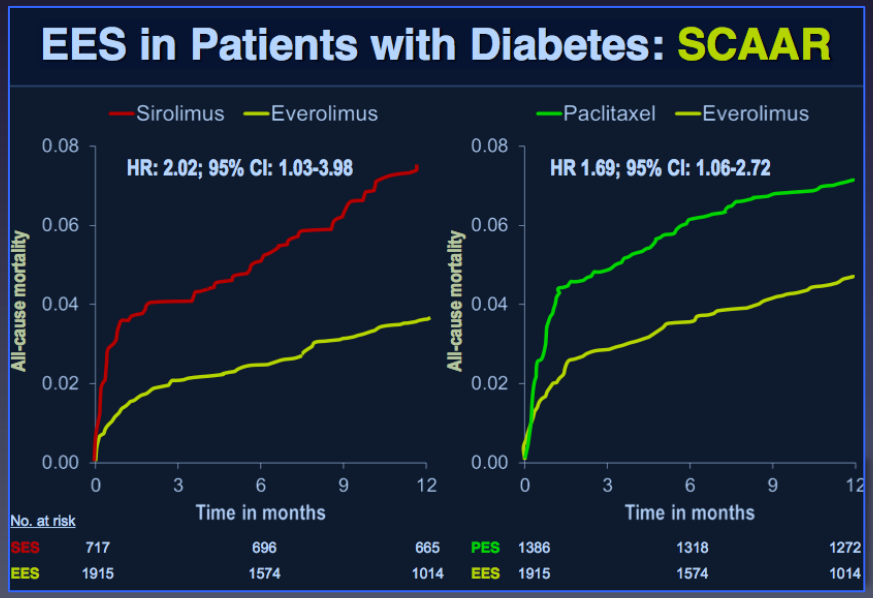
- Multiple risk factors for stent thrombosis*
- Role of individualized therapy*
- Length of DAPT*
- Cath lab considerations: IVUS or OCT imaging to assure lack of technical reasons for LST

Risk Factors for Stent Thrombosis

- ✧ Lack of adequate DAPT
- ✧ Underexpanded/malapposed stents
- • ACS presentation
- • Diabetes
- • Smaller vessel
- • Longer/overlapping stents
- • Clopidogrel non-responders
- • Clopidogrel use
- • Stent type



Basket LATE Trial (left), first suggested safety concern with DES vs. BMS (JACC 2006).
SCAAR Registry points toward improved safety with newer generation DES



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Comparison Among $P2Y_{12}$ Receptor Antagonist

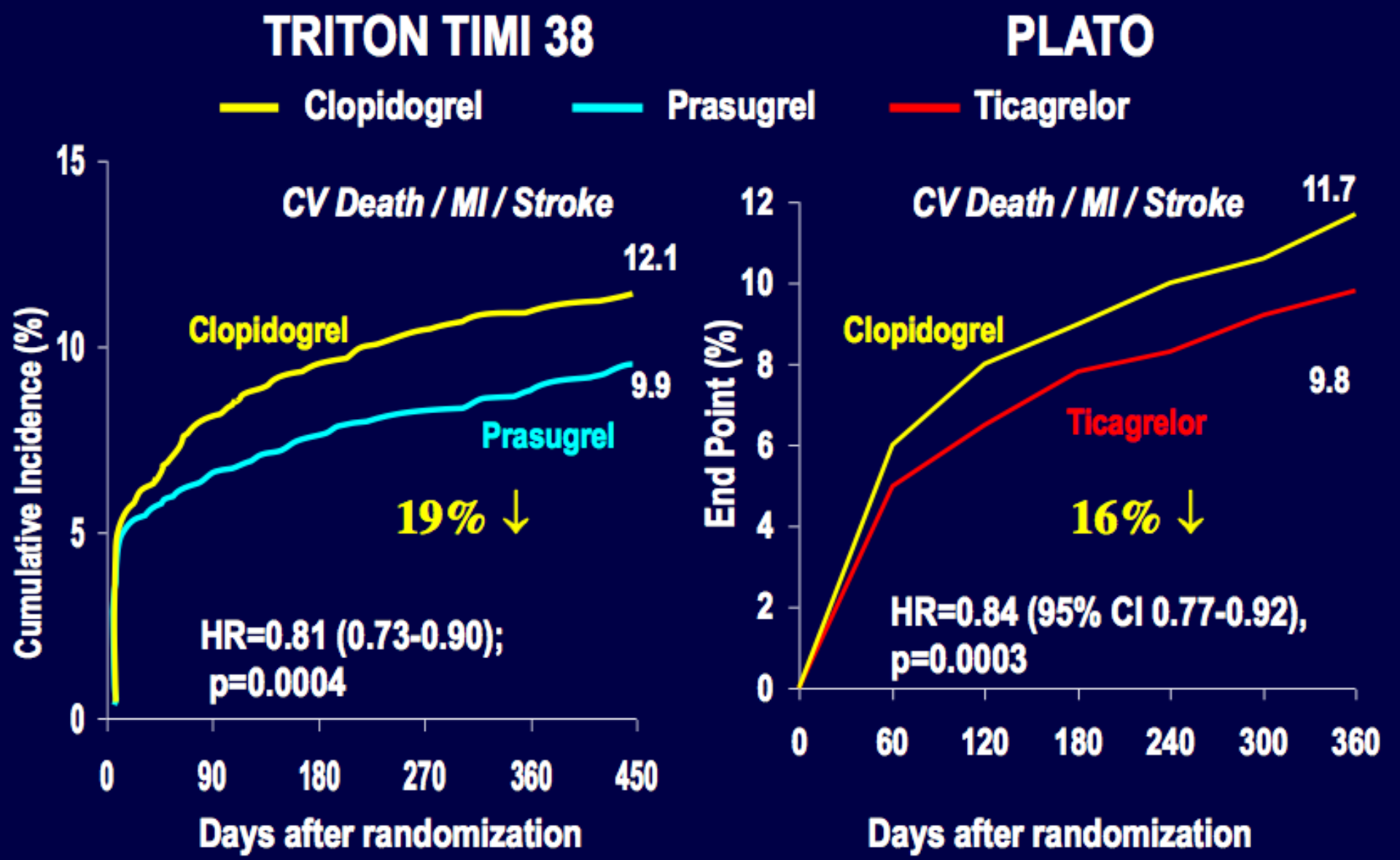
Clopidogrel

- Delayed onset of action
- Intermediate IPA
- Inter-individual variability

Prasugrel & Ticagrelor

- Rapid onset of action
- Higher levels of IPA
- Little interindividual variability
- Better clinical outcomes
- More bleeding

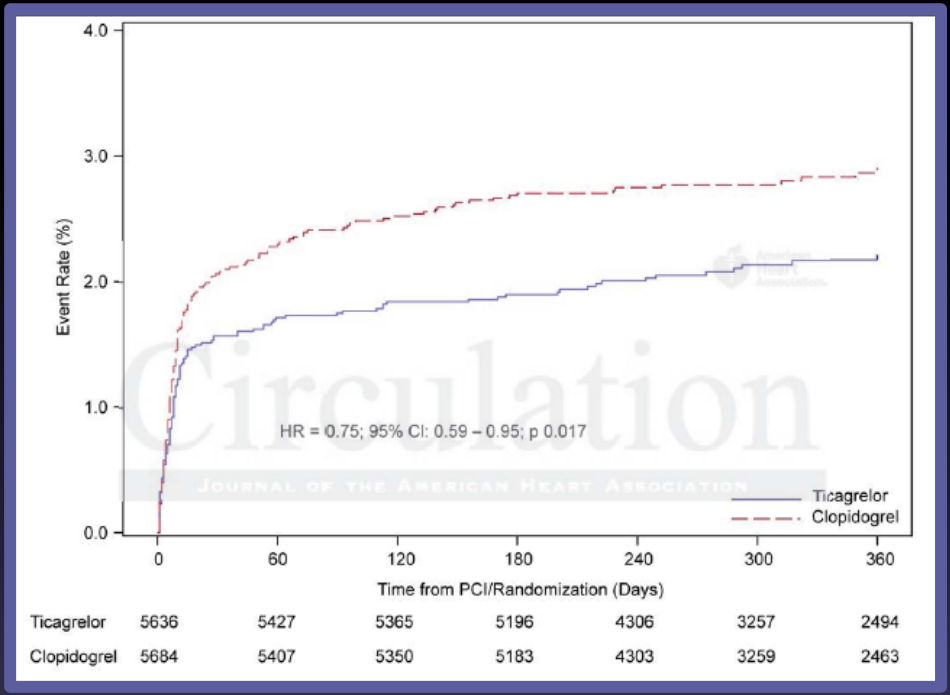
Primary Endpoint Events



Wiviott et al. N Engl J Med 2007;357:2001-2015

Wallentin et al. N Engl J Med 2009;361:1045-57

Stent Thrombosis in PLATO



Timing	RRR
Acute (<24 hrs)	0.93-1.01 (ns)
Subacute (24h-30 d)	0.60-.67 (p<0.05)
Late (> 30 d)	0.48-0.52 (p<0.05)

Range of RRR given represents RRR for definite ST - definite or probable ST

Clear reduction in incidence of ARC defined definite or probably stent thrombosis with ticagrelor

Steg et al. *Circulation* 2013; 128(10): 1055-65.
Also see Wiviott et al. Lancet 2008; 371(9621): 1353-63

Therapy in the Balance

Higher bleeding risk

Prior bleeding
Known GI conditions (ulcers, polyps, LGIB)
Concomitant medications: steroids, NSAIDs
Need for anticoagulation
Elderly
Women
ACS
Gain of function genotype (CYP 2c19 *17)

Higher risk of stent thrombosis

Premature cessation/ noncompliance with DAPT
ACS
Diabetes
Loss of function genotype (CYP 2C19 *2)

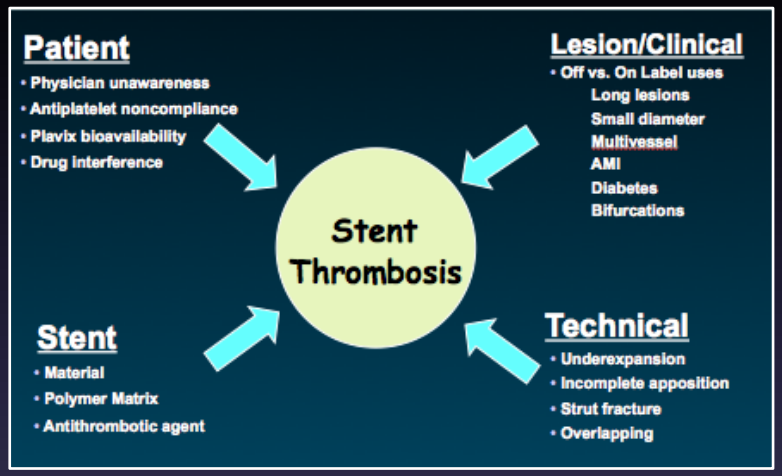
High On-Treatment Platelet Reactivity (HPR)

- Assessing Platelet Effect
  - Genotyping vs. Phenotype (platelet function testing)
  - Various functional assays (predictive of clinical outcomes)
    - VerifyNow P2Y12
    - Multiplate
    - VASP
    - Light transmission aggregometry
- HPR (in ACS) associated with increased:
  - CV mortality, nonfatal MI, early and late stent thrombosis

High On-Treatment Platelet Reactivity (HPR)

HPR explains 60% of early stent thrombosis

HPR ≠ diagnosis, but a risk factor for ischemic events



HPR may not be risk factor for ischemic events in low risk ACS/non-ACS settings

Trilogy ACS: Lower HPR with prasugrel DID NOT improve outcomes

Can We Use HPR to Guide Therapy?

GRAVITAS

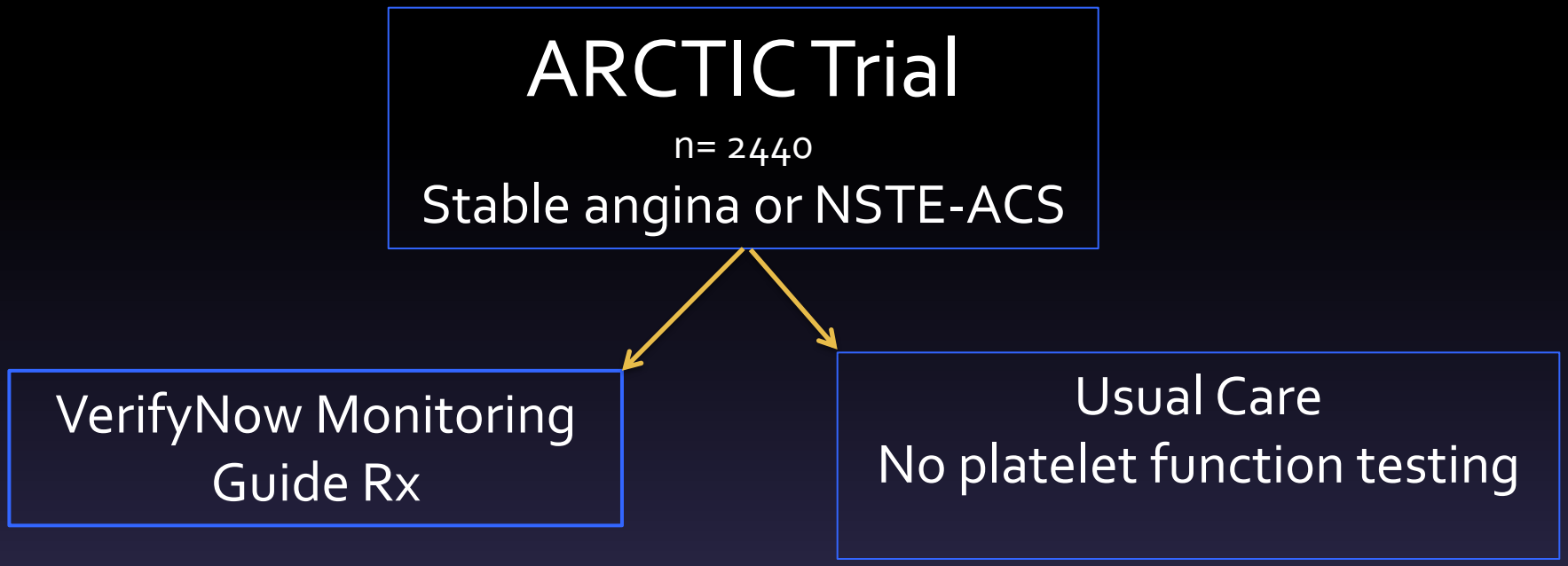
- 2214 pts with stable angina s/p PCI with HPR (PRU > 230)
- Assigned: standard vs. high dose clopidogrel
- 6 month results: no difference in death, MI, or ST

TRIGGER PCI

- 423 pts with stable angina s/p PCI with HPR (PRU>208)
- Assigned: clopidogrel or prasugrel
- Terminated early
- No difference in clinical events despite improved PRU

JAMA 2011; 305: 1097-1105
J Am Coll Cardiol 2012;

Can We Use HPR to Guide Therapy?



Algorithm included:
Increased clopidogrel
Increased aspirin
IIb/IIIa antagonism
Prasugrel only available at end of study

No difference in outcomes

Collet et al. N Eng J Med 2012; 367:2100-2109

Can We Use HPR to Guide Therapy?

TRANSLATE-POPS

ACS Patients

(TRANSLATE ACS Clinical Observation Trial)

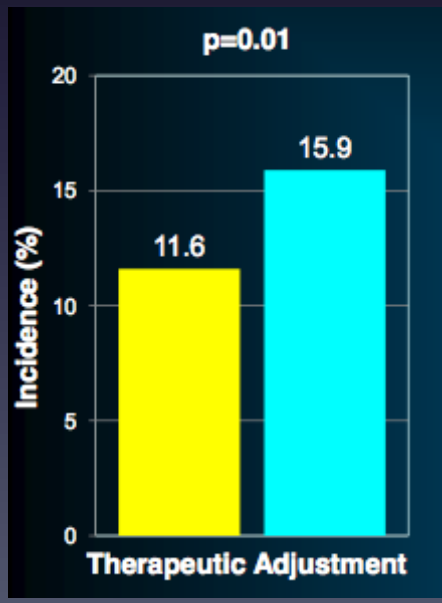
VerifyNow Testing offered
(at no charge)
Δ therapy at discretion of physician

VerifyNow Testing NOT provided

Initial therapy: 70% clopidogrel, 30% prasugrel
Approx 30% had PRU > 208

Results: ≈ 30% of pts in both groups had PRU > 208
Adjustments made slightly more in treatment group

No difference in early MACE or bleeding



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Can We Use HPR to Guide Therapy?

2010 ACC/AHA Expert Consensus Document: The evidence base is insufficient to recommend either routine genetic or platelet function testing at the preset time

2011 ACC/AHA PCI Guidelines: Platelet function testing may be considered in patients at high risk for poor clinical outcomes Level 2b, LOE C

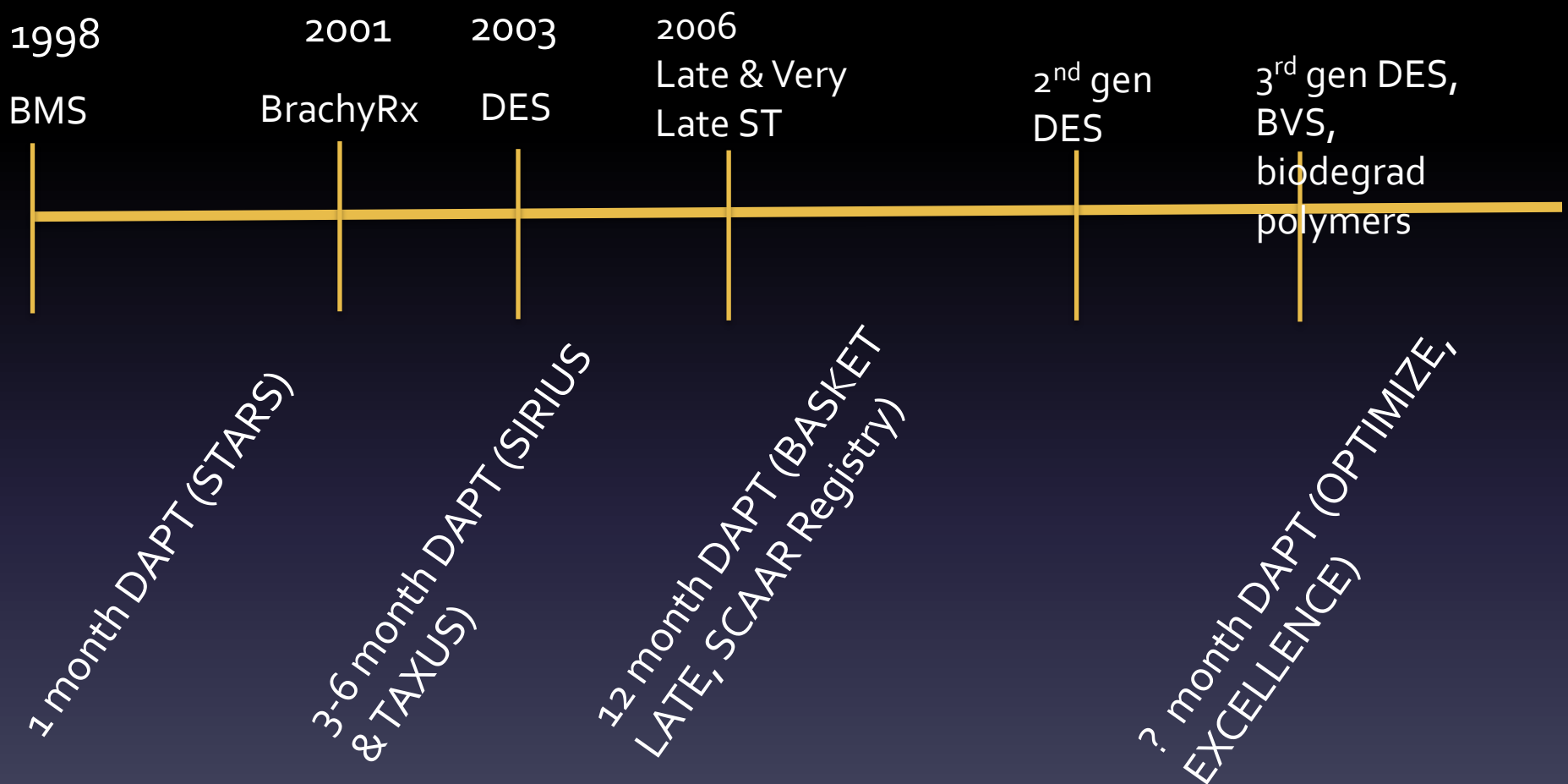
2012 ACC/AHA Update on UA/NSTEMI Focused Update: Platelet function testing to determine platelet inhibitory response in patients (with ACS) on thienopyridine treatment may be considered if results of testing may alter management (Class IIb. LOE B)

ESC Guidelines (NSTE-ACS): …platelet function testing "may be considered" in select cases where clopidogrel is used. Routine testing is "not recommended" because dose adaption of clopidogrel according to residual platelet reactivity failed to show any clinical benefit.

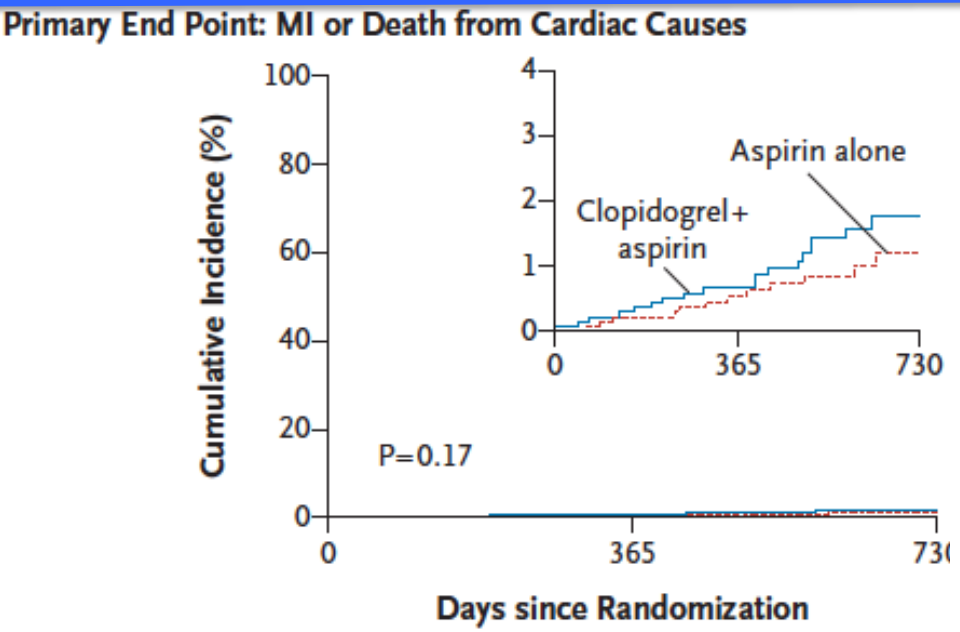
Summary: HPR

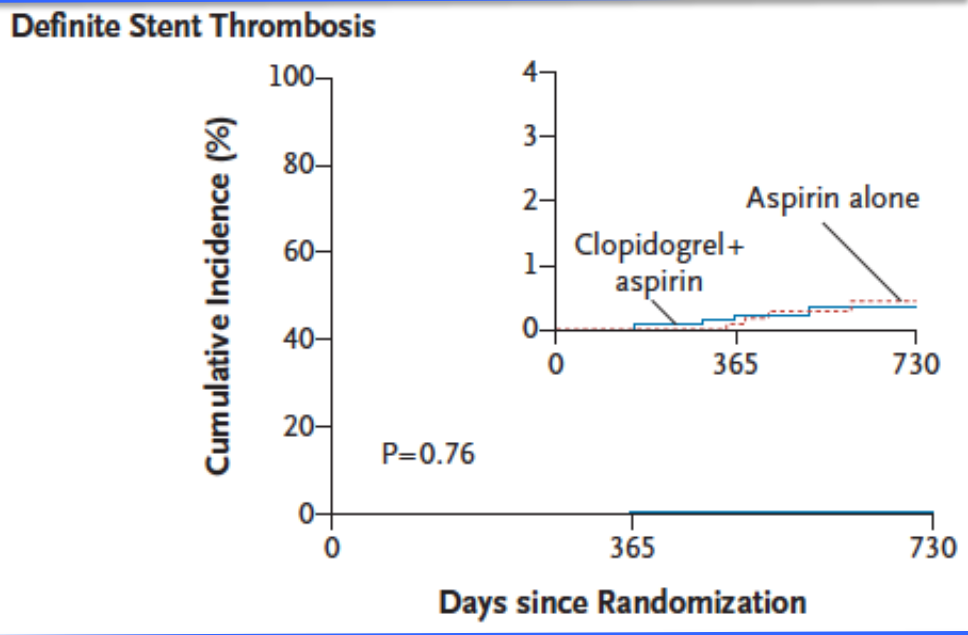
- HPR clearly a marker of increased ischemic events
  - Big question: is it modifiable?
- Prasugrel and ticagrelor associated with decreased ischemic events (vs. clopidogrel) in ACS (TRITON-TIMI 38, PLATO)
- No prospective data that platelet function test-guided therapy lowers ischemic events
- Limited data on Δ ing clopidogrel → newer agent

Duration of P2Y12 Blockade



REAL LATE + ZEST LATE





Park et al. NEJM 2010; 362:1374-82

OPTIMIZE Trial
Can we shorten the length of DAPT?

- Low-medium risk patients (neg TnI)
- Endeavor DES
- Assigned to 3 months vs. 12 months DAPT
- No difference in composite endpoint: death, MI, stroke, or major bleeding
- 3 months non-inferior to 12 months

JAMA, published online October 31, 2013

Future Trials

- DAPT Study
  - Any PCI with stent, n=20,645
  - 12 months vs. 30 months (if event free at 12 months)
- SMART DATE
  - Any ACS (stents not required), n=3,000
  - 6 vs. 12 months of DAPT
- DAPT-STEMI
  - STEMI patients with stent implantation, n=1.100
  - 6 vs. 12 months of DAPT
- NIPPON
  - Any PCI with Nobori stent, n=4,600
  - 6 vs. 18 months of DAPT
- GLOBAL LEADERS
  - Any PCI patients
  - DAPT x 1month, then ticagrelor alone vs continued DAPT
- EXCELLENCE

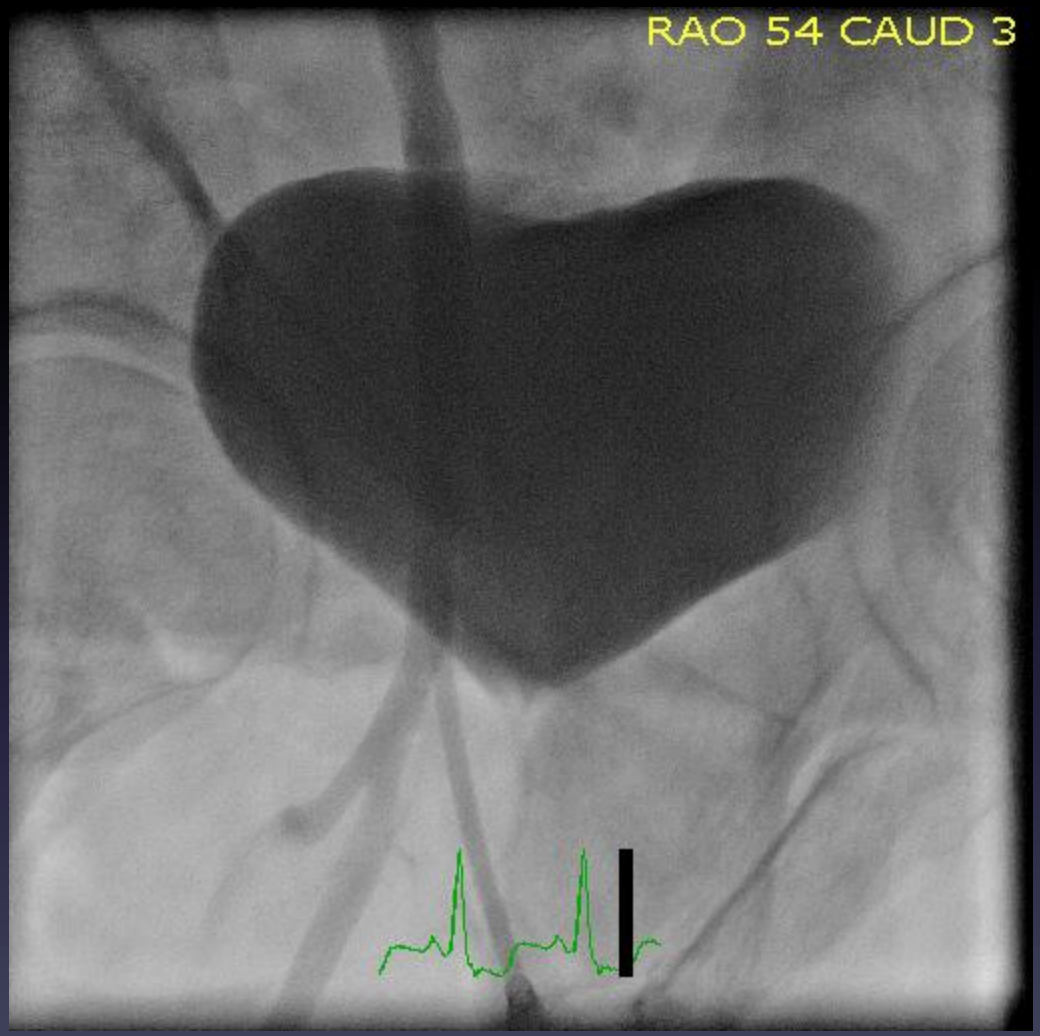
Duration of DAPT

- Standard of care: 12 months of DAPT in DES

  (if risk of bleeding is not increased)

- State-of-the-knowledge
  - Probably don't need DAPT beyond 12 months in most
  - Newer generation DES appear to have lower LT rates
  - ACS patients have higher rates of late/recurrent events
  - Low risk patients with Endeavor: 3 months may be sufficient

Thank You



I gotta go!....