Future Directions in Treatment of ST Segment Elevation Myocardial Infarction

Joint Coronary Revascularization

Busan, Korea December 13, 2014

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When you hear the positive results of a new drug on prevention of DVT (deep vein thrombosis) for patient undergoing knee surgery, what do you expect to hear:

2 years later

4 years later

6 years later?

- 1. Prevention of DVT for knee and hip procedure
- 2. Prevention and treatment of pulmonary embolism
- 3. Treatment of Unstable angina
- 4. Use in PCI
- 5. Treatment of ACS
- 6. Treatment of STEMI

Why this sequence ?

Demand of the markets

a. When benefits outweigh the risks

or b. when the rate of complications is down

PCI of LM versus CABG

a. When benefits outweigh the risks

or b. when the rate of complications is down

A. Four Metrics measuring the success of a hospital

a. Clinical outcome
b. Patient satisfaction
c. Financial health of the hospital
d. Operational efficiency

B. When Will A New Disruptive Technology Take Off?

1. Cheaper,
2. Easy to use
3. Comparable efficacy

A *disruptive technology* is a new one that emerges and displaces the old established technology and shakes up the industry.

1. P2 y12 inhibitors for PCI

- Substudy of 7544 STEMI patients with planned PCI from the PLATO Trial
- Ticagrelor was superior to clopidogrel
  - Primary endpoint (composite of MI, stroke, CV death)
  - Secondary endpoints (MI alone, total mortality, stent thrombosis)
- Major bleeding not increased
- Circulation. 2010;122:2131-2141

Pre-hospital ticagrelor ?

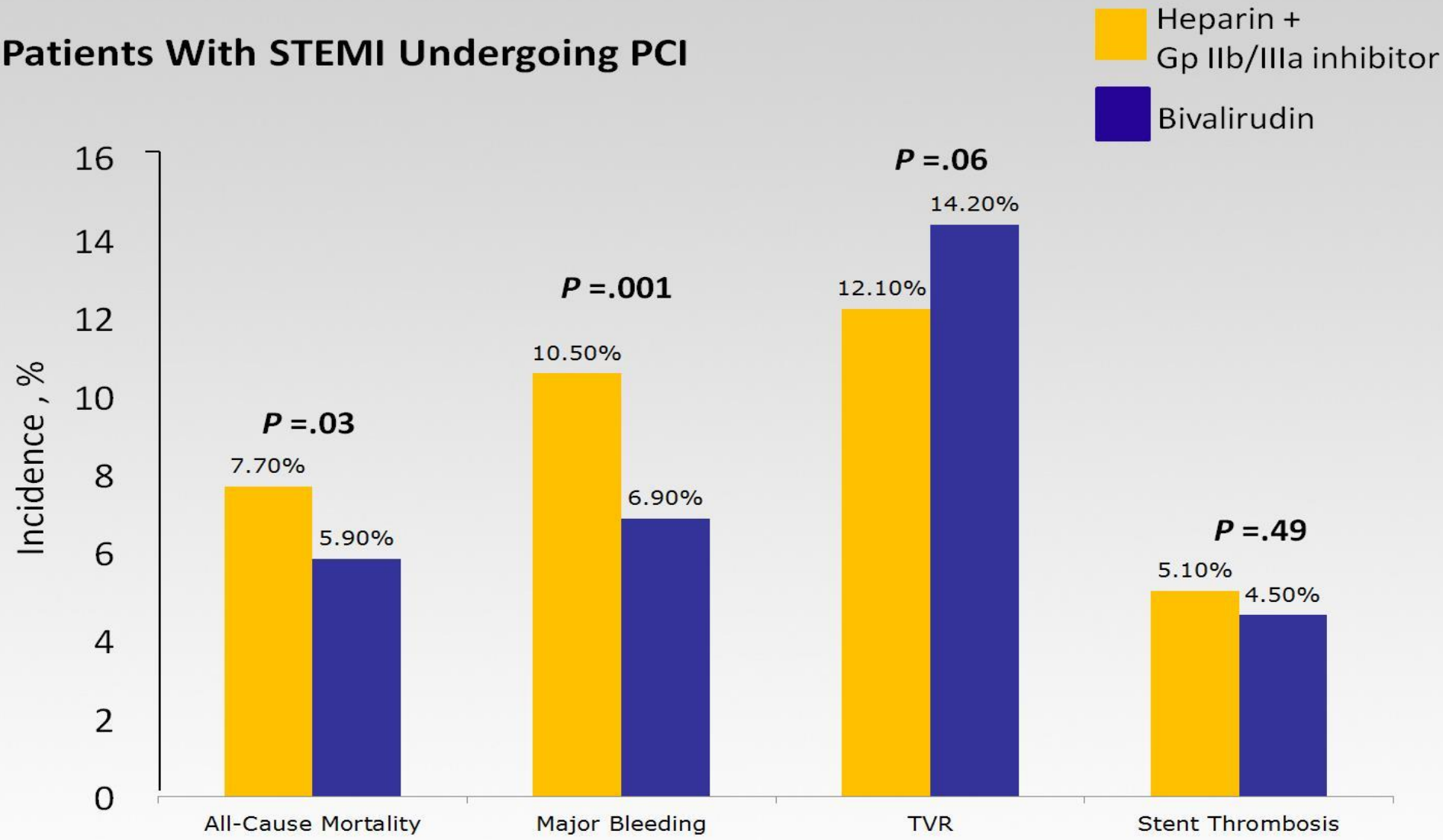
- ATLANTIC trial (N Engl J Med 2014;371:1016-27) 1862 STEMI patients with ambulance vs cath lab ticagrelor
- Ambulance group treated 31 minutes earlier
- No difference in pre-PCI coronary reperfusion (by ECG or TIMI flow)
- Stent thrombosis reduced
- No increased risk of bleeding

A. Number of patients with ACS is much higher compared with STEMI patients. Need higher market share

B. Why do we need to have upstream treatment? First contact with medical personnel and will continue to be given

2. Anticoagulant for PCI

Bivalirudin: HORIZONS-AMI



Thrombosis

Stone GW, et al. *Lancet.* 2011;377:2193-2204.[2]

theheart.org from WebMD

Medscape EDUCATION

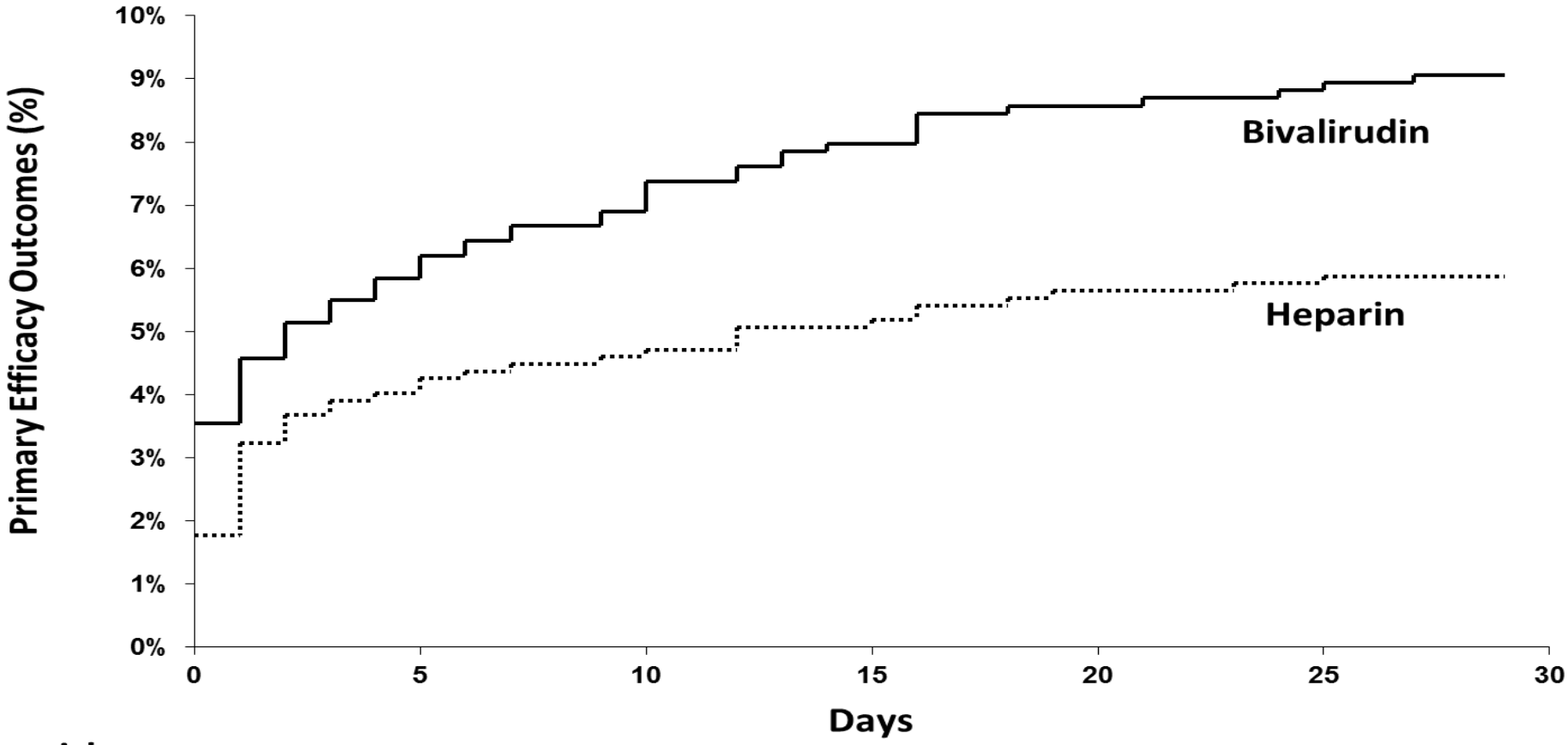
HEAT PPCI: *Heparin vs Bivalirudin in Primary PCI*

- Single center randomized controlled trial (Liverpool, UK)
- Feb 2012 – Nov 2013
- STEMI patients
  - Heparin 70 U/kg
  - Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion
  - Selective (bailout) abciximab
- Primary outcome at 28 days
  - MACE
  - Major bleeding
- 1917 pts screened, 1829 enrolled

HEAT PPCI: *Procedural characteristics*

- Radial access 80%
- P2Y12
  - Clopidogrel 11%
  - Prasugrel 27%
  - Ticagrelor 62%
- Abxicimab 14%
- PCI performed 82%

Timing of First MACE Event



No. at risk						
Heparin	907	871	866	862	857	856
Bivalirudin	905	853	844	835	830	828

Event curve shows first event experienced

HEAT PPCI: *Results*

(%)	Bivalirudin	Heparin	p Value
MACE	8.7	5.7	0.01
Reinfarction	2.7	0.9	
TLR	2.7	0.7	
Stent Thrombosis	3.4	0.9	0.001
Major bleed	3.5	3.1	0.59

BRIGHT Trial
Bivalirudin vs Heparin and Heparin + Tirofiban in Primary PCI

- Multicenter randomized controlled trial (China)
- 2194 AMI patients
  - Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr then 0.2 mg/kg/hr (234 min)
  - Heparin 100 U/kg
  - Heparin 60 U/kg + Tirofiban 10μg/kg bolus, 0.15μg/kg/min for 18-36 hrs
- Primary endpoint: NACE at 30 days
- Secondary endpoints
  - NACE at 1 year
  - MACCE at 30 days, 1 year
  - Bleeding at 30 days, 1 year

Han *TCT 2014*

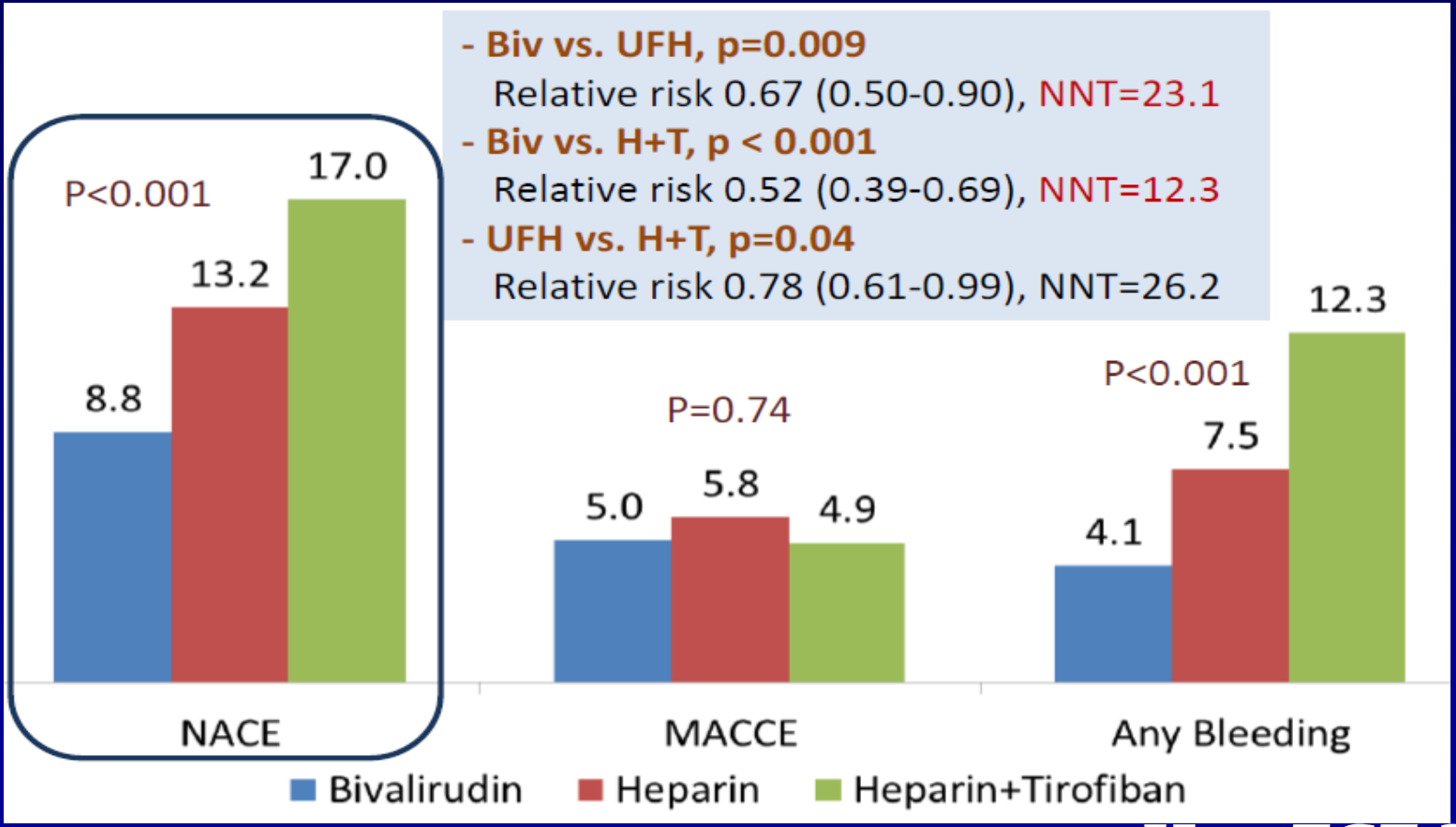
BRIGHT: *Procedural characteristics*

- STEMI 88%, NSTEMI 12%
- Radial access 78%
- Door to device time 66-70 min
- Clopidogrel 100%
- PCI performed 98%
- Stent 96%

Han *TCT 2014*

BRIGHT

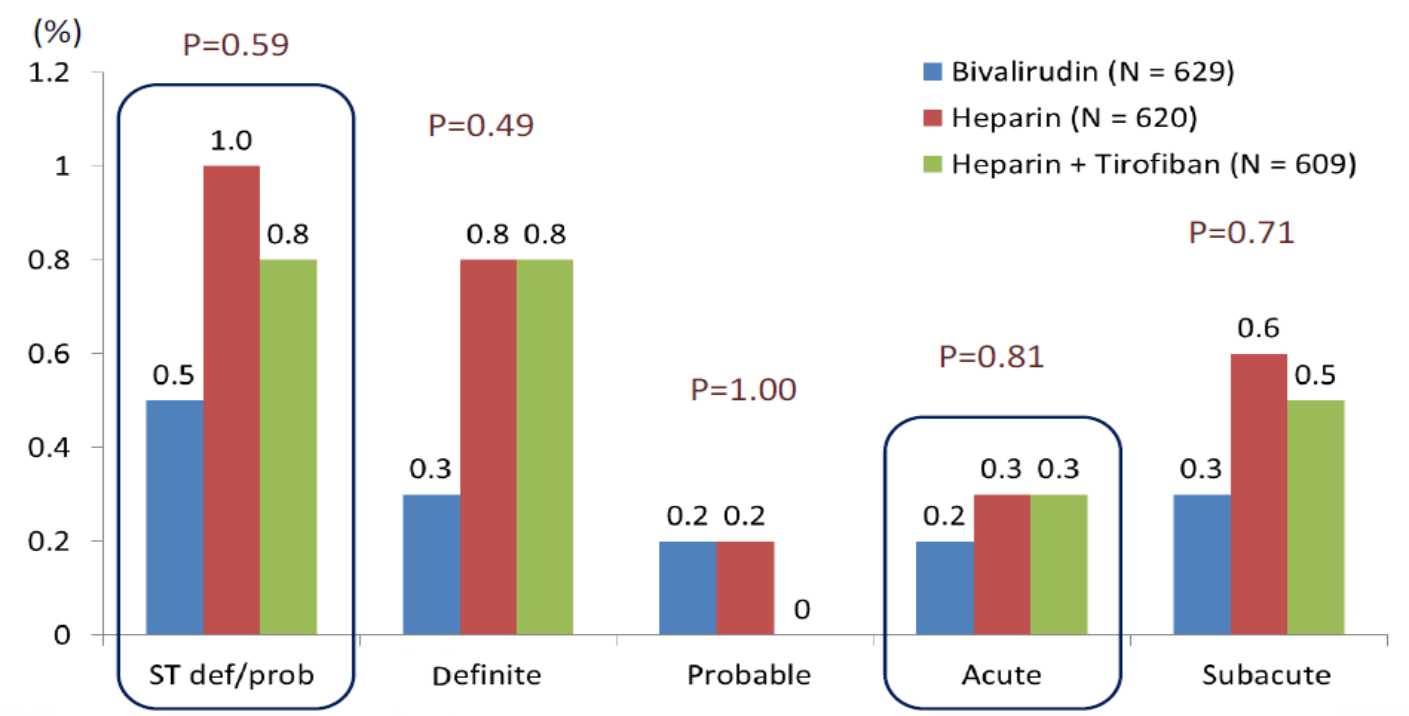
Primary and principal secondary endpoints at 30 days



Han *TCT 2014*

BRIGHT

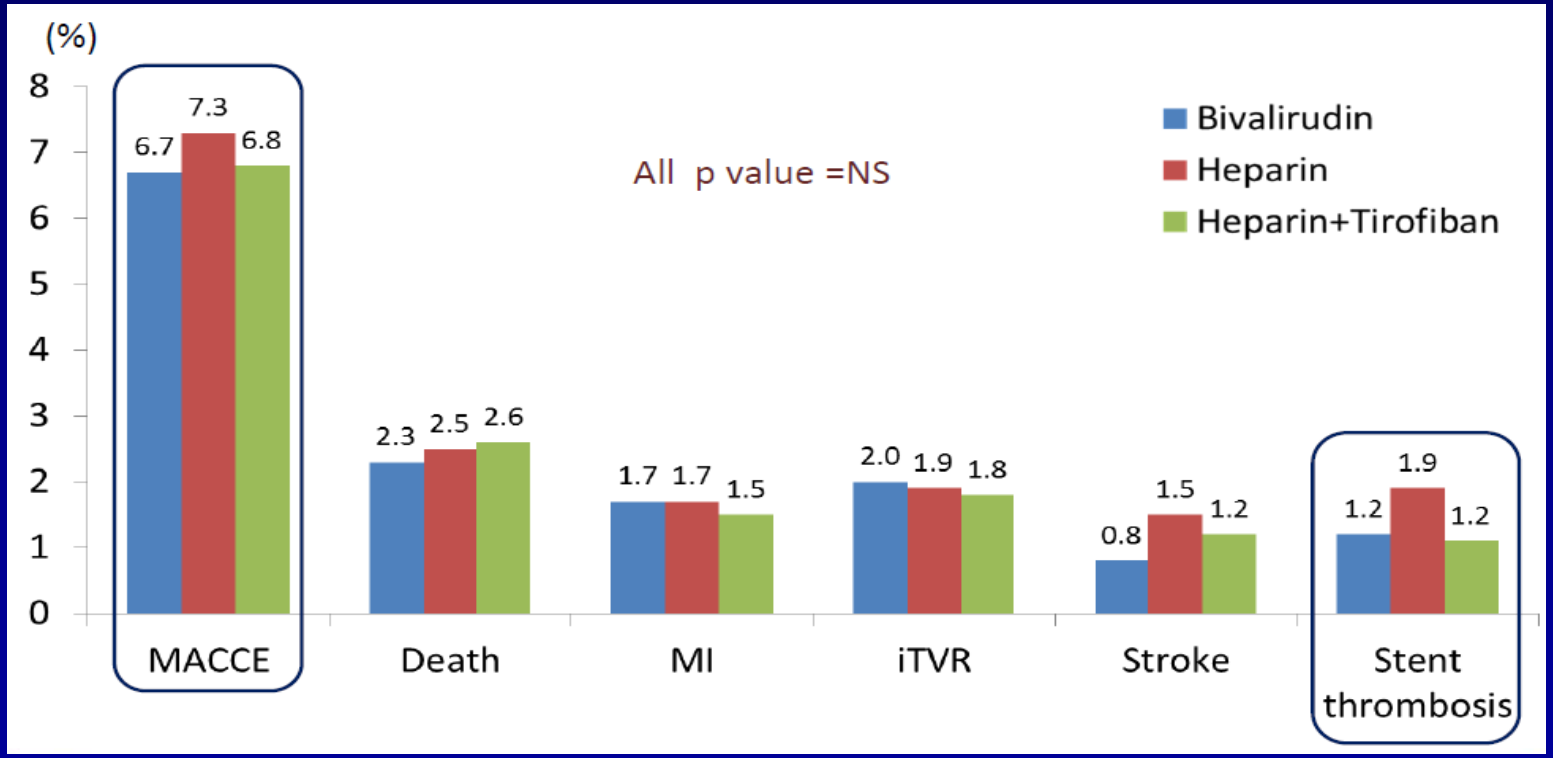
Stent thrombosis at 30 days – STEMI only



Han *TCT 2014*

BRIGHT

Major ischemic events at 1 year



Han *TCT 2014*

BRIGHT
Bleeding events at 30 days

Event	Bivalirudin (N = 735)	Heparin (N = 729)	Heparin + Tirofiban (N = 730)	P value (3-way)	P value (B vs H)	P value (B vs H+T)
Any bleeding	30 (4.1)	55 (7.5)	90 (12.3)	<0.001	0.005	<0.001
BARC 1 (%)	21 (2.9)	29 (4.0)	53 (7.3)	<0.001		
BARC 2 (%)	5 (0.7)	15 (2.1)	22 (3.0)	0.005		
BARC 3a (%)	4 (0.5)	7 (1.0)	6 (0.8)	0.59		
BARC 3b (%)	0 (0)	4 (0.5)	8 (1.1)	0.013		
BARC 5 (%)	0 (0)	0 (0)	1 (0.1)	0.67		
BARC 2-5 (%)	9 (1.2)	26 (3.6)	37 (5.1)	<0.001	0.003	<0.001
Major (BARC 3-5) (%)	4 (0.5)	11 (1.5)	15 (2.1)	0.04	0.07	0.01

Han *TCT 2014*

Putting HEAT and BRIGHT together…

- The mortality benefit for bivalirudin in primary PCI seen in HORIZONS-AMI was not confirmed in either HEAT or BRIGHT
- No MACE advantage for bivalirudin over heparin monotherapy
- Bivalirudin usage is associated with less bleeding than heparin 100 U/kg (BRIGHT) but is equivalent to heparin 70 U/kg (HEAT)
- Compared to heparin, bivalirudin usage results in increased rates of early stent thrombosis. This may be eliminated by continuing the bivalirudin for 4 hours post-PCI.

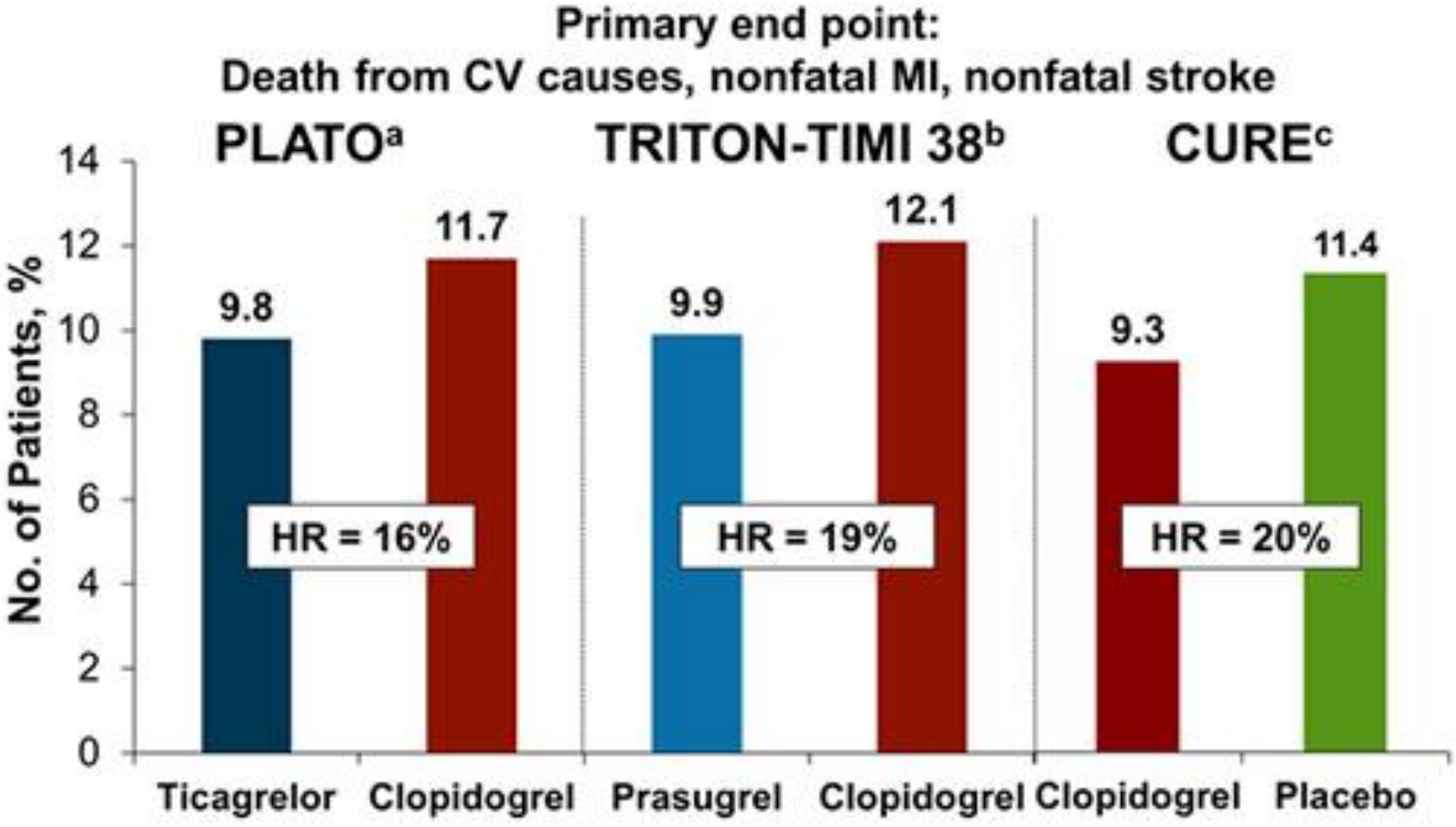
When Will A New Disruptive Technology Take Off?

1. Cheaper,
2. Easy to use
3. Comparable efficacy

3. Anticoagulant after PCI

PLATO, TRITON-TIMI 38, and CURE

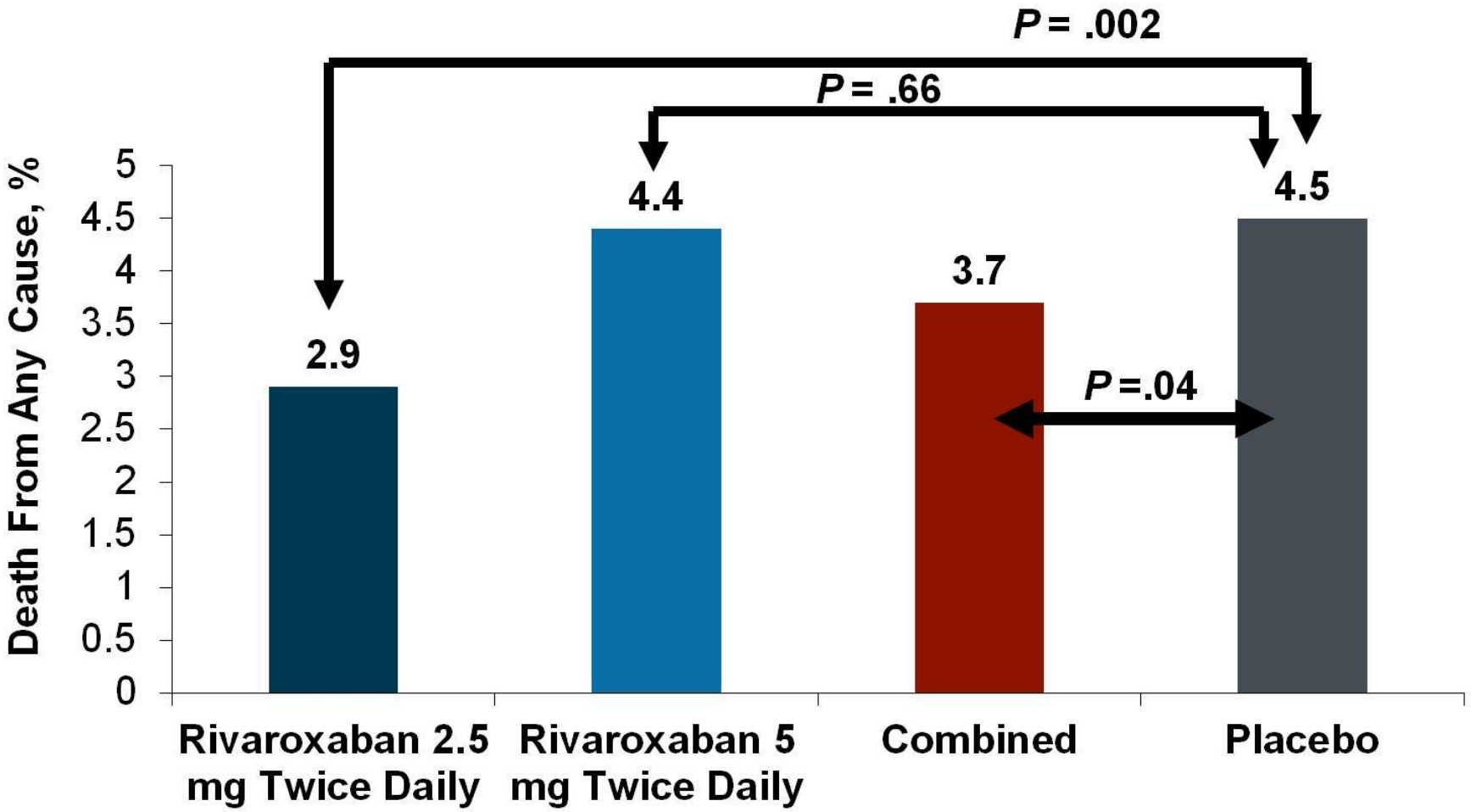
Residual Risk



a. Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057[3]; b. Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-2015[2]; c. Yusuf S, et al, *N Engl J Med*. 2001;345:494-502.[1]

ATLAS ACS 2—TIMI 51

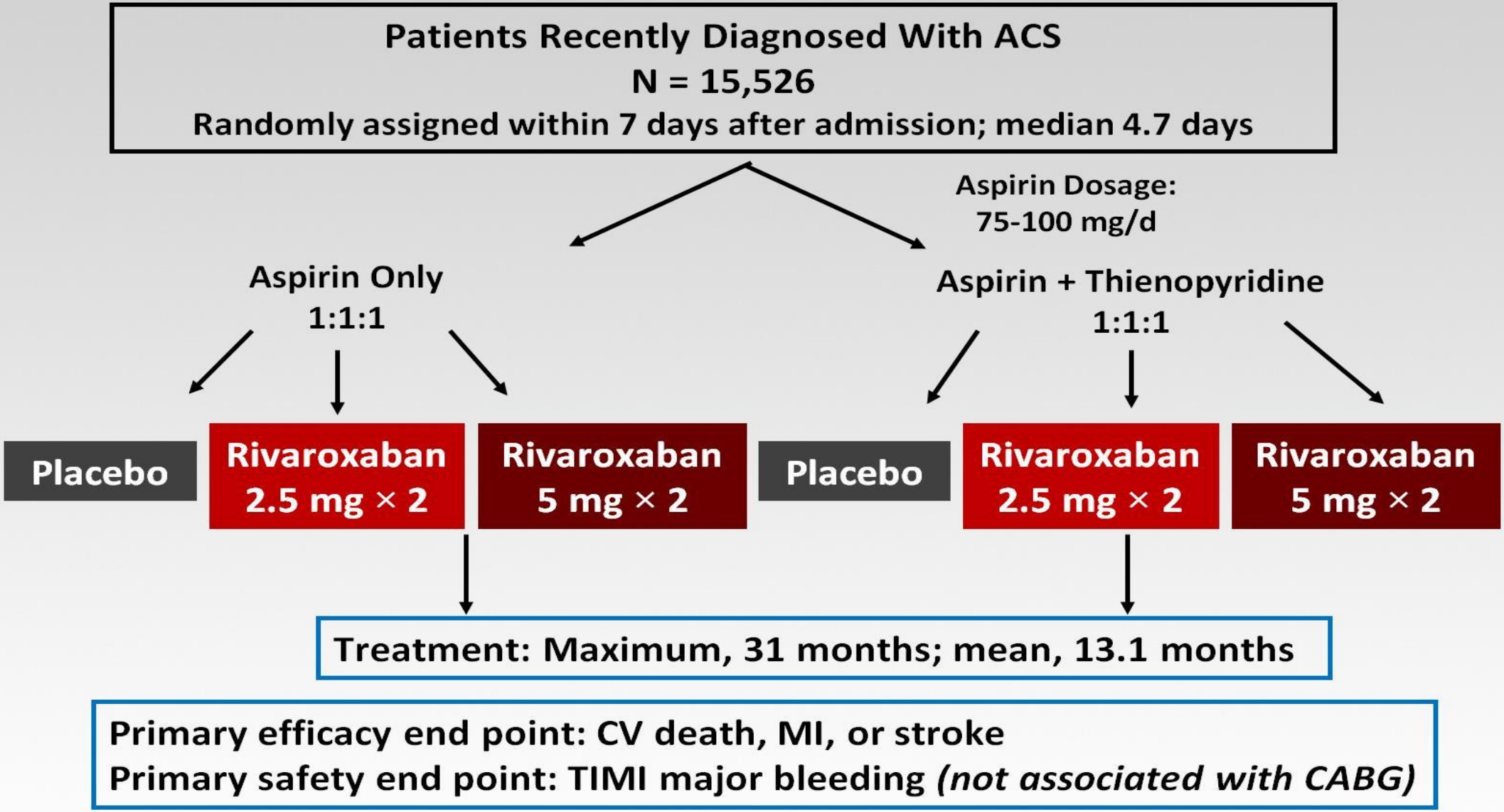
Mortality Benefit



P values represent mITT values.

Mega JL, et al. *N Engl J Med*. 2012;366:9-19.[26]

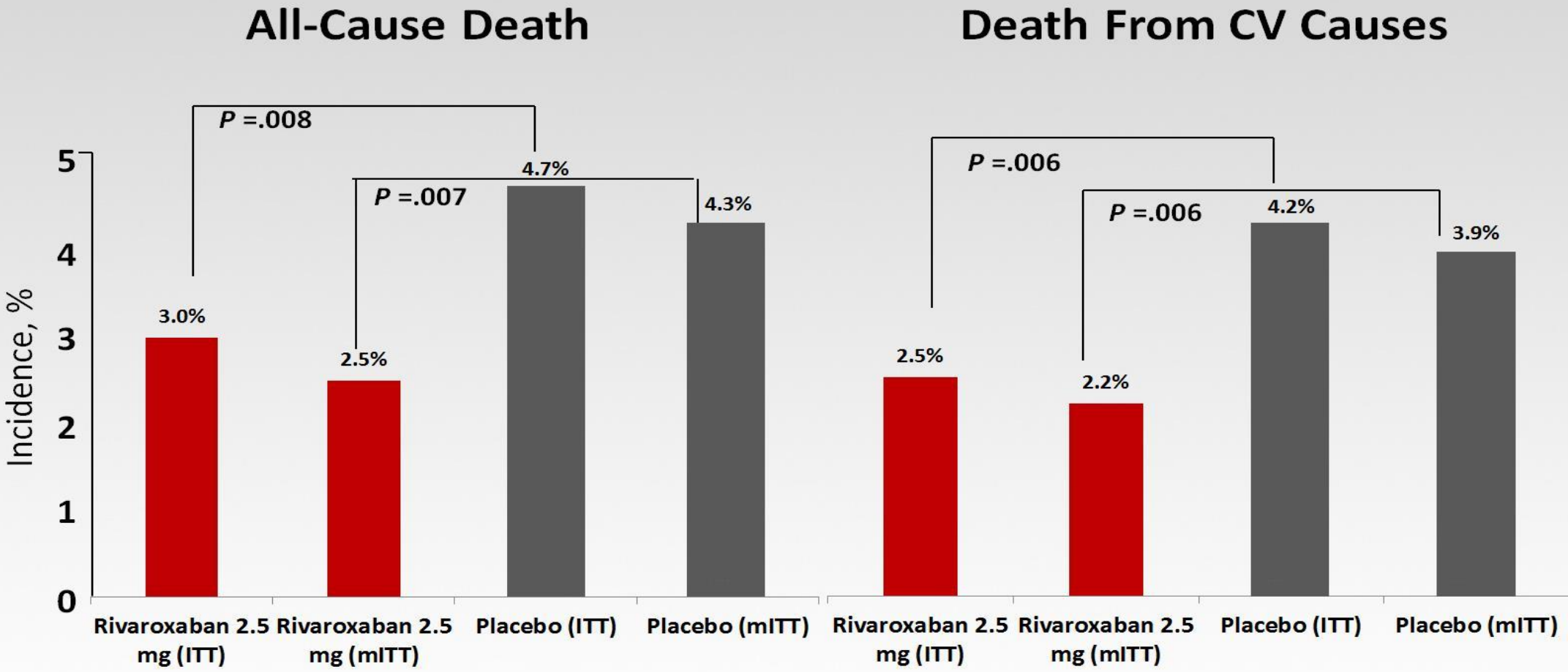
Rivaroxaban: ATLAS ACS 2-TIMI 51: Study Design



Gibson CM, et al. *Am Heart J.* 2011;161:815-821.[9]

ATLAS ACS 2-TIMI 51: Mortality Benefit With Very Low-Dose Rivaroxaban in STEMI Patients

N=7817



Mega JL, et al. *J Am Coll Cardiol* . 2013;61:1853-1859.[8]

Rivaroxaban: PIONEER AF-PCI

Patients With Documented AF Who Undergo PCI
N = 2,100

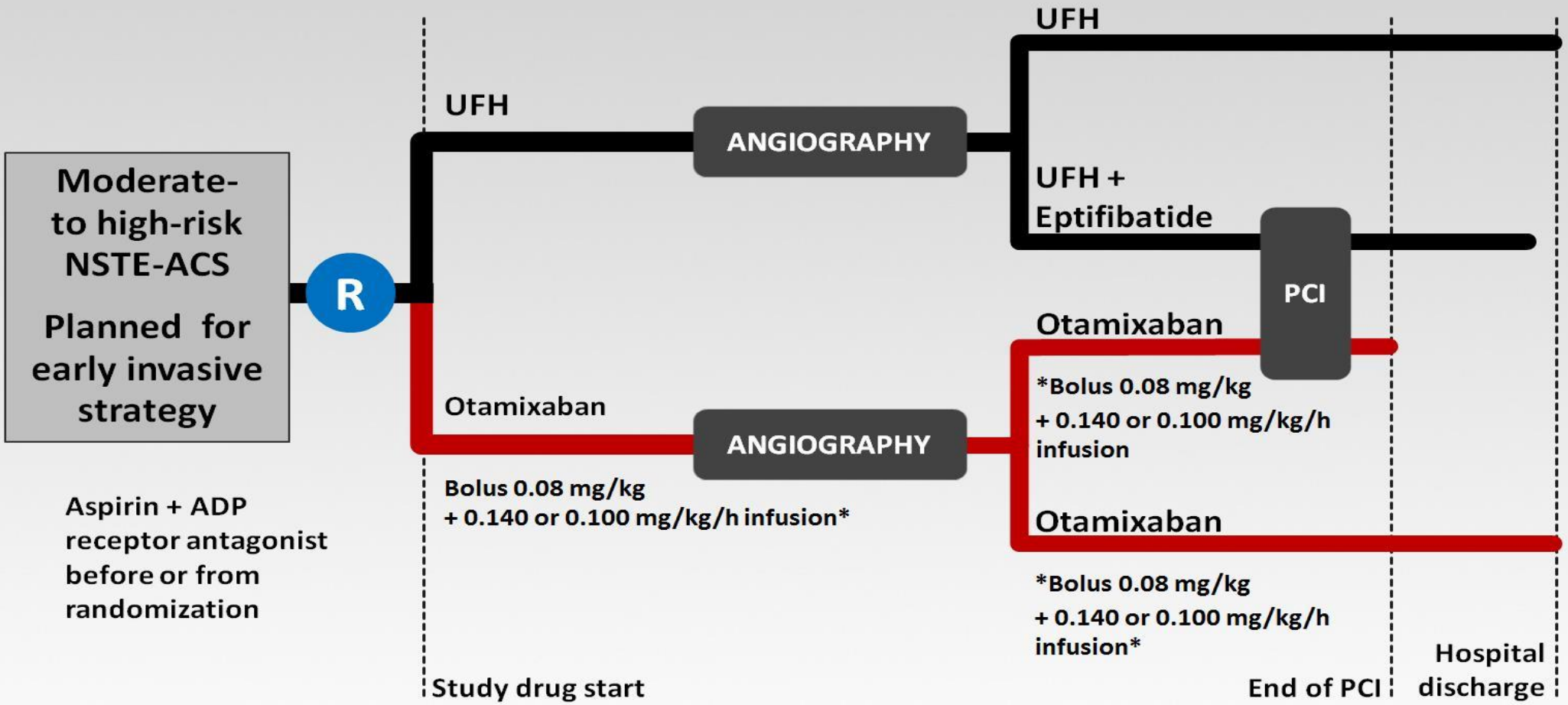
Rivaroxaban 2.5 mg twice daily + low-dose aspirin daily + clopidogrel 75 mg/d or prasugrel 10 mg/d or ticagrelor 90 mg tablet twice daily Followed by **rivaroxaban 15 mg** (or 10 mg in moderate renal impairment)/d + low-dose aspirin for 12 months	**VKA** daily (target INR 2.0 to 3.0) + plus low-dose aspirin + clopidogrel 75 mg/d or prasugrel 10 mg/d or ticagrelor 90 mg twice daily Followed by dose-adjusted **VKA** daily + low-dose aspirin for 12 months	**Rivaroxaban 15 mg** (or 10 mg in moderate renal impairment)/d + clopidogrel 75 mg/d or prasugrel 10 mg/d or ticagrelor 90 mg twice daily for 12 months

Primary outcome: Clinically significant bleeding at 12 months (composite of TIMI major bleeding, minor bleeding, and bleeding requiring medical attention)
Secondary outcome: Composite of CV death, MI, and stroke

clinicaltrials.gov.[10]

Otamixaban: TAO Study Design

June 4, 2013, update: The study did not meet its primary end point of superiority over current therapy and the investigational program for otamixaban will be discontinued.

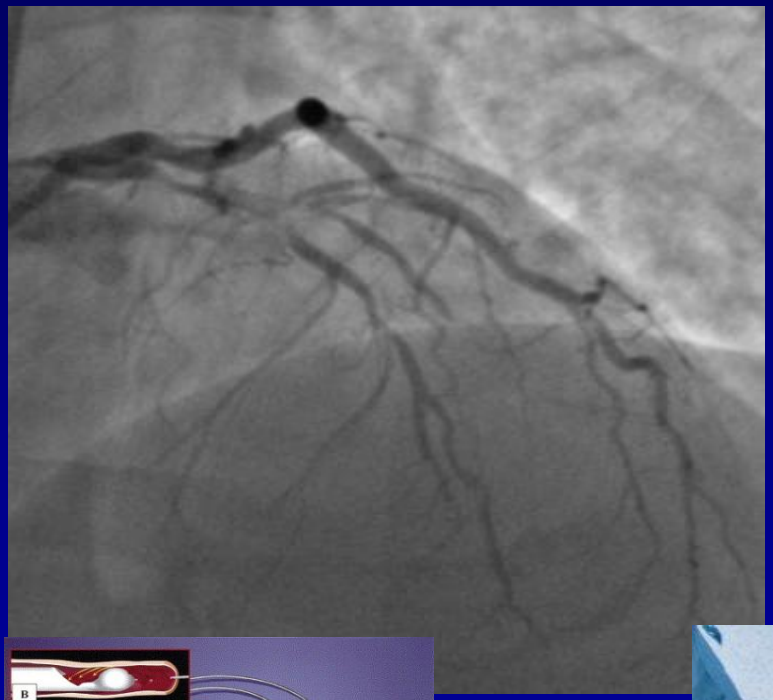


Primary efficacy end point: All-cause death or new MI to day 7; safety end point TIMI significant bleeding to day 7

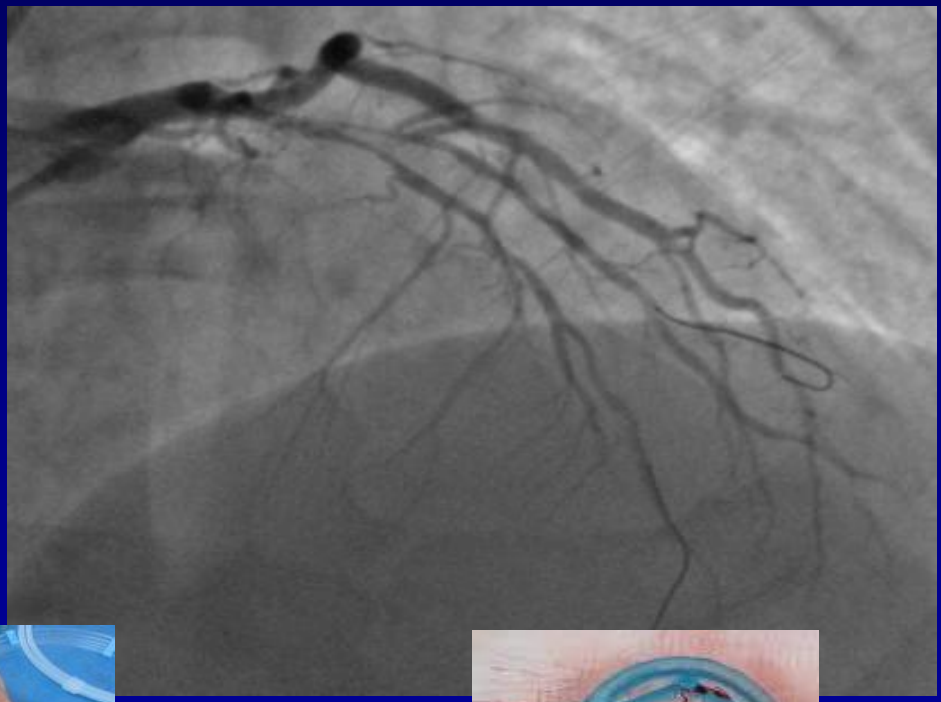
4. Thrombectomy

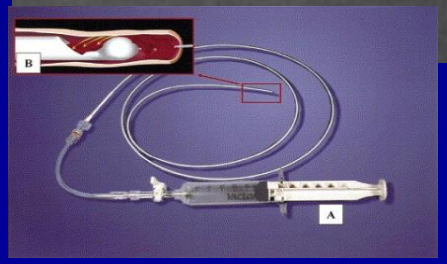
Manual aspiration thrombectomy is performed to the LAD and diagonal with improved flow

Before thrombectomy



After thrombectomy





TAPAS

- TAPAS trial: Manual aspiration of thrombus prior to balloon/stent (*NEJM* 2008;358:557-567)
  - Improved myocardial perfusion
  - Reduction of mortality at 1-year followup (*Lancet* 2008;371:1915-1920)

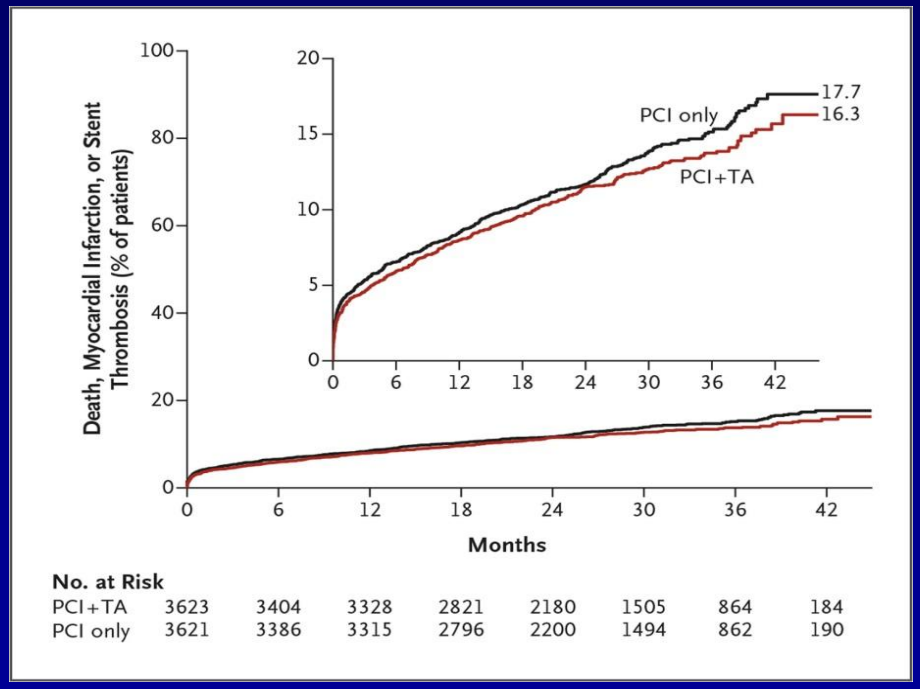
INFUSE AMI

- INFUSE-AMI *(JAMA* 2012;307:1817-26)
  - 452 patients at 37 sites with LAD STEMI
  - Evaluating intracoronary abciximab and manual aspiration thrombectomy
  - Primary end point: infarct size at 30 days by cardiac MRI
  - Small benefit for abciximab but not thrombectomy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction



- *7244 patients with STEMI PCI*
- *Aspiration thrombectomy + PCI vs PCI alone*
- *No reduction in early or late MACE*

Lagerqvist B et al. N Engl J Med 2014;371:1111-1120.

Thrombectomy in STEMI PCI

Conclusions

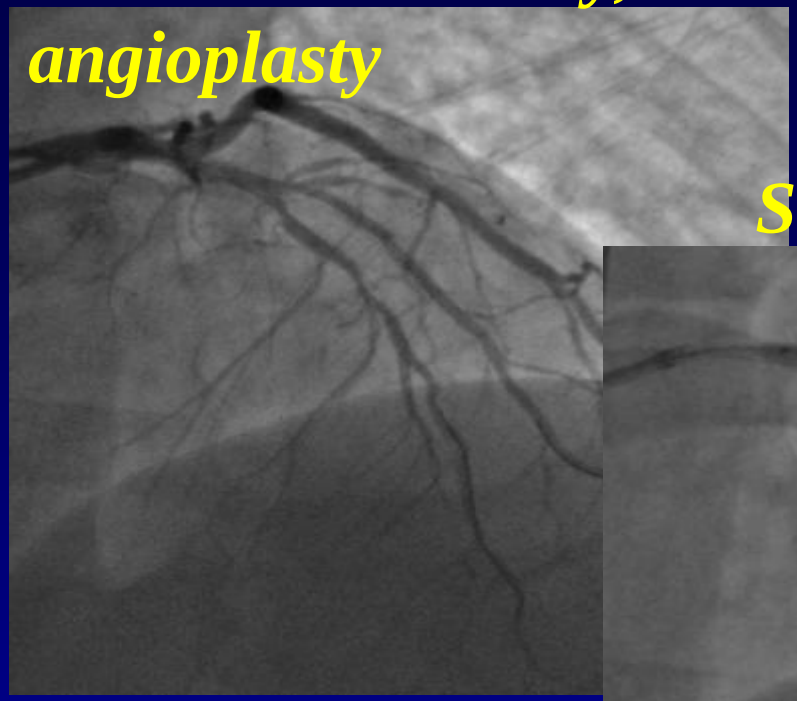
- Simple and safe procedure
- May improve procedural myocardial perfusion
- No early mortality reduction although possible improved mortality at 1 year (seen in TAPAS but not in TASTE)

Could not find the subset of patients who will need manual thrombectomy yet

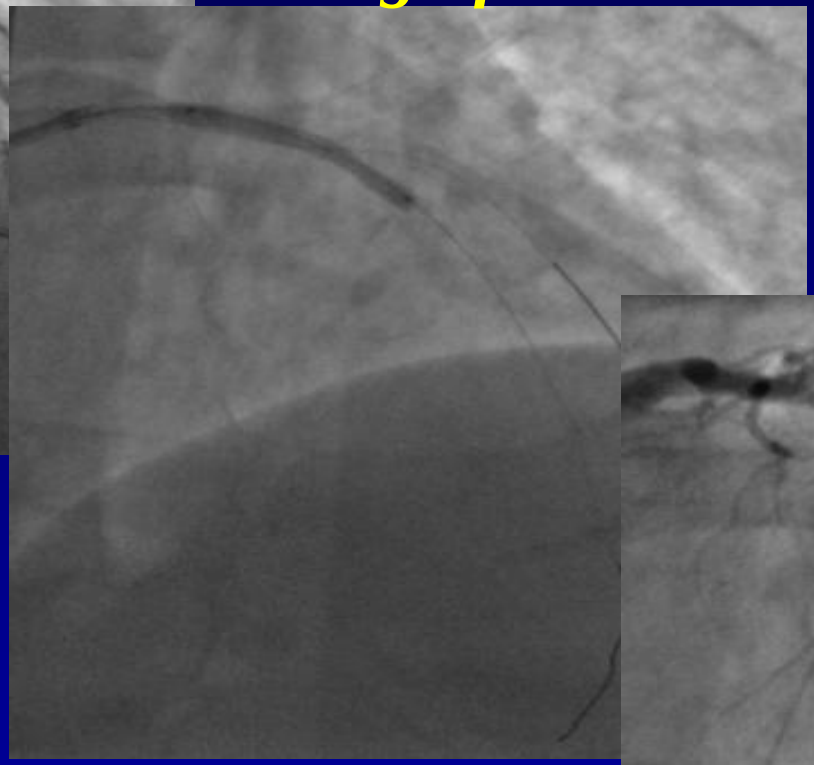
a. Clinical outcome
b. Patient satisfaction
c. Financial health of the hospital
d. Operational efficiency

5. PCI for non-Infarct Related artery

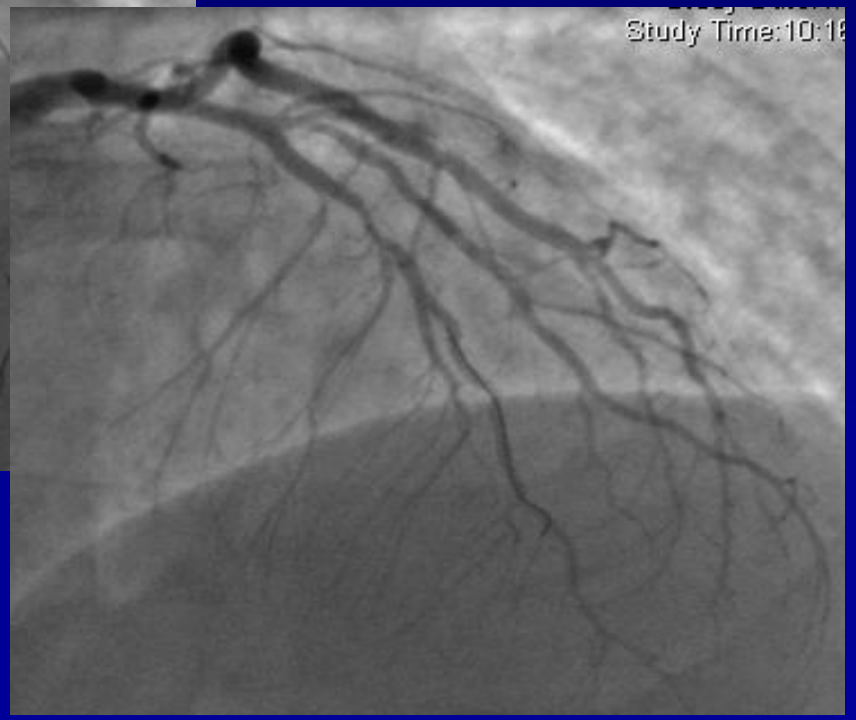
Post thrombectomy, angioplasty



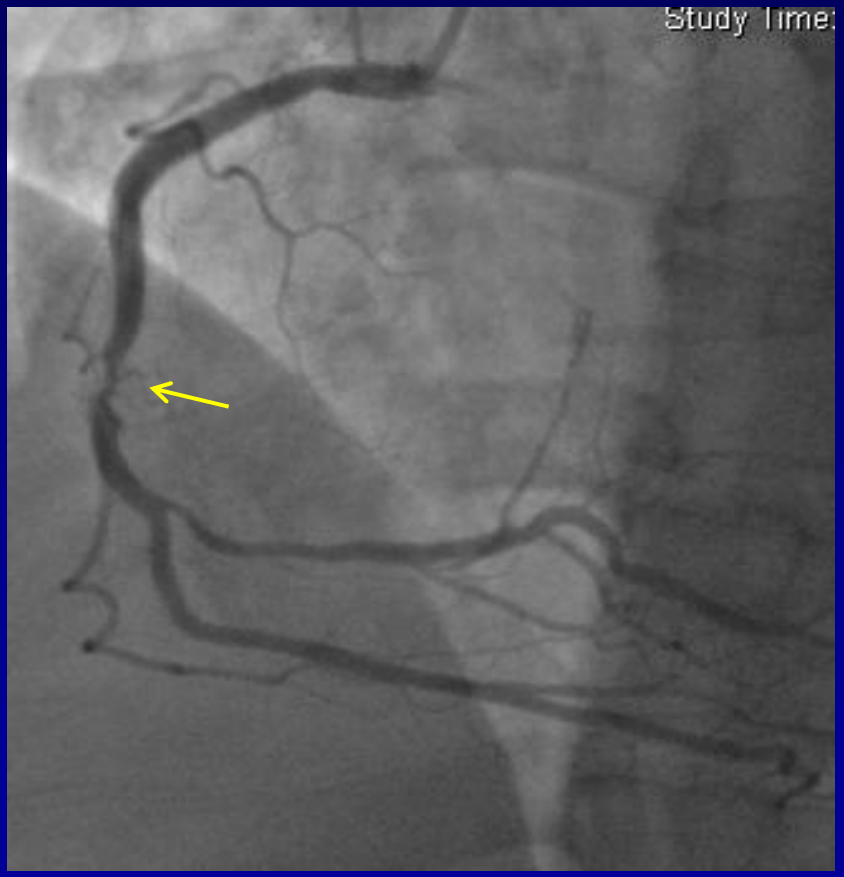
Stenting of LAD

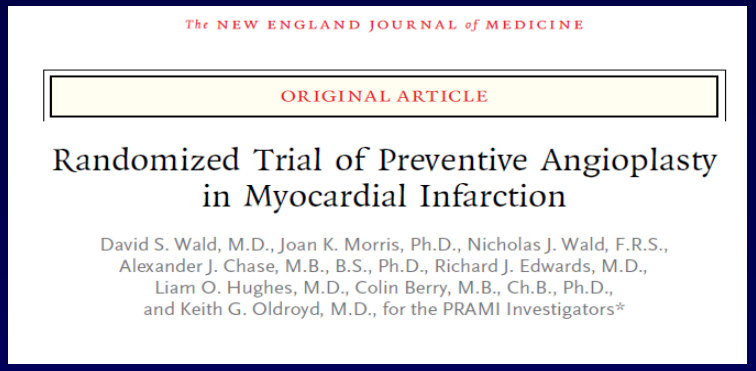


Post stent



How should the non-infarct vessel be treated?





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Preventive Angioplasty in Myocardial Infarction

David S. Wald, M.D., Joan K. Morris, Ph.D., Nicholas J. Wald, F.R.S., Alexander J. Chase, M.B., B.S., Ph.D., Richard J. Edwards, M.D., Liam O. Hughes, M.D., Colin Berry, M.B., Ch.B., Ph.D., and Keith G. Oldroyd, M.D., for the PRAMI Investigators*

- 465 STEMI patients with successful infarct artery PCI who also had ≥50% stenosis in at least one other vessel
  - 234 underwent immediate PCI of noninfarct vessels
  - 231 were treated with optimal medical therapy
- Endpoints: Primary: Composite of cardiac death, MI, or refractory angina
- Study was stopped early due to highly significant ($P<0.001$) difference favoring immediate PCI

PRAMI
Prespecified Clinical Outcomes

Outcome	Preventive PCI (N=234)	No Preventive PCI (N=231)	Hazard Ratio (95% CI)	P Value
	no. of events			
Primary outcome				
Death from cardiac causes, nonfatal myocardial infarction, or refractory angina†	21	53	0.35 (0.21–0.58)	<0.001
Death from cardiac causes or nonfatal myocardial infarction†	11	27	0.36 (0.18–0.73)	0.004
Death from cardiac causes	4	10	0.34 (0.11–1.08)	0.07
Nonfatal myocardial infarction	7	20	0.32 (0.13–0.75)	0.009
Refractory angina	12	30	0.35 (0.18–0.69)	0.002
Secondary outcomes				
Death from noncardiac causes	8	6	1.10 (0.38–3.18)	0.86
Repeat revascularization	16	46	0.30 (0.17–0.56)	<0.001

* All patients underwent infarct-artery PCI.
† Only the first event per patient is listed.

Wald DS et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1305520

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A *disruptive technology* is a new one that emerges and displaces the old established technology and shakes up the industry.

a. Heparin > bivalirudin
b. Anticoagulant after AMI.
c. Thrombectomy for special subset of patient
d. Non IRA PCI for special subsets of patients

Thank You