STEMI:

Eight Areas of Unmet Needs

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Disclosures

Research Grants/Support

Nanosphere

Haemonetics

Daiichi Sankyo/Lilly

CSL Pharmaceuticals

HCRI

NIH

Honoraria/Consulting

Pozen

Astra Zeneca

Daiichi Sankyo/Lilly

Accumetrics

Nanosphere

Boehringer

Merck

Medtronic

CSL

t2 Biosystems

Dr. Gurbel has patents in the field of platelet function testing

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The Core of Optimal STEMI Therapy:

"Reducing Total Ischemic Time"

Reperfusion Saves Myocardium in A Time-Dependent Fashion

Lives are Saved in A Time-Dependent Fashion

O'Gara PT et al *Circulation*. 2013;127:e362-425

The "Wavefront Phenomenon" of Myocardial Ischemic Cell Death

Duration of coronary occlusion

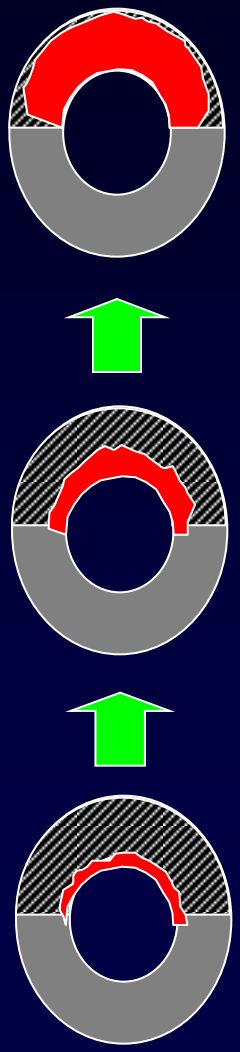
Myocardium at risk

Final infarct

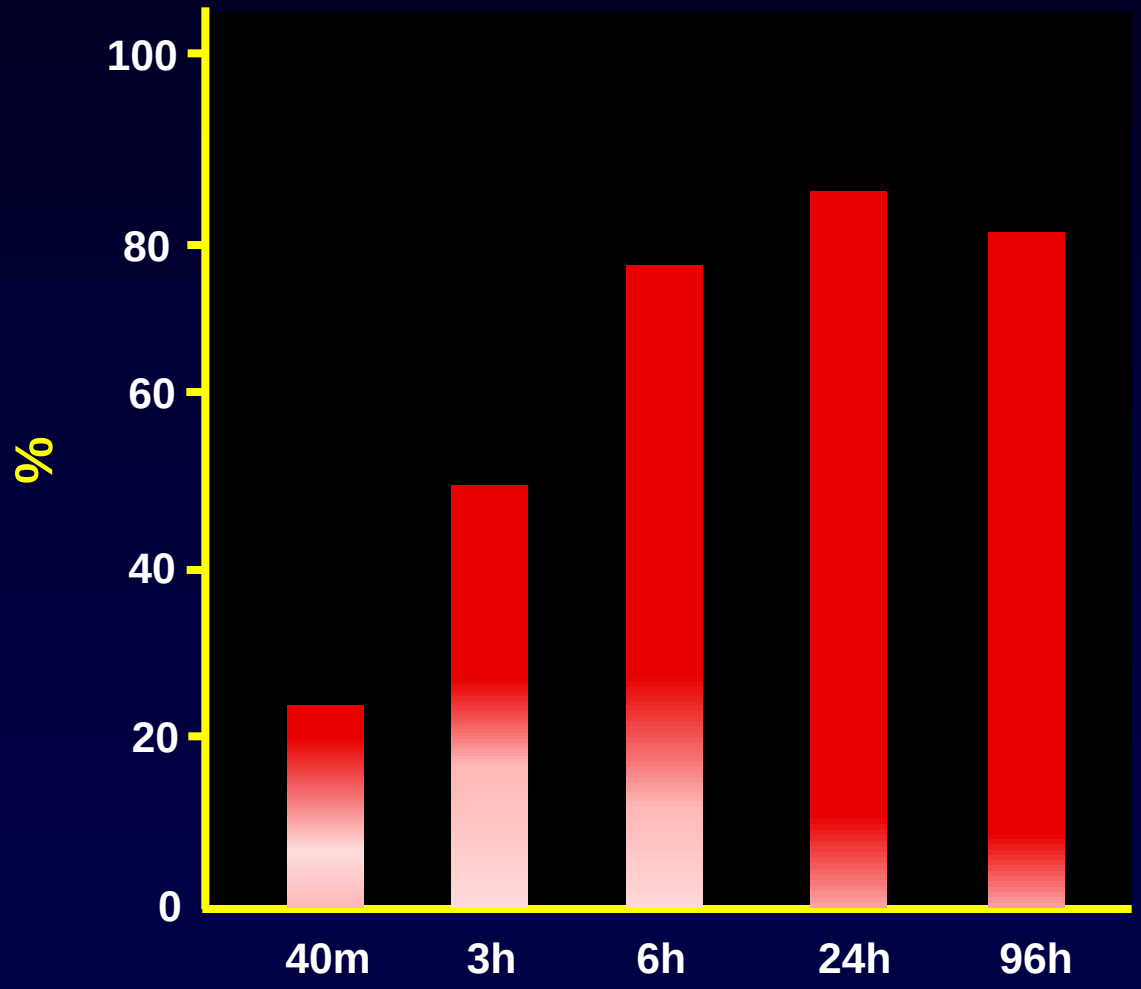
96 hours

3 hours

40 minutes



Transmural Necrosis



Reimer K, Jennings R et al. *Circulation.* 1977;56:786-794

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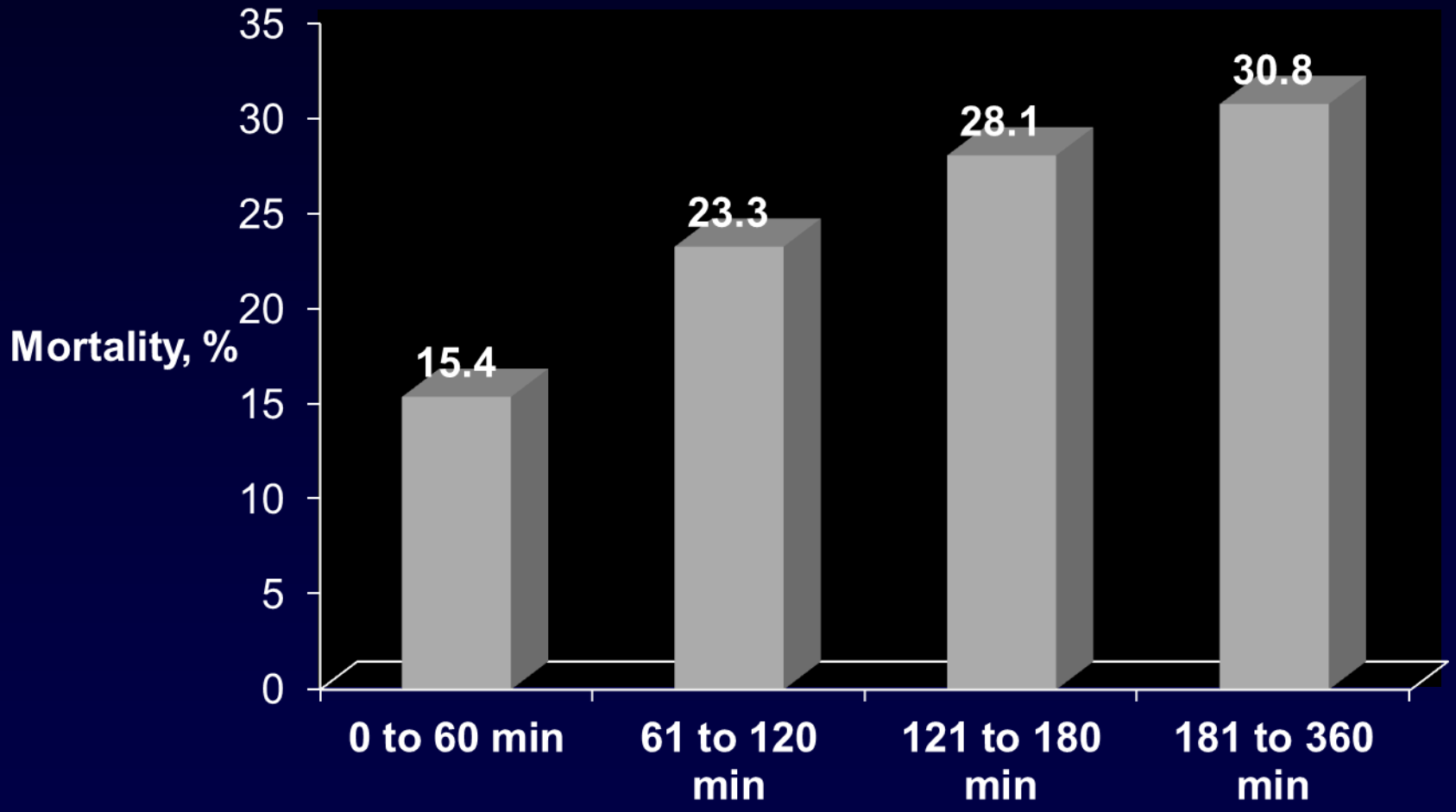
System Delay and Mortality in STEMI Patients



Terkelsen CJ et al. JAMA 2010;304:763-771

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The Core of Optimal STEMI Therapy:

Avoid Fibrinolytic Therapy if Possible:

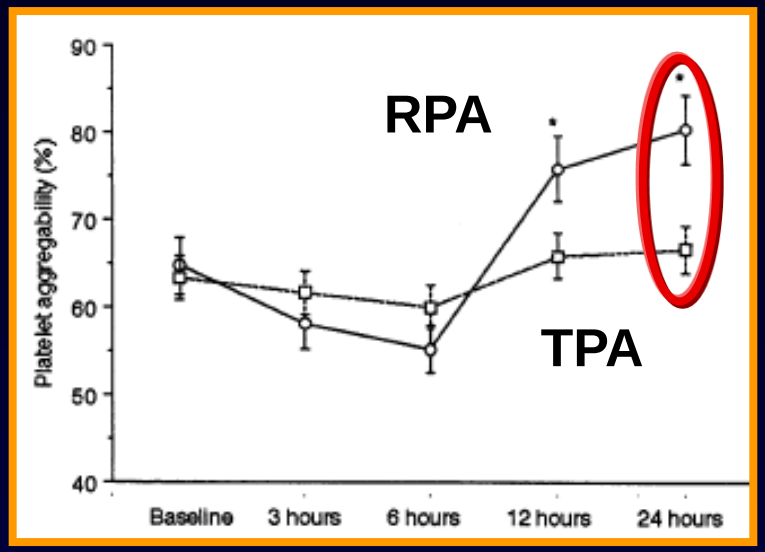
Incomplete Restoration of Flow

Intracranial Hemorrhage

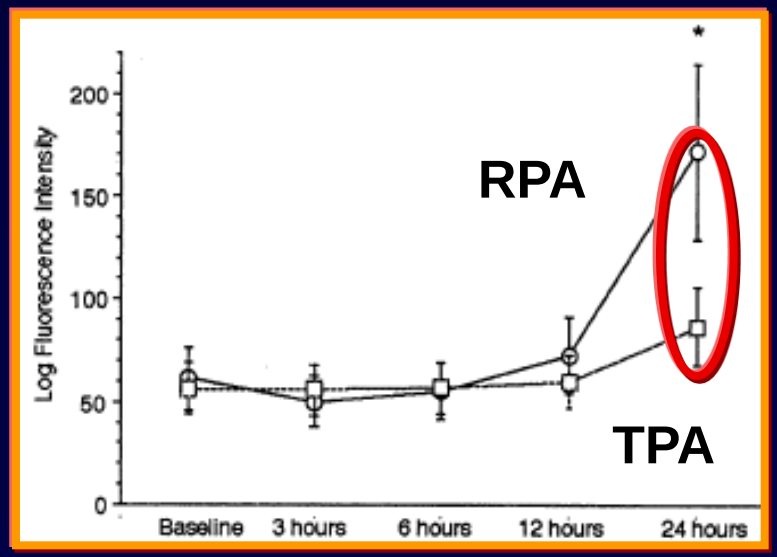
Enhancement of Platelet Reactivity

GUSTO-III Study:
Enhancement of Platelet Reactivity by Fibrinolytics

5uM ADP-Induced Aggregation



GPIIb/IIIa Receptor Activation



Gurbel PA et al, *J Am Coll Cardiol* 1998;31:1466–73

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8 Areas of Unmet Needs/Future Research

1) Patient Awareness

"Delays from symptom onset to STEMI care are unacceptably long"

-1.5 – 2.0 h delay (unchanged for last 10 y)

- women, black, elderly, medicaid

- EMS use 60%

  - 1/300 pts transported by private vehicle arrests en route.

  - pre-hosp ECG facilitates early reperfusion.

O'Gara PT et al *Circulation*. 2013;127:e362-425

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ALERTS Study: AngelMed Guardian System

Designed to reduce time to treatment and heart muscle damage

Background

- Detects progressive ST shifts and alerts patient
- Implanted like single-chamber pacemaker
- RV lead

Objective

- Demonstrate effectiveness in detection and alerting of rapidly progressive ST shifts.

Study Population

- High-risk ACS (e.g., unstable angina, STEMI or NSTEMI) or undergone or scheduled for CABG within 6 months of implantation
- One of the following: 1) Diabetes, 2) Compromised renal function, 3) TIMI Risk Score ≥3.

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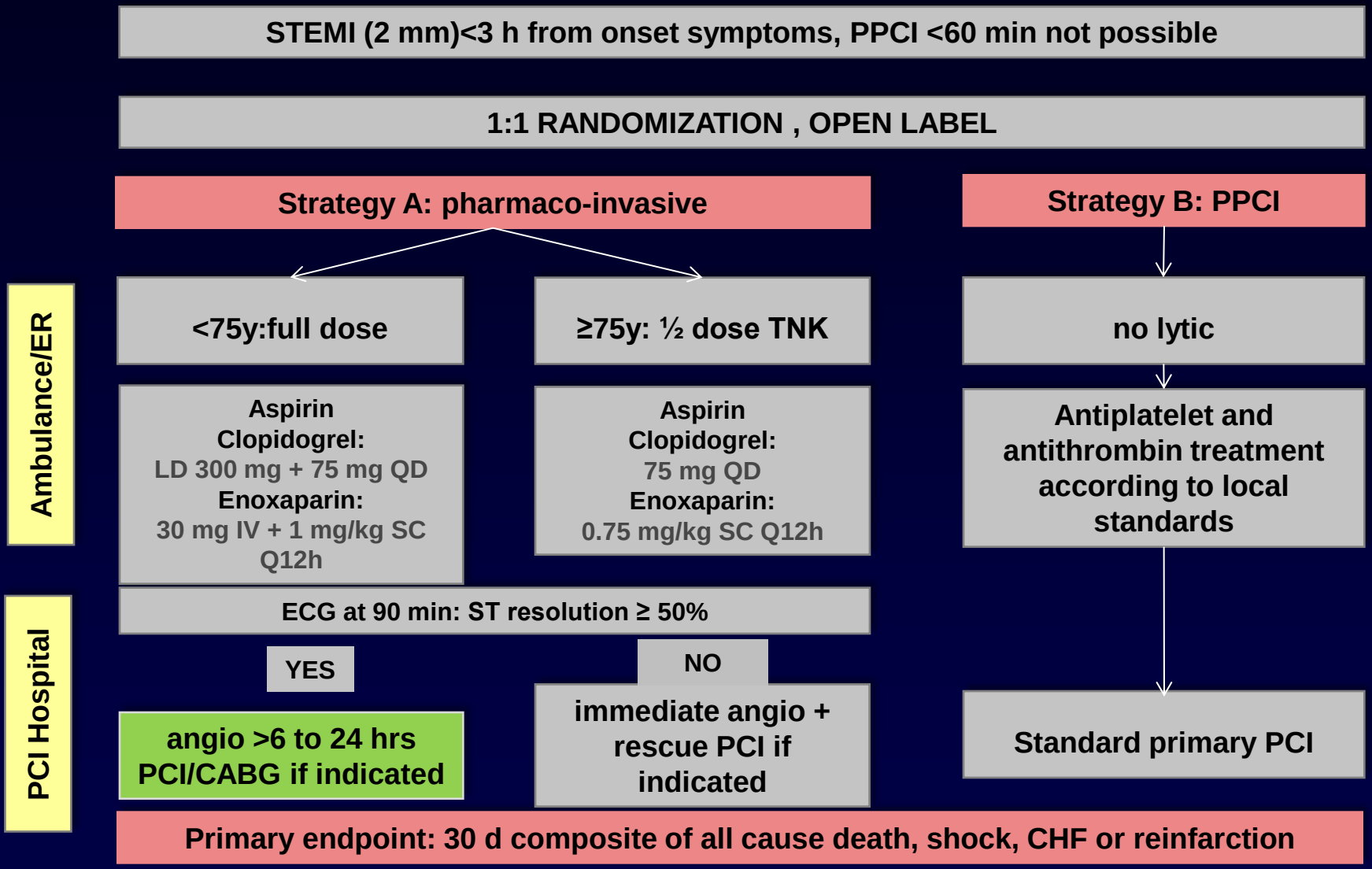
2) Regional Systems of Care

- Prehospital Emergency Medical Systems' protocols
- Out-of-hospital cardiac arrest
- Triage/transfer algorithms
- Rapid expert PCI availability
- Refinement of clinical / time-related factors for earlier lytic use + transfer for PCI
- *"Over-reliance on primary PCI"*
  - Waning familiarity with lytics
  - Only 10% of transferred pts had FMC-balloon <90 min (median 149 min)

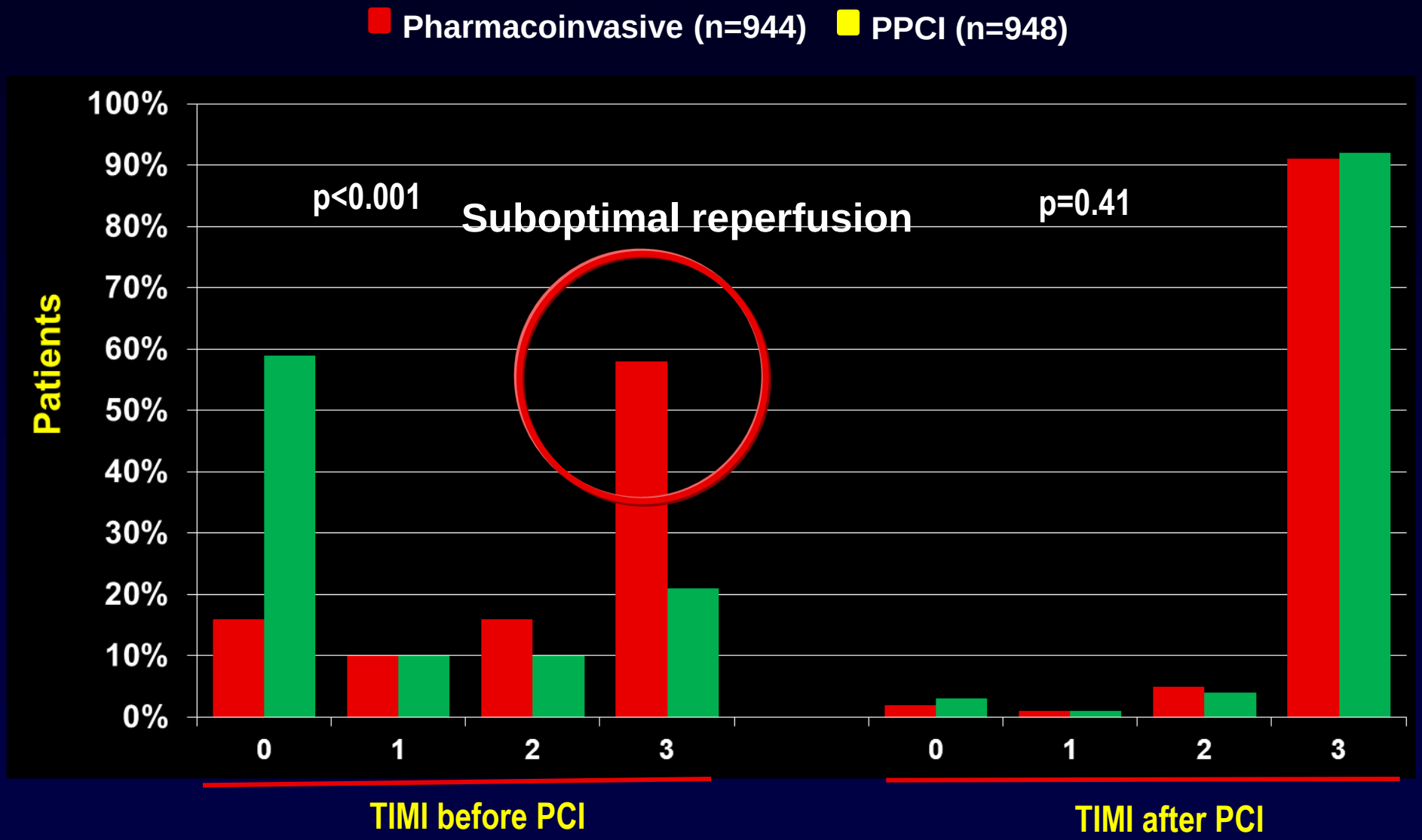
O'Gara PT et al *Circulation*. 2013 ;127:e362-425.

STREAM Trial: Study Protocol



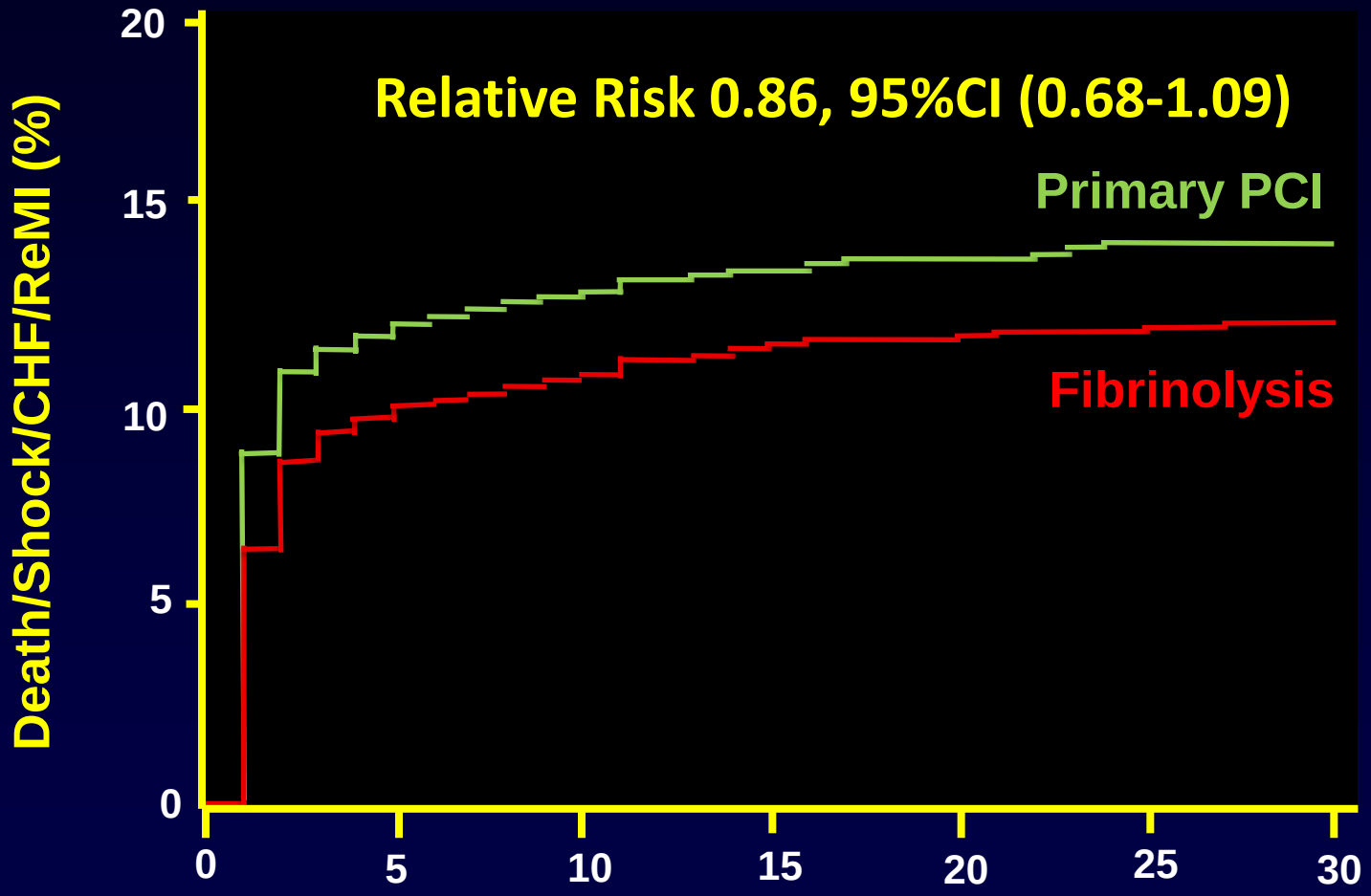
Armstrong PW et al. *N Engl J Med.* 2013;368:1379-87

STREAM Trial: TIMI Flow Rates



Armstrong PW et al. *N Engl J Med.* 2013;368:1379-87

STREAM Trial: Primary Endpoint



Armstrong PW et al. *N Engl J Med.* 2013;368:1379-87

STREAM Trial: Stroke Rates

	Pharmaco-invasive	PPCI	P-value
TOTAL POPULATION (N=1892)			
Total stroke	**15**/939 (1.60%)	**5**/946 (0.53%)	0.03
fatal stroke	**7**/939 (0.75%)	**4**/946 (0.42%)	0.39
Haemorrhagic stroke	**9**/939 (0.96%)	**2**/946 (0.21%)	0.04
fatal haemorrhagic stroke	**6**/939 (0.64%)	**2**/946 (0.21%)	0.18
POST AMENDMENT POPULATION (N=1503)			
Total stroke	**9**/747 (1.20%)	**5**/756 (0.66%)	0.30
fatal stroke	**3**/747 (0.40%)	**4**/756 (0.53%)	>0.999
Haemorrhagic stroke	**4**/747 (0.54%)	**2**/756 (0.26%)	0.45
fatal haemorrhagic stroke	**2**/747 (0.27%)	**2**/756 (0.26%)	>0.999

Armstrong PW et al. ***N Engl J Med.*** **2013;368:1379-87**

Author's Conclusion:

".. Early fibrinolysis .. coupled with timely angio resulted in effective reperfusion in pts presenting within 3h of sx onset unable to undergo PCI in 1 h"

Armstrong PW et al. *N Engl J Med.* 2013 ;368:1379-87

Editorialist's Conclusion:

"..Lack of superiority of fibrinolytic therapy .. coupled with increased intracranial hemorrhage ..make this an inferior strategy.. "

"STREAM trial shows us that that the best therapy for STEMI remains ….. a stent"

Bhatt DL. *N Engl J Med*. 2013;368:1446-7.

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Ongoing Tirofiban In Myocardial Infaction Evaluation

Acute myocardial infarction
diagnosed in ambulance or referral center
ASA + 600 mg clopidogrel + UFH

N=984
6/2006-11/2007

Placebo		Tirofiban*
	Transportation	
Angiogram	PCI center	Angiogram
Tirofiban provisional	PCI	Tirofiban cont'd

**Bolus: 25 µg/kg and 0.15 µg/kg/min infusion*

Van't Hof AW et al. *Lancet.* 2008;372:537-46.

Primary Endpoint

Residual ST deviation at 60 min.

	Placebo	Tirofiban	p- value
Readable ECG	94.1%	95.5%	0.358
Residual ST - deviation (mm)	4.8 ±6.3	3.6 ± 4.6	0.003
normal ECG	29.0%	35.5%	0.013
> 3 mm ST-deviation	45.1%	38.1%	0.035

Van't Hof AW et al. *Lancet.* 2008;372:537-46.

30d Clinical Secondary Endpoints

	Placebo n=477	Tirofiban n=473	p-value
Death/MI/uTVR or thrombotic bailout	32.9%	26%	0.020
Death	4.0%	2.3%	0.144
Recurrent MI	2.9%	2.7%	0.863
Stroke	1.5%	0.2%	0.069
Urgent TVR	4.2%	3.8%	0.761
Thromb. Bail out	28.5%	19.9%	0.002
Major bleeding	2.9%	4.0%	0.363

Van't Hof AW et al. *Lancet.* 2008;372:537-46.

3) Transfer/Management of Non-High Risk Pts After Lytic Treatment

"Transferring low risk patients for angiography with plan to revascularize is common

but,

evidence base for justification is limited"

4) Antithrombotic Therapy

- Role of platelet function testing and genotyping
- Gender, race and ethnic variability in outcomes
- Role of prasugrel, ticagrelor, Xa, IIa, and PAR-1 inhibitors
- Efficacy and safety of triple antithrombotic therapy in patients requiring anticoagulation
- Relation of access site to bleeding

O'Gara PT et al *Circulation*. 2013;127:e362-425.

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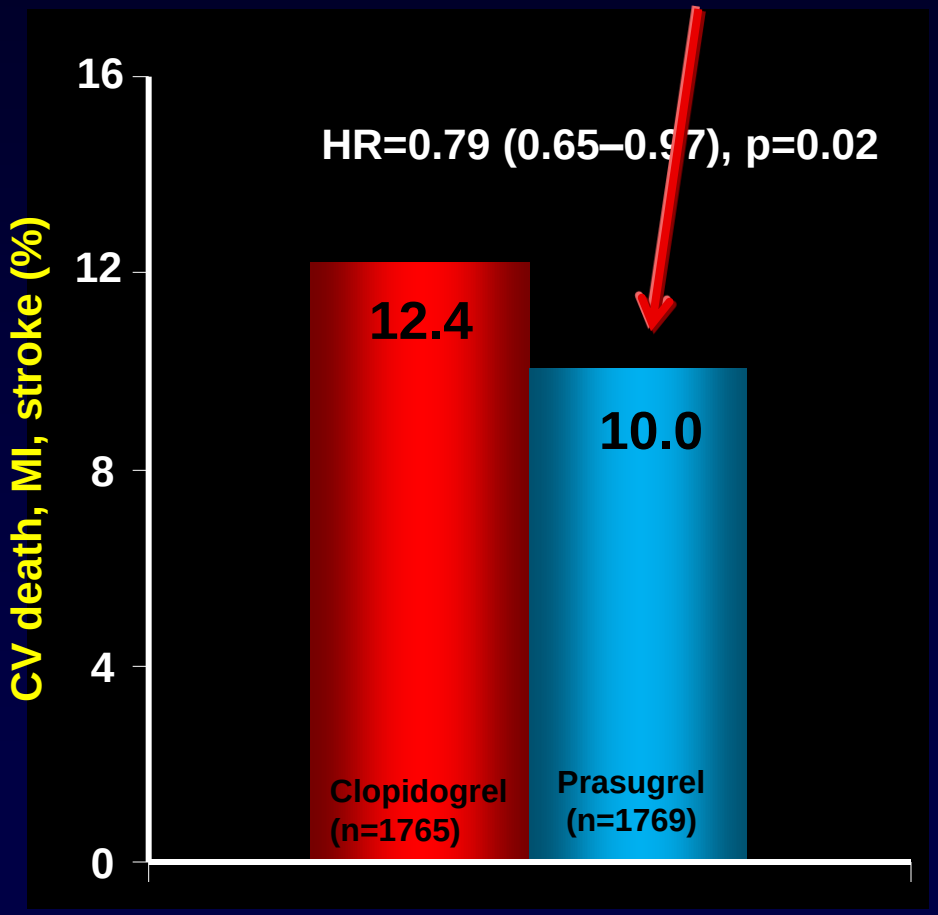
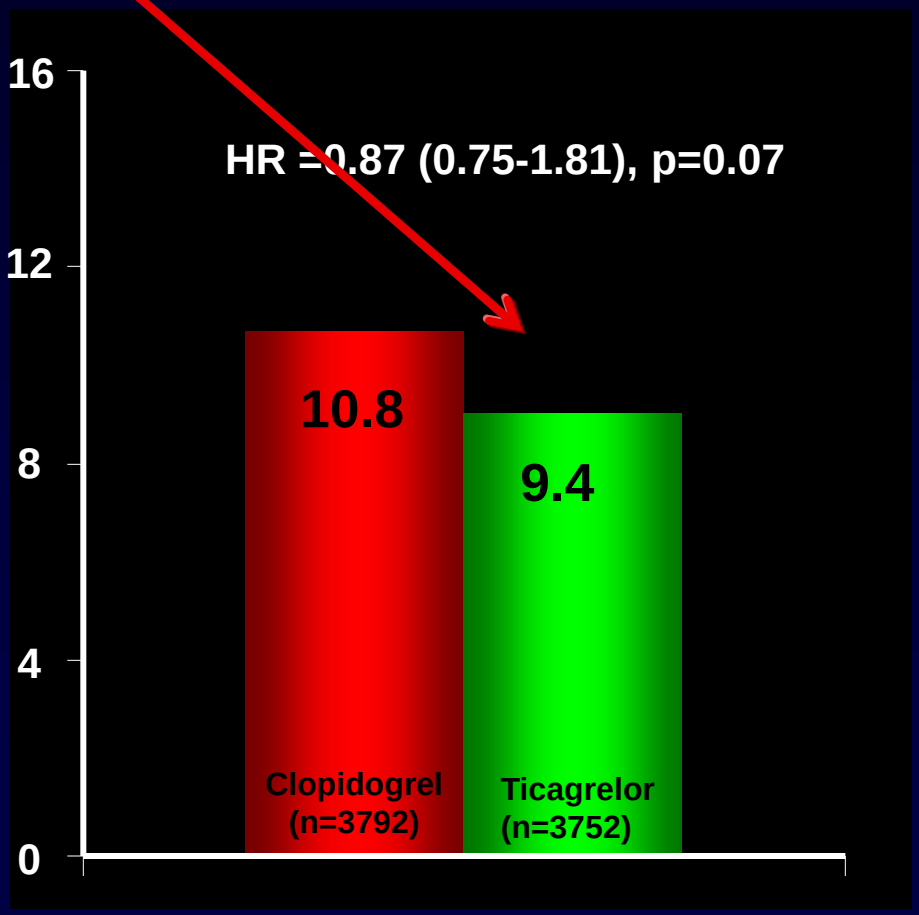
Prasugrel and Ticagrelor in STEMI
Primary Outcome

TRITON-TIMI-38 15 months

PLATO 12 months

TREATMENT FAILURE





Montalescot G et al. *Lancet* 2009;373:723-31

Steg PG et al. *Circulation* 2010;122:2131-

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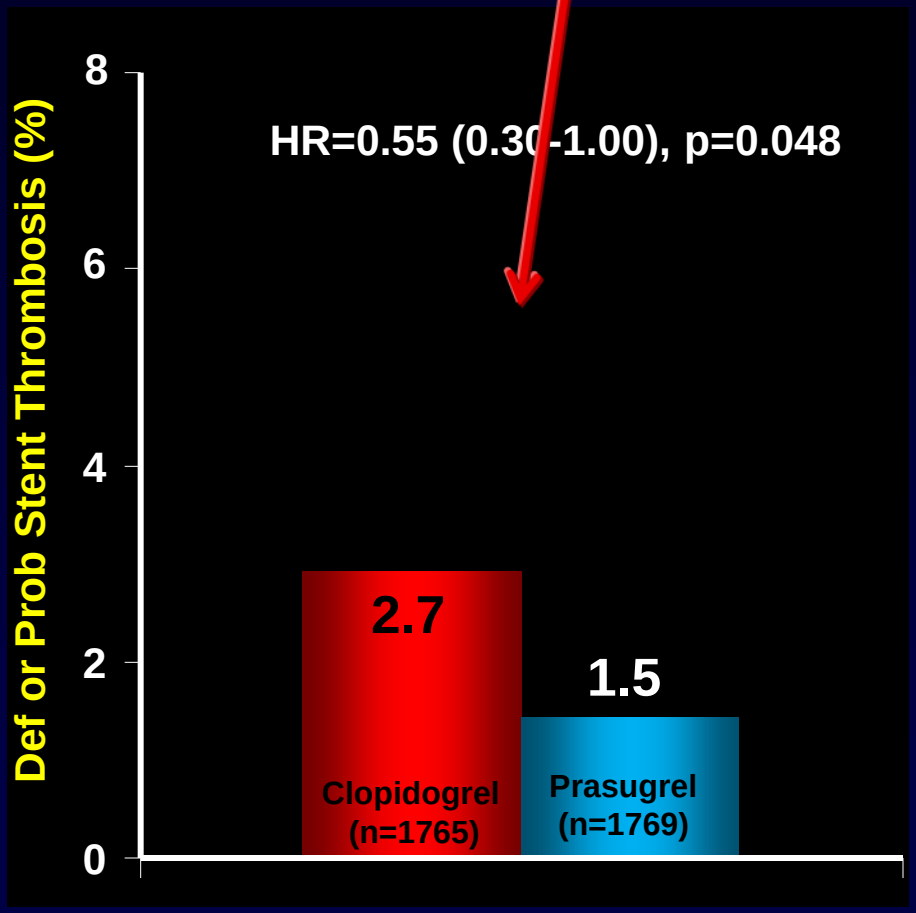
Prasugrel and Ticagrelor in STEMI

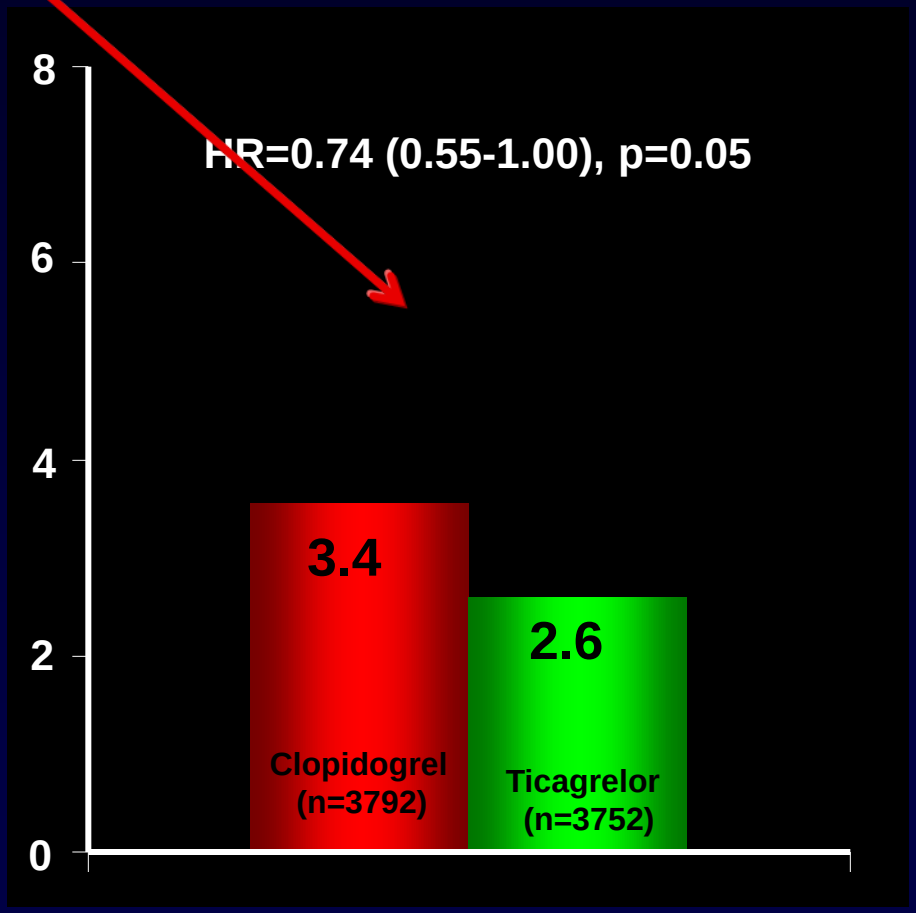
Stent Thrombosis (Def. or Prob.)

TRITON-TIMI-38 15 months

PLATO 12 months

TREATMENT FAILURE





Montalescot G et al. *Lancet* 2009;373:723-31

Steg PG et al. *Circulation* 2010;122:2131-

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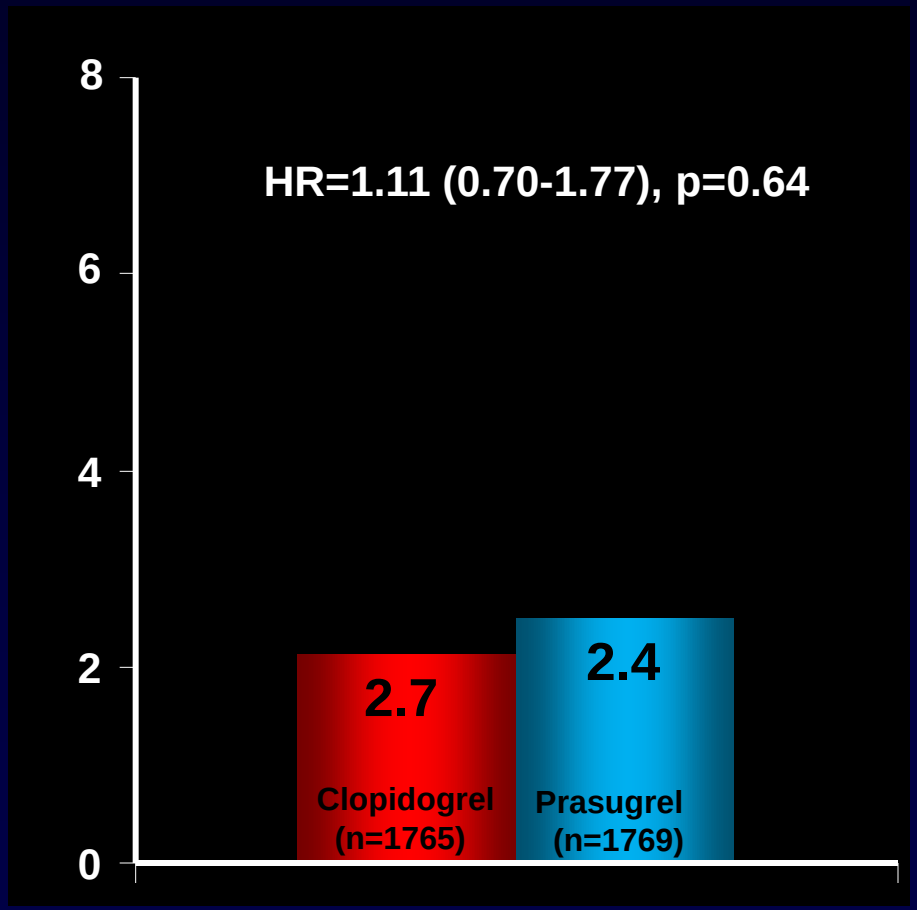
Prasugrel and Ticagrelor in STEMI

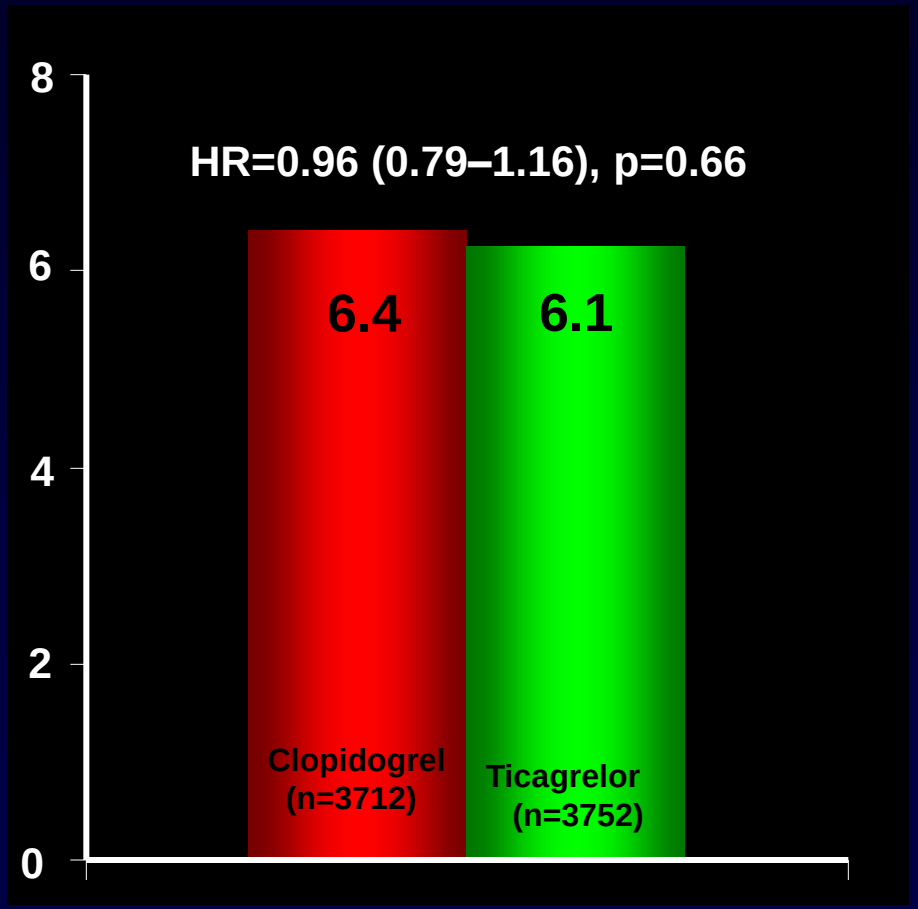
TIMI Major Bleeding

TRITON-TIMI-38 15 months



Montalescot G et al. *Lancet* 2009;373:723-31

PLATO 12 months



Steg PG et al. *Circulation* 2010;122:2131-

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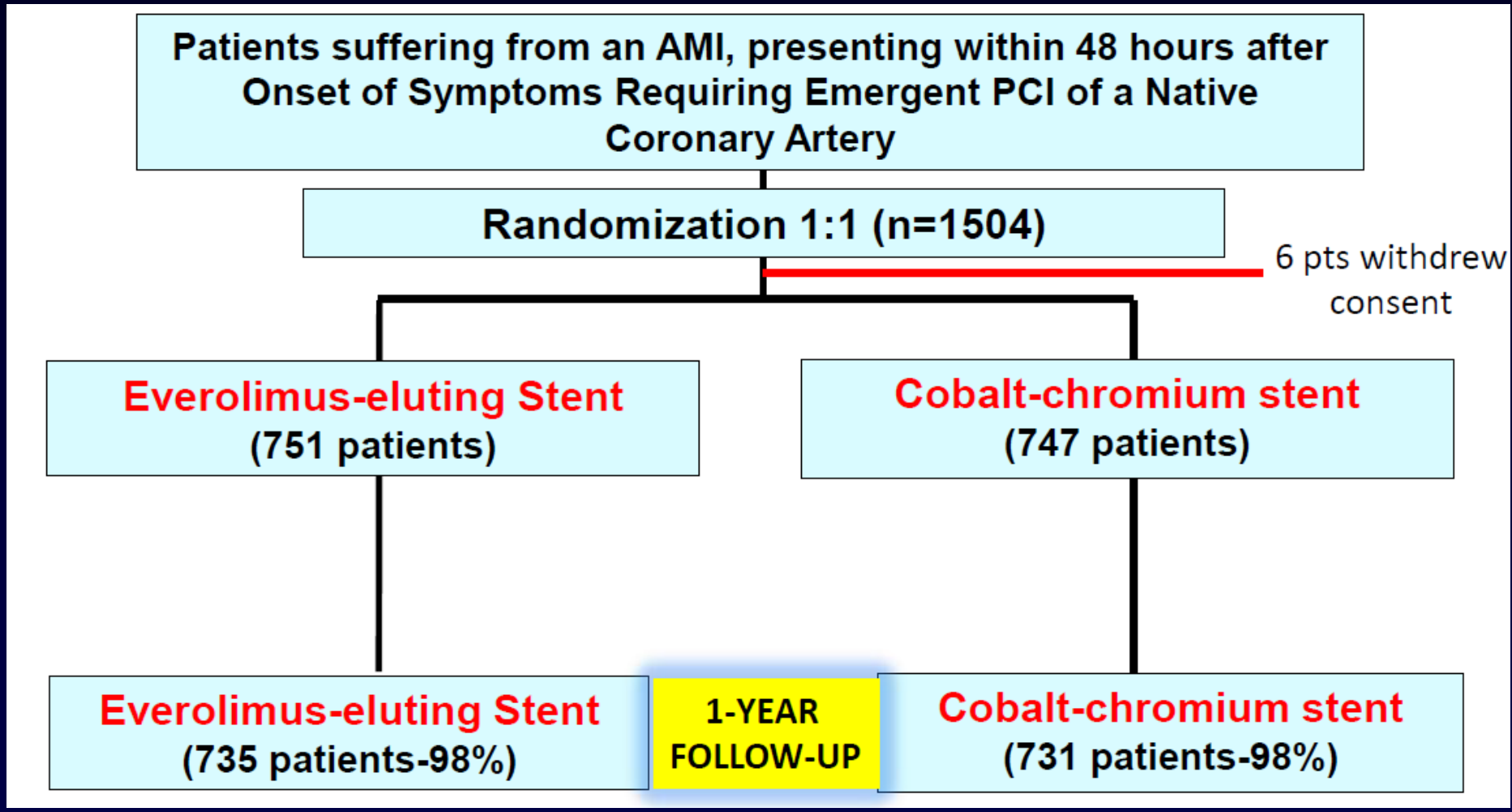
EXAMINATION Trial- Stent Thrombosis in New Era

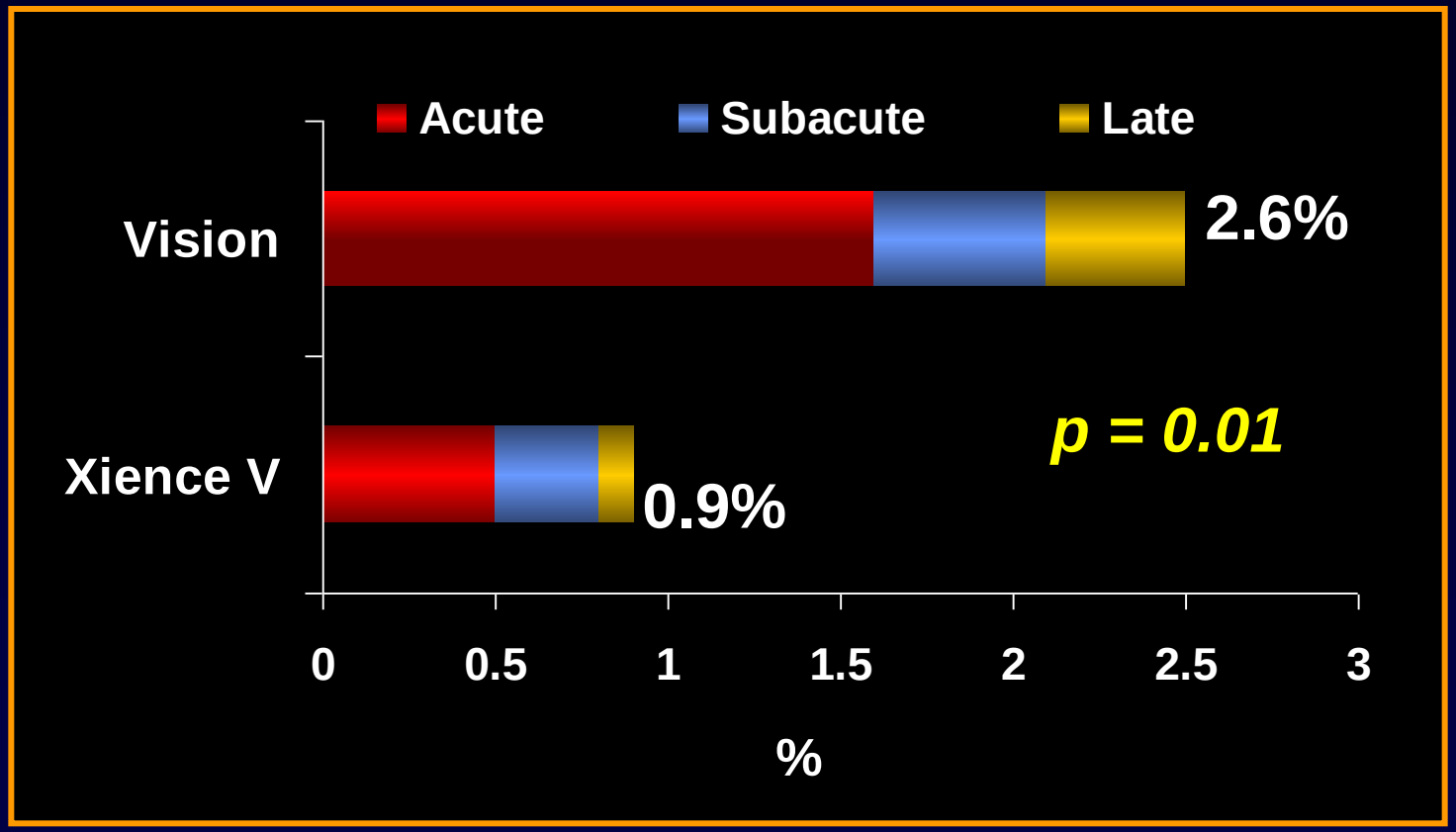


Sabate M. et al. *Lancet.* 2012;380:1482-90.

EXAMINATION Trial: Stent thrombosis still occurs with new generation DES

1504 pts with STEMI undergoing PCI within 48° (85% primary PCI within 12°) randomized to Xience V EES vs. Vision BMS

Stent thrombosis (Def/prob) within 1 year



Sabate M et al. *Lancet.* 2012;380:1482-90.

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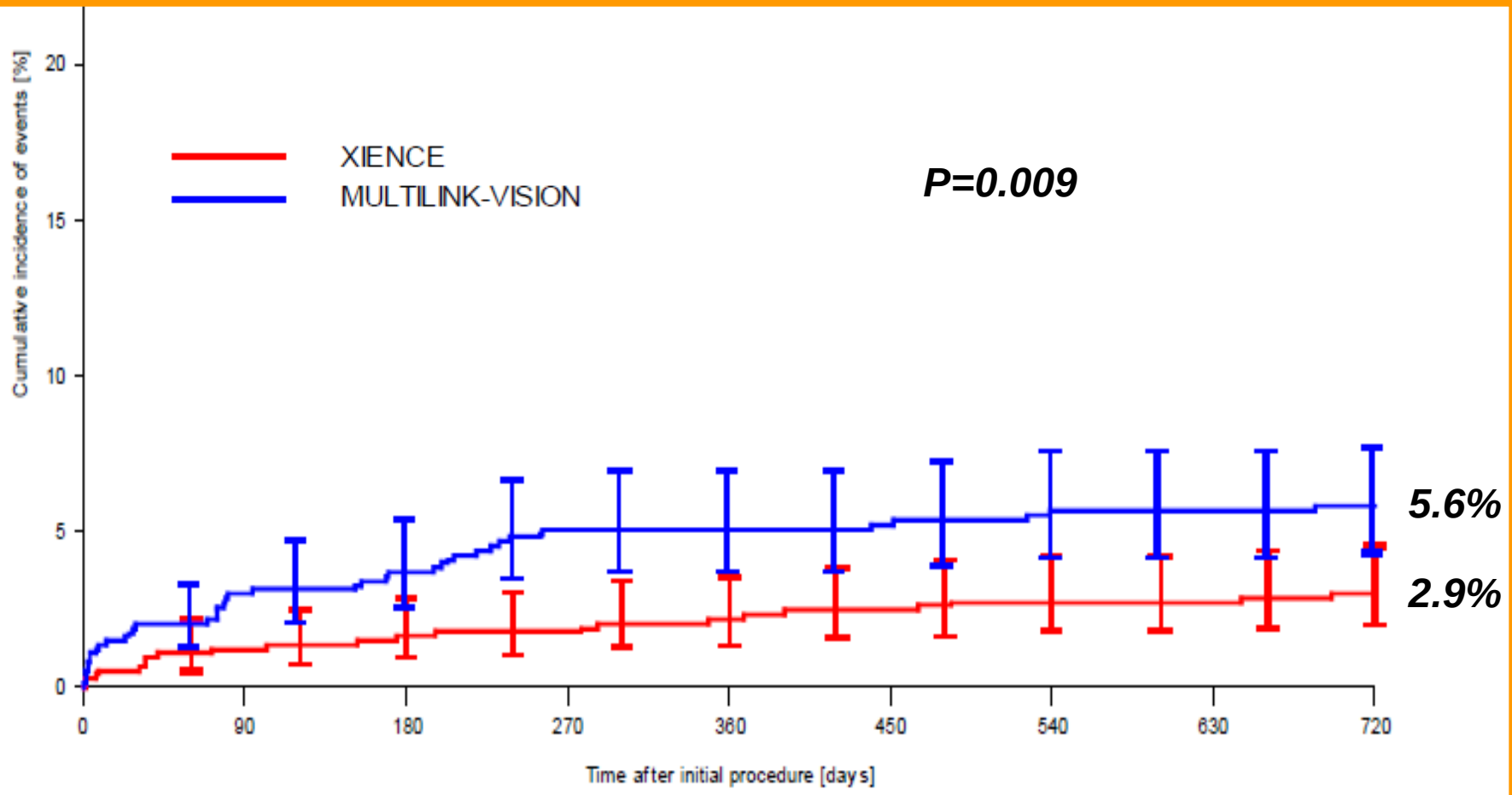
EXAMINATION Trial: TLR still occurs with new generation DES

Target Lesion Revascularization



Sabate M et al. *Lancet.* 2012;380:1482-90.

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5) No-reflow/Ischemia Reperfusion Injury

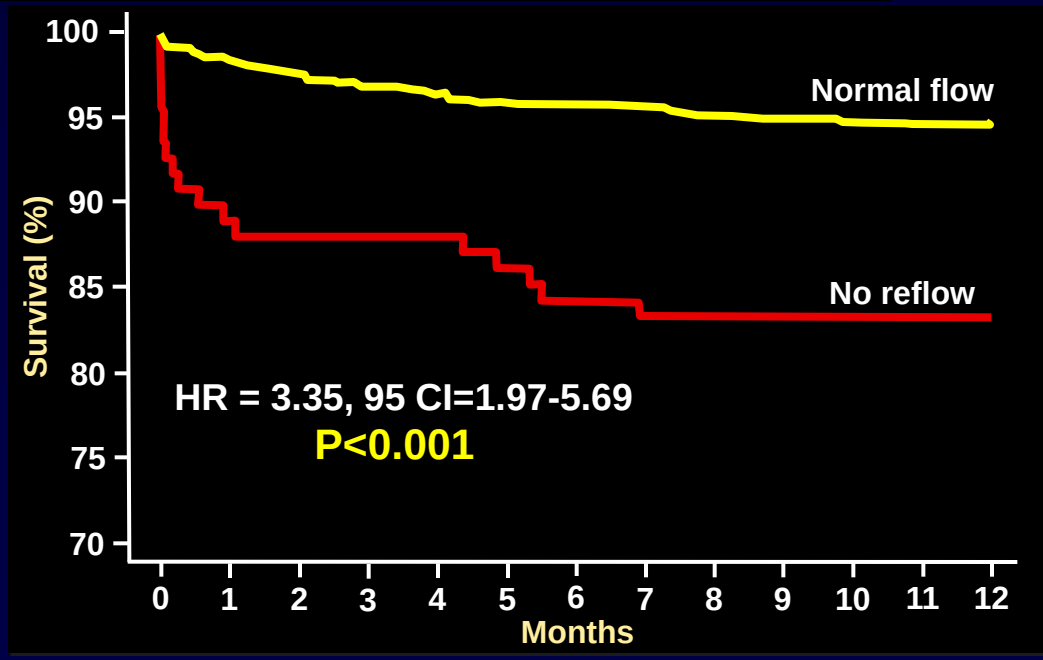
No-reflow developed in 108/1140 pts (9.5%)

* From pre-PCI and 7-14 day 99mTc-sestamibi imaging

	No reflow (n=108)	Normal flow (n=1032)	P value
Salvage index (median, [IQR])*	0.34 [0.15, 0.49]	0.55 [0.29, 0.81]	<0.001
Infarct size, 7-14d (median, [IQR])*	19% [10%, 34%]	9% [3%, 21%]	<0.001
LVEF, 6 months	48% ± 13%	54% ± 14%	<0.001

By multivariable analysis, no reflow was an independent predictor of 1-year mortality:

HR [95%CI] = 1.91 [1.11 to 3.30]



Ndrepepa G et al. *Circ CV Int.* 2010;3:27-33

Poor Reperfusion: Lack of ST-Segment Resolution as a Predictor of Death and MACE after Primary PCI in STEMI

The HORIZONS-AMI Trial

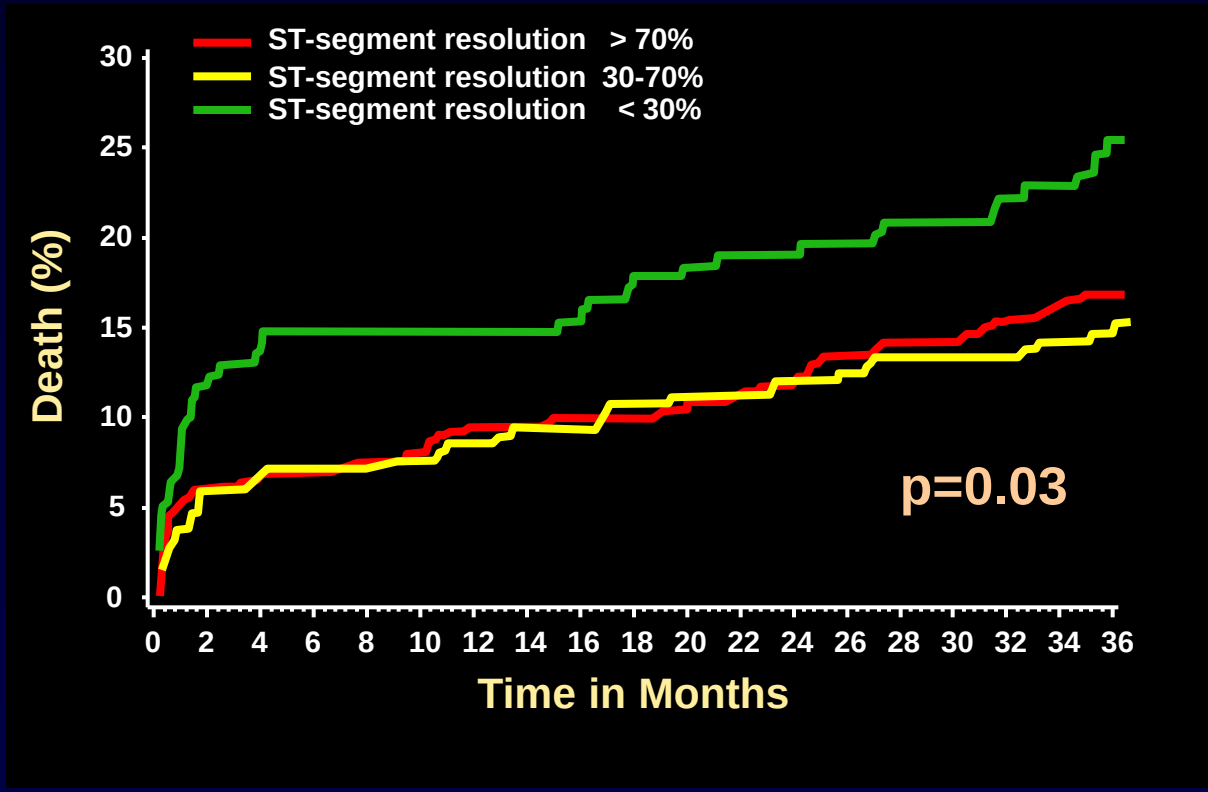
2,484 pts with interpretable baseline and 60-minute post-PCI ECGs

ST resolution at 60'

Complete (>70%)
1,258 (50.5%)

Partial (30%-70%)
712 (28.7%)

Absent (<30%)
514 (20.7%)



Farkouh ME et al. *Circ Cardiovasc Interv*. 2013;6:XX-XX.

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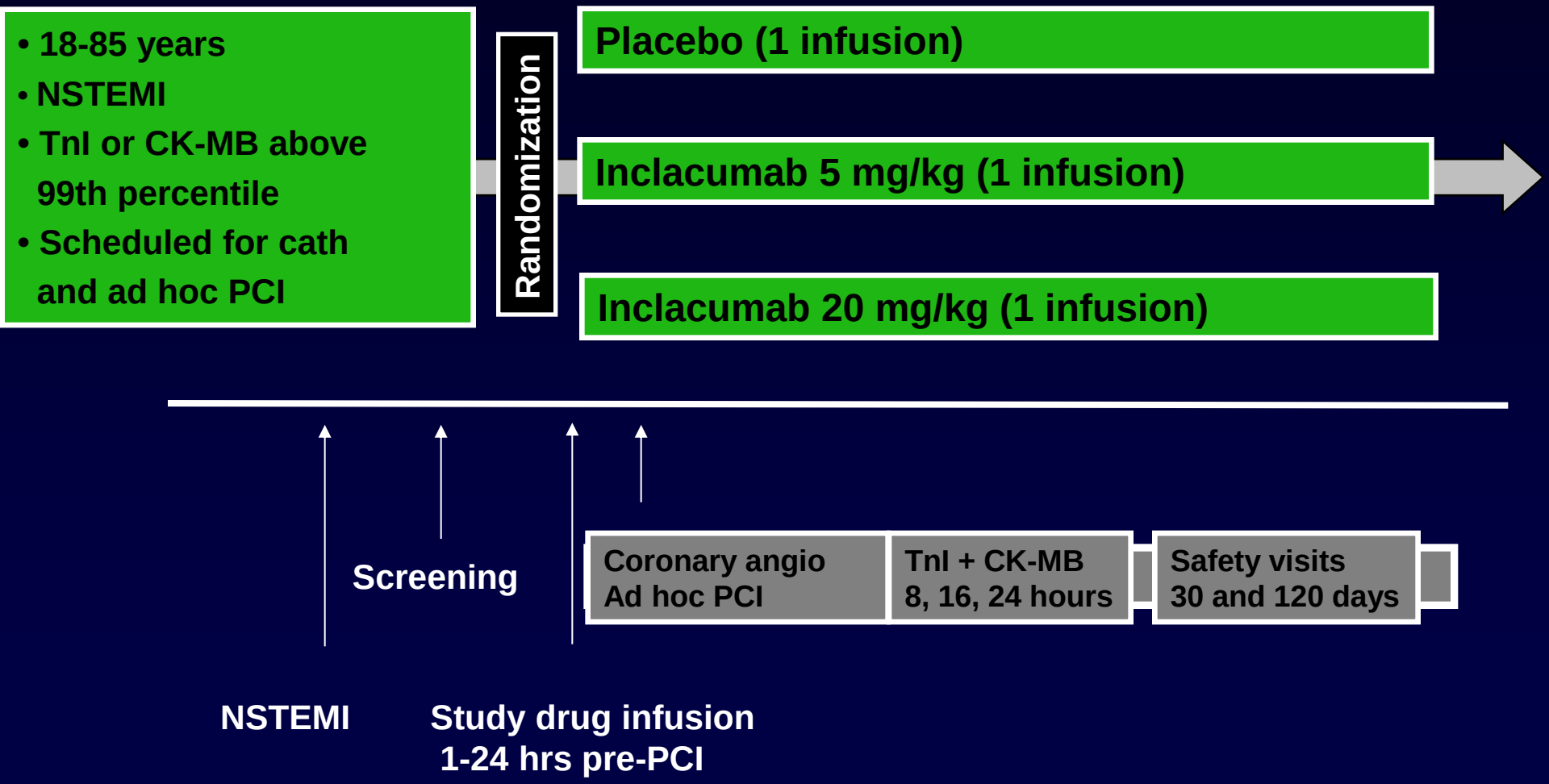
The SELECT-ACS Trial

Effects of the P-selectin antagonist inclacumab on myocardial damage after PCI for NSTEMI



Tardif J-C et al, *J Am Coll Cardiol.* 2013;61:2048–55

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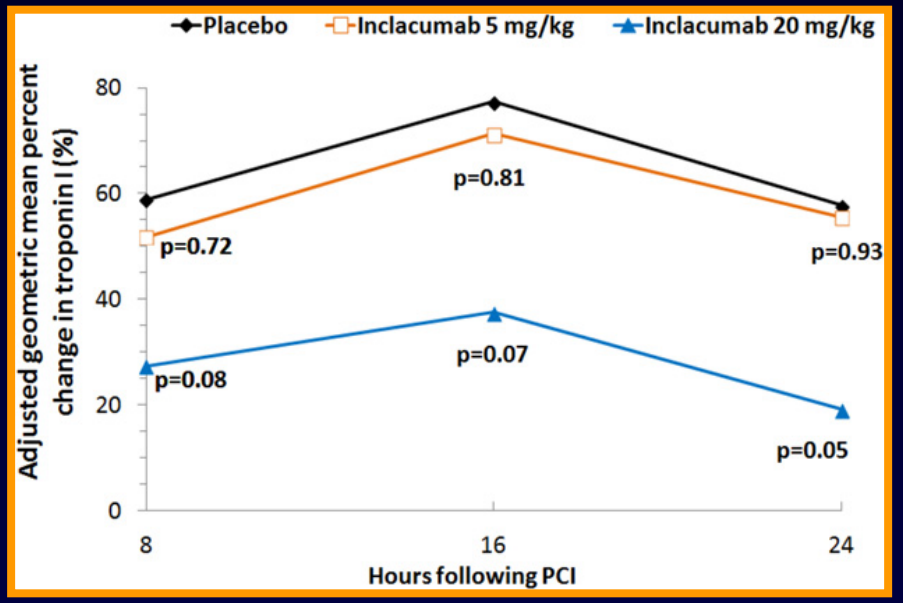
The SELECT-ACS Trial

Percent Change in Troponin I Over Time

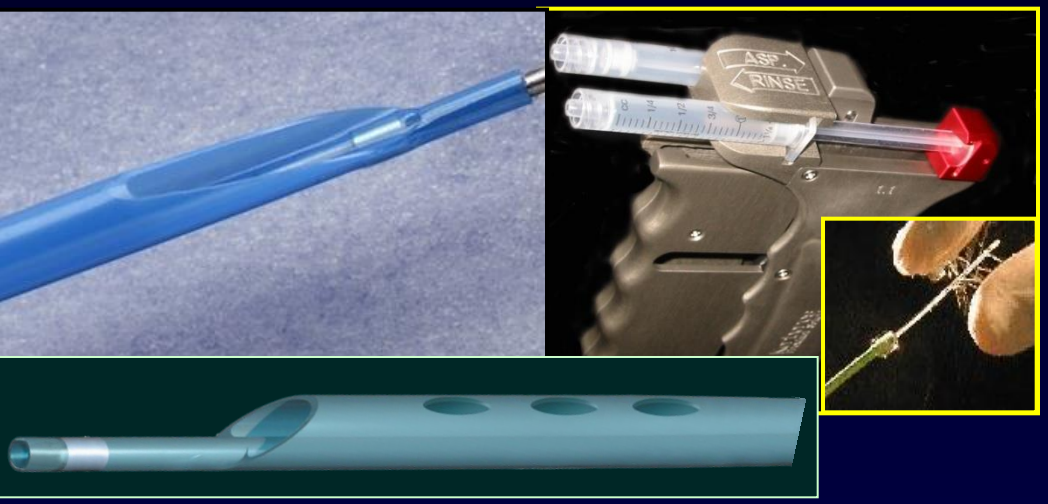


Tardif J-C et al, *J Am Coll Cardiol.* 2013;61:2048–55

Mechanical Approaches to Thrombus

Thrombus aspiration

(Rinspirator, Pronto, Export, Rescue, Diver CE, etc.)

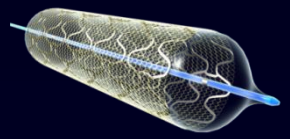


Thrombectomy

(AngioJet, X-Sizer)

Embolic protection (GuardWire, FilterWire, Proxis, etc.)

GuardWire,



*M*GUARD for *A*cute *ST* *E*levation*R*eperfusion

The MASTER Trial

STEMI with symptom onset within 12 hours at
432 pts at 50 sites in EU, Israel, Mexico and SA

R

PCI with BMS or DES

PCI with MGuard

Follow-up: 30 days, 6 months, 1 year

Primary endpoint: ST resolution at 60-90 minutes

Substudies:

MRI: 60 pts (30 in each arm) at 3-5 days

Angio FU: 60 pts in MGuard arm at 13 months

Stone GW et al. *J Am Coll Cardiol* . 2012;60:1975–84

MASTER trial: Angiographic Measures Post-PCI

	MGuard Stent (n = 217)	Control Stent (n = 216)	p Value
Device success*	208 (95.9)	214 (99.1)	0.03
Lesion success†	217 (100.0)	215 (99.5)	0.50
Angiographic success‡	199 (91.7)	178 (82.4)	0.004
Reference vessel diameter, mm§	3.20 (2.90–3.46)	3.16 (2.91–3.46)	0.99
Minimal luminal diameter, mm§			
In-stent	2.99 (2.73–3.25)	2.99 (2.69–3.31)	0.91
In-lesion	2.64 (2.40–2.96)	2.64 (2.36–2.95)	0.82
Diameter stenosis, %§			
In-stent	6.9 (4.2–10.5)	6.4 (3.9–10.3)	0.56
In-lesion	15.3 (9.6–21.2)	15.4 (10.8–21.2)	0.66
TIMI flow grade§			
0/1	4 (1.8)	12 (5.6)	0.01
2	14 (6.5)	25 (11.6)	0.06
3	199 (91.7)	179 (82.9)	0.006
Corrected TIMI frame count§	17.0 (12.0–23.0)	18.0 (13.0–22.0)	0.23
Myocardial blush grade§			
0/1	35 (16.1)	32 (14.8)	0.71
2	21 (9.7)	28/215 (13.0)	0.27
3	161 (74.2)	155/215 (72.1)	0.62
2/3	182 (83.9)	183 (84.7)	0.81
IPTE§	47 (21.7)	48/215 (22.3)	0.87

Stone GW et al. *J Am Coll Cardiol.* 2012;60:1975–84

6) Non-Infarct Artery Disease

"Need to clarify indications for and timing of non-infarct artery revascularization."

Class III harm-

"do not do non-infarct vessel PCI in a stable pt at time of primary PCI"

7) Prevention of Sudden Cardiac Death

- Prediction is imprecise

- Treatment decisions made on EF only

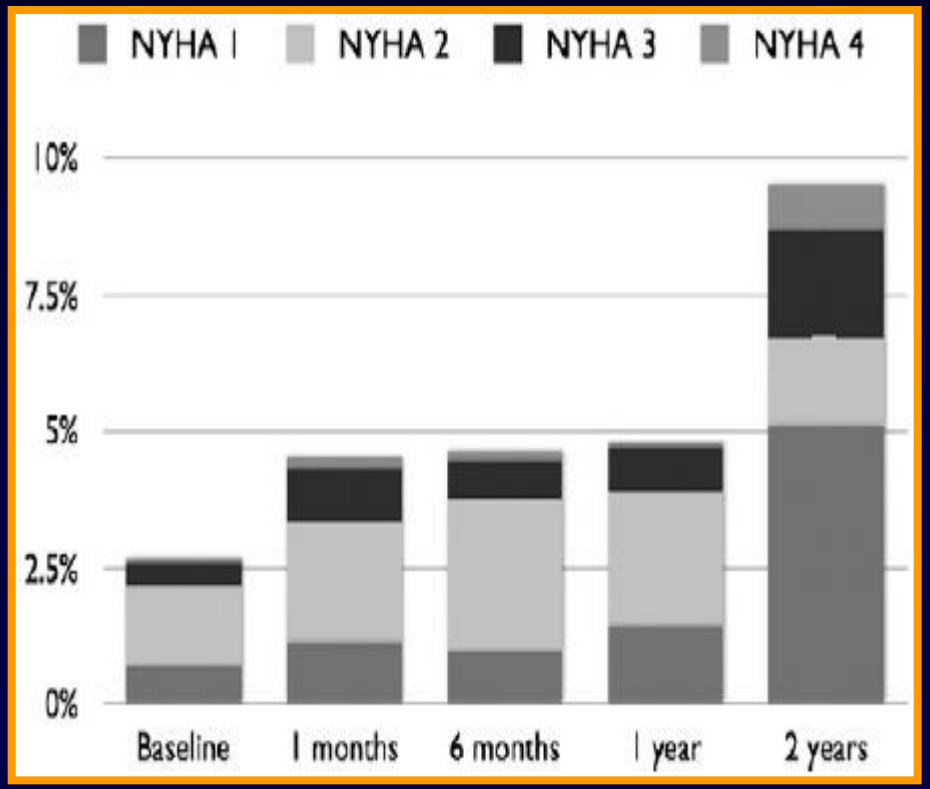
- Optimal therapy in the window after discharge not established

O'Gara PT et al *Circulation*. 2013 ;127:e362-425.

8) Prevention of Heart Failure/Cardiogenic Shock

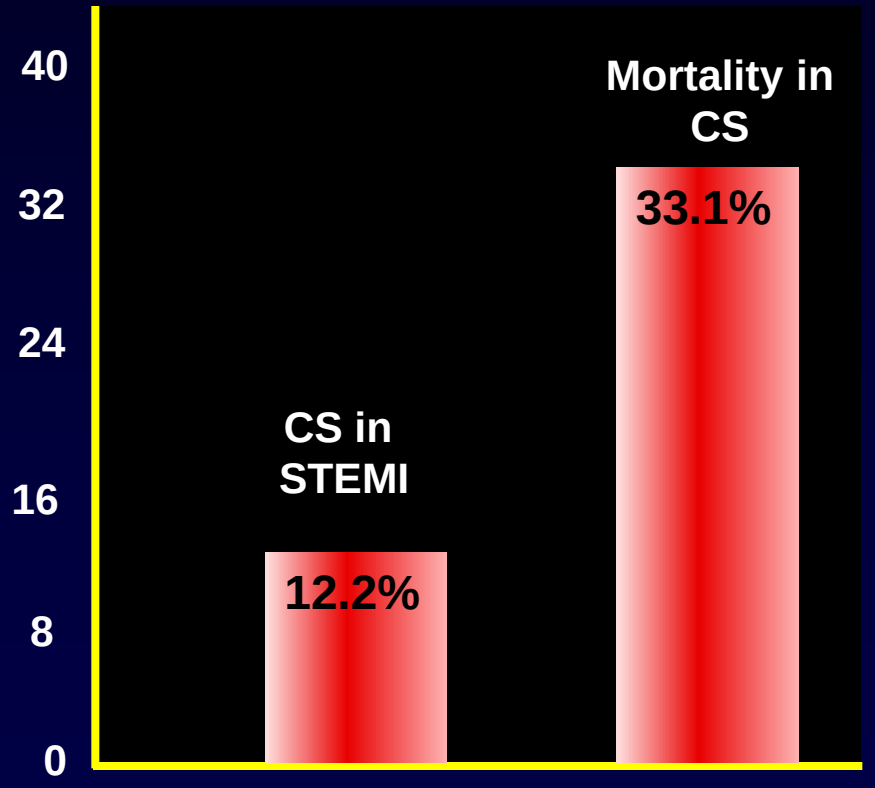
Frequency of CHF in STEMI

HORIZON-AMI Trial



Kelly DJ et al. *Am Heart J.* 2011;162:663-70

Cardiogenic shock



Anderson MI et al. AHA Scientific Sessions 2011

8)Prevention of Heart Failure/Cardiogenic Shock

Intraaortic Balloon Pump in Cardiogenic (IABP)- SHOCK II Trial

Outcome	IABP (N=300)	Control (N=298)	P Value	Relative Risk with IABP (95% CI)
	number (percent)			
Primary end point: all-cause mortality at 30 days	119 (39.7)	123 (41.3)	0.69	0.96 (0.79–1.17)
Reinfarction in hospital	9 (3.0)	4 (1.3)	0.16	2.24 (0.70–7.18)
Stent thrombosis in hospital	4 (1.3)	3 (1.0)	0.71	1.32 (0.30–5.87)
Stroke in hospital	2 (0.7)	5 (1.7)	0.28	0.40 (0.08–2.03)
Ischemic	2 (0.7)	4 (1.3)	0.45	0.49 (0.09–2.71)
Hemorrhagic	0	1 (0.3)	0.50	—
Peripheral ischemic complications requiring intervention in hospital	13 (4.3)	10 (3.4)	0.53	1.29 (0.58–2.90)
Bleeding in hospital*				
Life-threatening or severe	10 (3.3)	13 (4.4)	0.51	0.76 (0.34–1.72)
Moderate	52 (17.3)	49 (16.4)	0.77	1.05 (0.74–1.50)
Sepsis in hospital	47 (15.7)	61 (20.5)	0.15	0.77 (0.54–1.08)

Thiele H et al. *N Engl J Med* . 2012;367:1287-96.

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8)Prevention of Heart Failure/Cardiogenic Shock

Intraaortic Balloon Pump in Cardiogenic (IABP)- SHOCK II Trial

Authors' Conclusion:

"The use of intraaortic balloon counterpulsation did not significantly reduce 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction for whom an early revascularization strategy was planned."

Thiele H et al. *N Engl J Med* 2012;367:1287-96.

Editorialists' Conclusion:

"Given the concordance of data from the meta-analyses and the current trial, the data do not support the routine use of IABP in patients with acute myocardial infarction complicated by cardiogenic shock, and the level I guideline recommendation is now strongly challenged.

Members of guideline committees and clinicians should take note of another example of a recommendation that is based on insufficient data."

O'Connor CM, Rogers JG. *N Engl J Med.* 2012;367:1349-50.

Conclusions

We have a long way to go to optimize reperfusion in STEMI:

Major Limitations:

- Patient Education
- Transfer to dedicated PCI sites
- Antithrombotic therapy
- Catheter and fibrinolysis-induced reperfusion
  (no-reflow and ischemia-reperfusion injury)
- Treatment of shock

What we can do immediately to optimize reperfusion:

Practice Guideline Based Medicine!