

# Optimal ACS Management with Antiplatelet Agents

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# The 3 Most Important Advances in Antiplatelet Therapy for ACS

- Aspirin
- ADP antagonists
- Platelet GP IIb/IIIa receptor antagonists

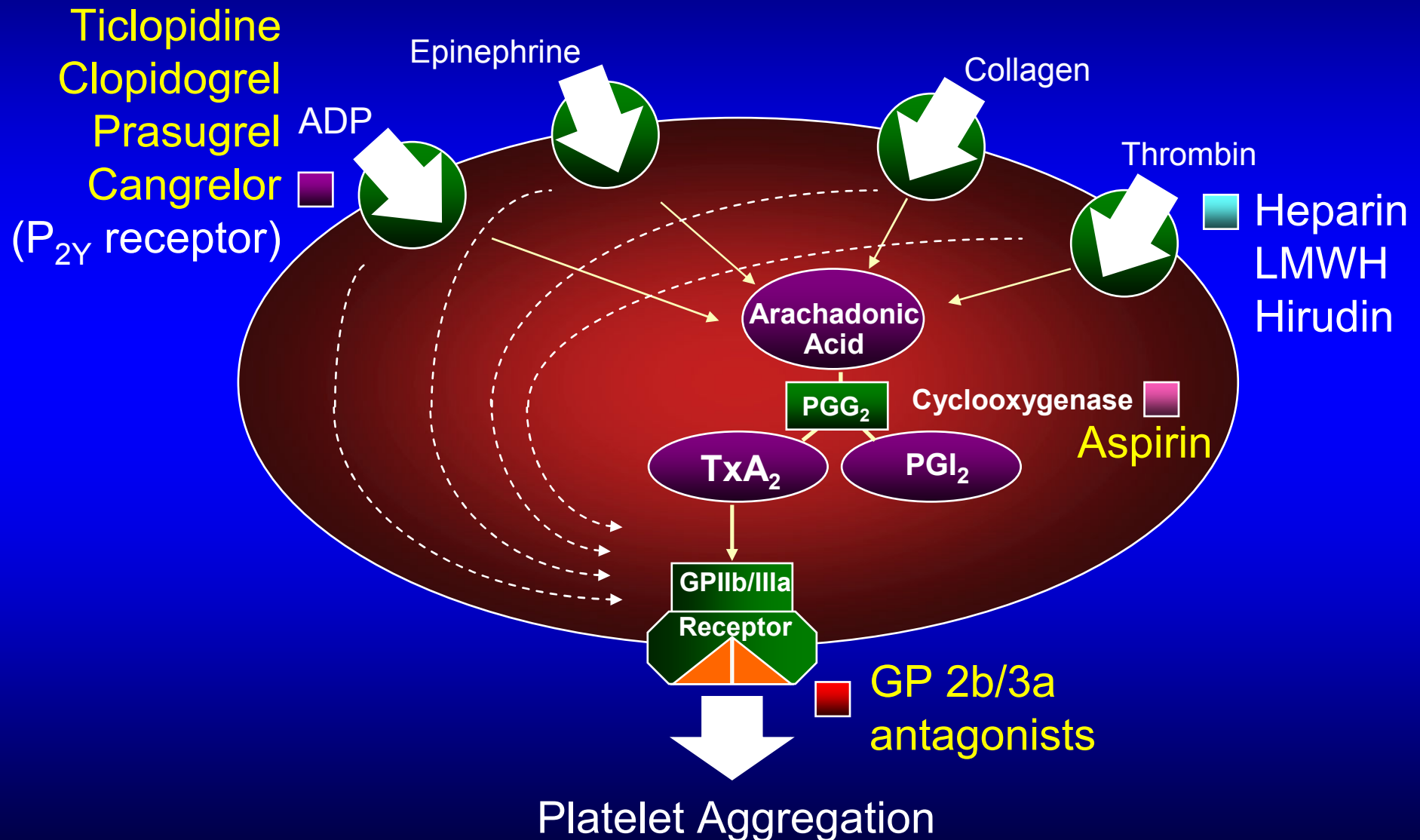
# 2007 ACC/AHA Guideline Recommendations

## Antithrombotic Therapy for Acute Coronary Syndromes

	Class I (Benefit >>> risk) (Highly recommended)	Class II		Class III (Risk ? Benefit) (Not recommended)
		IIa (Benefit >>risk) (Reasonably recommended)	IIb (Benefit ? risk) (May be considered)	
<b>Level A</b> (Multiple randomized clinical trials)	<ol style="list-style-type: none"> <li>Aspirin</li> <li>UFH or Enoxaparin</li> <li>Clopidogrel</li> <li>GPI during early PCI</li> <li>Early invasive Rx in stabilized high-risk pts</li> <li>Statins at any LDL level</li> </ol>			<ol style="list-style-type: none"> <li>Fibrinolytic therapy</li> <li>GPI (abciximab) during medical Rx</li> </ol>
<b>Level B</b> (Single randomized trial or nonrandomized studies)	<ol style="list-style-type: none"> <li>Early invasive Rx in unstable high-risk pts</li> <li>Fondaparinux (medical Rx)</li> <li>Bivalirudin (early PCI)</li> </ol>	<ol style="list-style-type: none"> <li>GPI + clopidogrel during early PCI in high-risk pts</li> <li>GPI (eptifibatide or tirofiban) during medical Rx</li> </ol>		
<b>Level C</b> (Consensus opinion, case studies, or standard of care)				

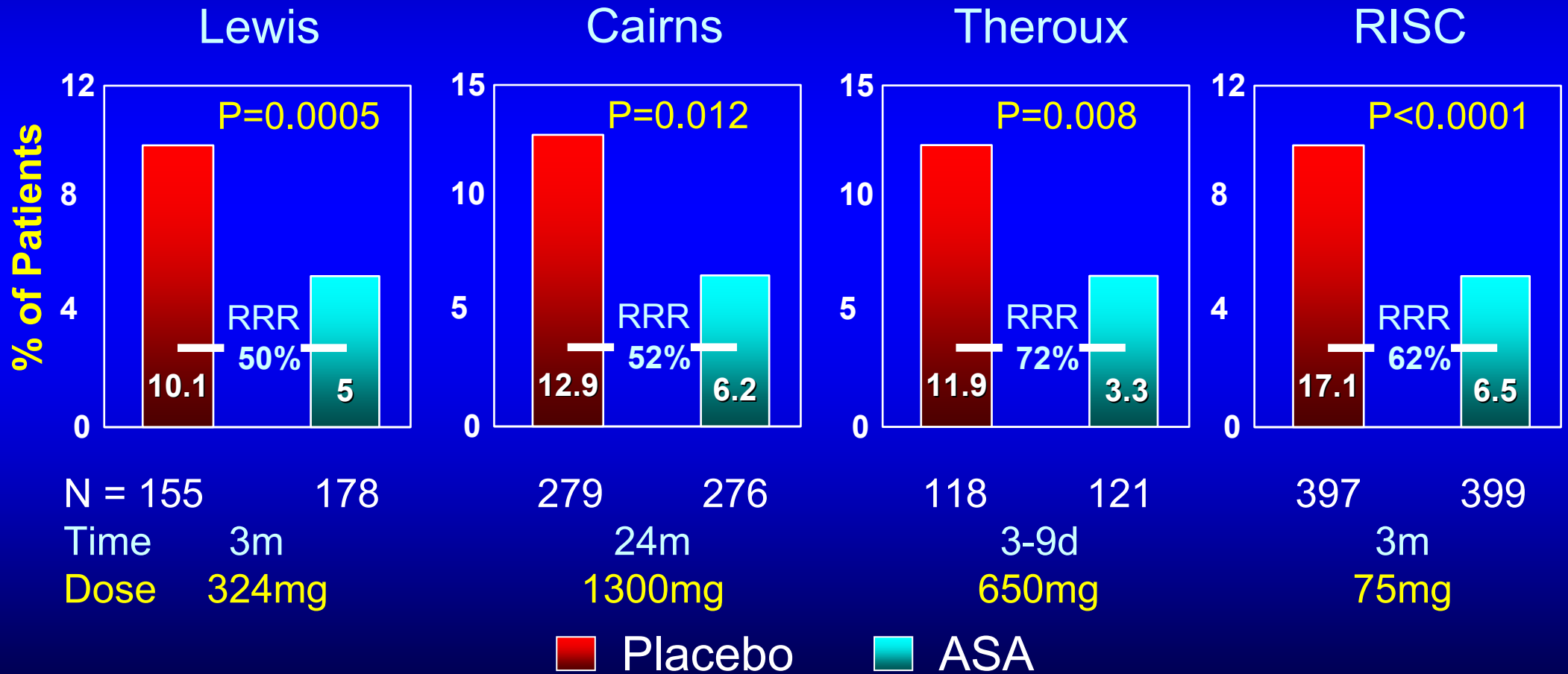
# Antiplatelet Agents

## Different Mechanisms of Action



# Effect of ASA in Non-ST Elevation MI and Unstable Angina

*Incidence of Death or Subsequent MI*



# Limitations of Aspirin

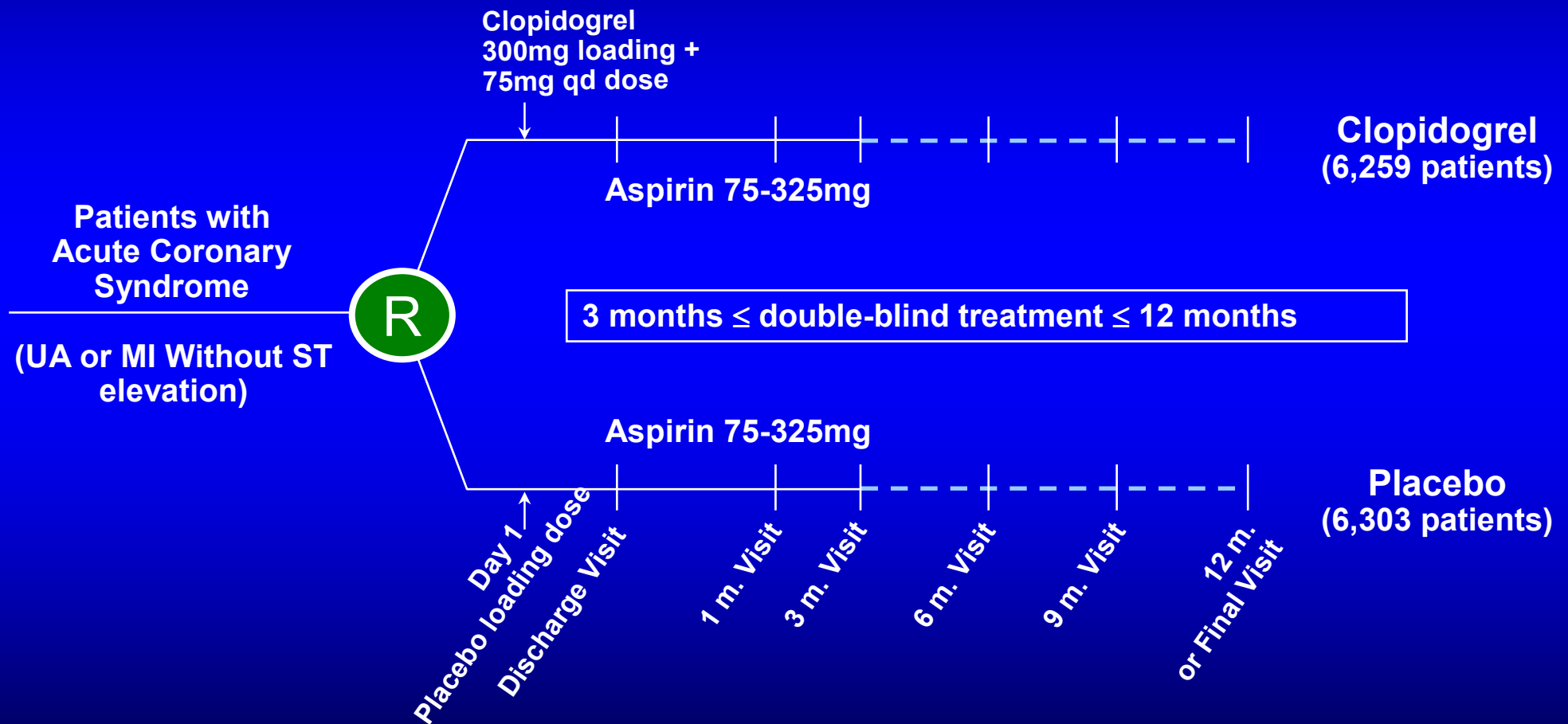
- Multiple pathways of platelet activation in vivo  
Thrombin, collagen, high shear stress activate platelets via non-cyclooxygenase pathways
- Catecholamines can overcome antiplatelet effect
- Platelet adhesion and thrombus formation not blocked
- Prothrombotic effect at higher doses  
Inhibition of vascular prostacyclin generation  
Inhibition of tPA (at doses >300 mg)

# New ACC/AHA Guidelines for Management of Unstable Angina/NSTEMI (2007)

- Early invasive strategy for high-risk patients (Class I, Level B)
- Add clopidogrel to aspirin and heparin (Class I, Level A)
- Add GP 2b/3a inhibitor (Class I, Level A) to clopidogrel (Class IIa, Level B) prior to angiography
- Add UFH or Enoxaparin (Class I, Level A) or bivalirudin or fondaparinux (Class I, Level B) to antiplatelet therapy with ASA and clopidogrel
- Statin Rx regardless of LDL-C (Class I, Level A)

*ACC/AHA Guidelines. August 14, 2007  
J Am Coll Cardiol. 2007;50:652-726*

# CURE Protocol



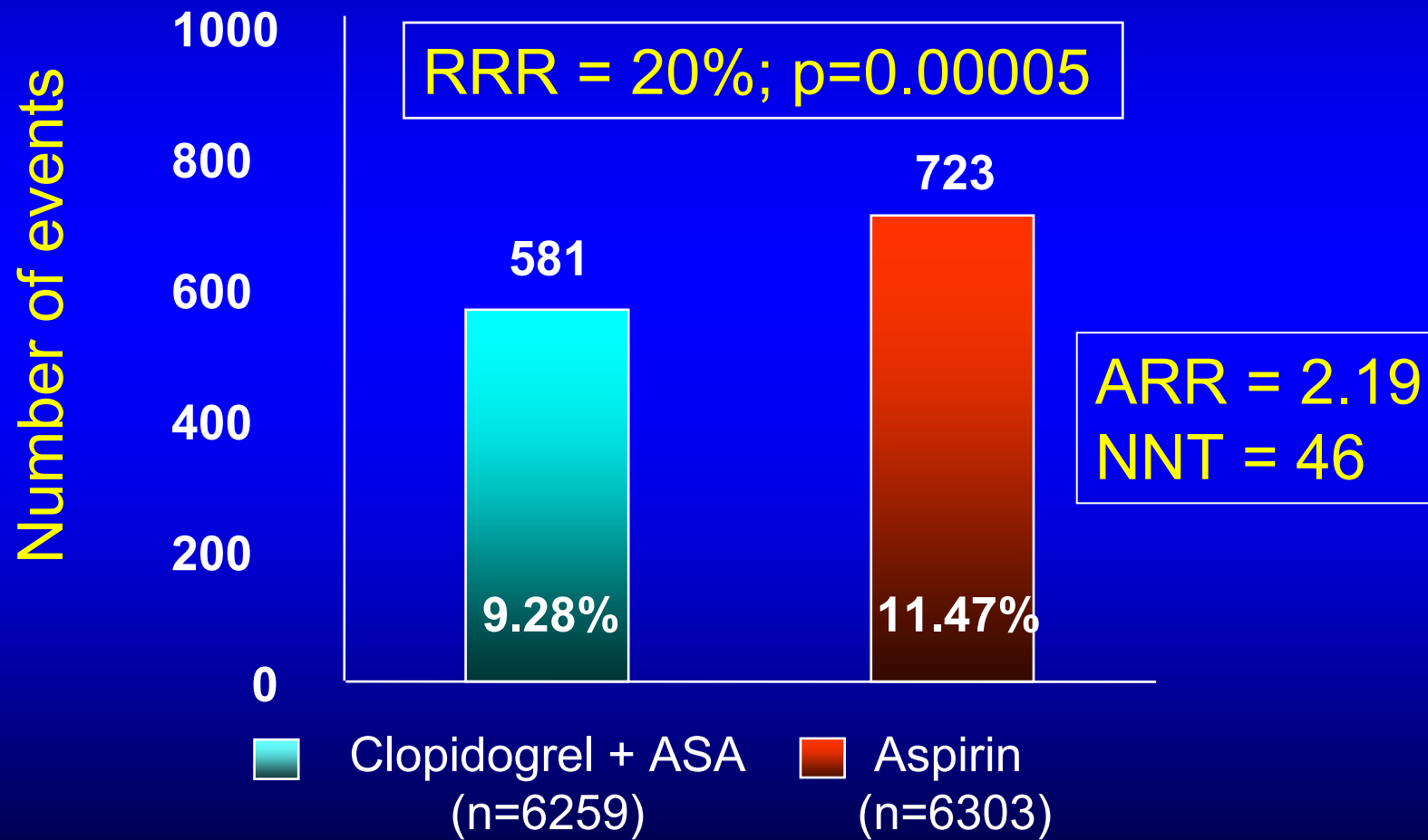
R=Randomization

The CURE Trial Investigators. *N Engl J Med.* 2001;345:494-502.

# CURE: Results

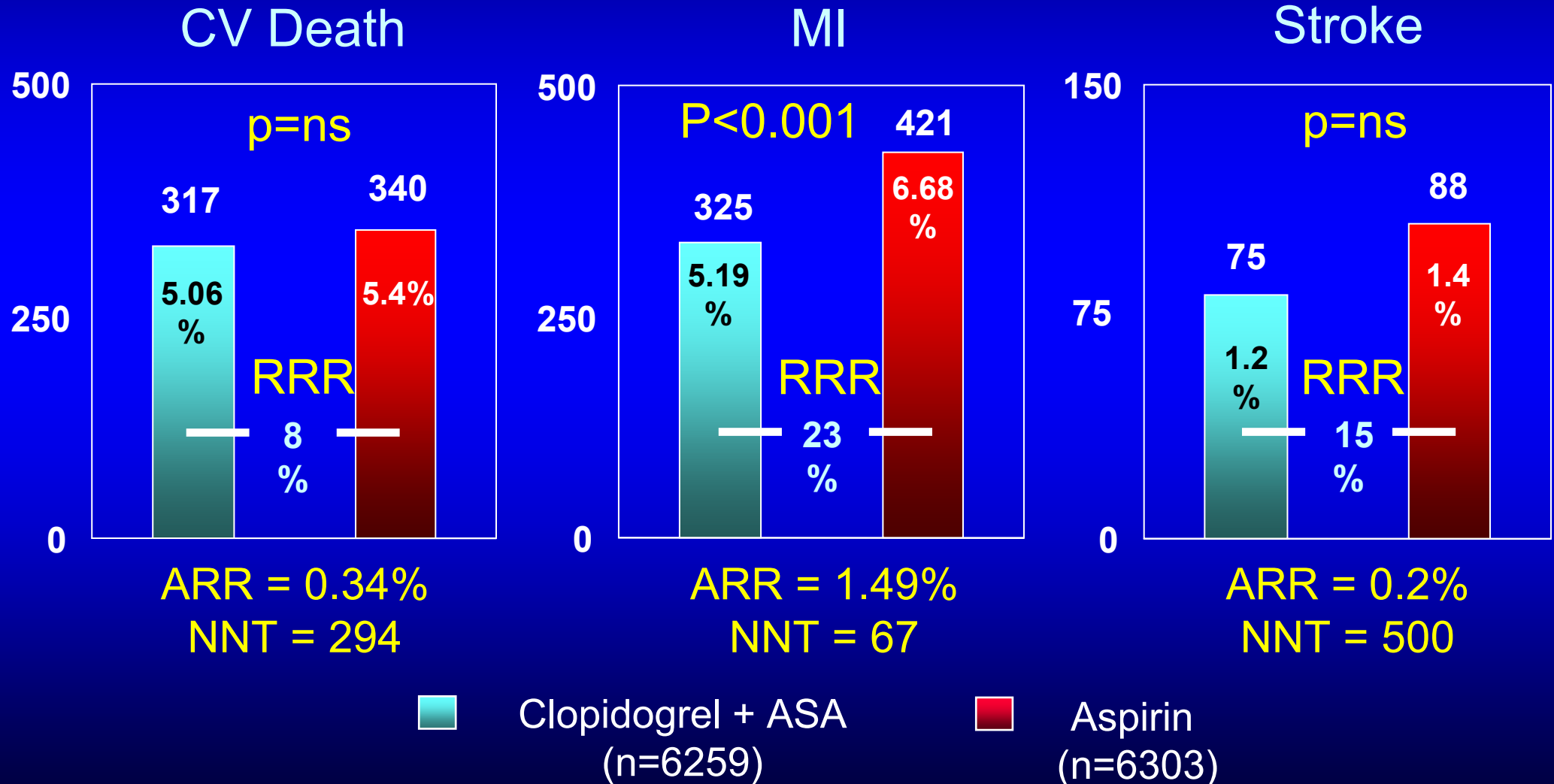
## Primary End-Point

CV Death, MI, Stroke



# CURE

## Treatment Effect by Individual Endpoint

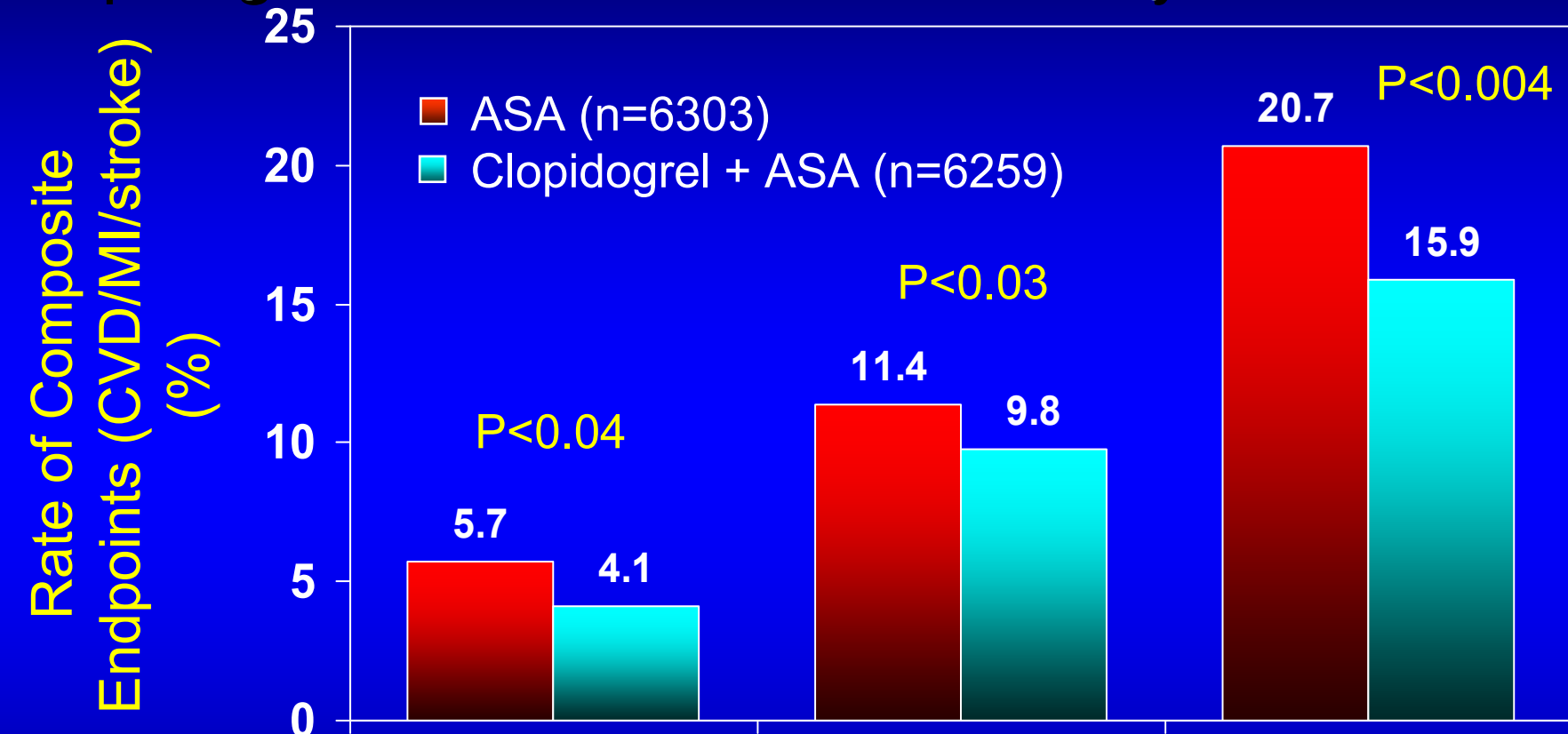


# Bleeding Complications in CURE

Endpoint	Aspirin (n=6303)	Aspirin + clopidogrel (n=6259)	Relative risk	p value
Major bleeding	2.7%	3.7%	1.34	0.003
Life-threatening bleeding	1.8%	2.2%	1.15	0.13
Minor bleeding	8.6%	15.3%	1.78	<0.001
Transfusions	2.2%	2.8%	1.28	0.03

# CURE Trial: Who Are Most Likely to Benefit?

## Clopidogrel+ASA vs ASA Stratified by TIMI-Risk Score



Risk Profile

No. of pts.

ARD

NNT

Low

26%

1.6

63

Intermediate

58%

1.6

63

High

16%

4.8

21

Budaj A et al, Circulation.2002;106:1622-1626

# Key Issues Regarding Clopidogrel Use

- How long to give it for optimum benefit?
- Is it necessary to pre-treat?
- When to stop prior to CABG?
- Should it be used with GP 2b/3a antagonists?
- What about clopidogrel resistance?

# Role of ADP Antagonists in Atherothrombosis

## Key Issues Regarding Clopidogrel Use in Clinical Practice

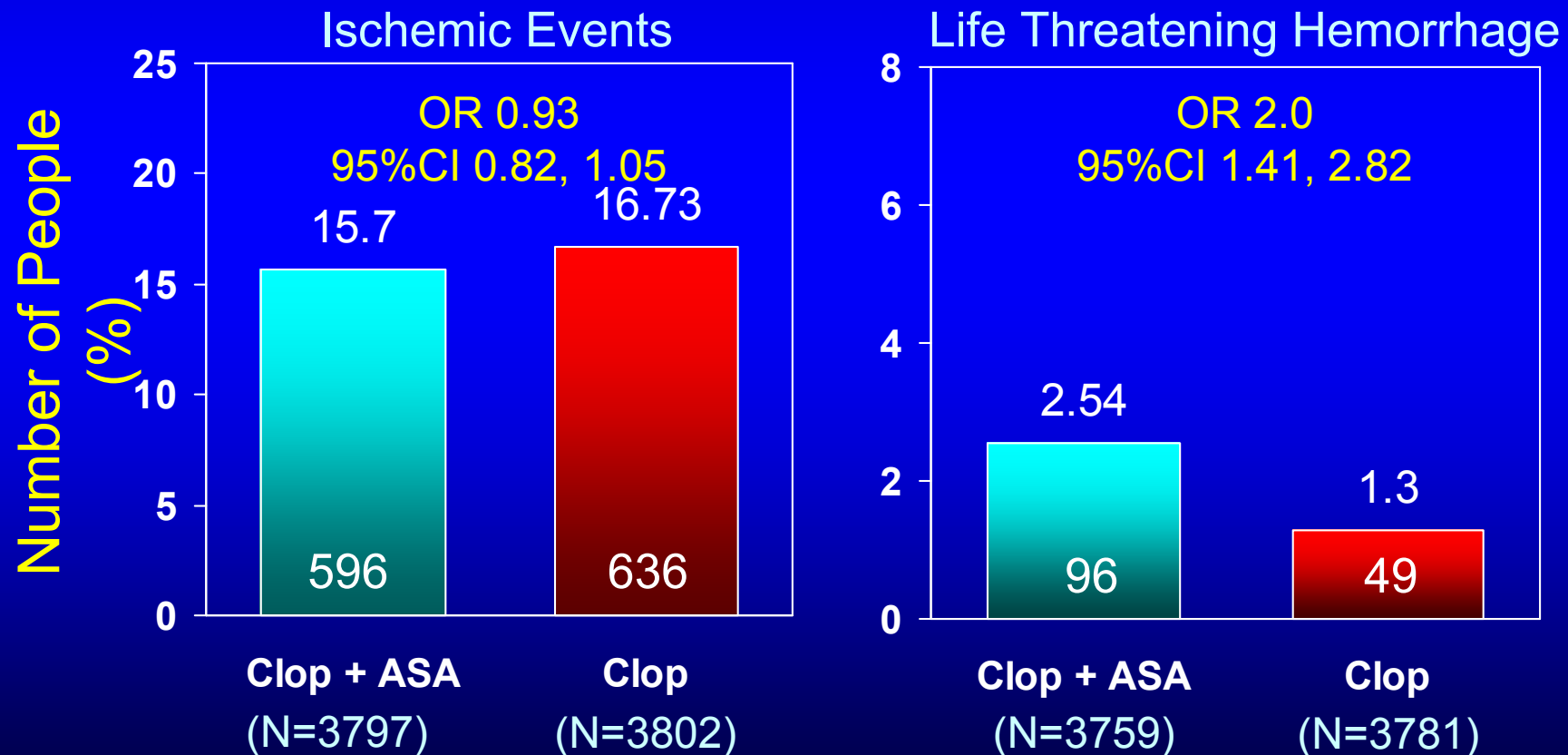
### *Duration of treatment*

- **Stable CVD:** No long-term benefit in patients with stable CVD or CV risk factors
- **UA/NSTEMI:**  $\leq 1$  month (**IA**),  $\leq 12$  months (**IB**) in high-risk pts at low-risk for bleeding
- **STEMI:** At least 1 month with fibrinolytic Rx; no direct studies with primary PCI
- **PCI:** At least 1 month (**IA**) and up to 12m (**IB**) with BMS; at least 12m (**IB**) with DES
- **Stroke:** Not recommended as first-line Rx unless a clear indication is also present

# Management of Atherothrombosis with Clopidogrel in High Risk Patients with Recent TIA or Ischemic Stroke

## MATCH Trial (N=7,599)

MI, ischemic stroke, vascular death, or rehospitalization for an acute ischemic event at 18 months



Diener HC et al, Lancet 2004;364:331-337.

# Antiplatelet Therapy Following Stenting

## AHA/ACC/SCAI/ACS/ADA Science Advisory 2007

### Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents

A Science Advisory From the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, With Representation From the American College of Physicians\*

Cindy L. Grines, MD, FACC; Robert O. Bonow, MD, FAHA, FACC;  
Donald E. Casey, Jr, MD, MPH, MBA, FACP; Timothy J. Gardner, MD, FAHA, FACC, FACS;  
Peter B. Lockhart, DDS, FDS RCSEd; David J. Moliterno, MD, FAHA, FSCAI, FACC;  
Patrick O’Gara, MD, FAHA, FACC; Patrick Whitlow, MD, FAHA, FACC

**Abstract**—Dual antiplatelet therapy with aspirin and a thienopyridine has been shown to reduce cardiac events after coronary stenting. However, many patients and healthcare providers prematurely discontinue dual antiplatelet therapy, which greatly increases the risk of stent thrombosis, myocardial infarction, and death. This advisory stresses the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent and educating the patient and healthcare providers about hazards of premature discontinuation. It also recommends postponing elective surgery for 1 year, and if surgery cannot be deferred, considering the continuation of aspirin during the perioperative period in high-risk patients with drug-eluting stents. (*J Am Coll Cardiol* 2007;49:734–9)

**Key Words:** AHA Scientific Statements ■ thrombosis ■ myocardial infarction ■ stents ■ myocardial stunning

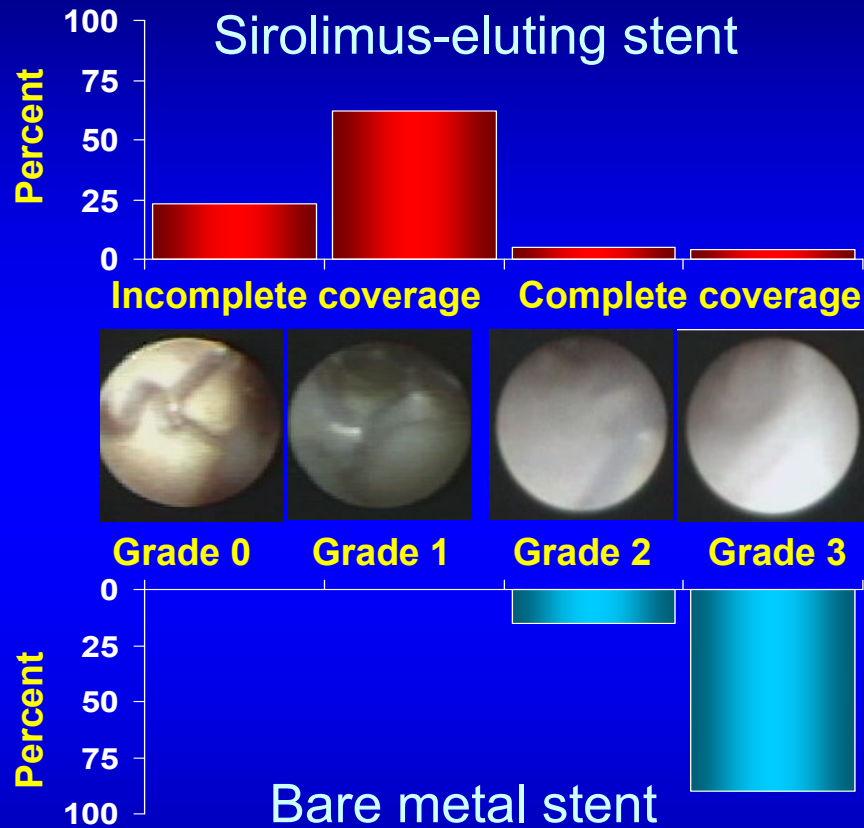
# Clinical Importance of Stent Thrombosis

## “Real-World” and RCT Experience

Study	Stent type	Confirmation of stent thrombosis	Duration	Death	Death or MI
<b>Cutlip, 2001</b> (N=6186)	<b>BMS</b>	Angiogram or clinical	6 m	21%	<b>70%</b>
<b>Heller, 2001</b> (N=1855)	<b>BMS</b>	Angiogram plus acute MI	9m	17%	<b>100%</b>
<b>Iakovou, 2005</b> (N=2229)	<b>DES</b>	Angiogram or clinical	9 m	<b>45%</b>	<b>93%</b>
<b>Ong, 2005</b> (N=2016)	<b>DES</b>	Angiogram plus clinical	1 m	<b>25%</b>	<b>100%</b>
<b>Kuchulakanti, 2006</b> (N=2974)	<b>DES</b>	Angiogram	6 m	<b>31%</b>	<b>NA</b>
<b>Mauri, 2007</b> (N=4545)	<b>DES</b>	Angiogram plus clinical	4y	<b>31%</b>	<b>100%</b>

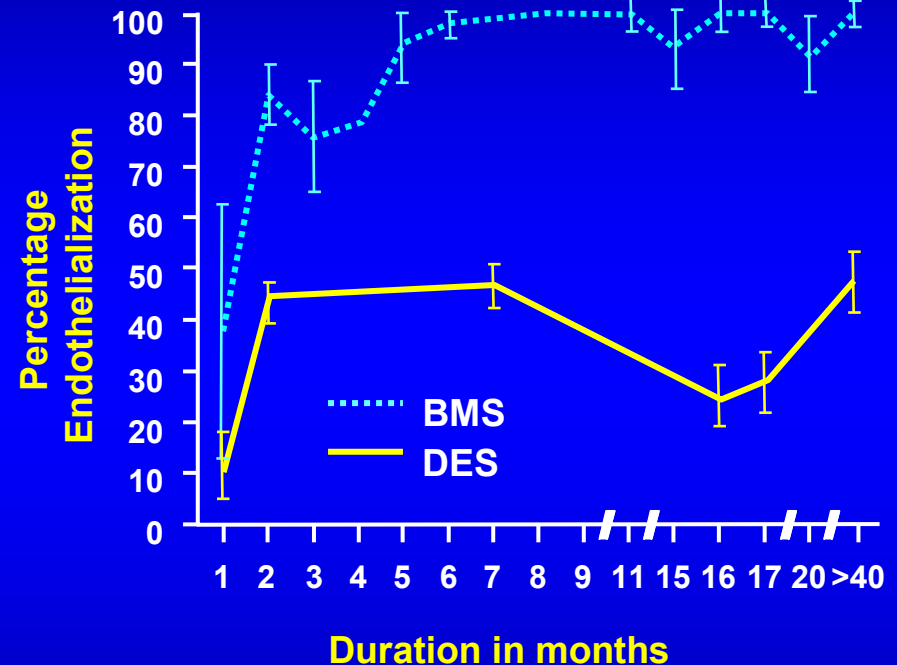
Cutlip D, et al. Circulation 2001;103:1967; Iakovou I, et al. JAMA 2005;293:2196  
 Kuchulakanti PK et al. Circulation. 2006;113:1108-1113;  
 Ong, et al. JACC 2005;45;2088-2092; Mauri L et al. NEJM 2007;356:1020-9

# Incomplete Strut Endothelialization With DES?



**Angioscopy at 8 months post SES implantation**

Kotani J et al. *JACC*. 2006;47:2108



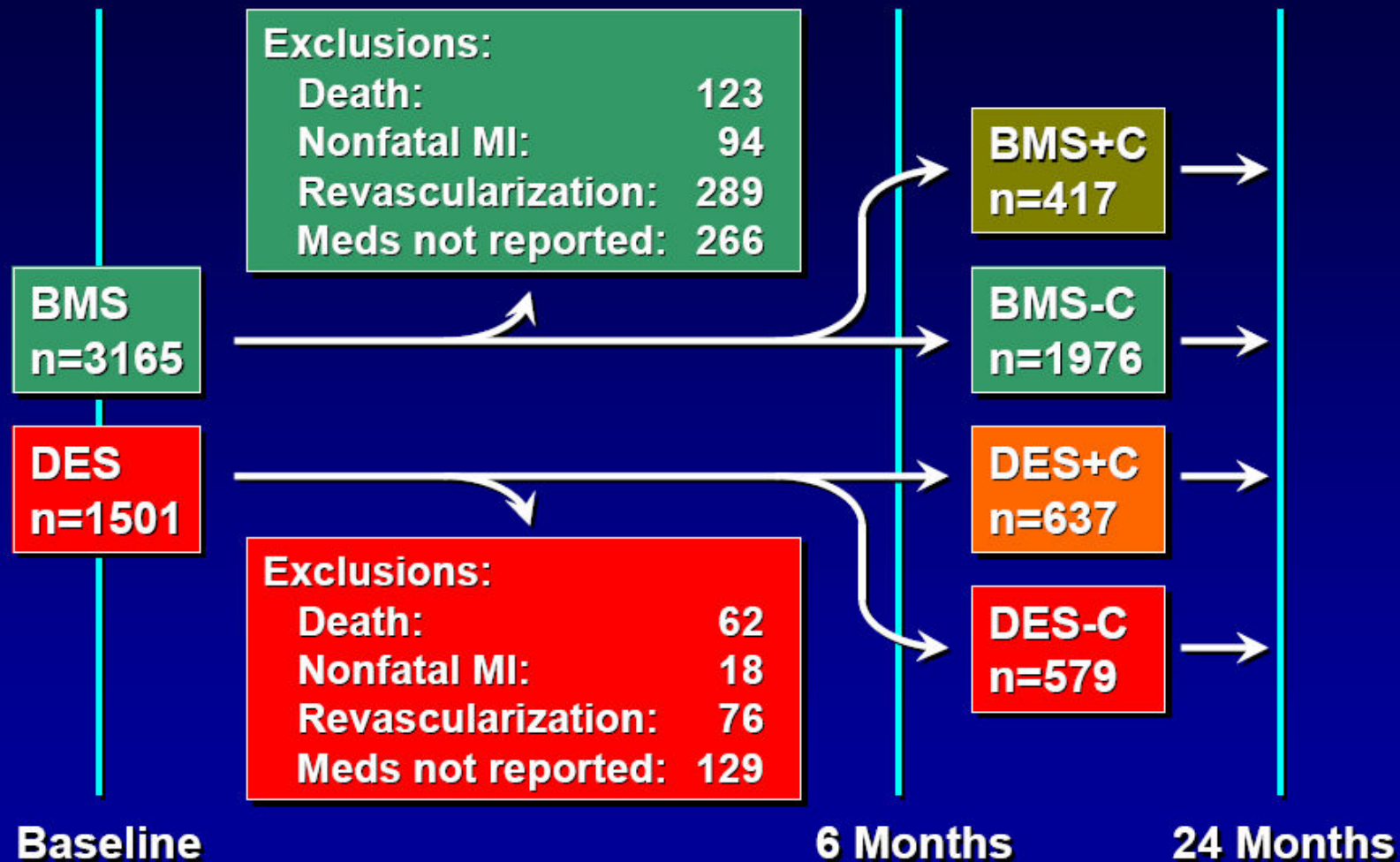
**Virmani autopsy data**

Joner M et al. *JACC*. 2006;48:193.

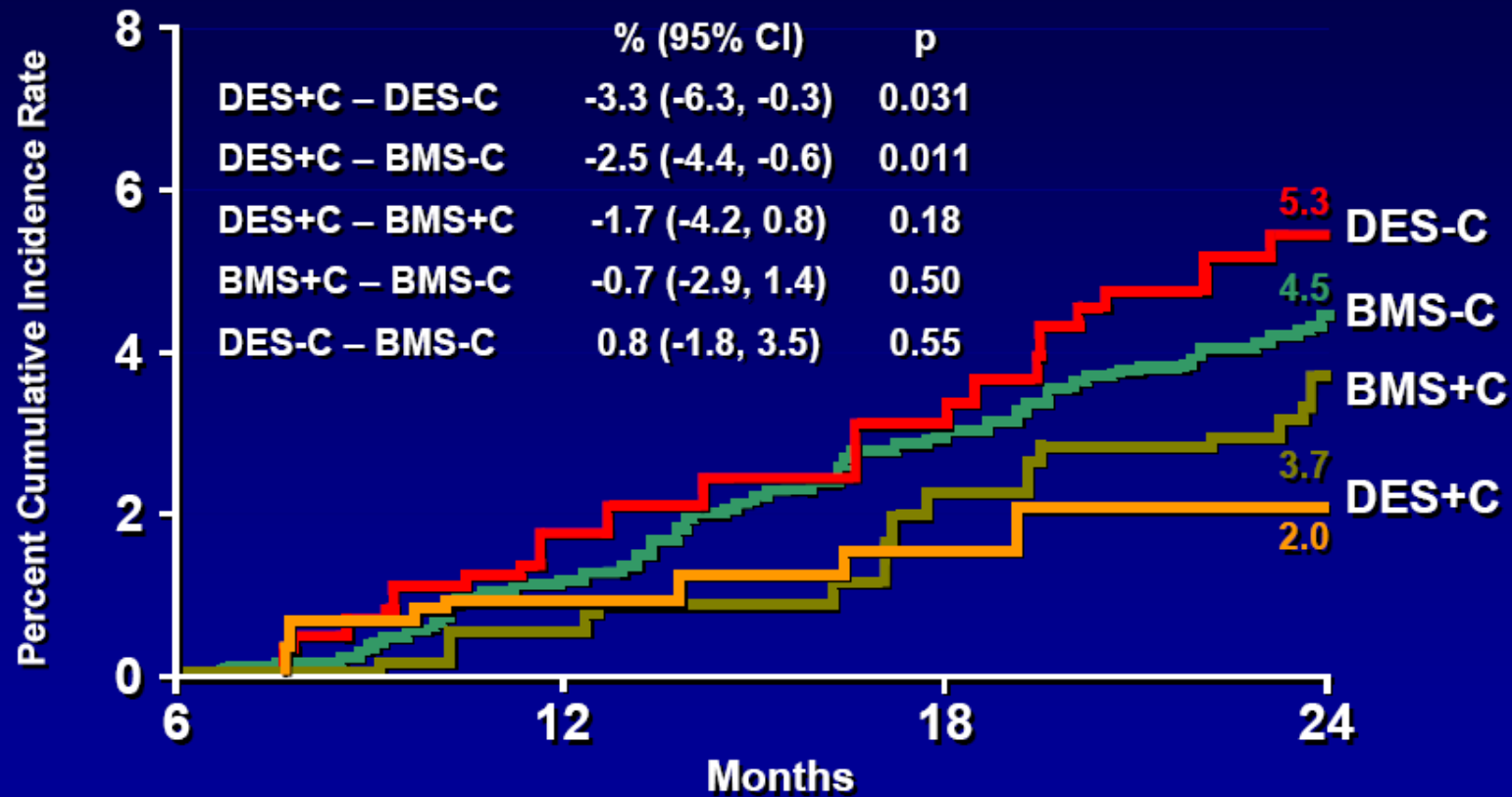


**Longer period of anti-platelet therapy is needed after DES**

## 6-Month Landmark View

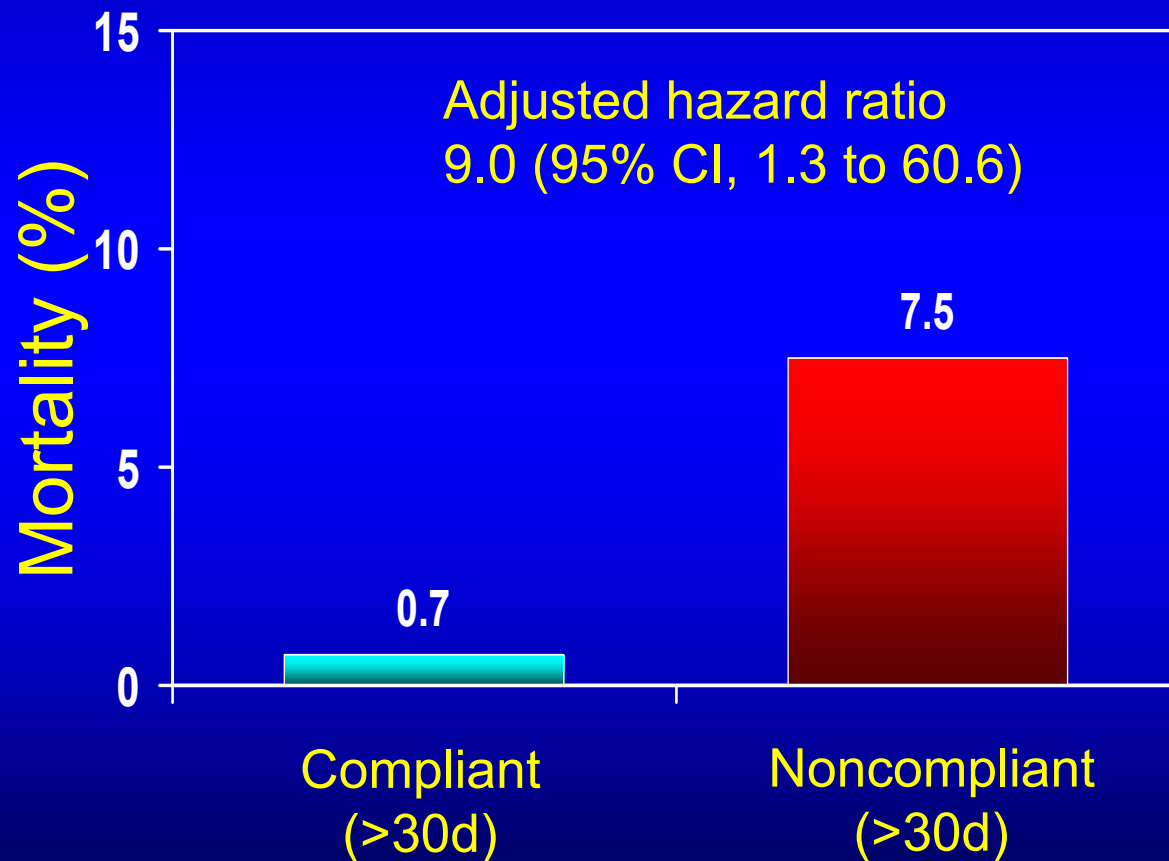


## 6-Month Landmark Analysis Adjusted Cumulative Mortality Rates



# The PREMIER Registry

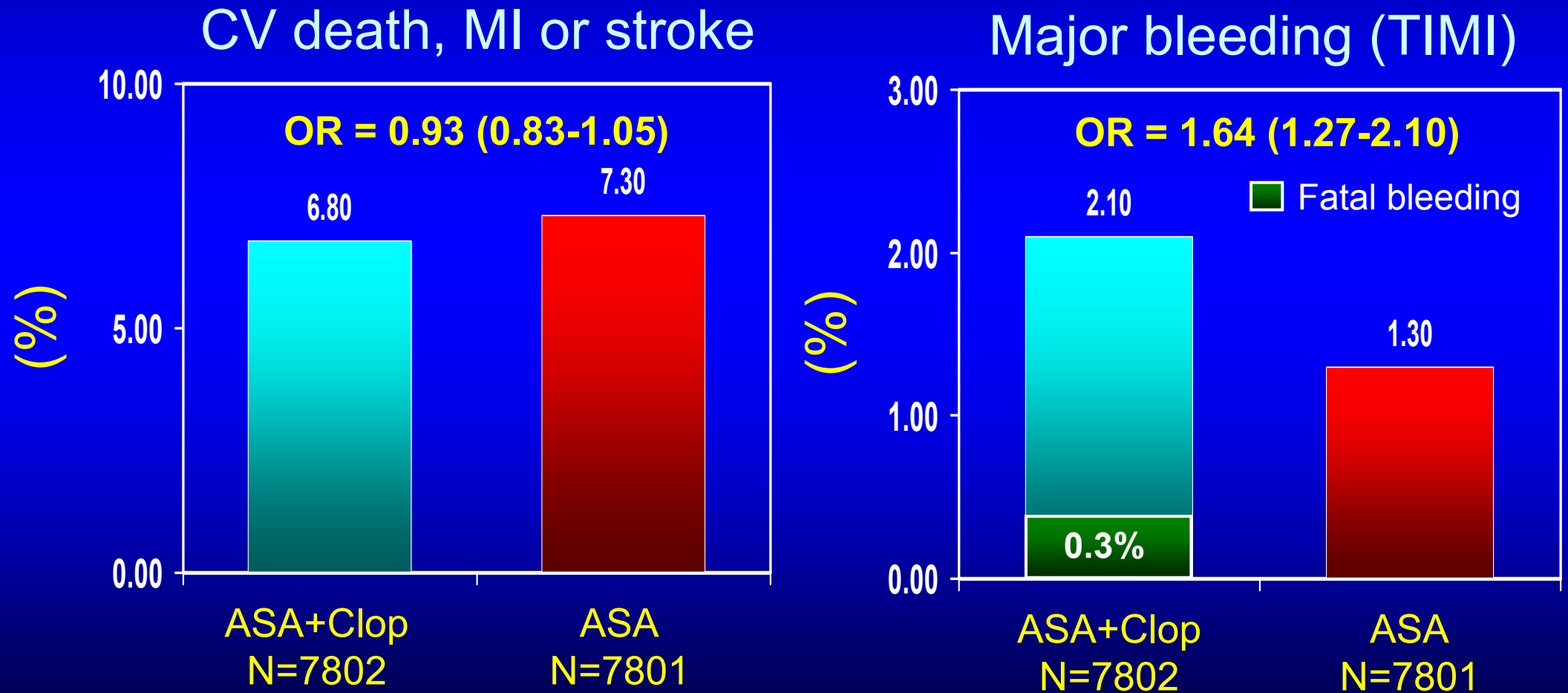
## Prevalence, Predictors, and Outcomes of Premature Discontinuation of Clopidogrel Therapy After DES



- 500 patients post MI
- 68 (13.6%) stopped Rx <30d
- Predictors of nonadherence:
  - Age
  - Socioeconomic, educational and marital status
  - Discharge instructions

# Long-Term Clopidogrel Plus Aspirin Treatment

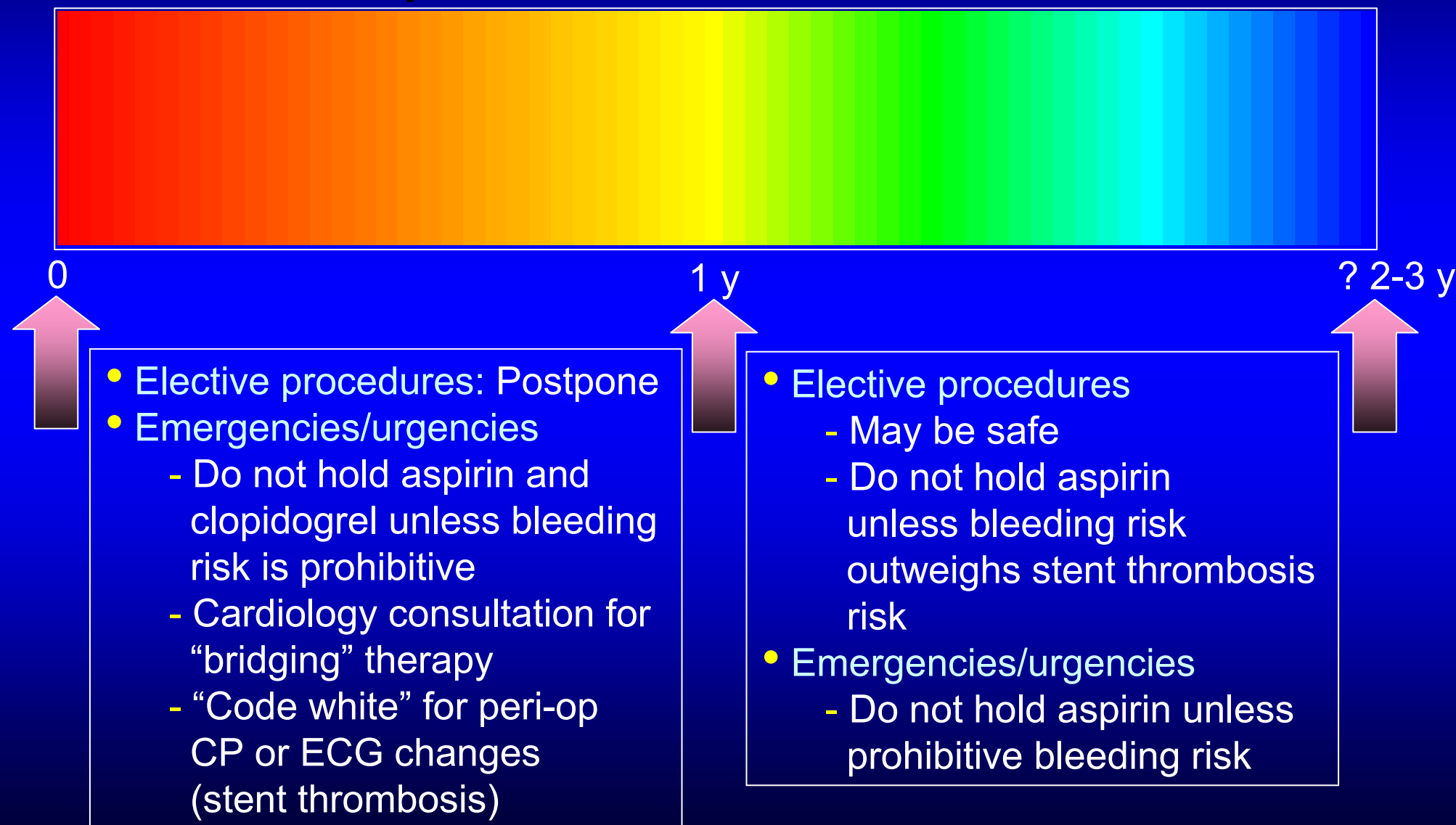
## Results of The CHARISMA Trial (28m)



Bhatt DL et al, *NEJM* 2006

# Timing of Surgery/Invasive Procedures Post-DES

## Special Considerations



# “Bridging” Therapy Post-DES (Multidisciplinary Approach)

## Do's

- Formal **pre-op** evaluation 1 wk prior
- **Communication** between surgeon, anesthesiologist & cardiologist is key
- Hold clopidogrel **5-7d** prior
- Do not hold aspirin unless prohibitive bleeding risk (increase to 325mg)
- Admit in-patient 3-4 days prior
- Initiate **IV short-acting GP 2b/3a** (**eptifibatide** or  **tirofiban**) without loading dose
- Monitor CBC daily for plt count
- Stop GP 2b/3a **10-12h prior** to procedure (5-6 half-lives)
- Check plt count &/or function 2h prior
- Restart clopidogrel (300-600 mg loading dose) >24h post-op

## Dont's

- Don't use abciximab (long half-life)
- Heparin, including LMWH, unlikely to be effective
- Antiplatelet agents such as dipyrimadole or aggrenox should be avoided
- Platelet transfusions not helpful

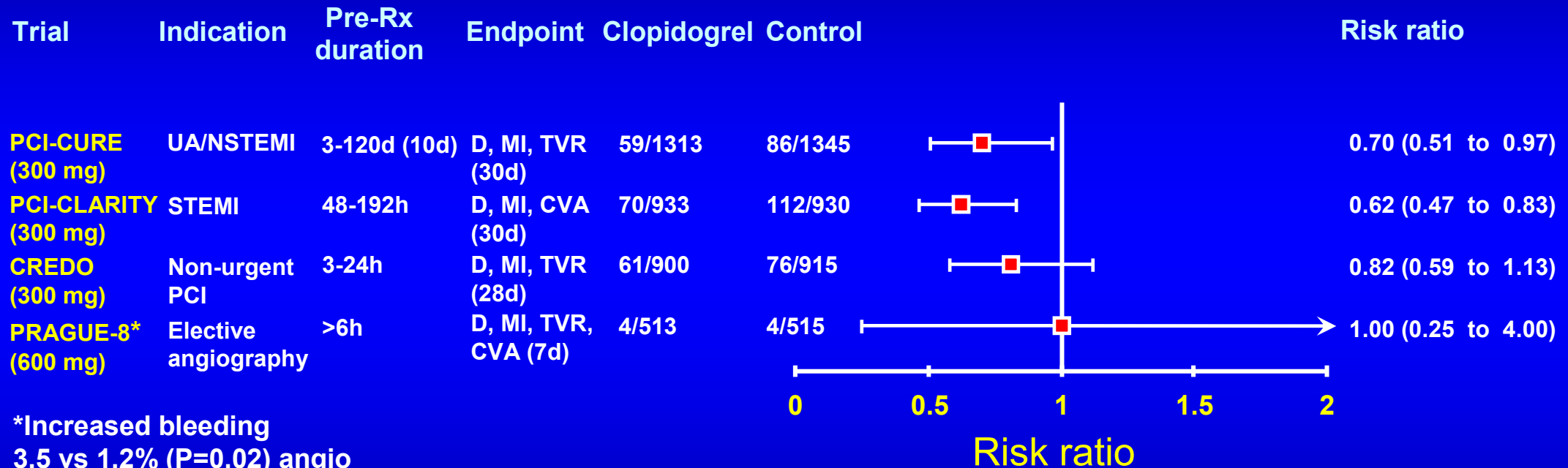
## Don't know's

- Platelet function assay
- Random donor plts (apheresis)
- Investigational ADP antagonist, IV cangrelor (phase III trials)

# Key Issues Regarding Clopidogrel Use

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- Is it necessary to pre-treat?
- When to stop prior to CABG?
- Should it be used with GP 2b/3a antagonists?
- What about clopidogrel resistance?

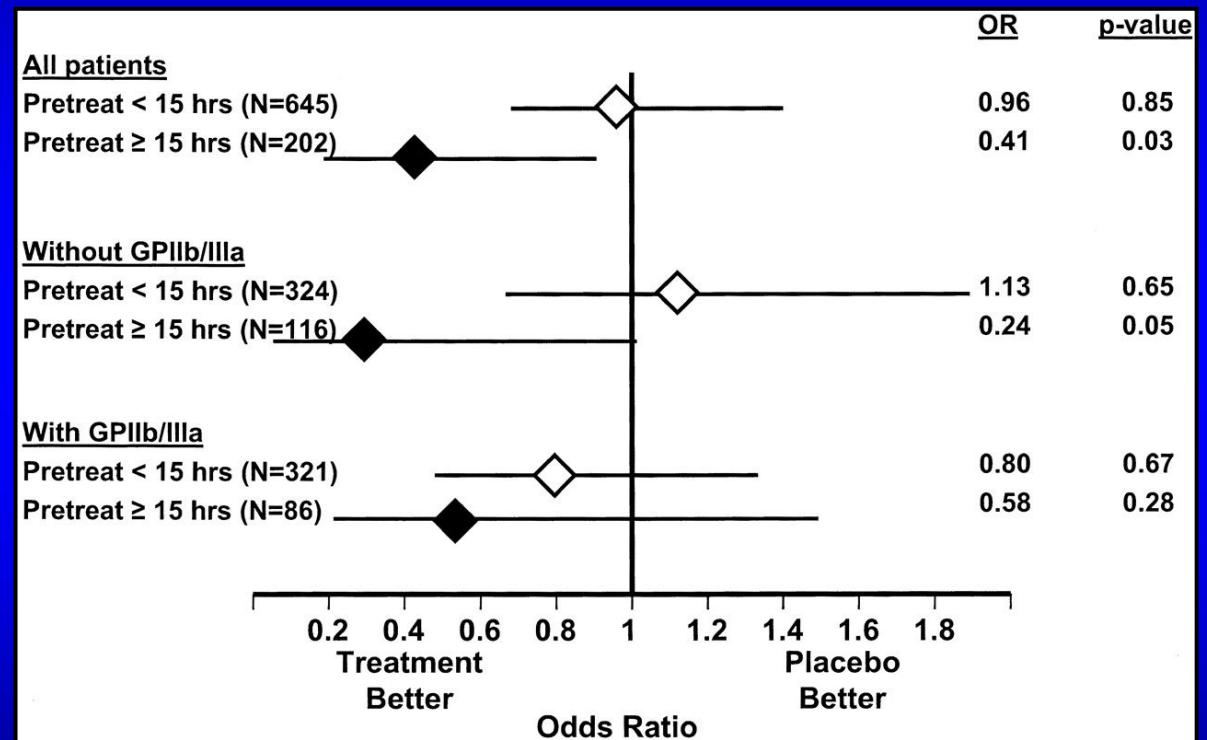
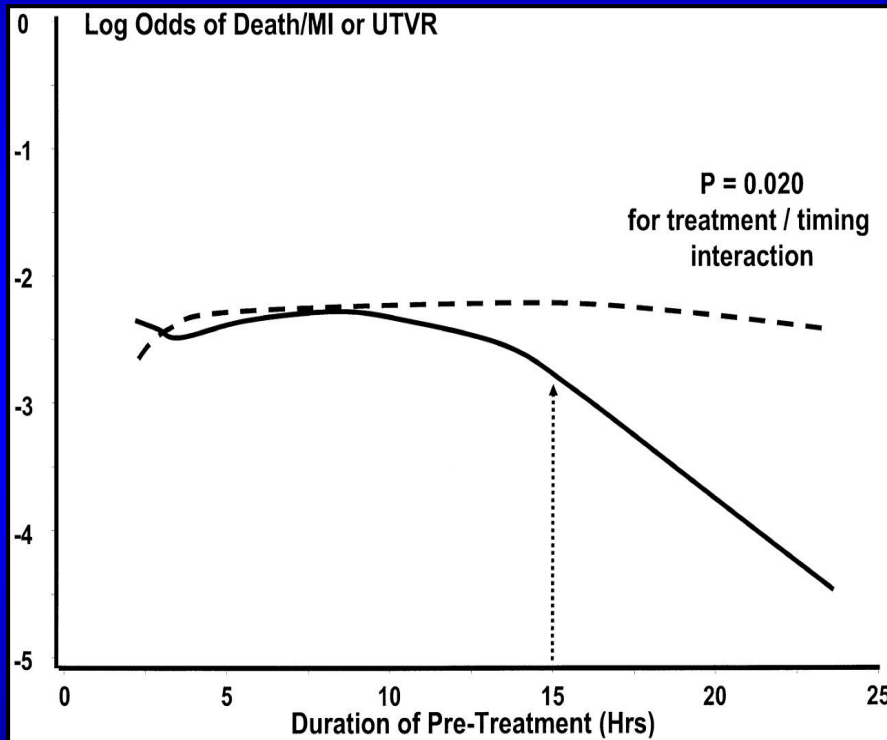
# Clopidogrel Pre-treatment Fact or Fashion



\*Increased bleeding  
3.5 vs 1.2% (P=0.02) angio  
7.2 vs 0.7% (P=0.006) PCI

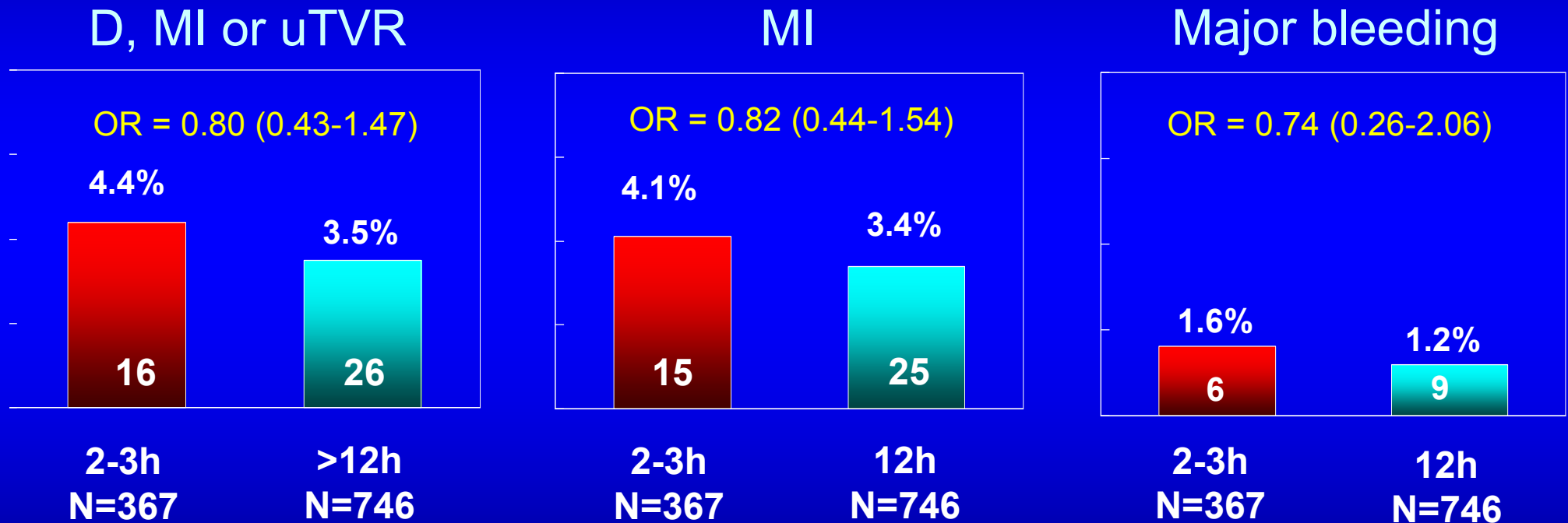
**No definite benefit with pretreatment, but a potential risk for increased bleeding associated with PCI and CABG**

# Optimal Timing of Clopidogrel Pre-Treatment (300mg): CREDO Post hoc Analysis Results at 28 days



**Pretreatment with 300mg loading for at least 15h and ideally 24h**

# Optimal Timing of Clopidogrel Pre-Treatment (600mg): ISAR-REACT Post hoc Analysis Results at 30 days



**No time-dependence with 600mg loading dose ± GP2b/3a**

# Role of ADP Antagonists in Atherothrombosis

## Key Issues Regarding Clopidogrel Use in Clinical Practice

### *Pre-treatment ?*

- Favorable data in retrospective analysis (EPISTENT, ESPRIT, TARGET)
- Pretreatment hypothesis not validated in the only prospective assessment (CREDO)
- Guideline recommendations:
  - ESC: 600 mg loading 2-6h pre-PCI (IC)
  - ACC/AHA: 300 mg loading dose 6h pre-PCI without (IA) or with (IIa, B) GP IIb/IIIa in ACS
  - ACCP: 300 mg loading dose 6h pre-PCI without (IA)
- Prudent to rule out surgical CAD before pretreatment to avoid bleeding risk
- A properly designed clinical trial is warranted to provide unequivocal support

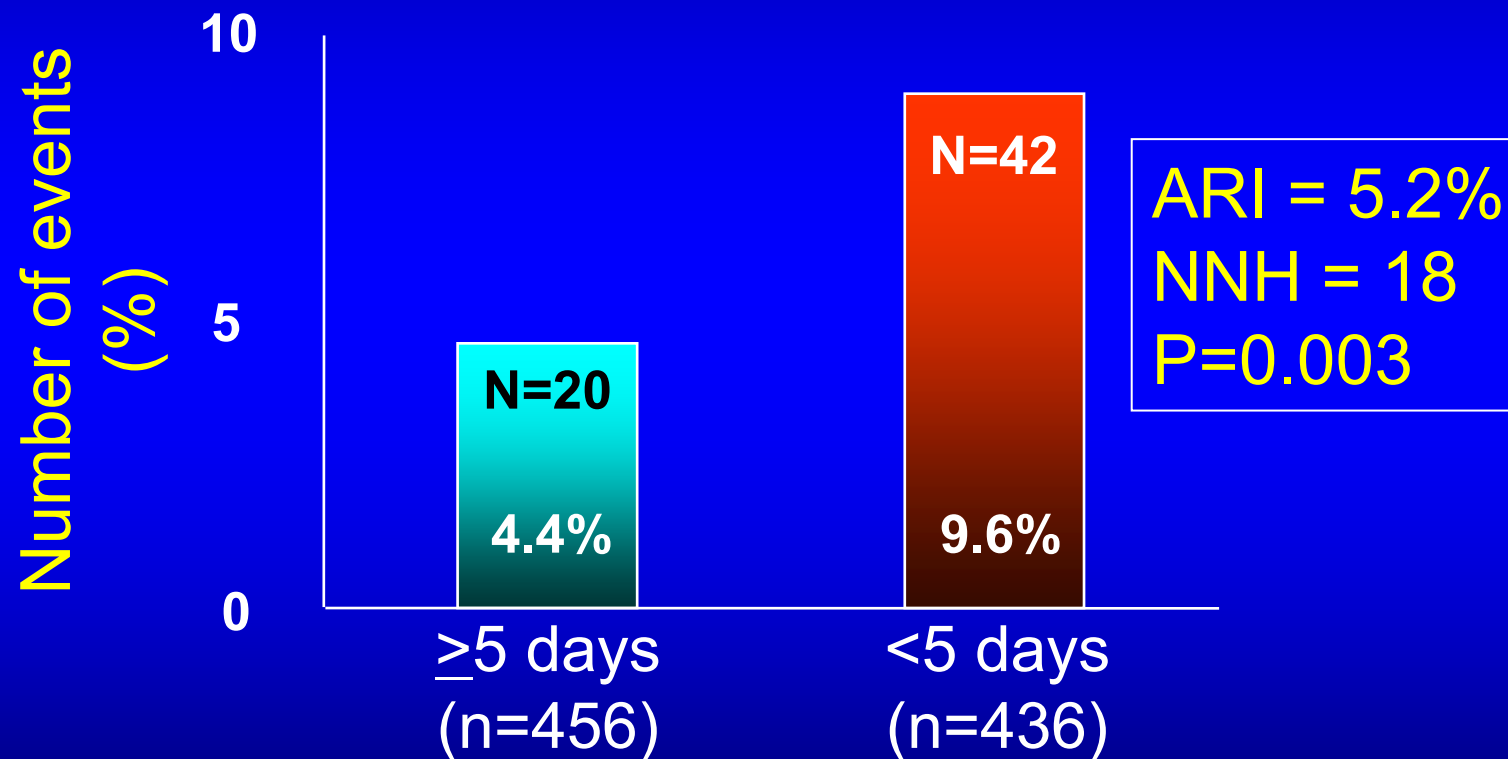
# Key Issues Regarding Clopidogrel Use

- How long to give it for optimum benefit?
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- When to stop prior to CABG?
- Should it be used with GP 2b/3a antagonists?
- What about clopidogrel resistance?

# Key Issues Regarding Clopidogrel Use in ACS

When Should Clopidogrel be Stopped Prior to CABG?

## Major Bleeding



**At least 5 days and preferably 7 days (I, B)**

# Key Issues Regarding Clopidogrel Use

- How long to give it for optimum benefit?
- Is it necessary to pre-treat?
- When to stop prior to CABG?
- Should it be used with GP 2b/3a antagonists?
- What about clopidogrel resistance?

# ISAR-REACT 2 Trial: Study Design

2022 patients with an episode of angina within the preceding 48 hours and an elevated troponin T level or new ST-segment depression of  $\geq 0.1$  mV or transient ( $< 20$  minutes) ST-segment elevation of  $\geq 0.1$  mV or new or presumed new bundle-branch block; significant angiographic lesions in a native coronary vessel or venous bypass graft amenable to and requiring a PCI  
**Placebo Controlled. Randomized. Blinded.**  
24% female, mean age 66 years, mean follow-up 30 days

Pre-treatment with high dose (600mg) clopidogrel at least 2 hours pre-procedure

**Abciximab**

(usual bolus or infusion dose)

n=1012

**Placebo**

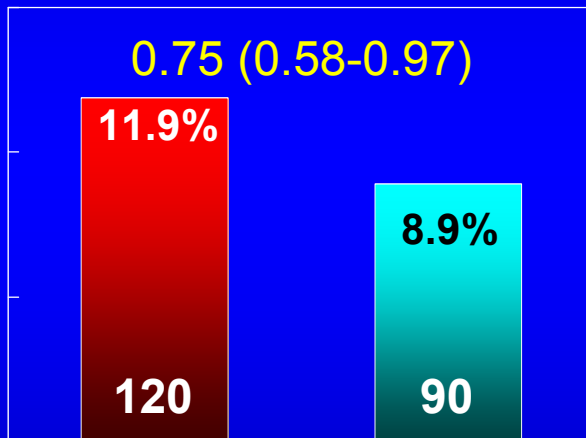
n=1010

- **Primary Endpoint:** Composite of death, MI, and urgent target vessel revascularization (TVR) due to myocardial ischemia within 30 days
- **Secondary Endpoint:** In-hospital major and minor bleeding

# ISAR-REACT 2

## Results at 30 days

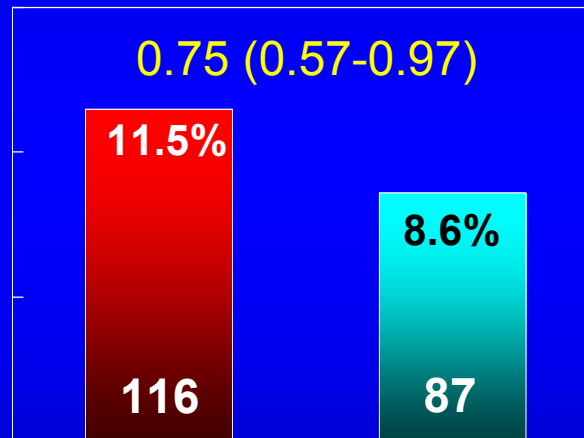
### D, MI or uTVR



Placebo  
N=1,010

Abciximab  
N=1,012

### Death or MI



Placebo  
N=1,010

Abciximab  
N=1,012

### Major bleeding

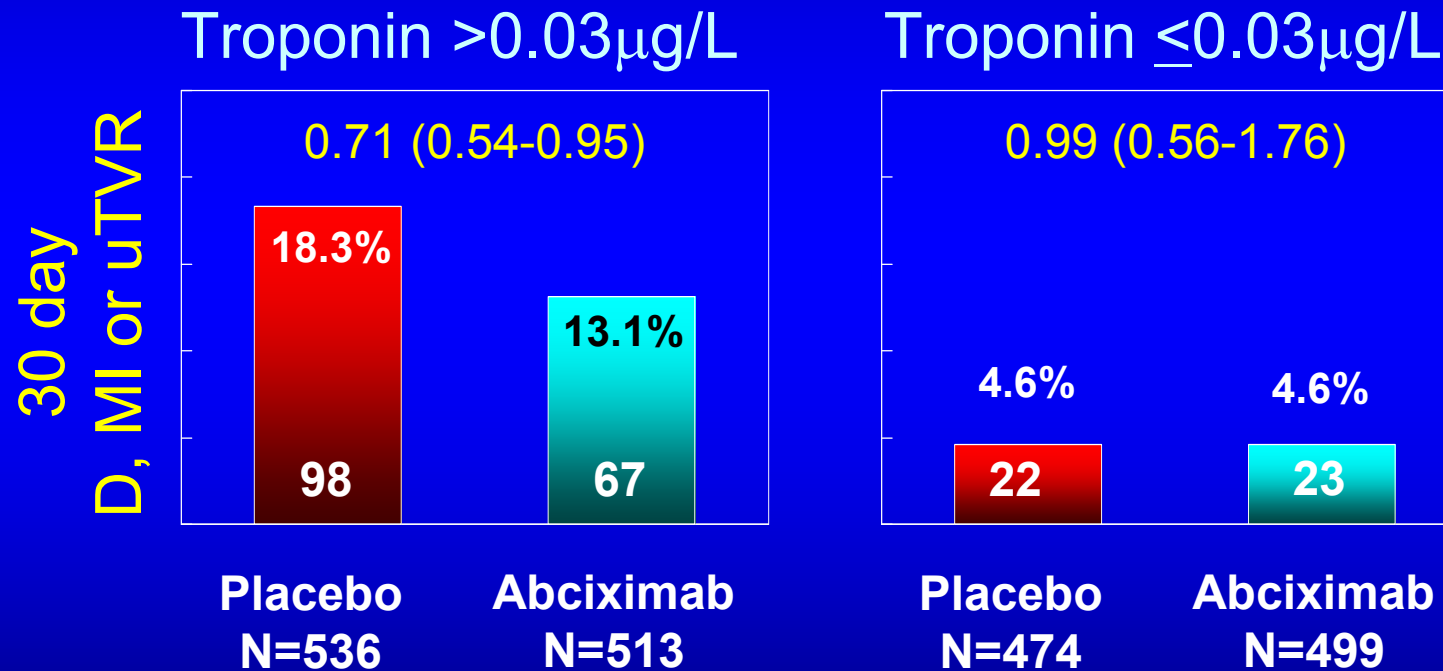


Placebo  
N=1,010

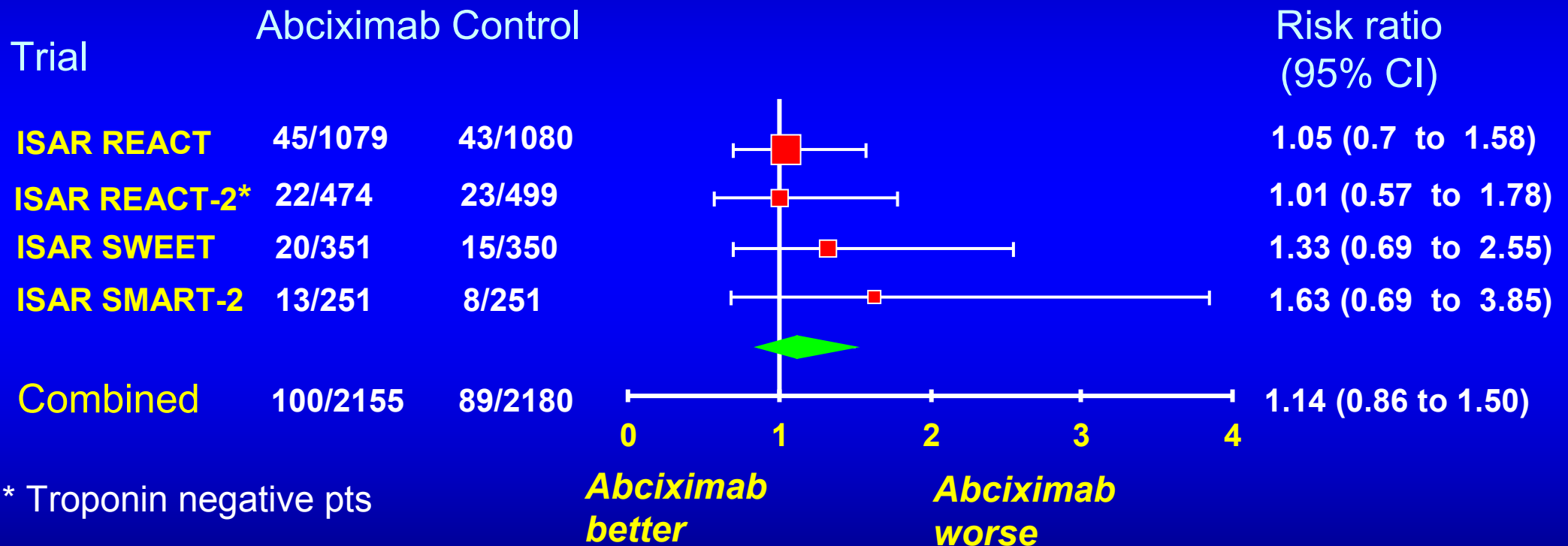
Abciximab  
N=1,012

# ISAR-REACT 2

## Results Stratified by Baseline Troponin



# Impact of Triple Antiplatelet Rx in Non-urgent PCI (ASA, Clopidogrel, Abciximab) Death, MI or Urgent TVR at 30 days

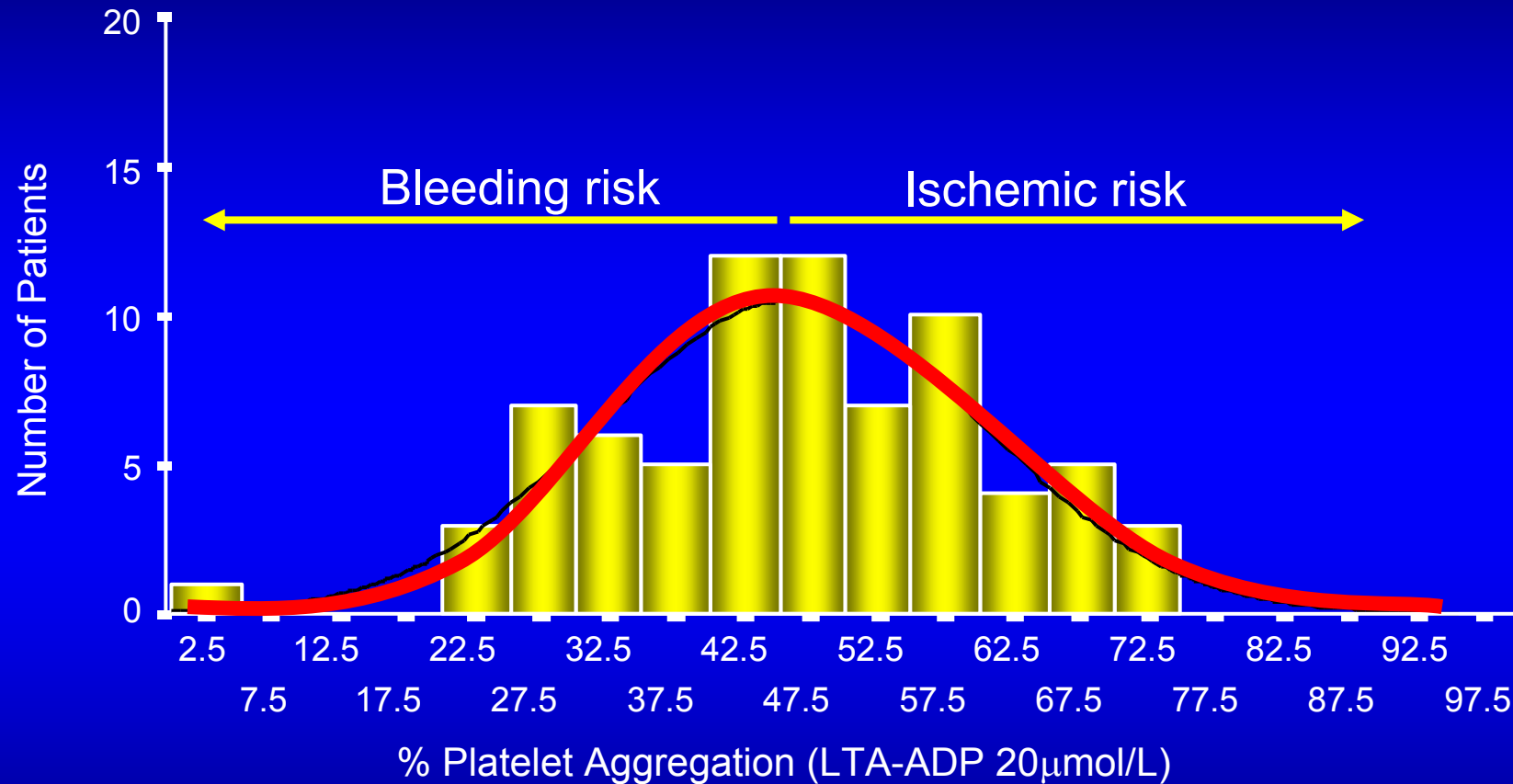


Adjunctive therapy with GP 2b/3a not effective and safe in stable pts

# Key Issues Regarding Clopidogrel Use

- How long to give it for optimum benefit?
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- When to stop prior to CABG?
- Should it be used with GP 2b/3a antagonists?
- What about clopidogrel resistance?

# Individual Response Variability to Dual Antiplatelet Rx in the Steady State Phase



~ 5-30% incidence of 'hyporesponsiveness' to clopidogrel

## Genetic Factors

- Polymorphisms of CYP
- Polymorphisms of GPIa
- Polymorphisms of P2Y<sub>12</sub>
- Polymorphisms of GPIIb/IIIa

# Clopidogrel Response Variability

## Clinical Factors

- Failure to prescribe/poor compliance
- Under-dosing
- Poor absorption
- Drug-drug interactions involving CYP3A4
- Acute coronary syndrome
- Diabetes mellitus/insulin resistance
- Elevated body mass index

## Cellular Factors

- Accelerated platelet turnover
- Reduced CYP3A metabolic activity
- Increased ADP exposure
- Up-regulation of the P2Y<sub>12</sub> pathway
- Up-regulation of the P2Y<sub>1</sub> pathway
- Up-regulation of P2Y-independent pathways  
(collagen, epinephrine, TXA<sub>2</sub>, thrombin)

# Clinical Relevance of Clopidogrel Non-responsiveness

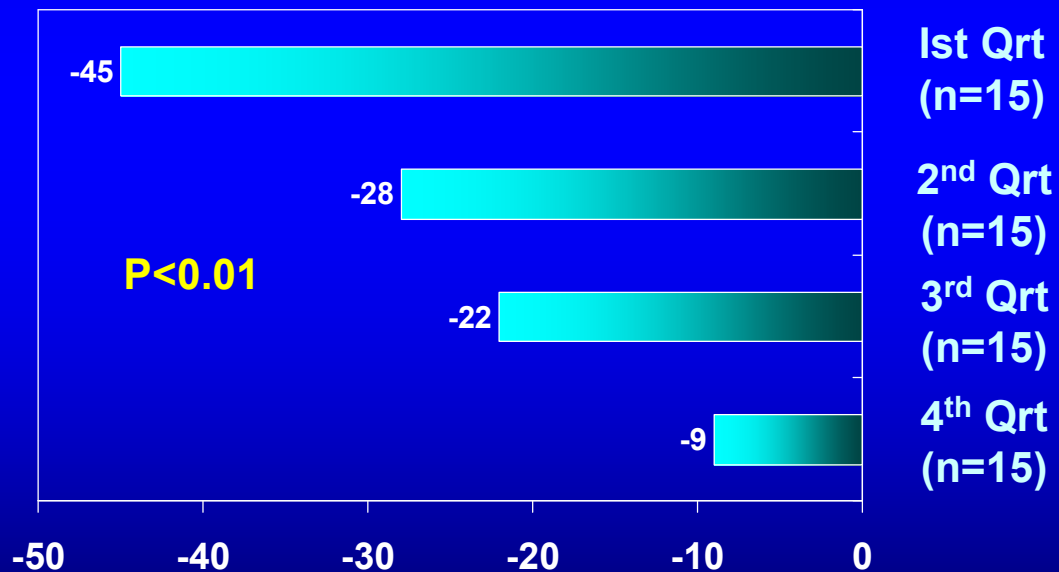
## Post-Stent Ischemic Events and Periprocedural Infarction

	N	Functional Parameter	Clinical Relevance
Matezky et al. Circulation 2004	60	↑ platelet aggregation (4 <sup>th</sup> quartile)	Post-primary PCI ischemic events (6 months)
Gurbel et al. JACC 2005	192	↑ periprocedural platelet aggregation	Post-PCI ischemic events (6 months)
Gurbel et al. Circulation 2005	120	↑ periprocedural platelet aggregation	Myonecrosis and inflammation marker release
Cuisset et al. J Thromb Haemost 2006	106	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Lev et al. JACC 2006	120	↑ clopidogrel/aspirin-resistant patients	Post PCI-myonecrosis
Cuisset et al. JACC 2006	292	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Hocholzer et al. JACC 2006	802	↑ platelet aggregation (3 <sup>rd</sup> & 4 <sup>th</sup> quartiles)	Post-PCI ischemic events (30 days)
Geisler et al. Eur Heart J 2006	379	↓ platelet inhibition	Post-PCI ischemic events (3 months)
Bliden et al. JACC 2007	100	↑ platelet aggregation	Post-PCI ischemic events (12 months)

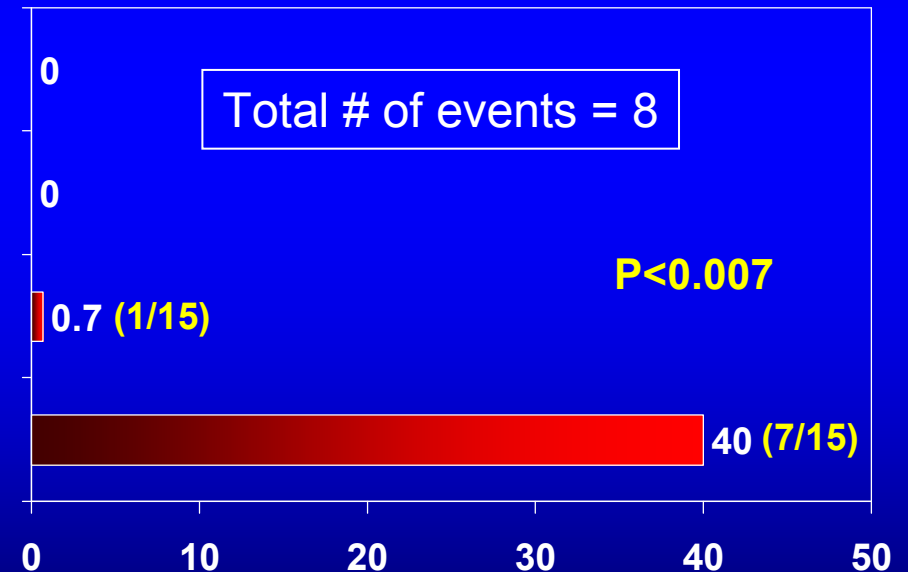
# Clopidogrel Resistance

- 60 patients with STEMI undergoing primary PCI <6h
- Aspirin, heparin, eptifibatide during PCI
- Clopidogrel 300 mg load post-PCI, 75 mg daily x3 months

### Inhibition of ADP-induced Aggregation @ 6 days (%)



### Recurrent CVS Events @ 6 months (%)



# Role of ADP Antagonists in Atherothrombosis

## Key Issues Regarding Clopidogrel Use in Clinical Practice

### *Clopidogrel resistance*

- Unclear entity with unclear definition (variable “responsiveness” or true “resistance”)
- Unclear diagnosis (? optimum test)
- Unclear mechanism
- Unclear clinical relevance (? prediction of clinical outcomes; ? titration of drug Rx)
- Not recommended by ISTH, ACCP, ESC
- A thorough assessment of the phenomenon is indicated

# Novel P2Y12 ADP Receptor Antagonist

Drug	Type	Route	Action	Dose	Mean Platelet Inhibition (Time Required)	Trials (Phase III)
<b>Prasugrel (CS-747)</b>	Thienopyridine (3 <sup>rd</sup> gen) – requires hepatic conversion to active metabolite	Oral	Irreversible binding	60 mg loading dose, 10 mg maintenance dose	≈ 70% (<1 hour)	<b>TRITON</b>
<b>AZD6140</b>	Cyclopetyl-triazolopyrimidine – Direct inhibition	Oral	Competitive binding	90 mg bid	≈ 95% (2-4 hours)	<b>PLATO</b>
<b>Cangrelor (ARC-669931MX)</b>	ATP analogue – Direct inhibition	Parenteral	Competitive binding	4 µg/kg/min	≈ 95% (few minutes)	<b>CHAMPION</b>

***More potent and less variability!!***

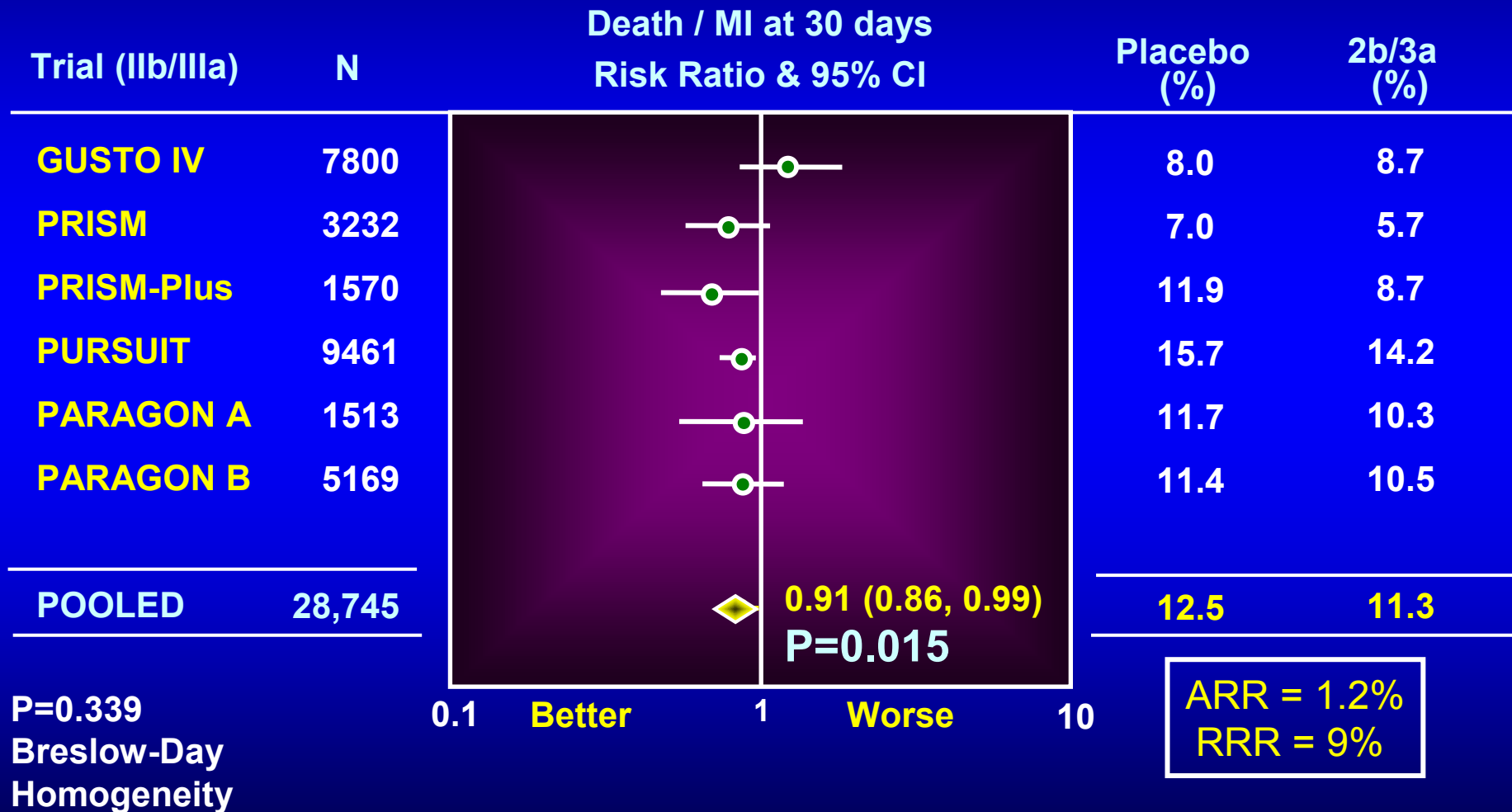
# New ACC/AHA Guidelines for Management of Unstable Angina/NSTEMI

- Early invasive strategy for high-risk patients (Class I, Level B)
- Add clopidogrel to aspirin and heparin (Class I, Level A)
- Add GP 2b/3a inhibitor (Class I, Level A) to clopidogrel (Class IIa, Level B) prior to angiography
- Add UFH or Enoxaparin (Class I, Level A) or bivalirudin or fondaparinux (Class I, Level B) to antiplatelet therapy with ASA and clopidogrel
- Statin Rx regardless of LDL-C (Class I, Level A)

*ACC/AHA Guidelines. August 14, 2007  
J Am Coll Cardiol. 2007;50:652-726*

# Clinical Importance vs Statistical Significance

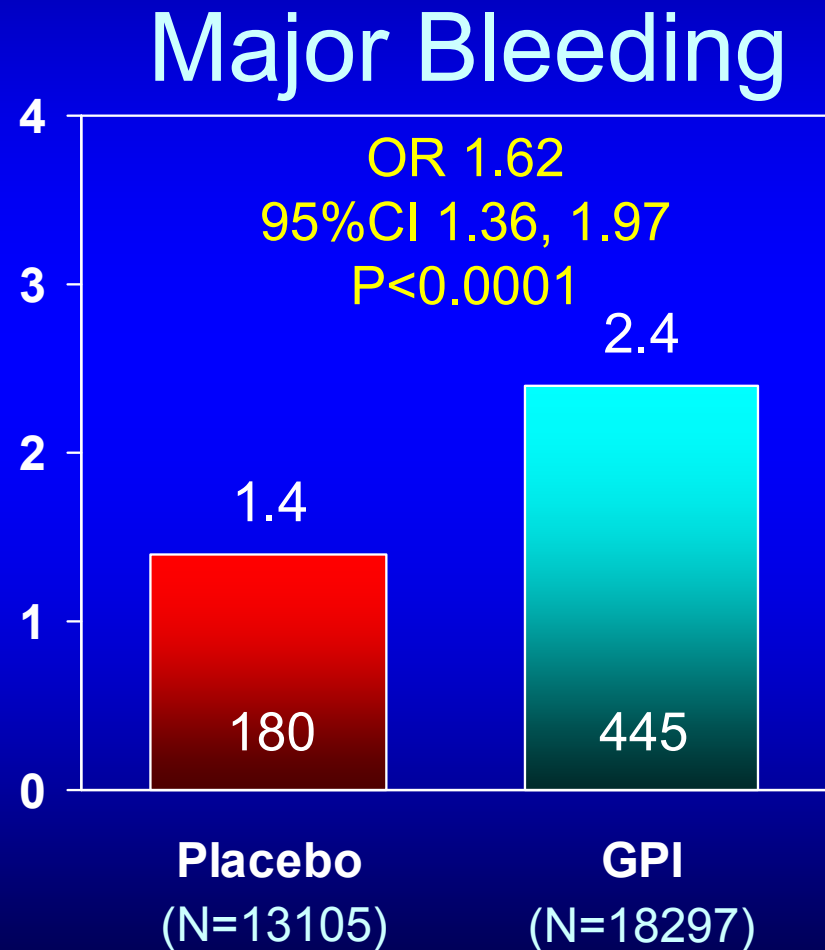
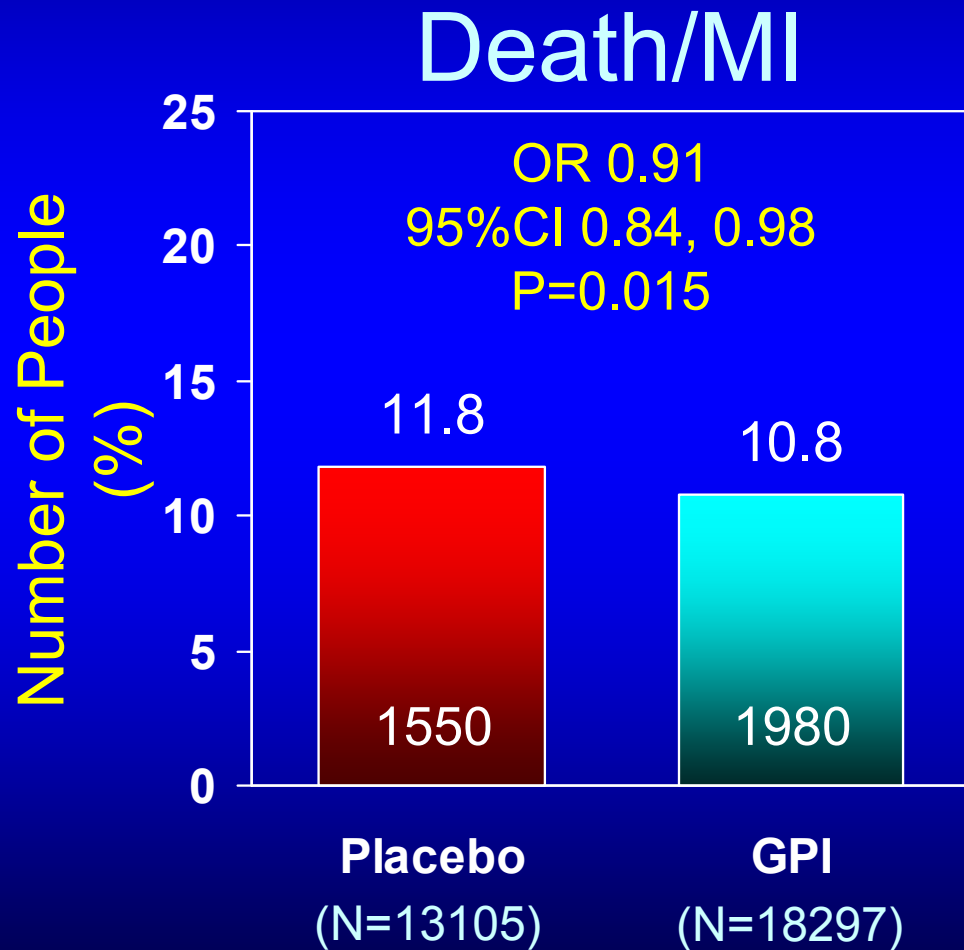
## Impact of GP IIb/IIIa Inhibitor on Death or MI



Boersma et al, Lancet 2002;359:189-1198.

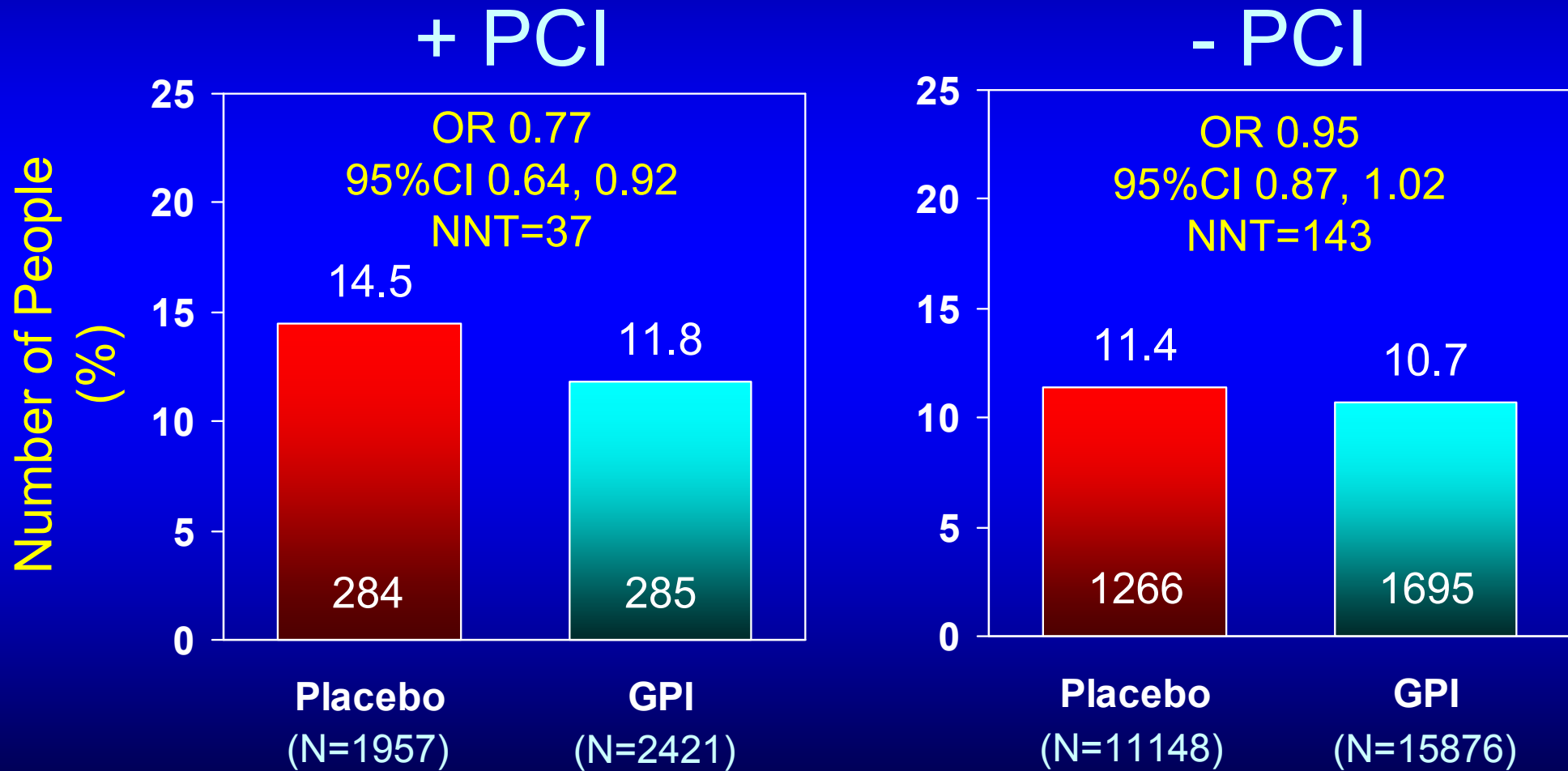
# GP 2b/3a Inhibitors in ACS (N=31,402)

## 30-Day Death/MI and Bleeding Complications



# GP 2b/3a Inhibitors in ACS (N=32,402)

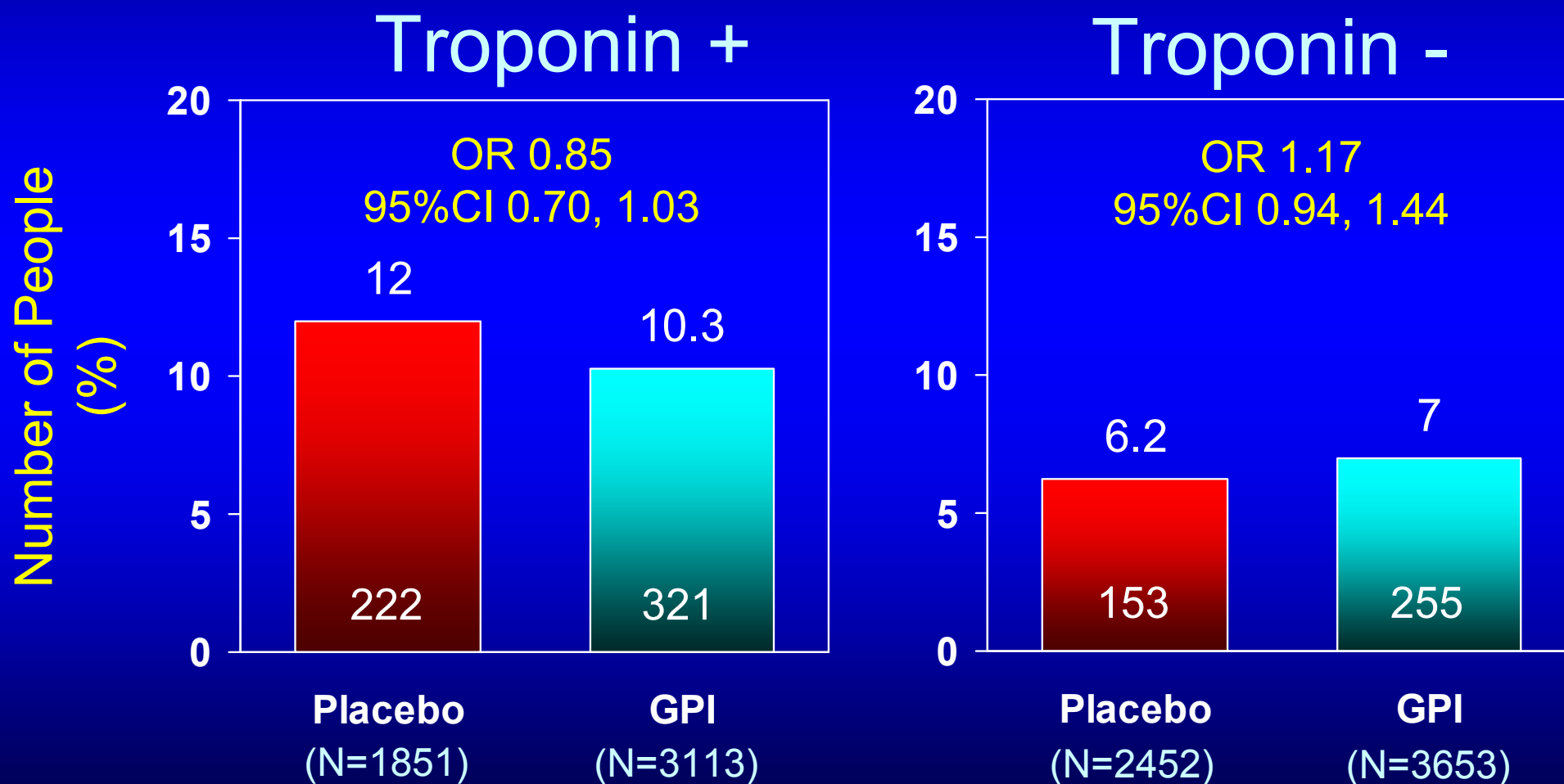
## 30-Day Death/MI According to PCI Within 5d (14%)



Boersma et al, Lancet 2002;359:189-1198.

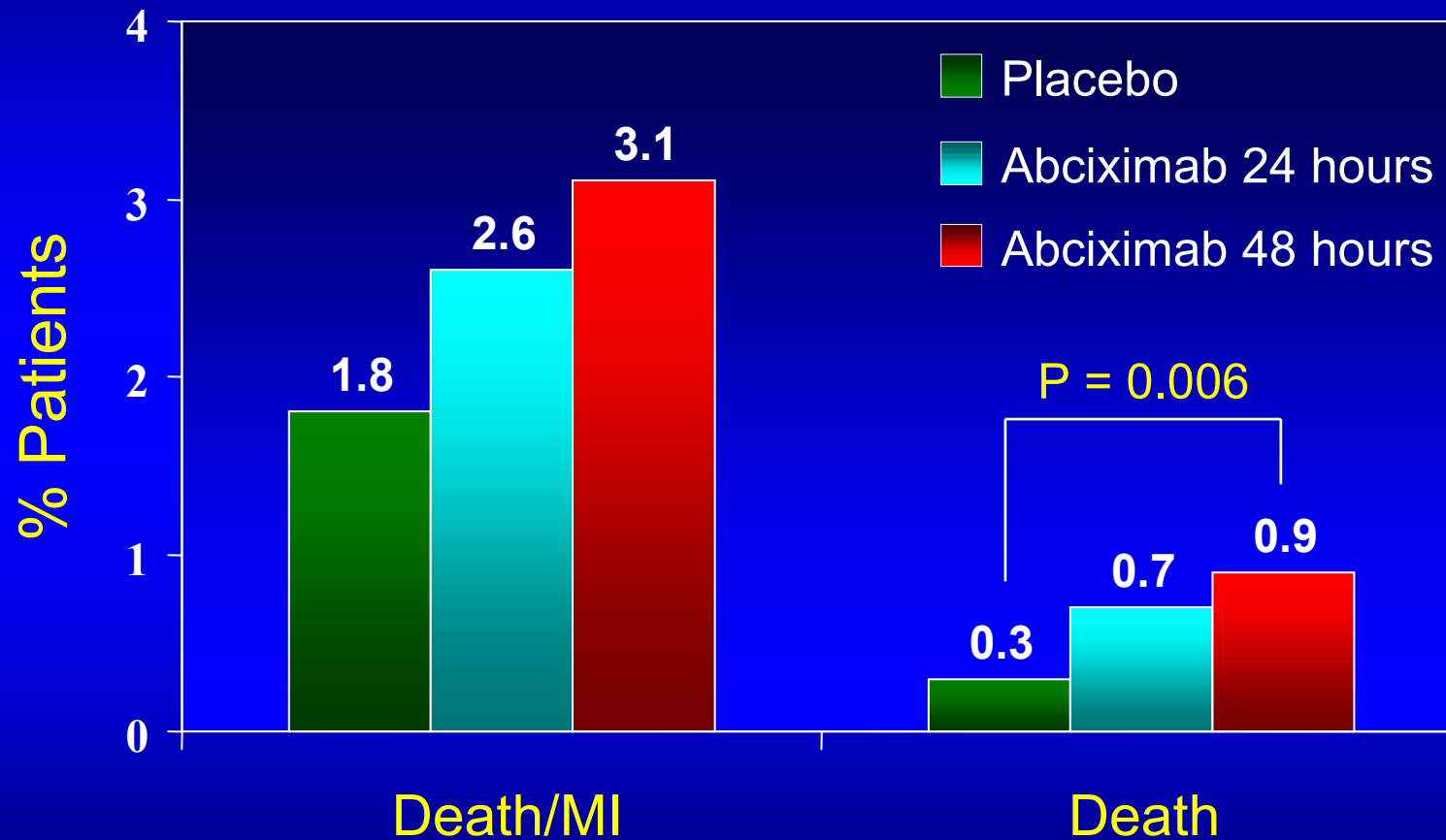
# GP 2b/3a Inhibitors in ACS (N=32,402)

## 30-Day Death/MI According to Troponin Status (35%)



Boersma et al, Lancet 2002;359:189-1198.

# GUSTO IV-ACS: 48-hour Outcomes



*Lancet 2001*

# Key Points Regarding GP IIb/IIIa Inhibitors in ACS

- Should be considered in high-risk patients oriented to an early invasive strategy (I, A); abciximab for upstream Rx if no appreciable delay in angiography (I, B)
- Small molecules (tirofiban & eptifibatide) approved for medical stabilization therapy (IIa, B)
- Combination Rx with ASA, heparin and clopidogrel may have a favorable risk-benefit in high-risk pts - ↑ TnI (IIa, B)
- Abciximab is contraindicated for medical therapy (Class III)

# Optimal ACS Management with Antiplatelet Agents

## Conclusion

- Aspirin and clopidogrel are the most used, effective, safe and cost-effective therapies
- GP IIb/IIIa inhibitors offer significant benefits with potential of cost-effectiveness in high-risk patients
- Newer therapies look promising (prasugrel, cangrelor, AZD6140)
- Strategies for risk stratification and optimization of cost-benefit-risk profile are worthwhile goals

“The aim of science is not only to  
open the door to endless wisdom  
but also to put a limit to endless error”

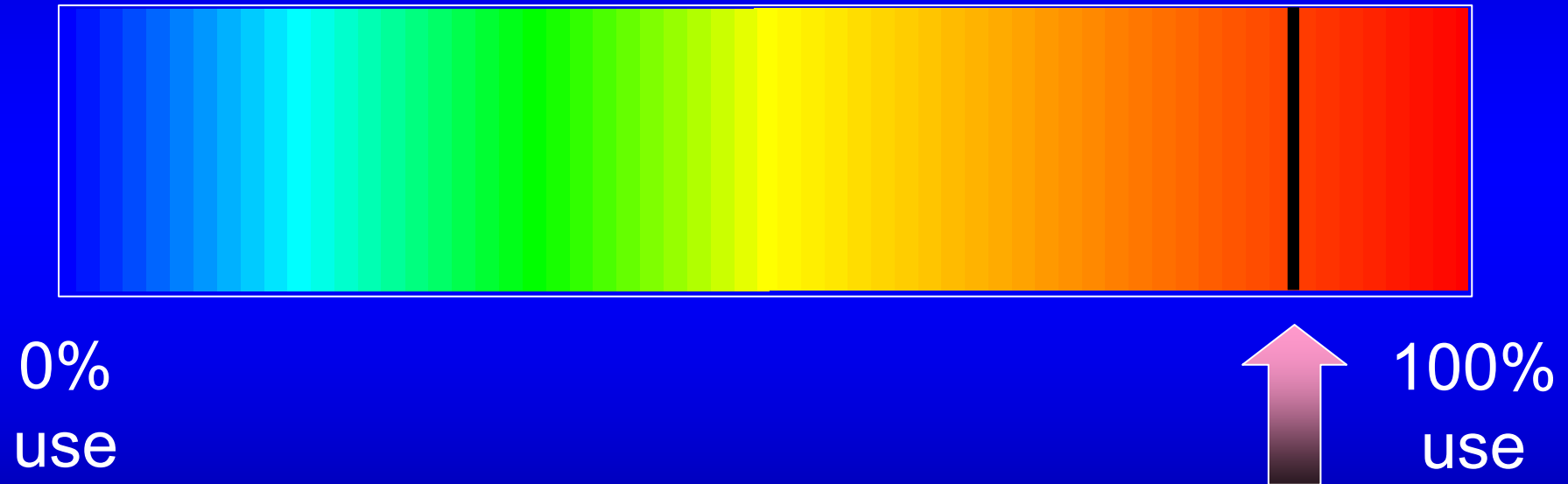
Galileo



Given our limited understanding of the exact mechanism and incidence of stent thrombosis, our inability to accurately identify at-risk patients and the lack of effective and safe therapies to mitigate this risk, the most prudent strategy to limit this rare but potentially life-threatening complication at the current time is a **selective, thoughtful and evidence-based** application of drug-eluting stents in clinical practice

# Balancing Risk and Benefit

DES Utilization: 2006



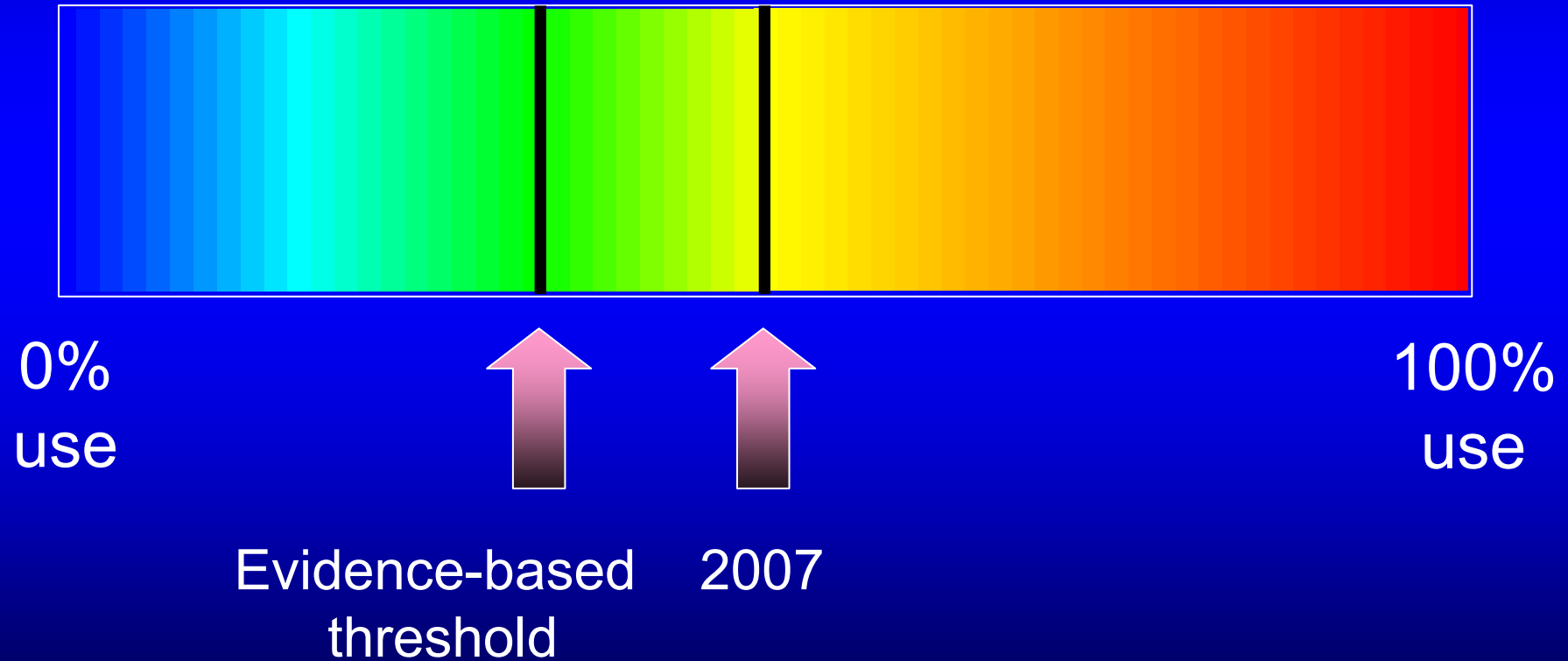
~60% "off-label"

(TAXUS ARRIVE 1, BASKET-LATE)

(↑ stent thrombosis = 2-3%)

# Balancing Risk and Benefit

## DES Utilization: 2007



# Role of Clopidogrel in CHD

Trial

CHARISMA

CURE

CREDO  
PCI-CURE  
PCI-CLARITY

CLARITY  
COMMIT



Indication

**Stable CVD**  
*MI*  
*Stroke*  
*PAD*

**ACS**  
*UA/NSTEMI*

**PCI**  
*Stable CAD*  
*UA/NSTEMI*  
*STEMI*

**STEMI**

Duration

28 months

9 months

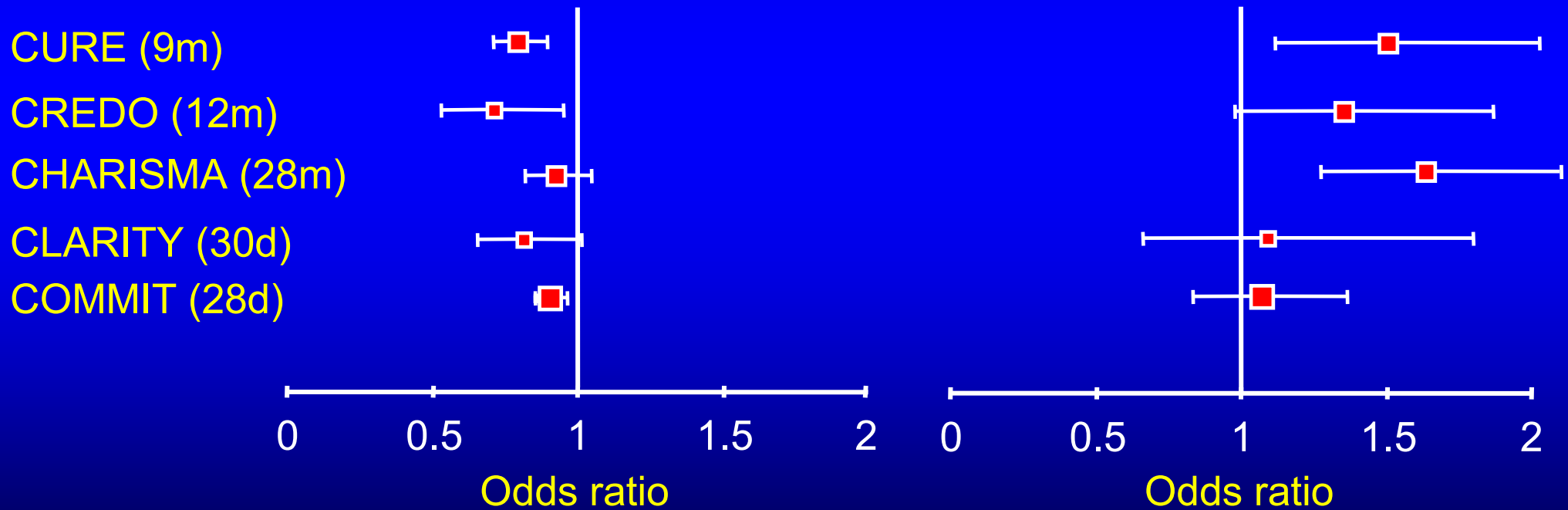
1-12 months

8-28 days

# Role of Clopidogrel in CHD

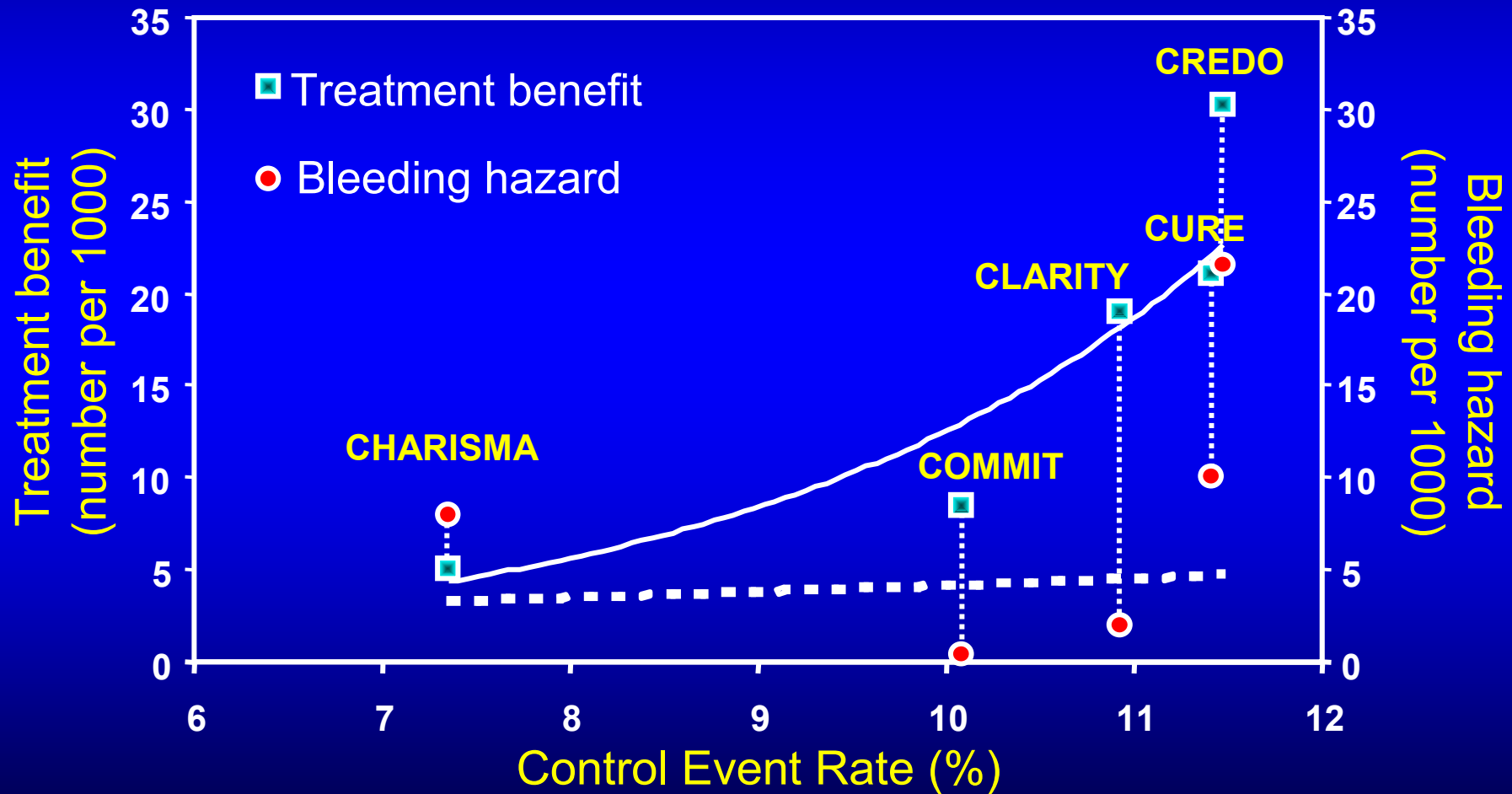
*CV Death, MI or Stroke*

*Major Bleeding*



# Role of Clopidogrel in CHD

## Benefit-Risk Profile



Eshaghian, Kaul et al. *Ann Int Med* 2007

# Therapeutic Options in ACS (2007 Update)

USAP/NSTEMI

ASA + Clopidogrel (**CURE**)

High-risk

Convenient, reliable, safe,  
as good as UFH

No

Yes (**FRISC II, TIMI 18-TACTICS, ICTUS**)

Medical  
stabilization Rx

Aggressive strategy  
Cor angio within 24-48h

UFH or  
LMWH (enoxaparin)  
(**SYNERGY, A-to-Z**)  
GP IIb/IIIa  
(Abciximab if no delay)

UFH or  
LMWH or  
Fondaparinux  
(**FRIC  
ESSENCE  
TIMI-11B  
FRAXIS  
OASIS-5**)

+ GP IIb/IIIa +  
(**GUSTO IV-ACS  
ACUTE-2**)

Safe  
? efficacy

PCI eligible

↓ Safety  
= efficacy

>12-24h minimum

Yes

No

Stress test  
(LVEF >40%)

↓ Safety  
= efficacy

PTCA/Stent

CABG or  
Medical Rx

Safe, effective,  
'Bridge'-Rx

+

-

Cath Lab

Medical Rx

GP IIb/IIIa + heparin  
(**SYNERGY, A-to-Z**)  
Bivalirudin  
(**ACUITY**)

LMWH (dalteparin)  
(**FRISC-II**)

(don't switch to UFH)