2009 Update

Management of
Acute Myocardial Infarction
(ACC/AHA & ESC Updated Guidelines)

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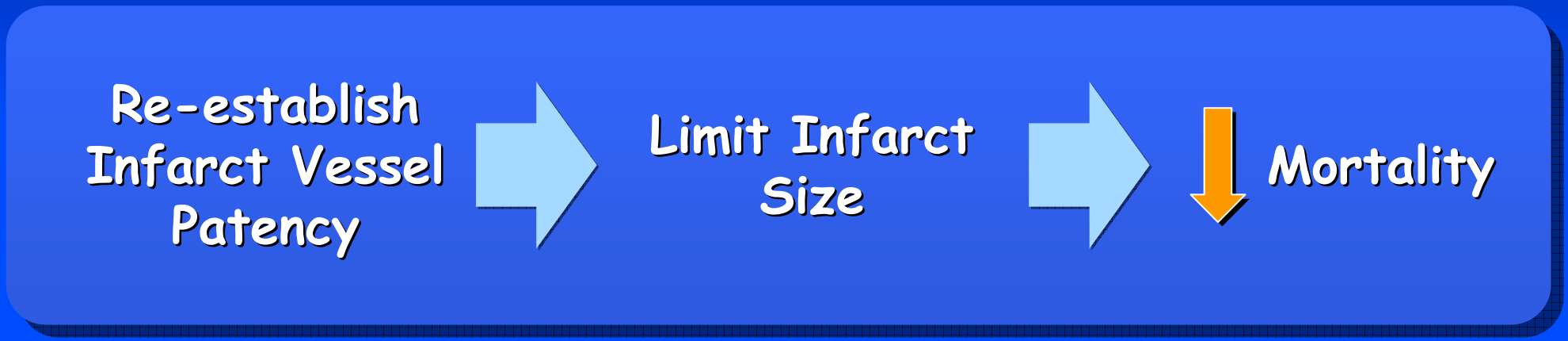
Myocardial Reperfusion for AMI Patients

The Paradigm

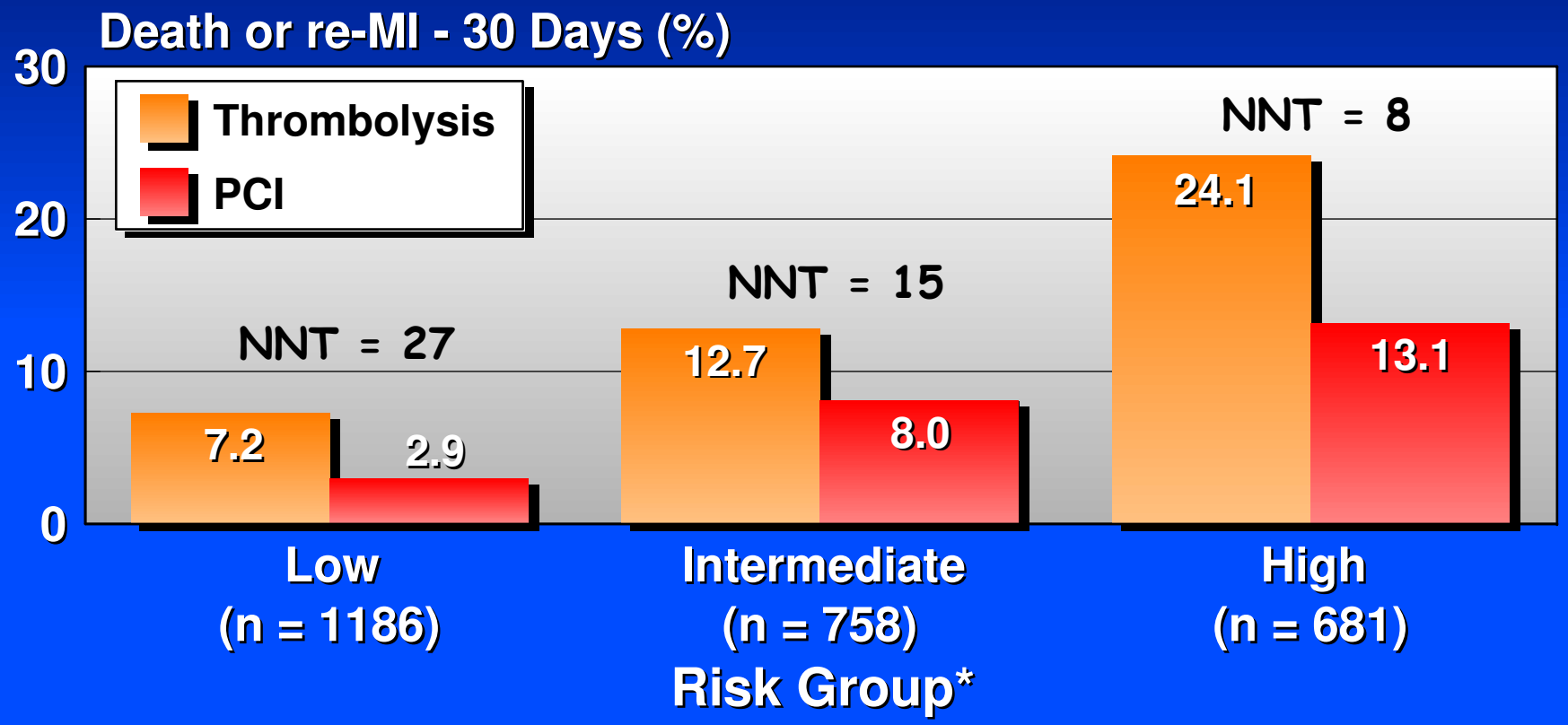


Management of Acute MI

- **Reperfusion therapy**
- Adjunctive antithrombotic therapy
- Adjunctive mechanical therapy
- Reperfusion Injury

Primary PCI vs Fibrinolysis in Acute MI

Pooled Analysis of Randomized Trials



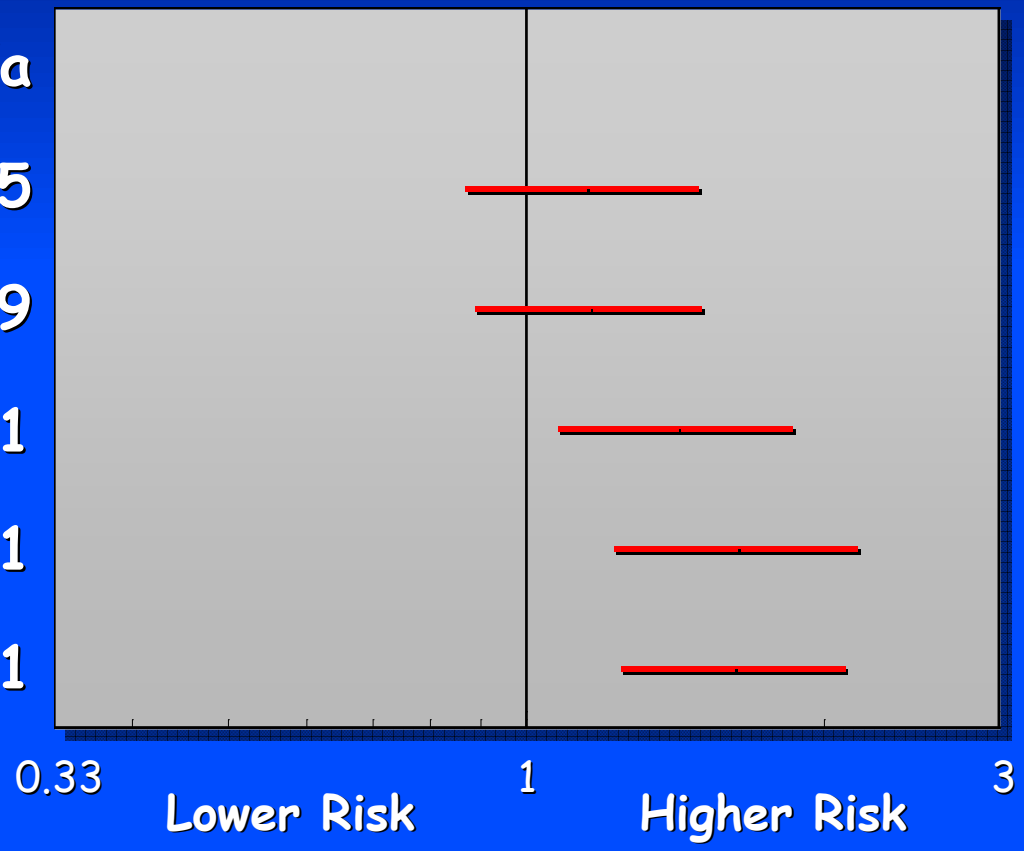
*Based upon age, anterior MI, prior MI, SBP <115 mm Hg, pulse > 85 bpm

PCAT Collaborators. AHJ 2003;145:47.

Primary PCI in AMI: NRMI-2 Registry

27,080 Patients: "Door to Balloon" Time

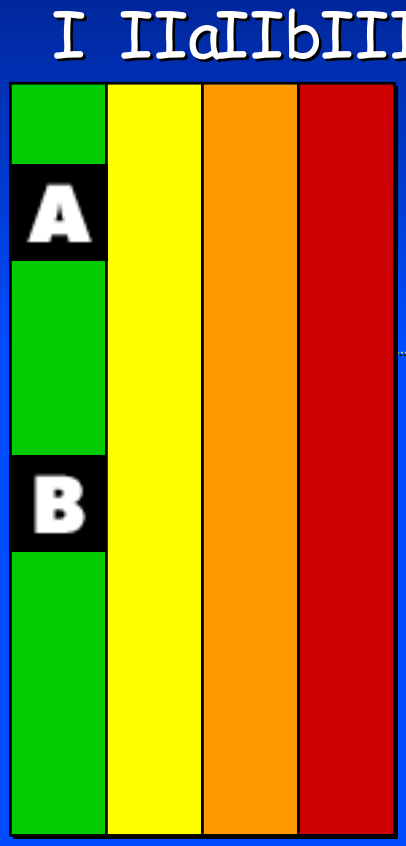
Time (min)	p-value	Mortality OR (95% CI)	Mortality
0-60	n/a		4.2%
61-90	0.35		4.6%
91-120	0.29		5.1%
121-150	0.01		6.7%
151-180	<0.001		8.5%
>180	<0.001		7.9%



Cannon et al. JAMA 2000;283:2941.

ACC-AHA STEMI Guidelines

PCI vs Fibrinolysis in Acute MI



Primary PCI if available within 90 min

Fibrinolysis within 30 min if pt presents to hospital without PCI capability, unless pt can be transferred to undergo PCI within 90 min of first medical contact

Antman EM. J Am Coll Cardiol 2008;51:210-47.

ESC Guidelines

Reperfusion Therapy: Primary PCI

Recommendations	Class	LOE
▪ Preferred reperfusion treatment if performed by an experienced team as soon as possible after FMC	I	A
▪ Time from FMC to balloon should be < 2 h in any case and < 90 min in pts presenting early (e.g. < 2 h) with large infarct and low bleeding risk	I	B
▪ Indicated for patients in shock and those with contraindications to fibrinolytic therapy irrespective of time delay	I	B
<u>Rescue PCI</u>		
▪ After failed fibrinolysis in patients with large infarcts if performed within 12 h	IIa	A

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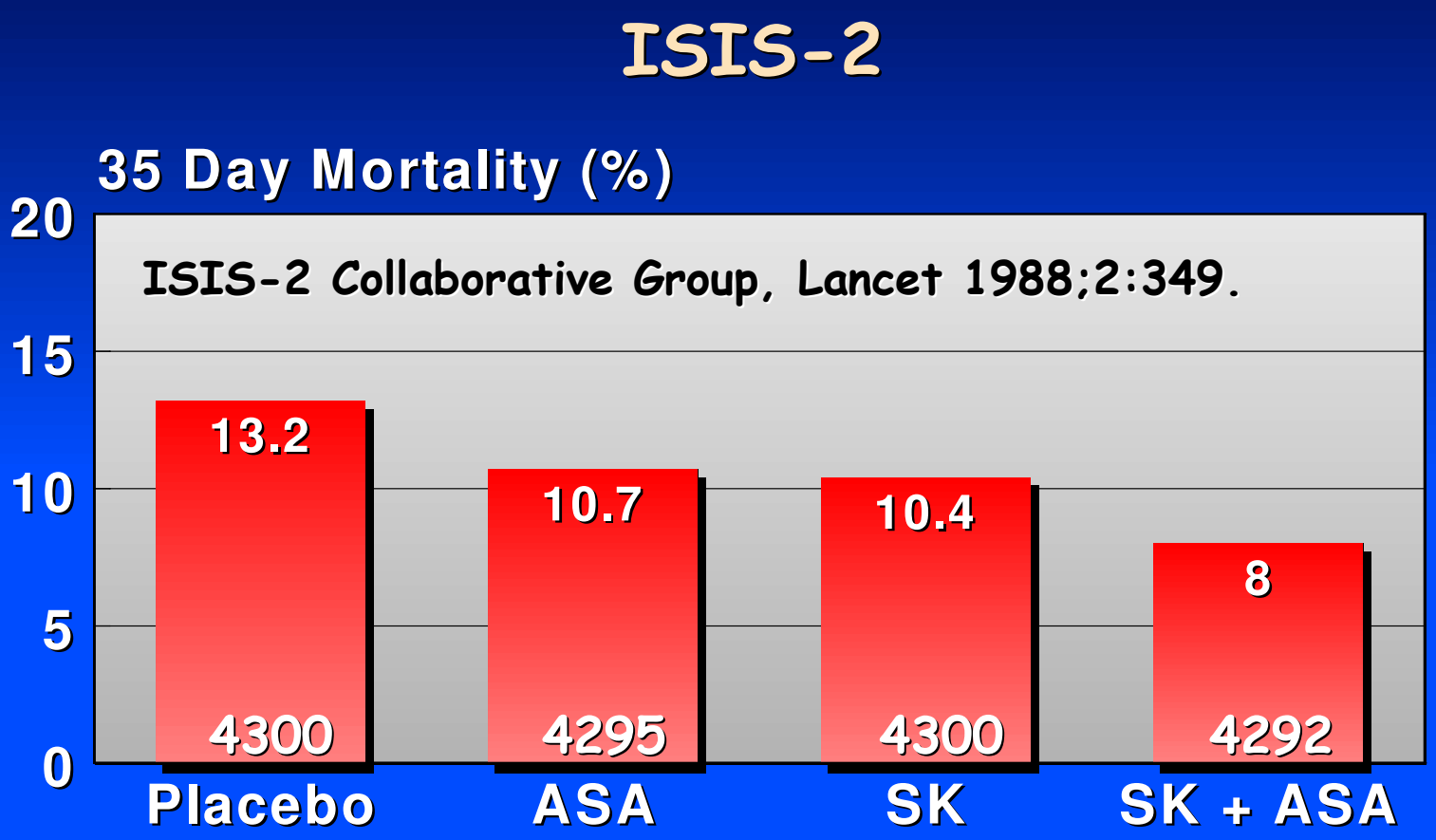
Management of Acute MI

- Reperfusion therapy
- **Adjunctive antithrombotic therapy**
- Adjunctive mechanical therapy
- Reperfusion Injury

Aspirin in Acute MI

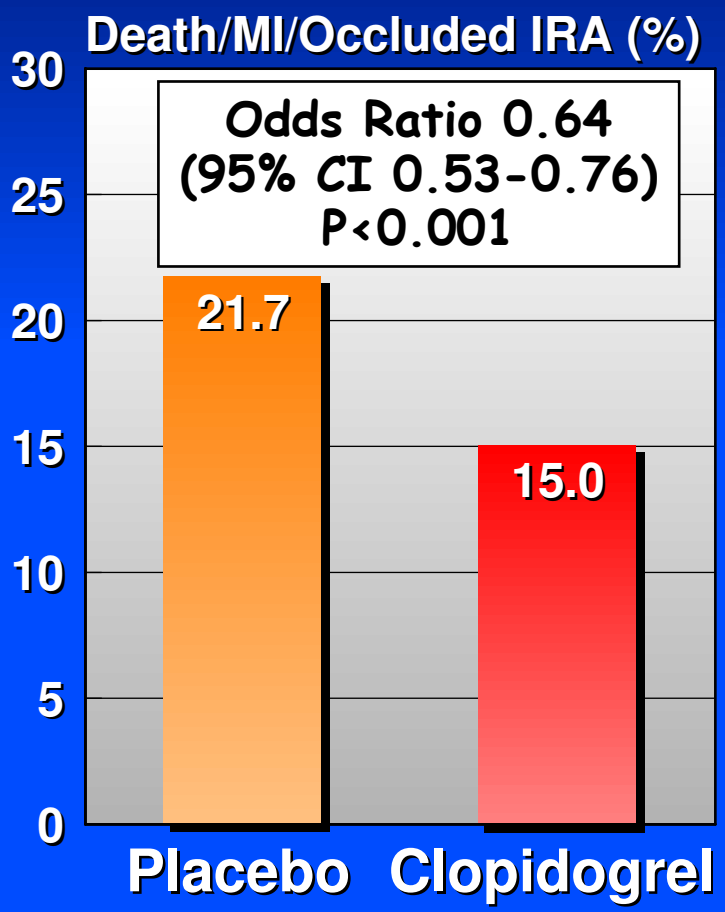


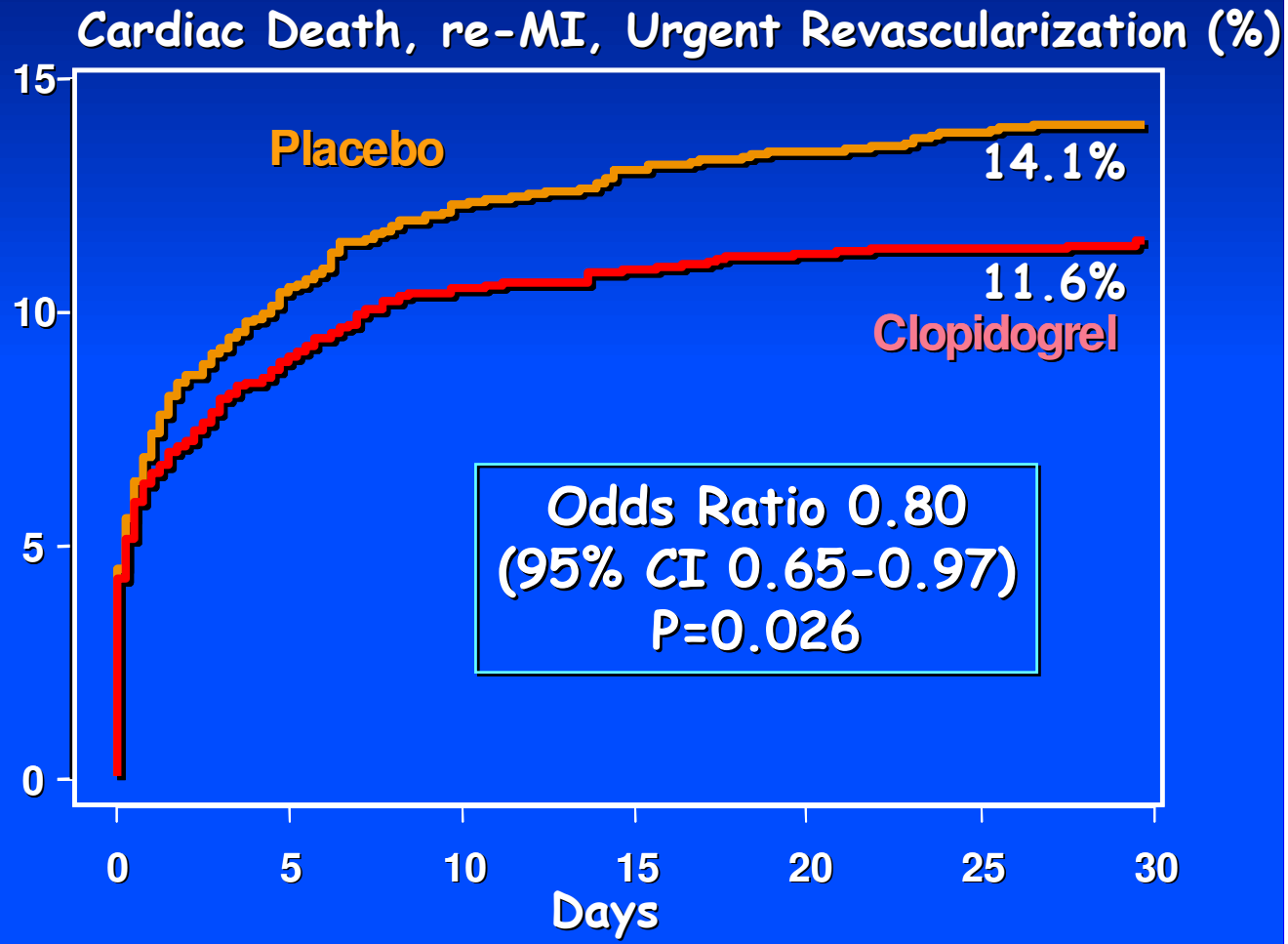
Class I, LOE A:
Aspirin daily indefinitely after STEMI in all pts without true aspirin allergy.
Initial dose – 165-325 mg. Maintenance dose – 75-162 mg.

Thienopyridines in Acute MI

CLARITY TIMI 28

Clopidogrel in STEMI





Sabatine MS et al. NEJM 2005; 352: 1179.

Recommendations for the use of Thienopyridines

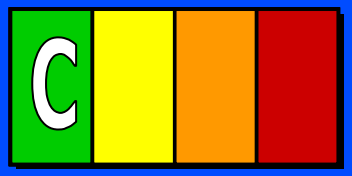
- The optimal loading dose of clopidogrel has not been established
- Randomized clinical trials using >300mg of clopidogrel as a loading dose for PCI in STEMI or UA/NSTEMI have not rigorously established superior safety or efficacy
- Clopidogrel is a prodrug which must undergo hepatic conversion to its active metabolite for platelet inhibition, a process taking several hours.

Recommendations for the use of Thienopyridines

MODIFIED Recommendation

A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:

I IIa IIb III



Clopidogrel at least 300 mg to 600mgt should be given as early as possible before or at the time of primary or non-primary PCI.

Recommendations for the use of Thienopyridines

MODIFIED Recommendation

Prasugrel 60 mg should be given as soon as possible for primary PCI.

TRITON-TIMI 38: Study Design

Wiviott SD et al AHJ 152: 627,2006
Adapted with permission from E.Antman

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,600

Double-blind

CLOPIDOGREL	PRASUGREL
300 mg LD/ 75 mg MD	60 mg LD/ 10 mg MD

✓Median duration of therapy - 12 months

1º endpoint: CV death, MI, Stroke

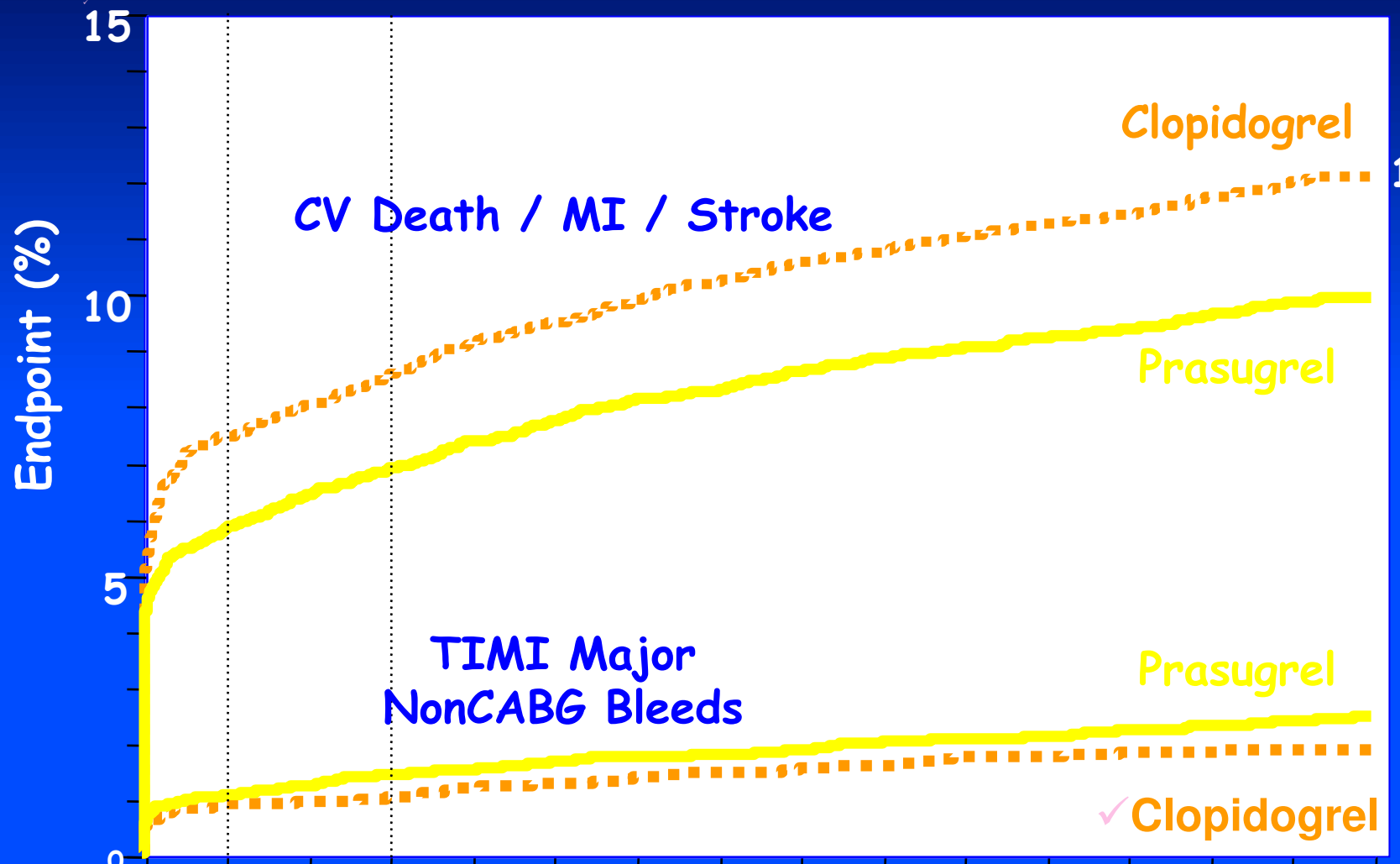
2º endpoints: CV death, MI, Stroke, Rehosp-Rec Isch
CV death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)

Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

TRITON: Results

Balance of Efficacy and Safety



↓ 138 events

12.1 Clopidogrel

9.9 Prasugrel

HR 0.81
(0.73-0.90)
P=0.0004
NNT = 46

↑ 35 events

2.4 Prasugrel

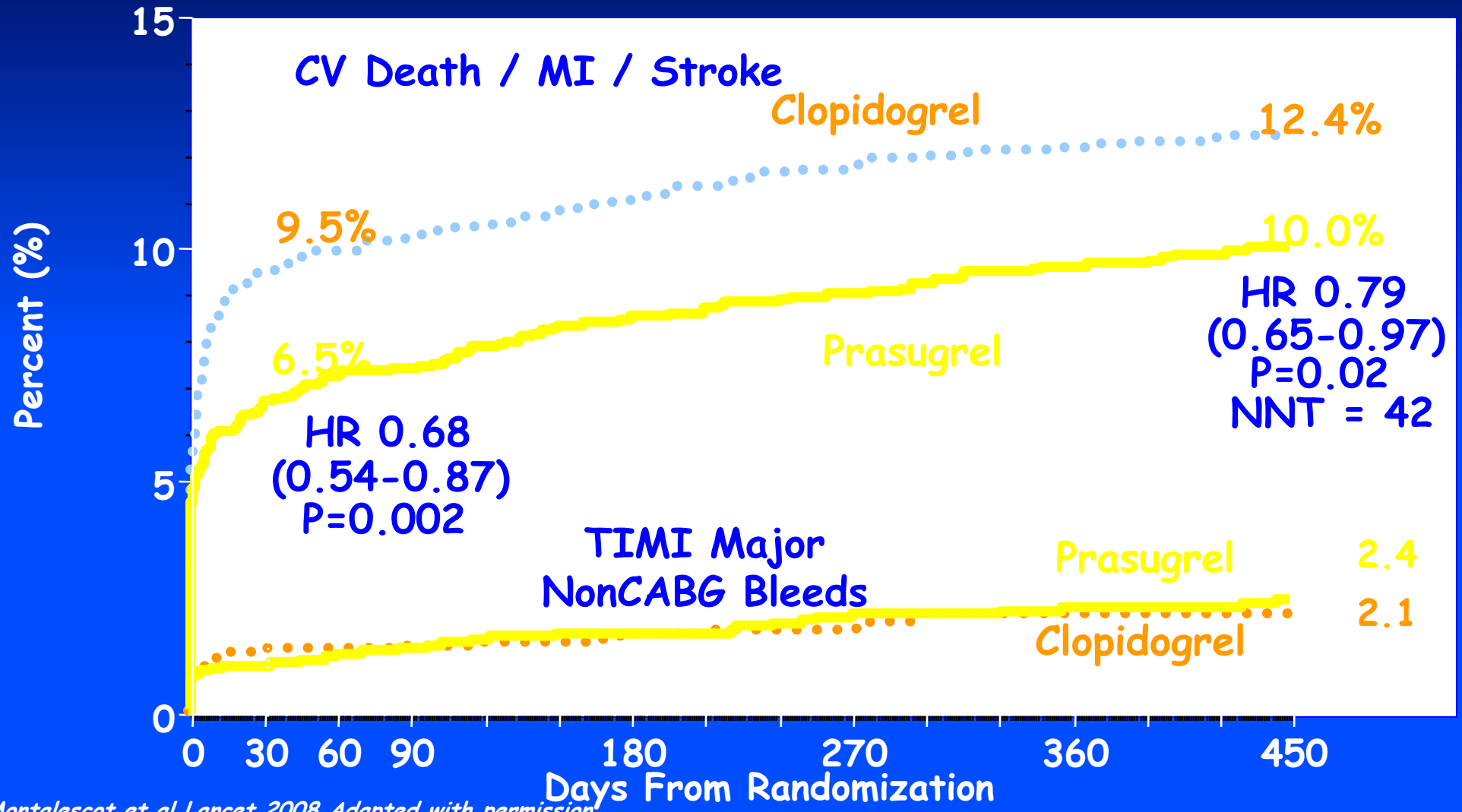
1.8 Clopidogrel

HR 1.32
(1.03-1.68)
P=0.03
NNH = 167

Adapted with permission from Wiviott SD et al NEJM 357:2007

TRITON TIMI-38

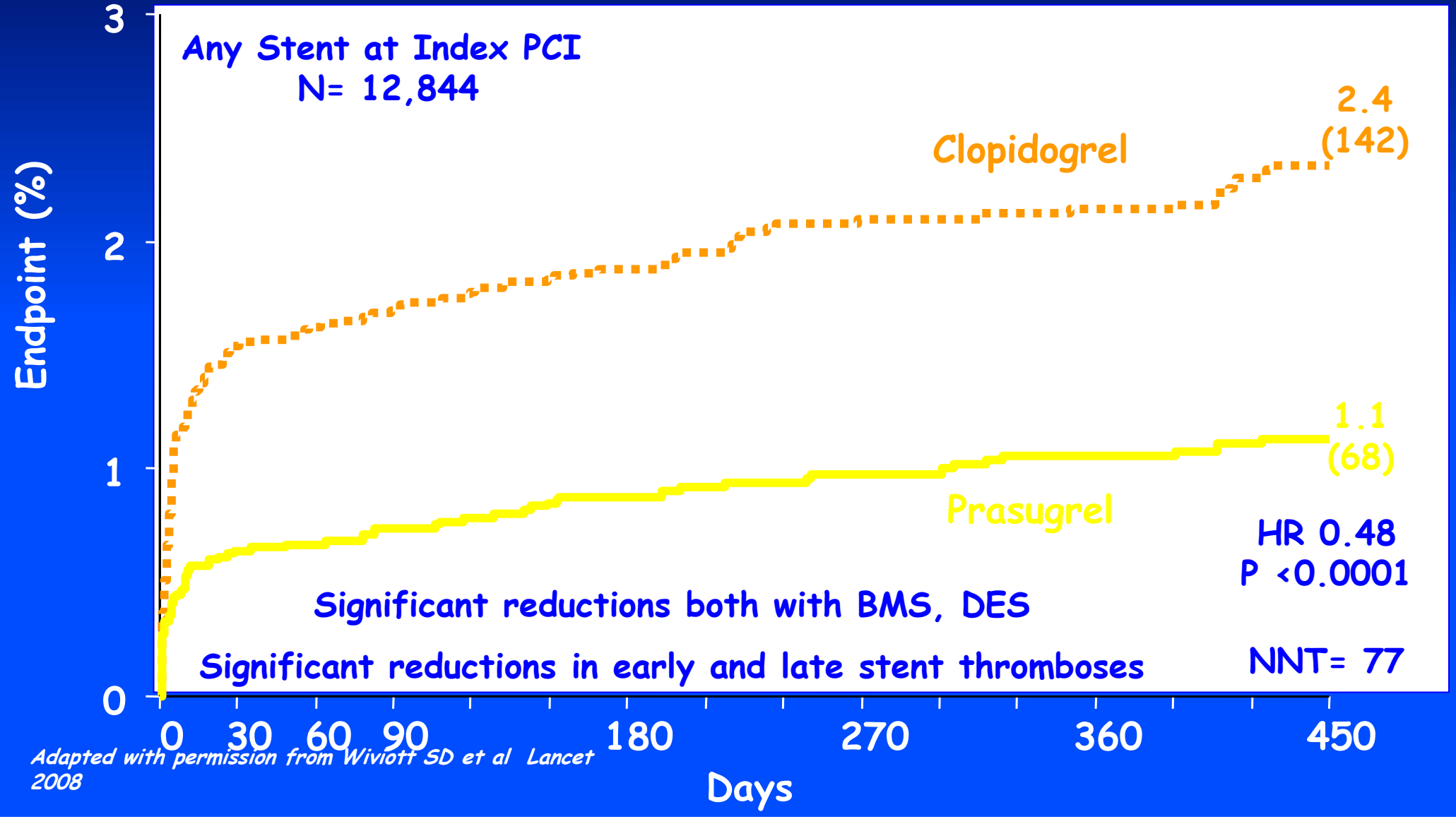
STEMI Cohort N=3534



Montalescot et al Lancet 2008. Adapted with permission from Antman EM.

TRITON TIMI-38

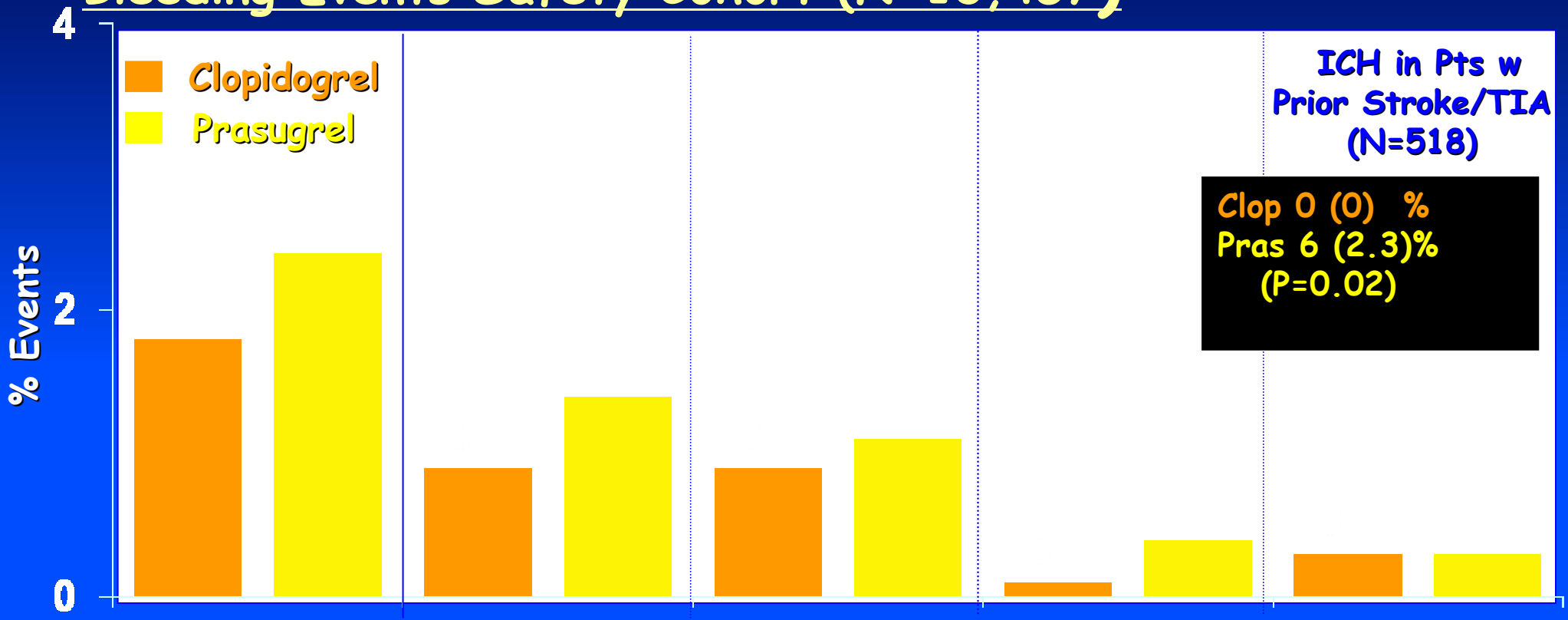
Stent Thrombosis (ARC Definite + Probable)



Adapted with permission from Wiviott SD et al Lancet 2008

TRITON TIMI-38:

Bleeding Events Safety Cohort (N=13,457)



Wiviott SD et al NEJM 357: 2001, 2007.
Adapted with permission from Antman EM.

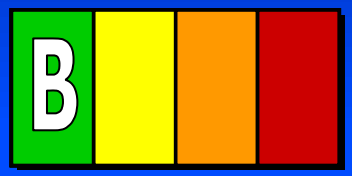
The duration of Thienopyridine Therapy

Thienopyridines

MODIFIED Recommendation

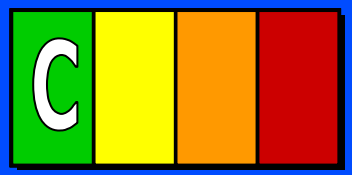
The duration of thienopyridine therapy should be as follows:

I IIa IIb III



a. In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg daily† or prasugrel 10 mg daily should be given for at least 12 months;

I IIa IIb III

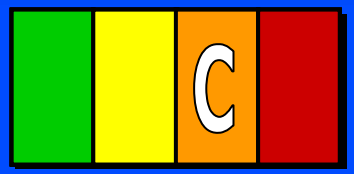


b. If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered.

Thienopyridines and DES

MODIFIED
Recommendation

I IIaIIbIII

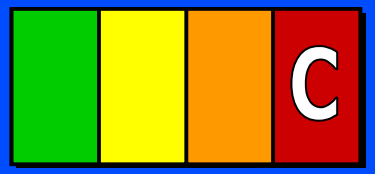


Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients undergoing drug-eluting stent placement

Thienopyridines

NEW Recommendation

I IIa IIb III

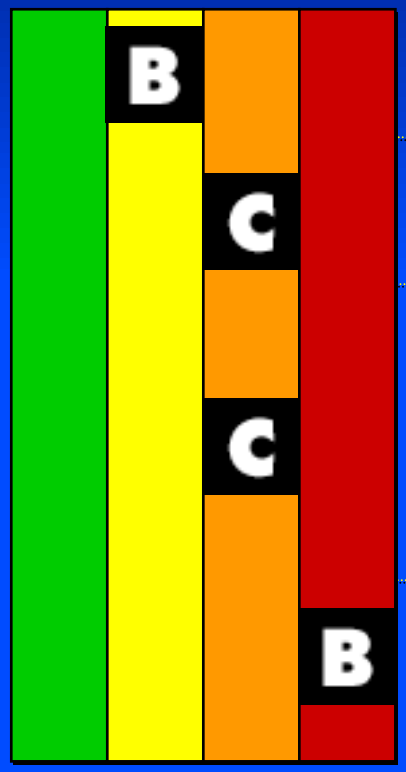


In STEMI patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned, *prasugrel is not recommended as part of a dual antiplatelet therapy regimen*

Recommendations for the Use of Glycoprotein IIb/IIIa Receptor Antagonists in STEMI

ACC-AHA STEMI Guidelines

GP IIb/IIIa Inhibitors in Acute MI



Abciximab as early as possible before primary PCI

Eptifibatide or tirofiban before primary PCI

Facilitated PCI without full dose fibrinolytic if pt high risk, PCI not available within 90 min, bleeding risk is low

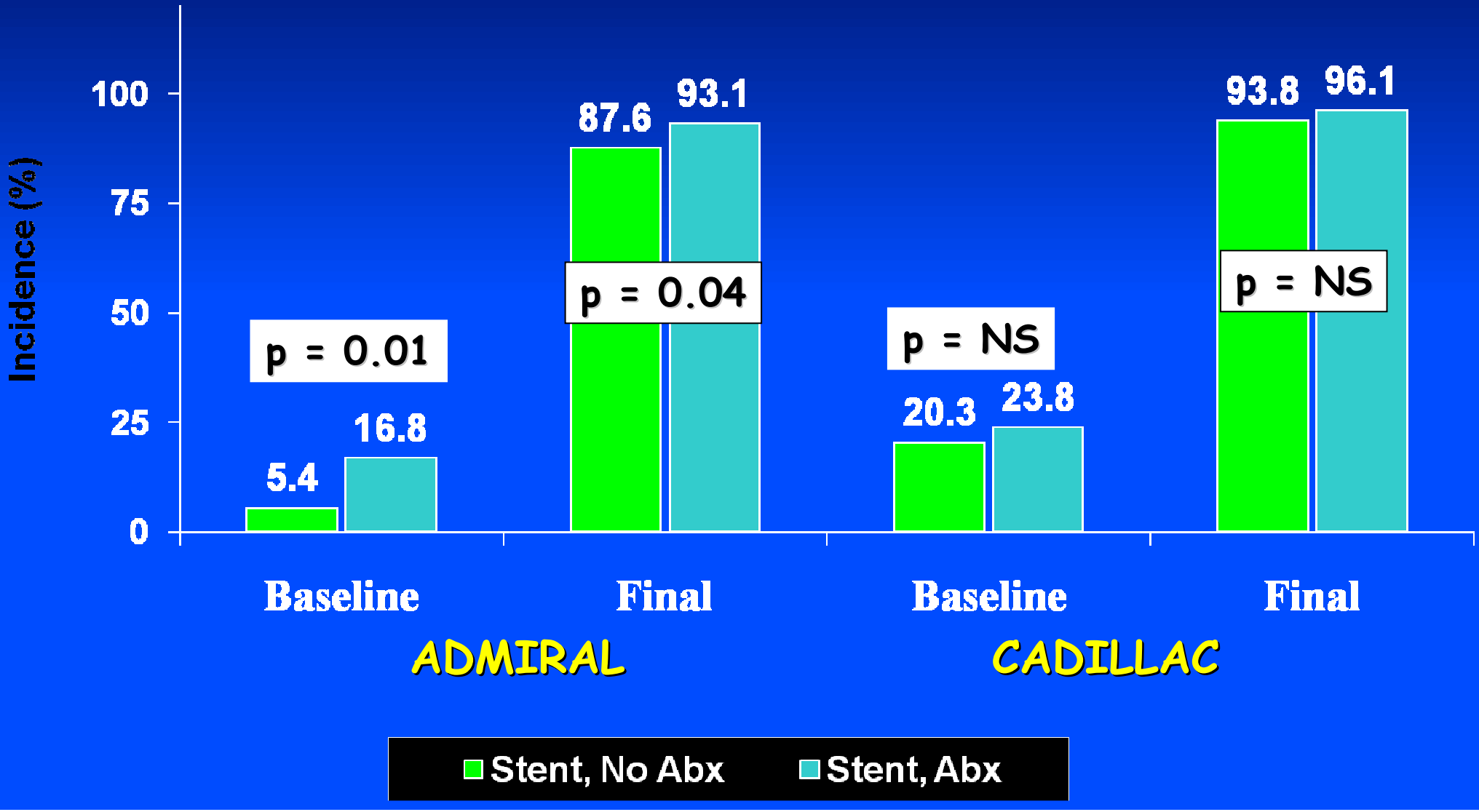
Planned full-dose lytic followed by immediate PCI

Antman EM. 2004 STEMI Practice Guidelines
Antman EM. JACC 2008;51:210-47.

ADM IRAL and CADILLAC

TIMI 3 Flow

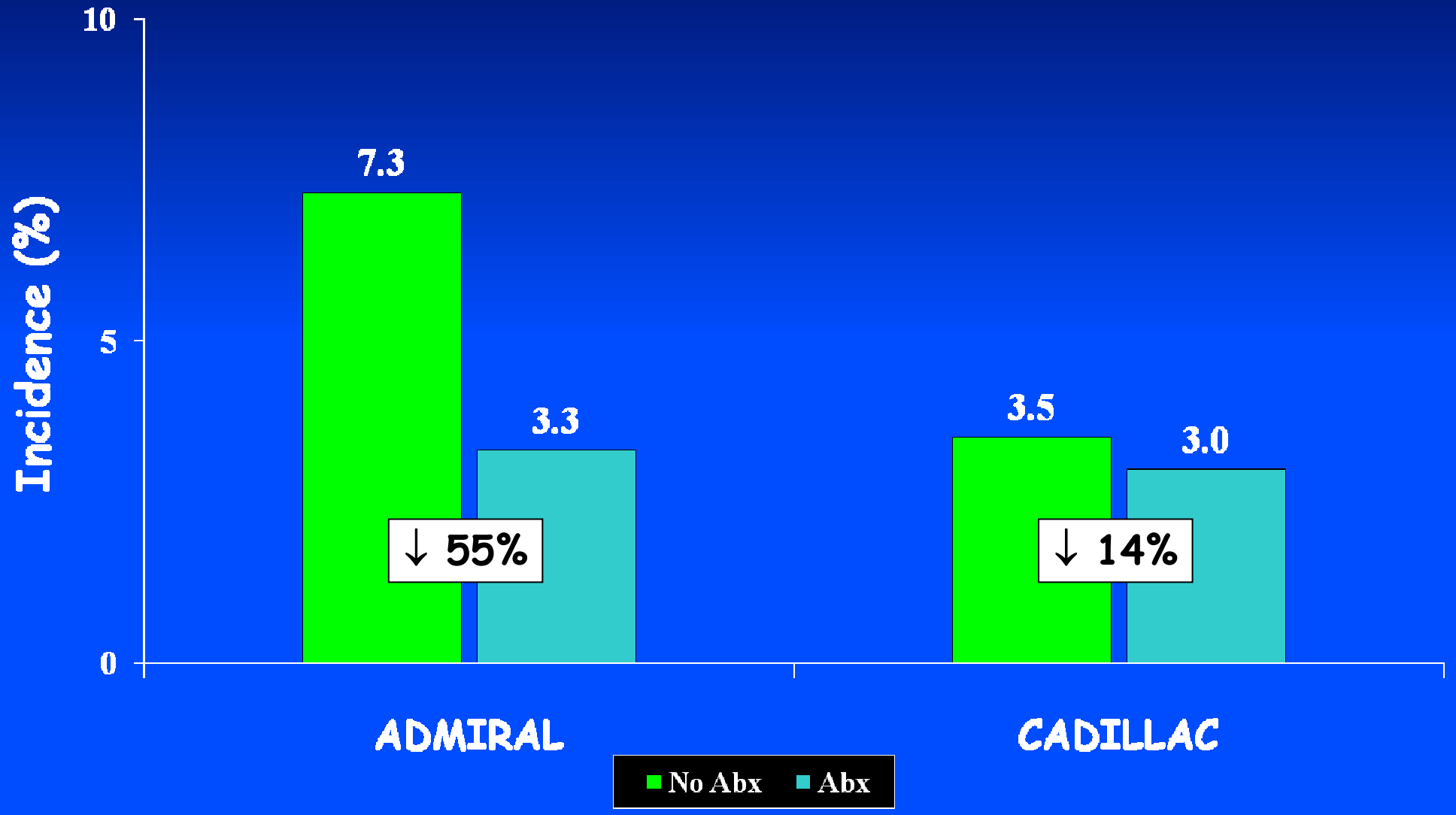
Stone et al. Circ 2000; 102: II-664,
Barragan et al Circ 2000; 102: II-662



ADM IRAL and CADILLAC

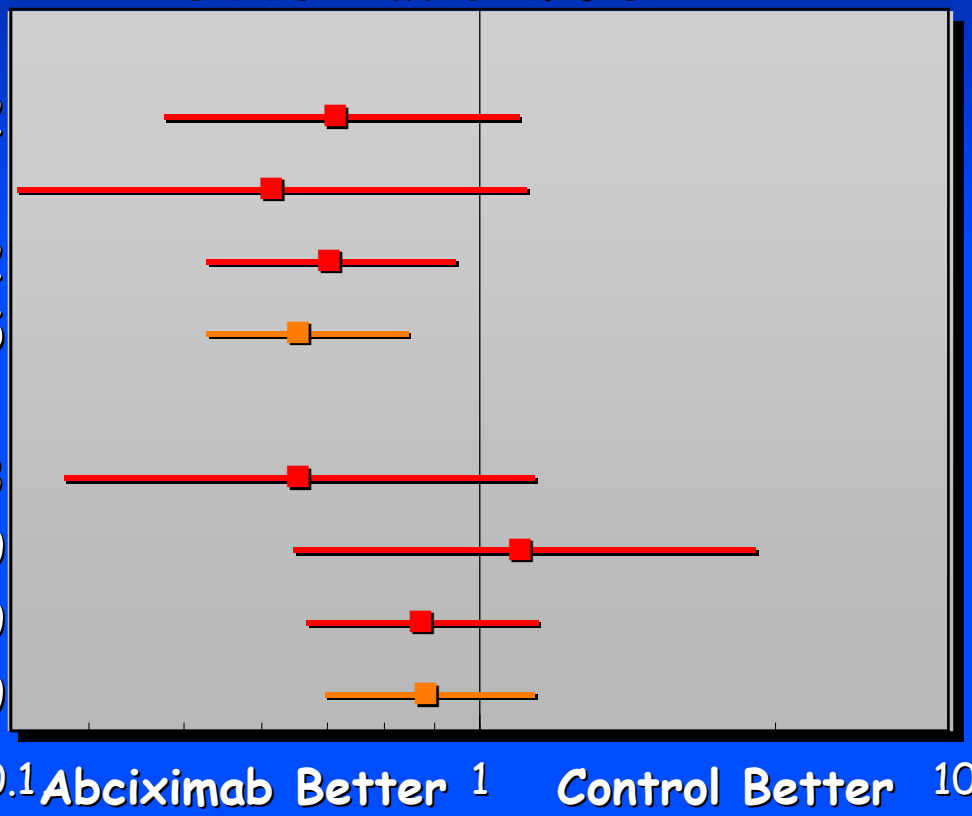
6 Month Mortality

Stone et al. Circ 2000; 102: II-664,
Barragan et al Circ 2000; 102: II-662



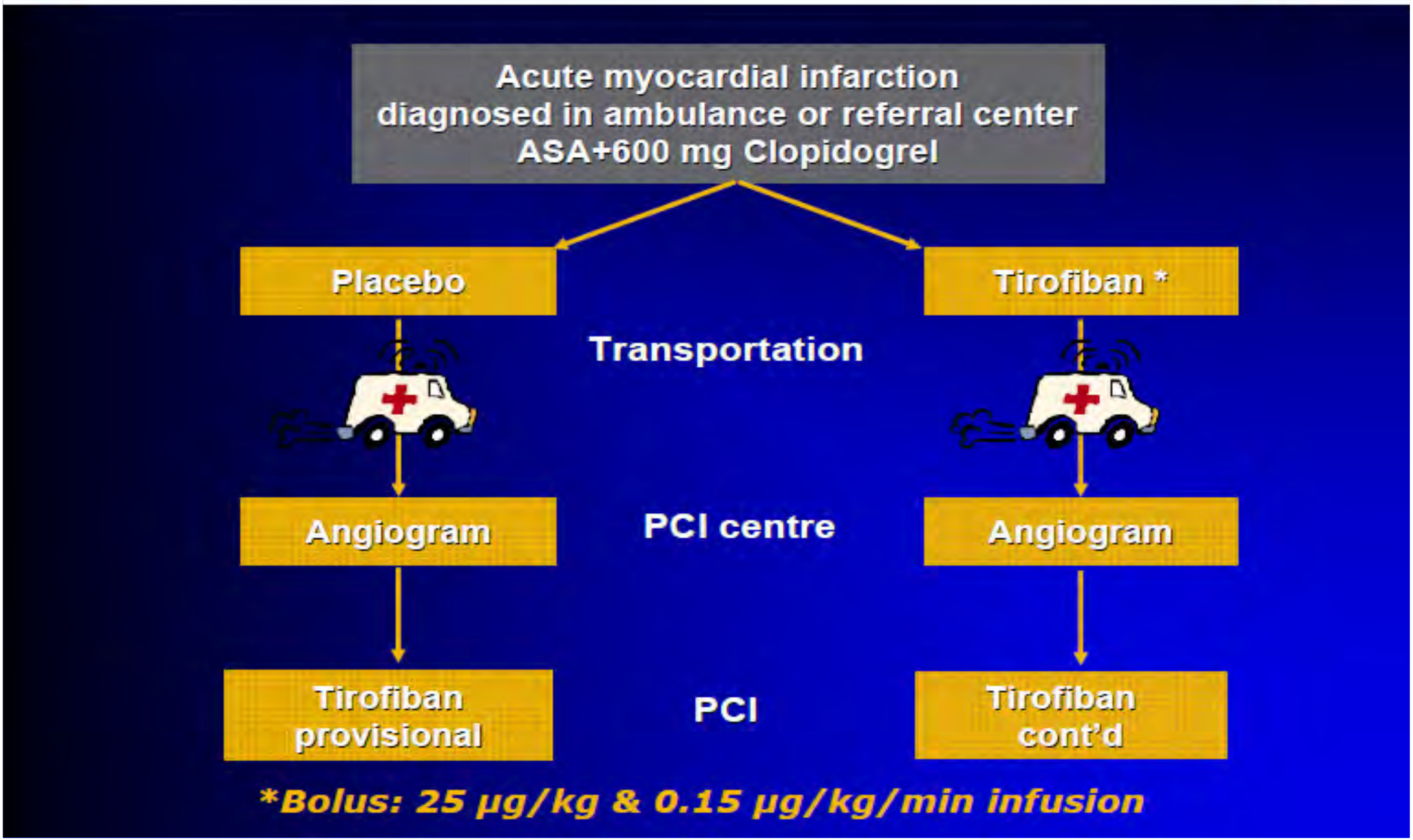
Abciximab During Primary PCI for AMI

Meta-Analysis of 3755 Patients in 6 RCT's

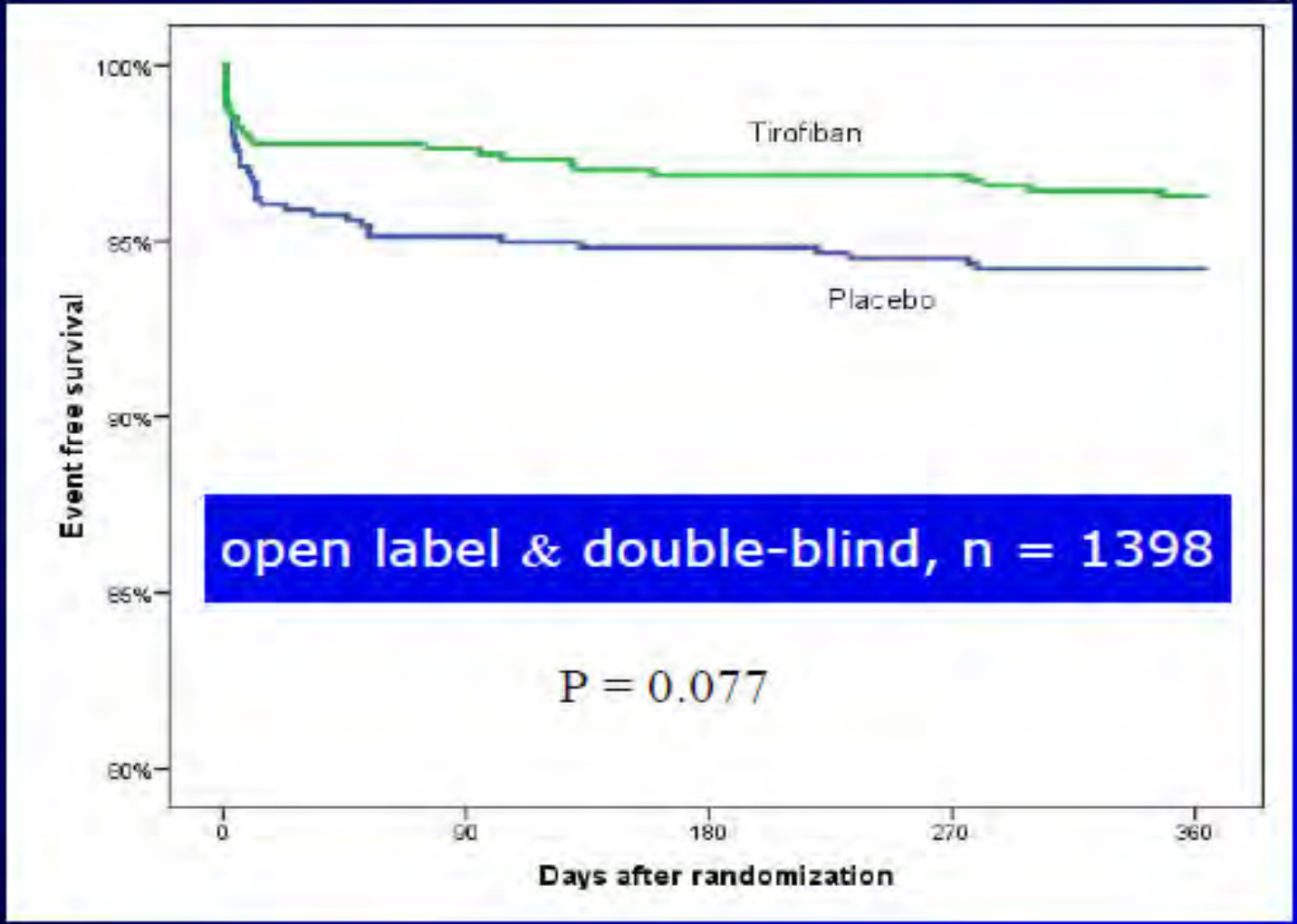


Endpoint	p-value	Abciximab	Control
Stent (n = 2226)			
Death	0.12	3.8%	5.1%
Re-MI	0.11	1.6%	2.6%
TVR	0.02	8.5%	11.6%
MACE	0.005	13.7%	19.1%
Balloon (n = 1529)			
Death	0.13	3.0%	4.5%
Re-MI	0.70	3.9%	3.6%
TVR	0.30	16.6%	18.6%
MACE	0.30	21.8%	23.9%

Araujo et al. AHJ 2004;148:937.


Acute myocardial infarction
diagnosed in ambulance or referral center
ASA+600 mg Clopidogrel
Placebo
Tirofiban *
Transportation
Angiogram
PCI centre
Angiogram
Tirofiban
provisional
PCI
Tirofiban
cont'd
*Bolus: 25 µg/kg & 0.15 µg/kg/min infusion

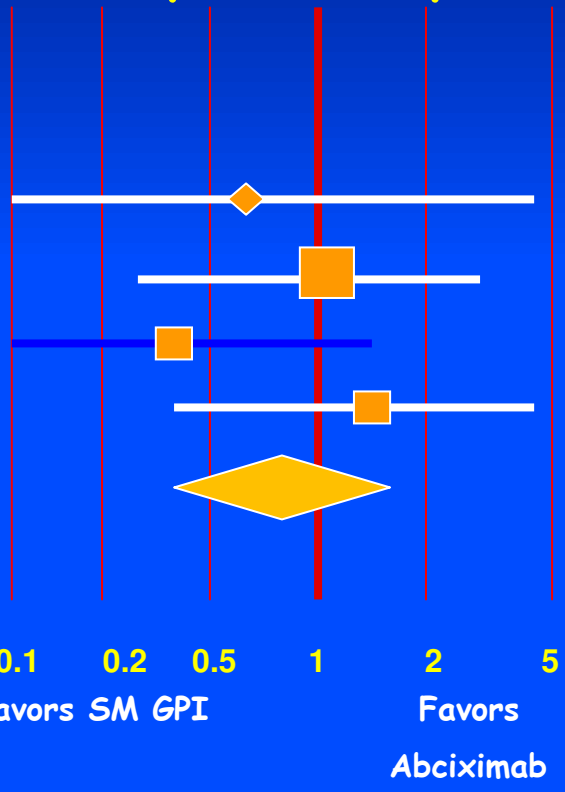
All-Cause Mortality 1-Year



Use of Glycoprotein IIb/IIIa Receptor Antagonists in STEMI

Study Name	Year	Statistics	p-value	Dead/Total	
				SM GPI	Abciximab
Valgimigli	2005	**0.667** (0.11-4.09)	**0.661**	2/87	3/88
EVA-AMI	2007	**1.017** (0.36-2.86)	**0.974**	8/226	7/201
MULTISTRATEGY	2008	**0.438** (0.13-1.44)	**0.173**	4/372	9/372
FATA	2008	**1.367** (0.43-4.35)	**0.596**	7/351	5/341
		0.843 (0.46-1.55)	**0.584**		

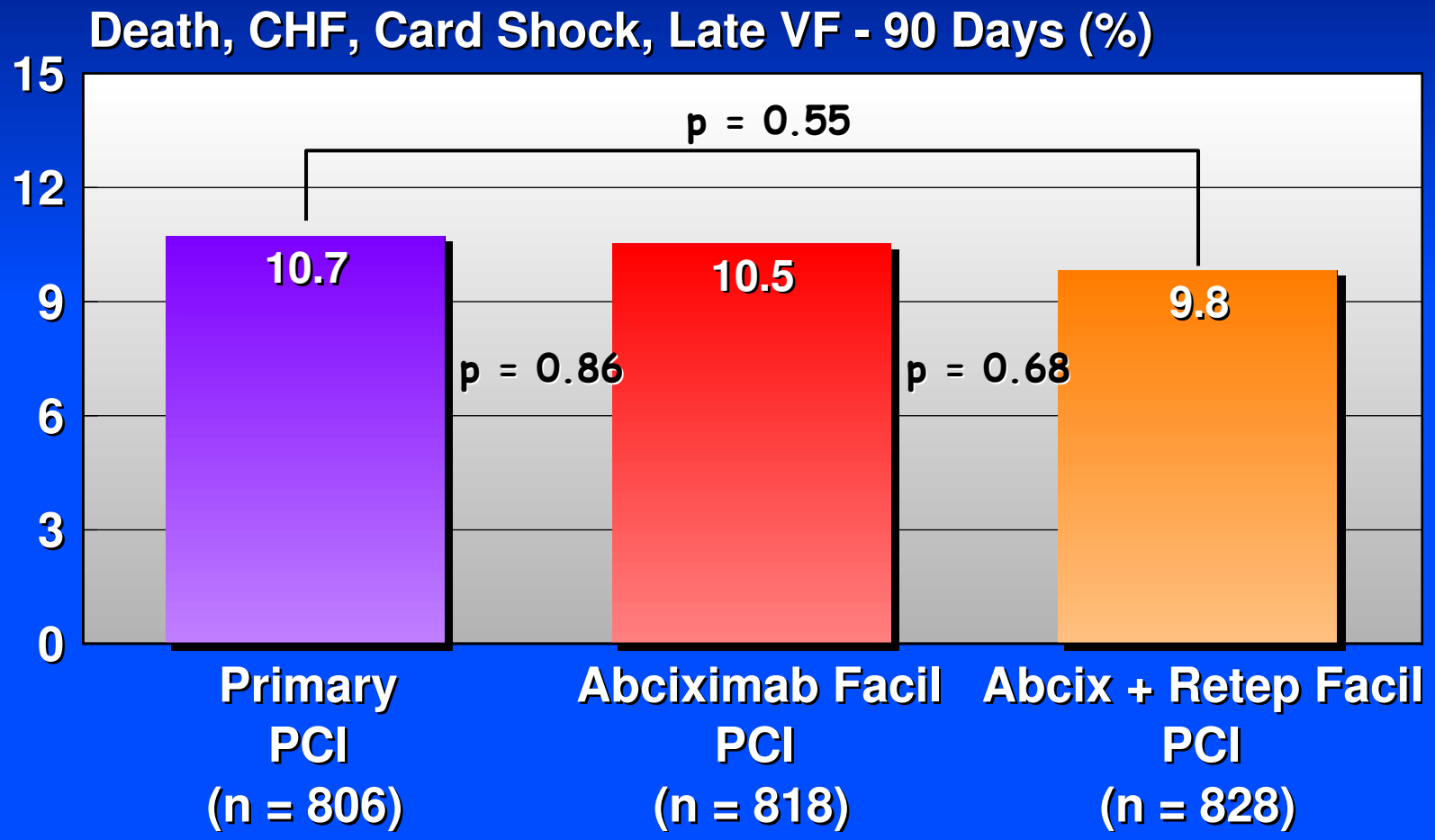
OR and 95% CI of 30-day Mortality



Grum et al. Small Molecule GP IIb/IIIa Inhibitors primary PCI. *Circ Cardiovas Intervent.* 2009;2:230-2236.

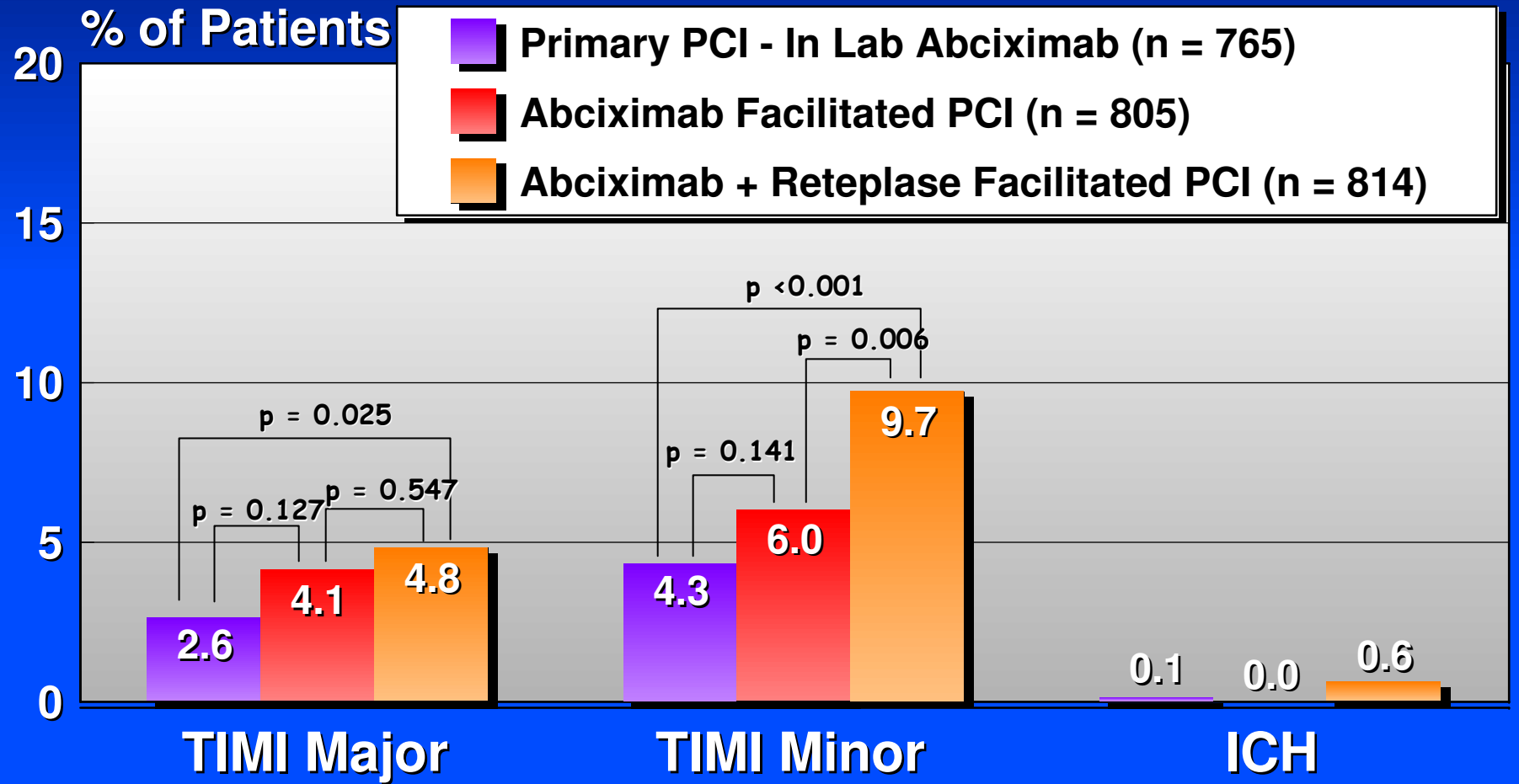
FINESSE Trial

Primary Composite Endpoint



FINESSE Trial

Hemorrhagic Complications



BRAVE 3: Study design

TREATMENT:	pre-PCI treatment with clopidogrel (600 mg), followed by abciximab vs. placebo
INCLUSION:	suspected acute MI (ST change or LBBB) within 24 h of symptom onset
EXCLUSION:	high risk for bleeding, prior stroke,shock, trauma, thrombolytics, hypertension, relevant hematologic deviations
1° OUTCOMES:	infarct size, death, stroke, urgent revascularization of affected artery

Mehilli et al. *Circ.* 2009;119:1933-1940

Effects of Abciximab

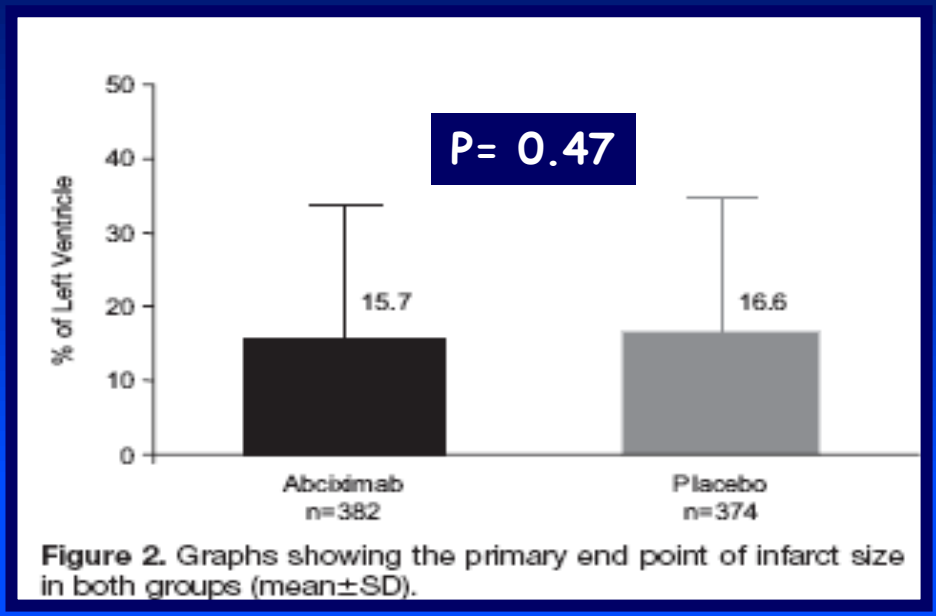


Figure 2. Graphs showing the primary end point of infarct size in both groups (mean±SD).

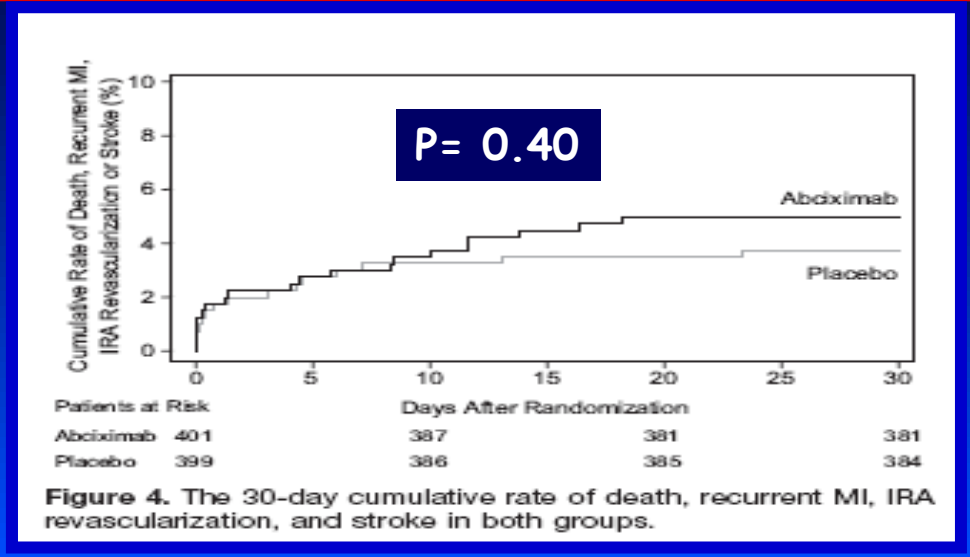


Figure 4. The 30-day cumulative rate of death, recurrent MI, IRA revascularization, and stroke in both groups.

Table 4. Thirty-Day Clinical Events

	Abciximab (n=401), n (%)	Placebo (n=399), n (%)	*P*
Death	13 (3.2)	10 (2.5)	0.53
Recurrent MI	6 (1.5)	6 (1.5)	0.99
IRA revascularization	3 (0.8)	4 (1)	0.70
Death, recurrent MI, IRA revascularization	19 (4.7)	14 (3.5)	0.38
Stroke	1 (0.3)	1 (0.3)	1.0
TIMI major bleeding	7 (1.8)	7 (1.8)	0.99
TIMI minor bleeding	15 (3.7)	7 (1.8)	0.09
Blood transfusion	12 (3.0)	13 (3.3)	0.83
Profound thrombocytopenia	6 (1.5)	0	0.03

No significant difference in infarct size or major bleeding

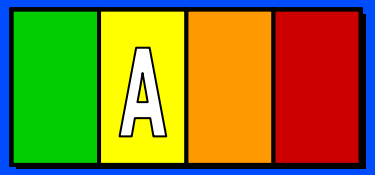
Mehilli et al. *Circ.* 2009;119:1933-1940

Use of Glycoprotein IIb/IIIa Receptor Antagonists in STEMI

Modified Recommendation

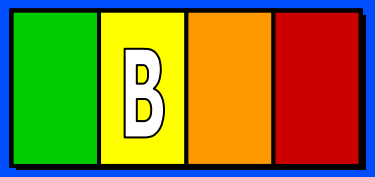
It is reasonable to start treatment with glycoprotein IIb/IIIa receptor antagonists at the time of primary PCI (with or without stenting) in selected patients with STEMI:

I IIa IIb III



abciximab

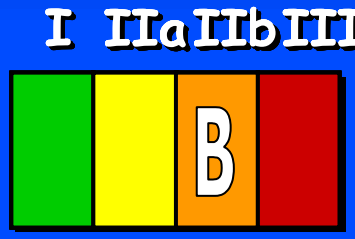
I IIa IIb III



tirofiban and eptifibatide

Use of Glycoprotein IIb/IIIa Receptor Antagonists in STEMI

Modified Recommendation

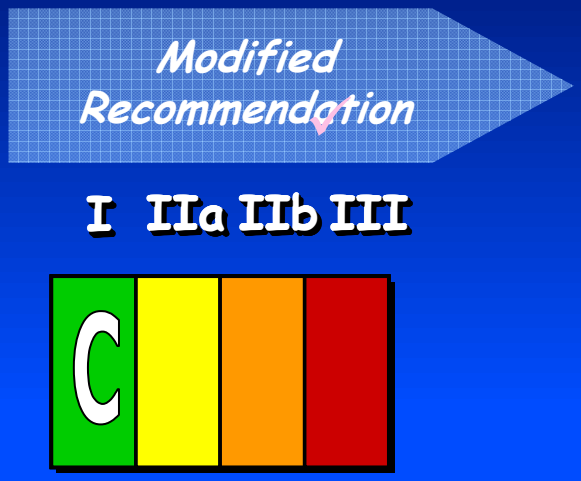


The usefulness of glycoprotein IIb/IIIa receptor antagonists (as part of a preparatory pharmacologic strategy for patients with STEMI prior to arrival in the cardiac catheterization laboratory for angiography and PCI) is uncertain.

Facilitated PCI without full dose fibrinolytic if pt high risk, PCI not available within 90 min, bleeding risk is low

Recommendations for Use of Parenteral Anticoagulants in Patients with STEMI

Use of Parenteral Anticoagulants in STEMI



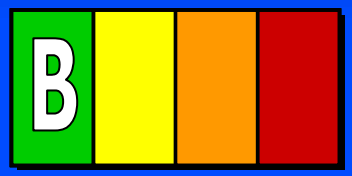
For patients proceeding to primary PCI, who have been treated with ASA and a thienopyridine, recommended supportive anticoagulant regimens include:

a. For prior treatment with UFH, additional boluses of UFH should be administered as needed to maintain therapeutic activated clotting time levels, taking into account whether GP IIb/IIIa receptor antagonists have been administered

Use of Parenteral Anticoagulants in STEMI (cont.)

Modified Recommendation

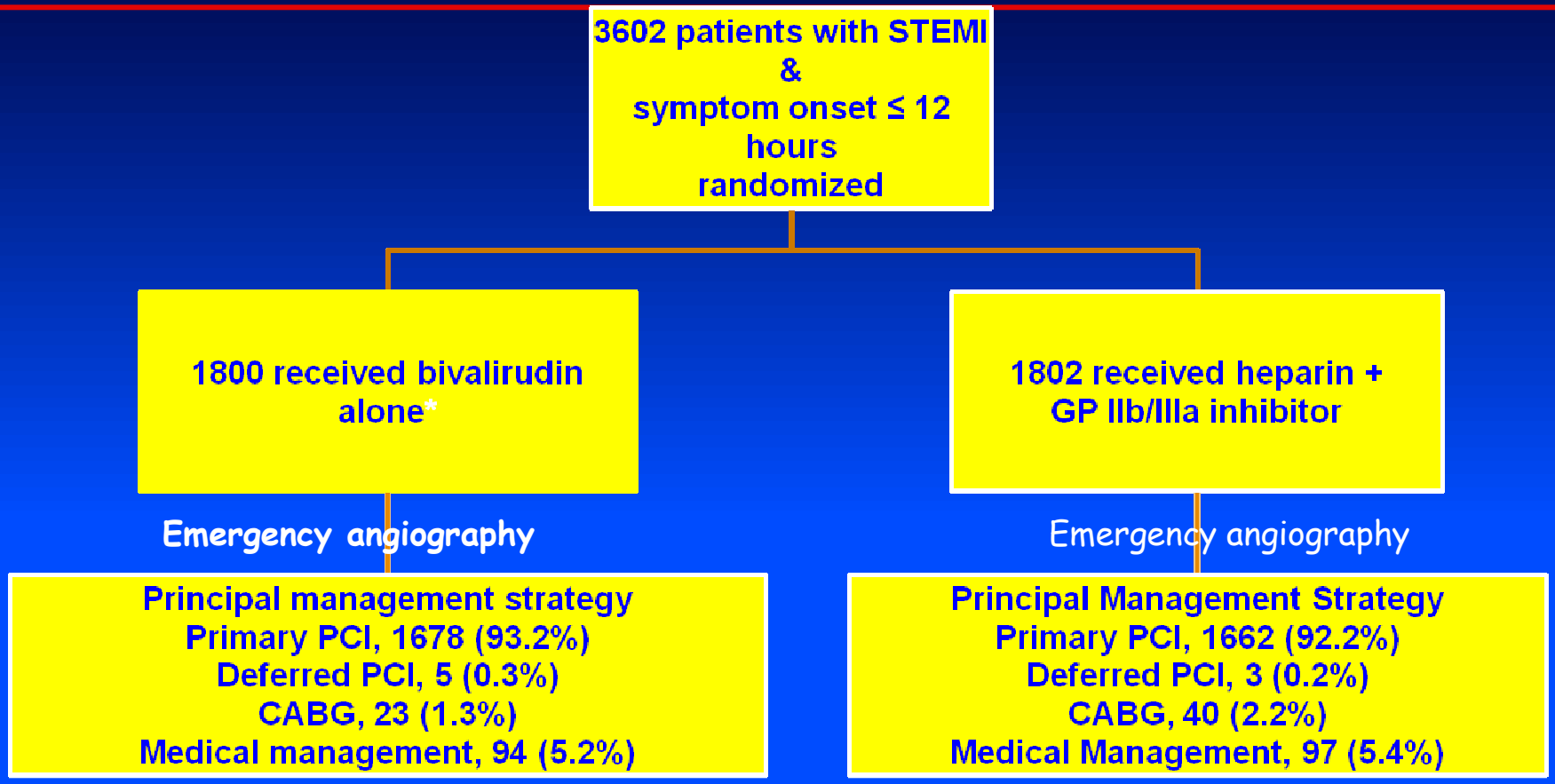
I IIa IIb III



For patients proceeding to primary PCI, who have been treated with ASA and a thienopyridine, recommended supportive anticoagulant regimens include:

b. Bivalirudin is useful as support for primary PCI with or without prior treatment with heparin.

HORIZONS-AMI: Design

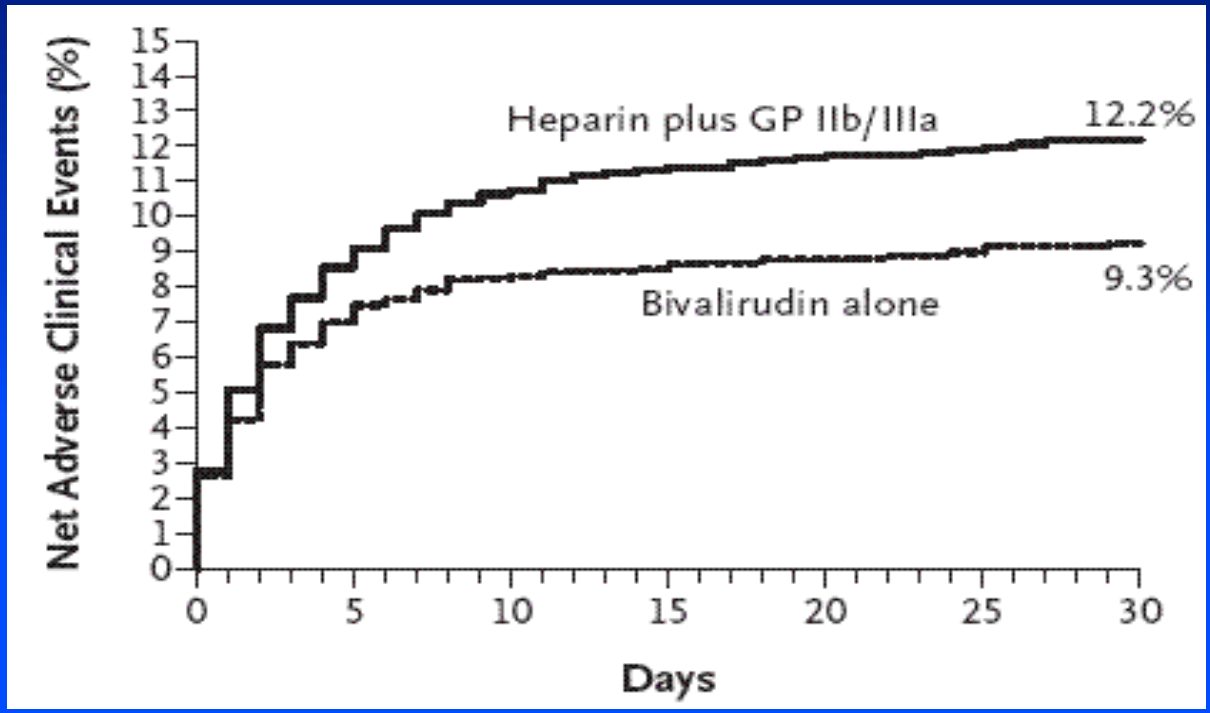


Endpoints: Composite of net adverse clinical events (NACE)

Included major bleeding plus MACE (a composite of CVD death, reinfarction, target-vessel revascularization for ischemia, and stroke within 30 days)

Stone et al. N Eng J Med. 2008;358:2218-30.

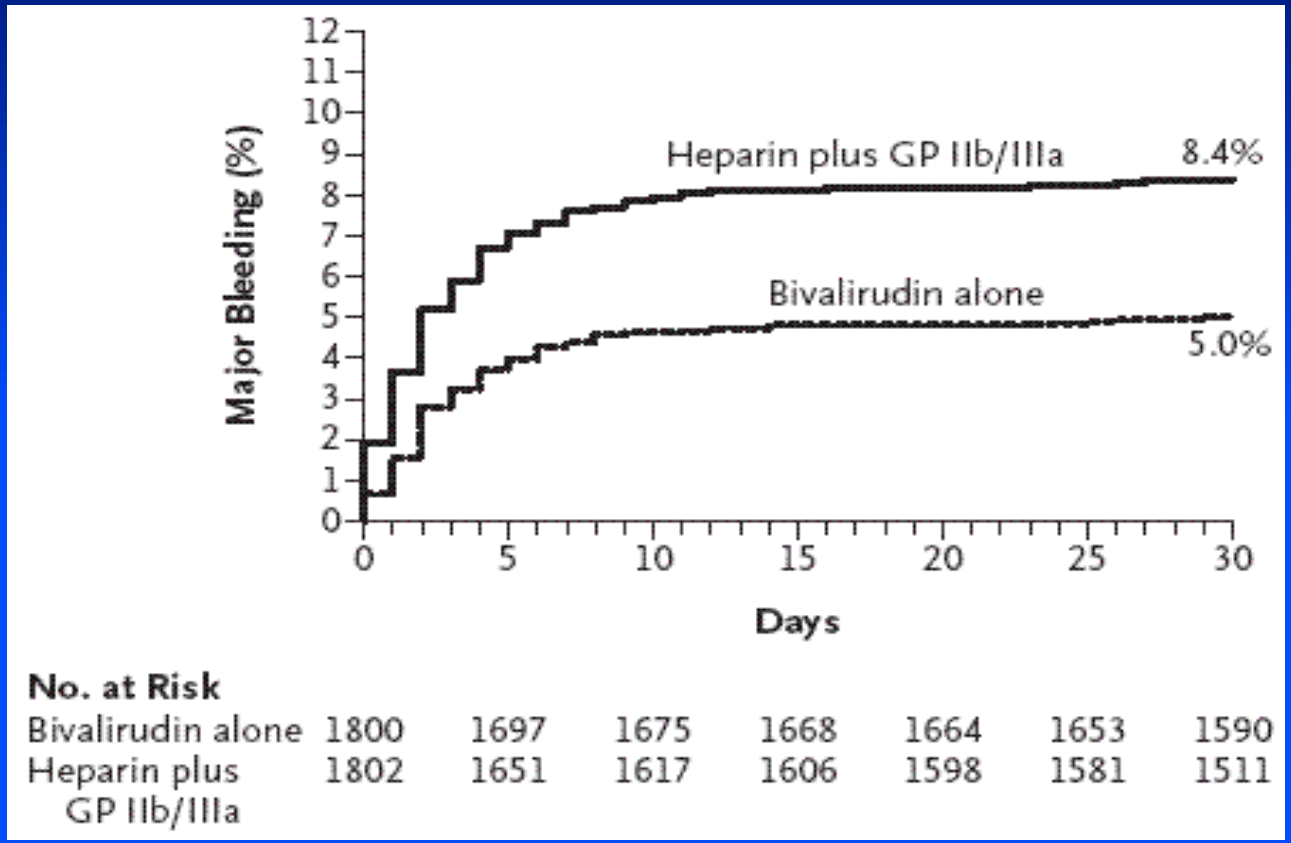
HORIZONS-AMI: Time-to-Event Curves through 30 days: Net Adverse Clinical Events



Treatment with bivalirudin alone compared with UFH + GP IIb/IIIa Inhibitors resulted in reduced 30-day rates of net adverse clinical events [HR=0.75, (0.62-0.92); p=0.006]

Stone et al. N Eng J Med. 2008;358:2218-30.

HORIZONS-AMI: Time-to-Event Curves through 30 days: Major Bleeding



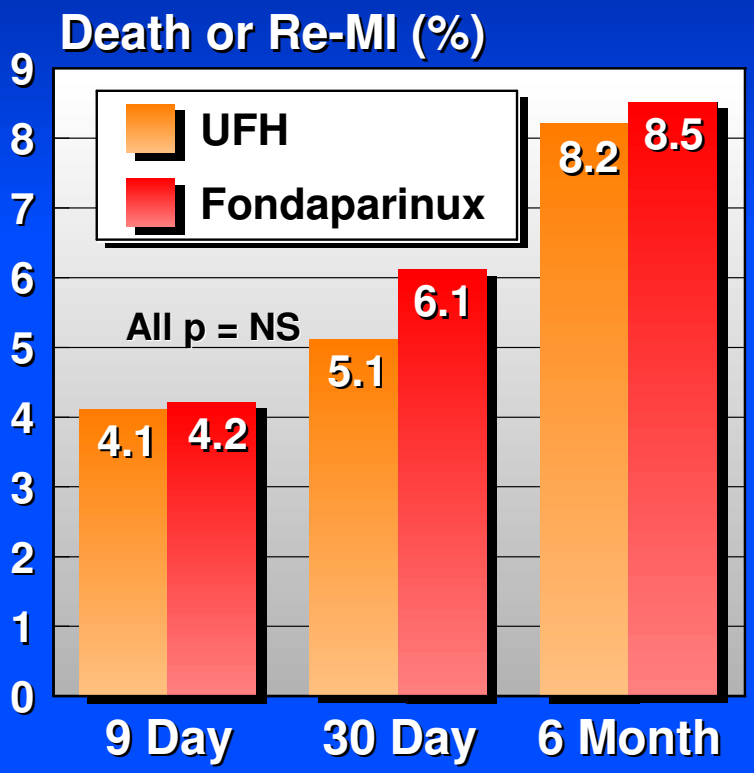
HR=0.59 (0.45-0.76); p<0.0001

* 40% less bleeding in Bivalirudin group at 30 days

Stone et al. N Eng J Med. 2008;358:2218-30.

OASIS-6

Fondaparinux vs Heparin in STEMI
Primary PCI Subgroup (N = 3768 pts)



	UFH n=1898	Fonda n=1890	p-value
Procedural heparin	100%	20.8%	-
Death or re-MI	93	114	N.S.
Severe bleeding	9	16	N.S.
Guide catheter thrombus	0	22	<0.001
Coronary complication	225	270	0.04

OASIS-6 Investigators. JAMA 2006;295.

Use of Parenteral Anticoagulants in STEMI Patients Proceeding to Primary PCI: Modified Class I Recommendations

- Bilvalirudin added as an acceptable anticoagulant for primary PCI
- Unfractionated heparin (UFH) administration guided by:
  - Therapeutic activated clotting time (ACT) levels

    Prior administration of GP IIb/IIIa receptor antagonists
- Enoxaparin and fondaparinux unchanged from 2007 STEMI Focused Update

ESC Guidelines: Primary PCI Adjunctive Therapies

Antithrombin co-therapy		
heparin	I	C
bivalirudin	IIa	B
fondaparinux	III	B

Management of Acute MI

- Reperfusion therapy
- Adjunctive antithrombotic therapy
- **Adjunctive mechanical therapy**
- Reperfusion Injury

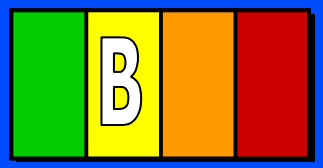
ESC Guidelines:

Recommendations	Class	LOE
Adjunctive devices		
thrombus aspiration	IIb	B

Thrombus Aspiration During PCI for STEMI

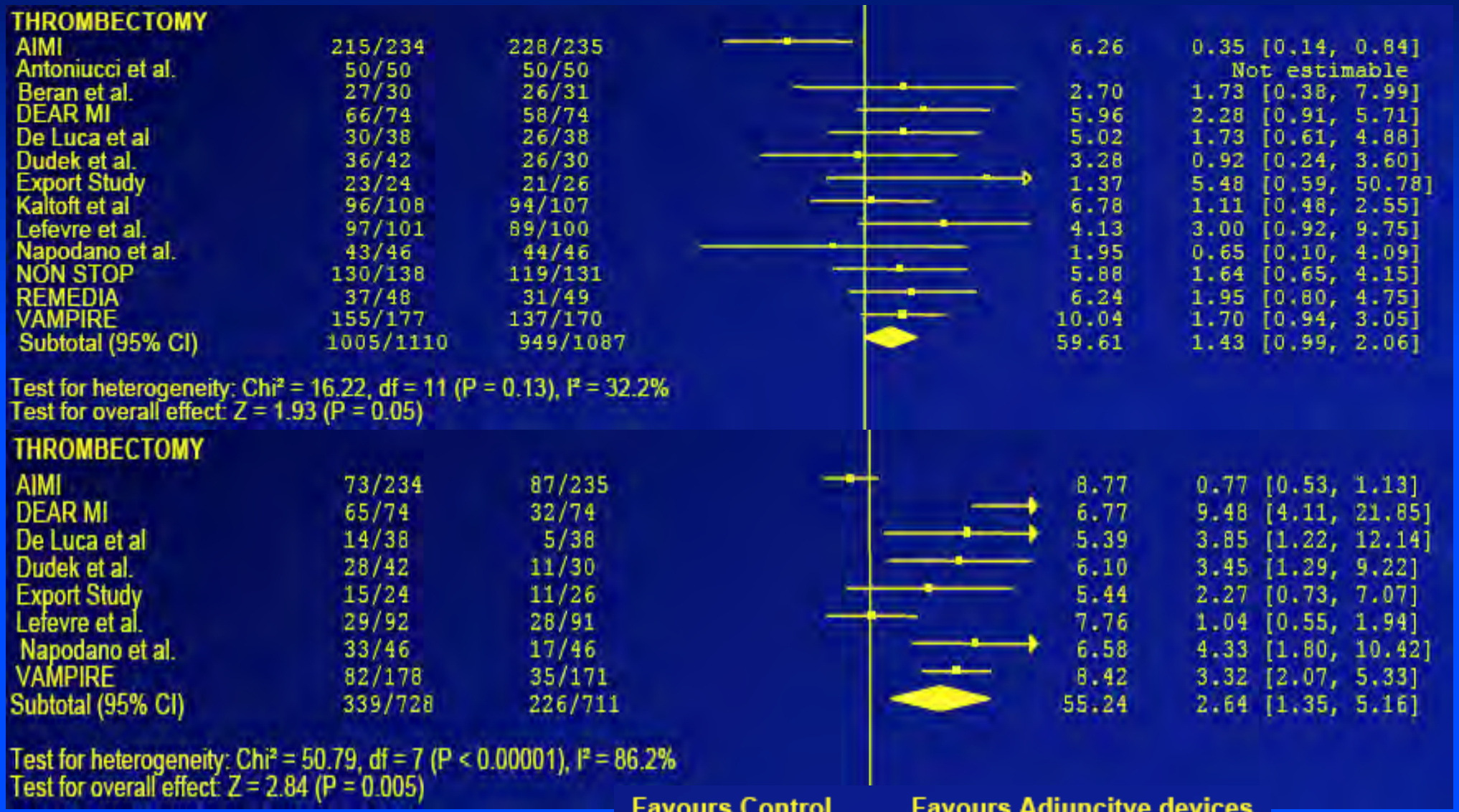
NEW Recommendation

I IIaIIbIII



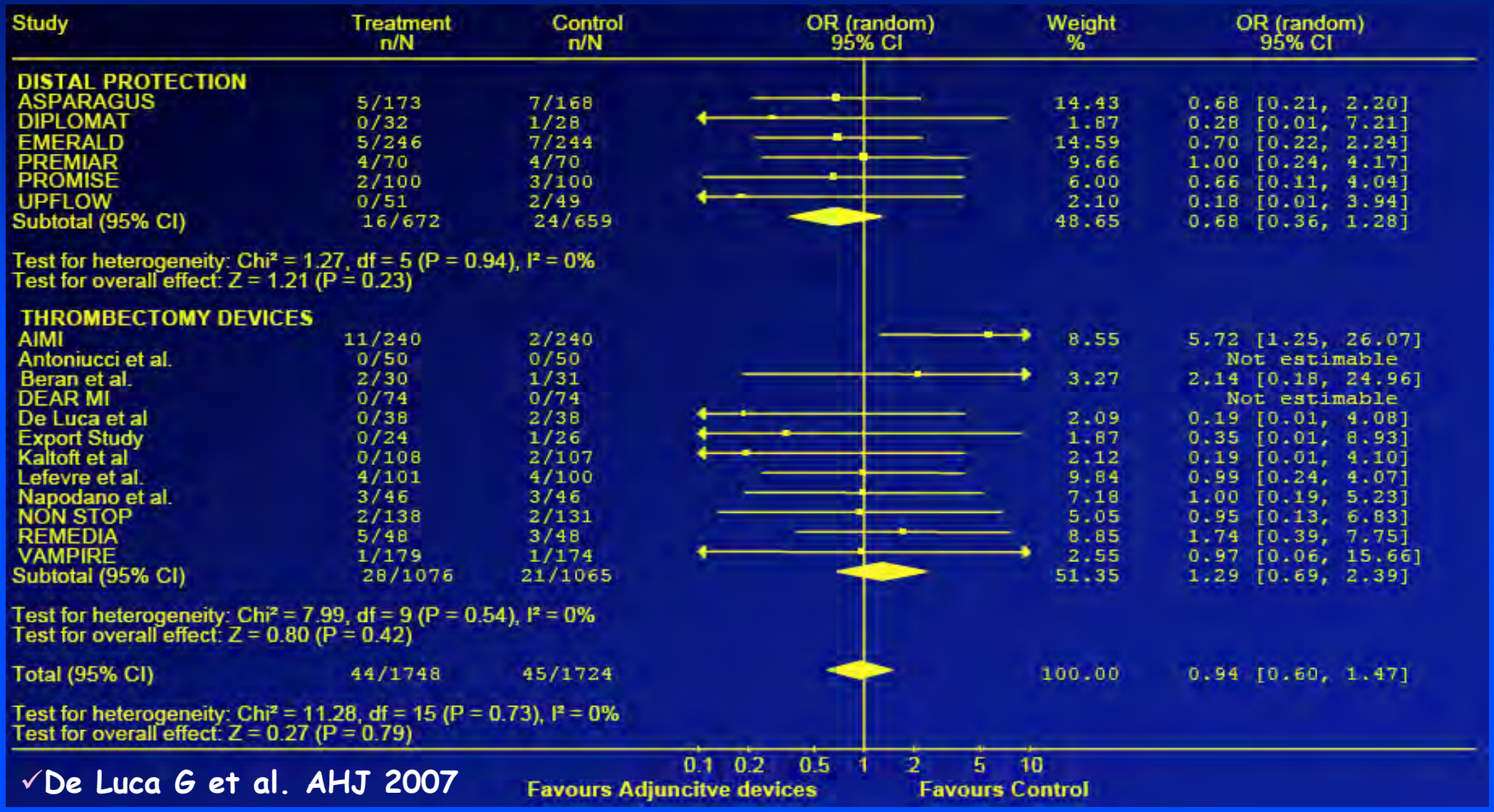
Aspiration thrombectomy is reasonable for patients undergoing primary PCI

PREVENTION OF DISTAL EMBOLIZATION IN AMI: A META-ANALYSIS TIMI 3 FLOW & MPG 3



✓De Luca G et al. AHJ 2007

PREVENTION OF DISTAL EMBOLIZATION IN AMI: A META-ANALYSIS - 30 DAYS MORTALITY



✓De Luca G et al. AHJ 2007

TAPAS Study

- A total of 1071 patients were randomly assigned to the thrombus-aspiration group or the conventional-PCI group before undergoing coronary angiography.

- Angiographic and electrocardiographic signs of myocardial reperfusion, as well as clinical outcome were assessed .

Svilaas T et al. *N Engl J Med* 2008; 358:557-567.

Myocardial reperfusion as assessed by angiography and electrocardiography

End point	Thrombus aspiration during PCI (%)	Conventional PCI (%)	p
Myocardial blush grade 0 or 1	17.1	26.3	<0.001
Complete resolution of ST-segment elevation	56.6	44.2	<0.001
Absence of persistent ST-segment deviation	53.1	40.5	<0.001

Svilaas T et al. *N Engl J Med* 2008; 358:557-567.

Outcomes at one year by treatment group, aspiration vs no aspiration, in TAPAS

End point	Stenting with predilatation, n=536 (%)	Aspiration before stenting, n=535 (%)	p
Death	7.9	4.2	0.040
Death/ nonfatal reinfarction	11.6	6.7	0.016

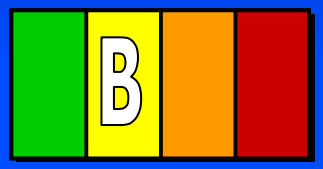
Svilaas T et al. *N Engl J Med* 2008; 358:557-567.

Recommendations for the use of DES in STEMI

Use of stents in STEMI

NEW Recommendation

I IIaIIbIII



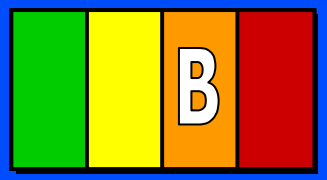
It is reasonable to use a drug-eluting stent as an alternative to a bare-metal stent for primary PCI in STEMI

* Consideration for the use of stents (DES or BMS) in STEMI should include the ability of the patient to comply with prolonged dual antiplatelet therapy, the bleeding risk in patients on chronic oral anticoagulation, and the possibility that the patient may need surgery during the ensuing year

Use of stents in STEMI

MODIFIED Recommendation

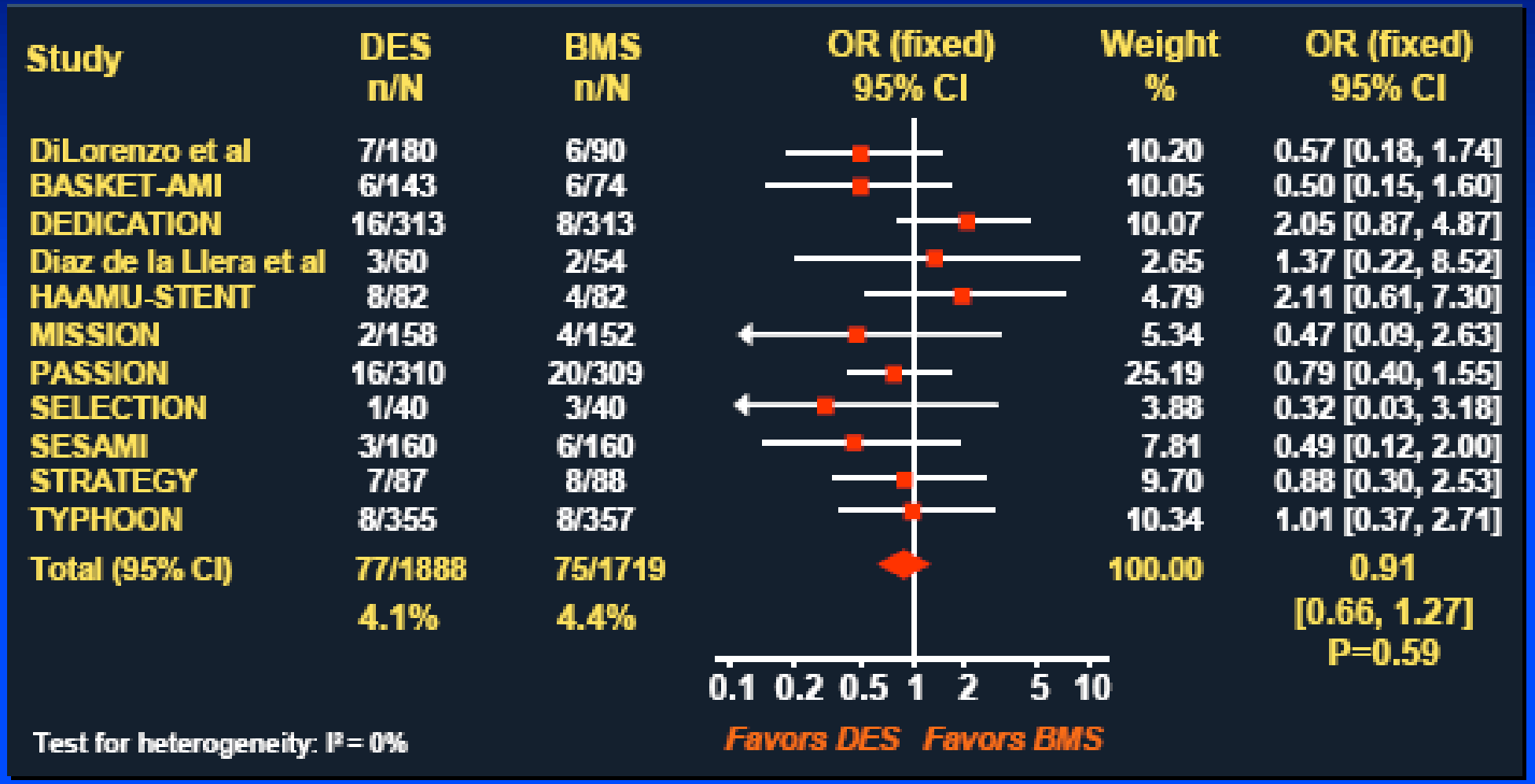
I IIaIIbIII



A DES may be considered for clinical and anatomic settingst in which the efficacy/safety profile appears favorable

11 DES vs. BMS RCTs in AMI (n=3,607)

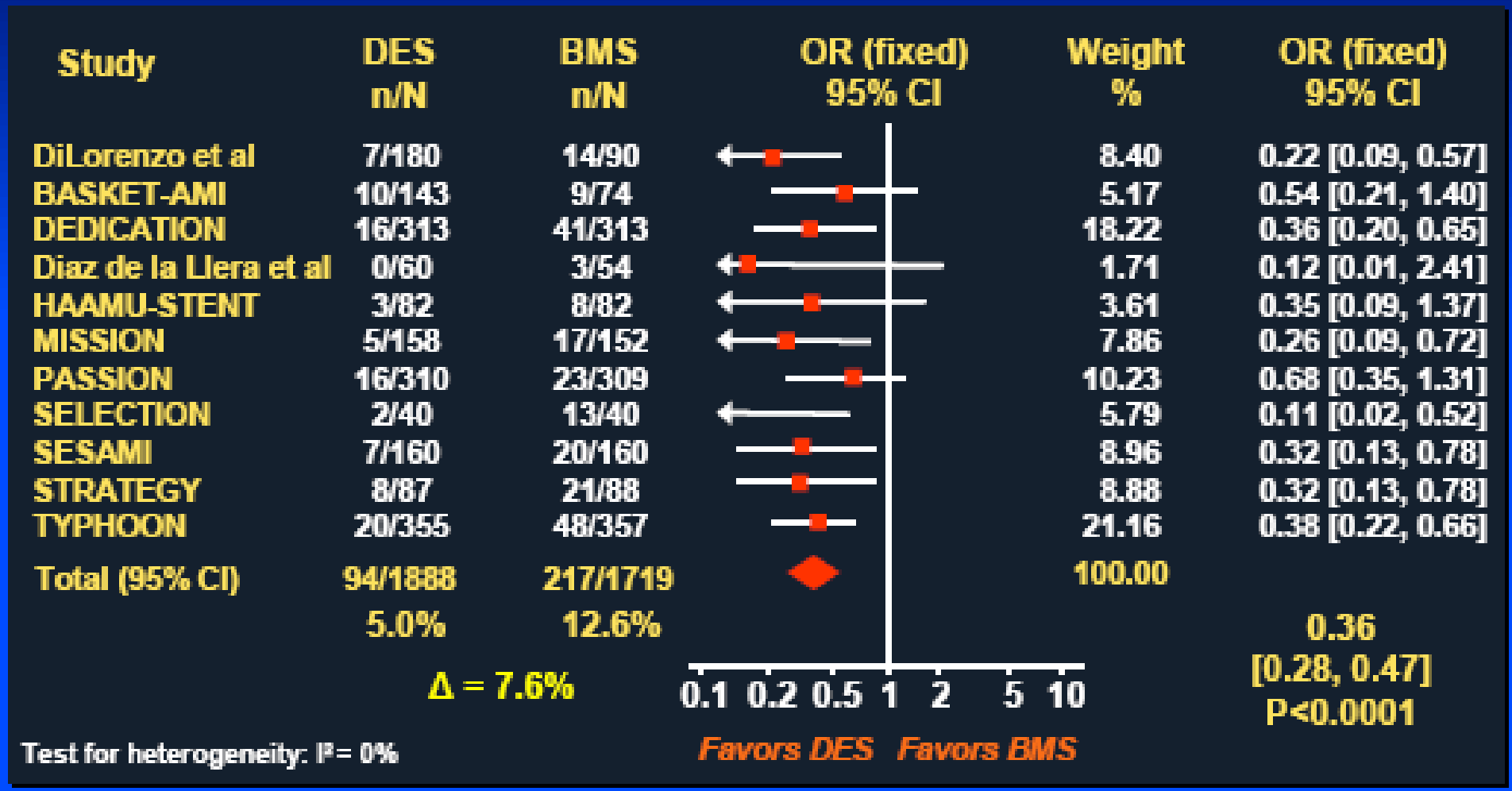
Death at 12 Months



De Luca G et al. *Int J Cardiol 2008*

11 DES vs. BMS RCTs in AMI (n=3,607)

TVR at 12 Months

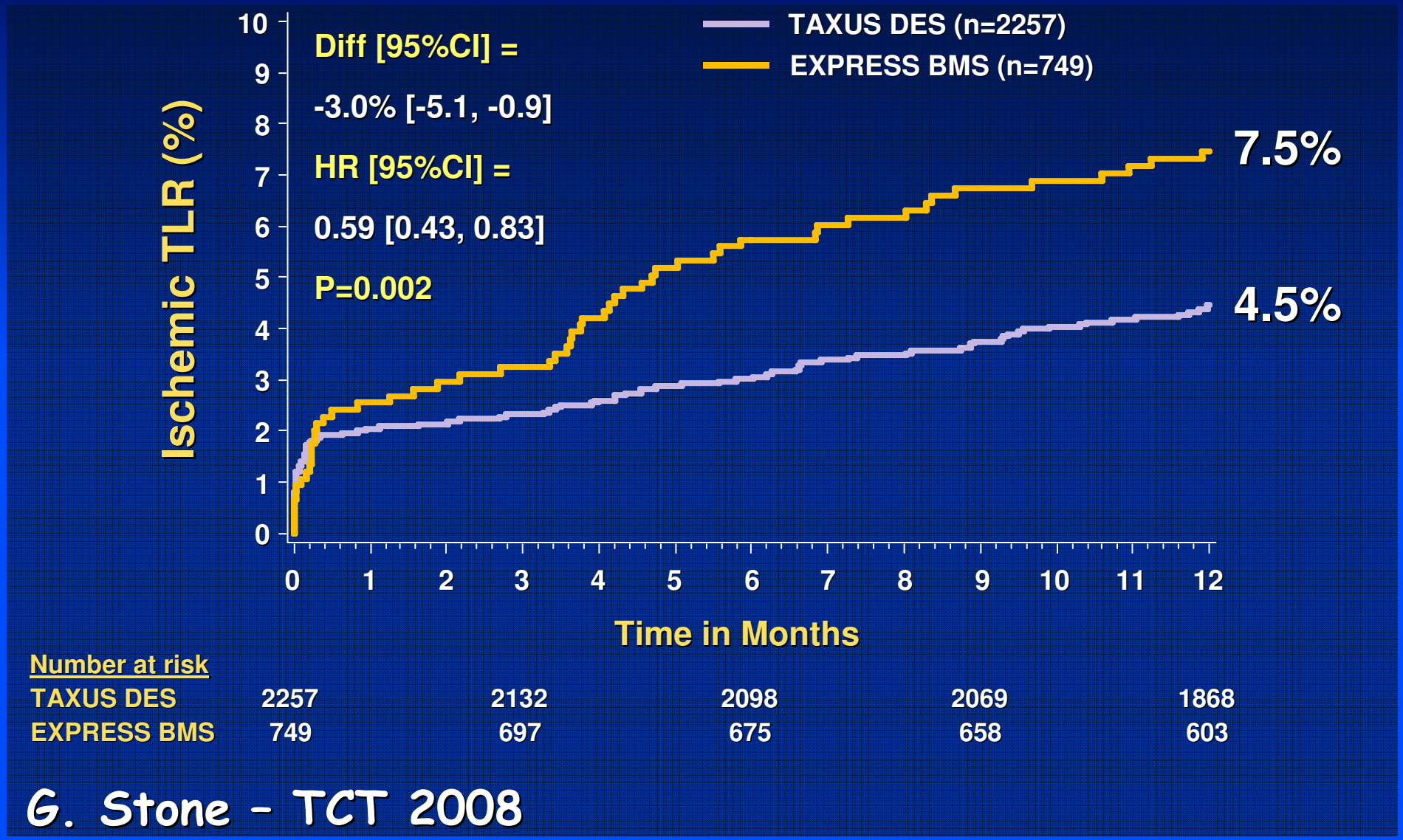


De Luca G et al. *Int J Cardiol 2008*

Primary Efficacy Endpoint:

Ischemic TLR

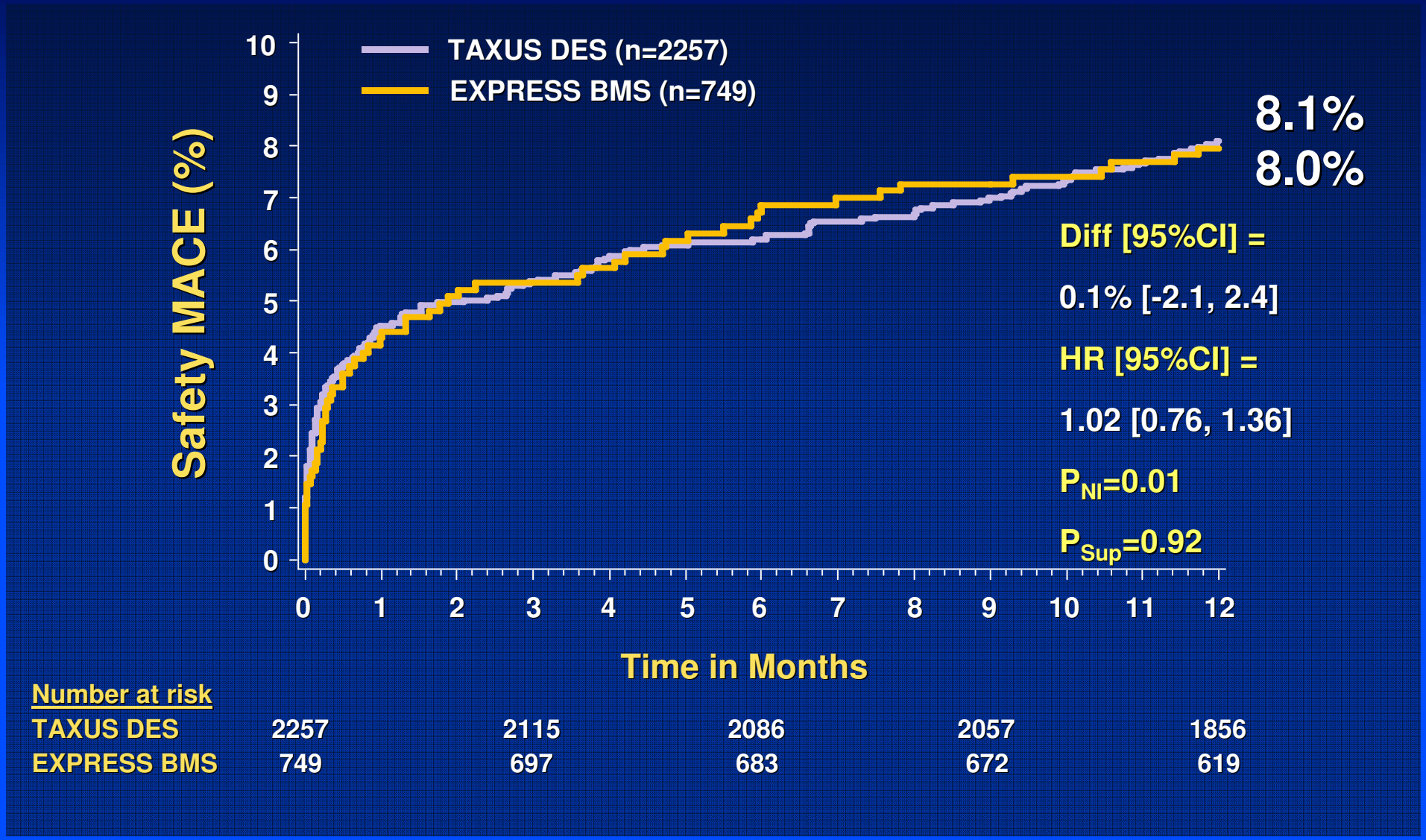
HORIZONS AMI



G. Stone - TCT 2008

Safety MACE*

HORIZONS AMI

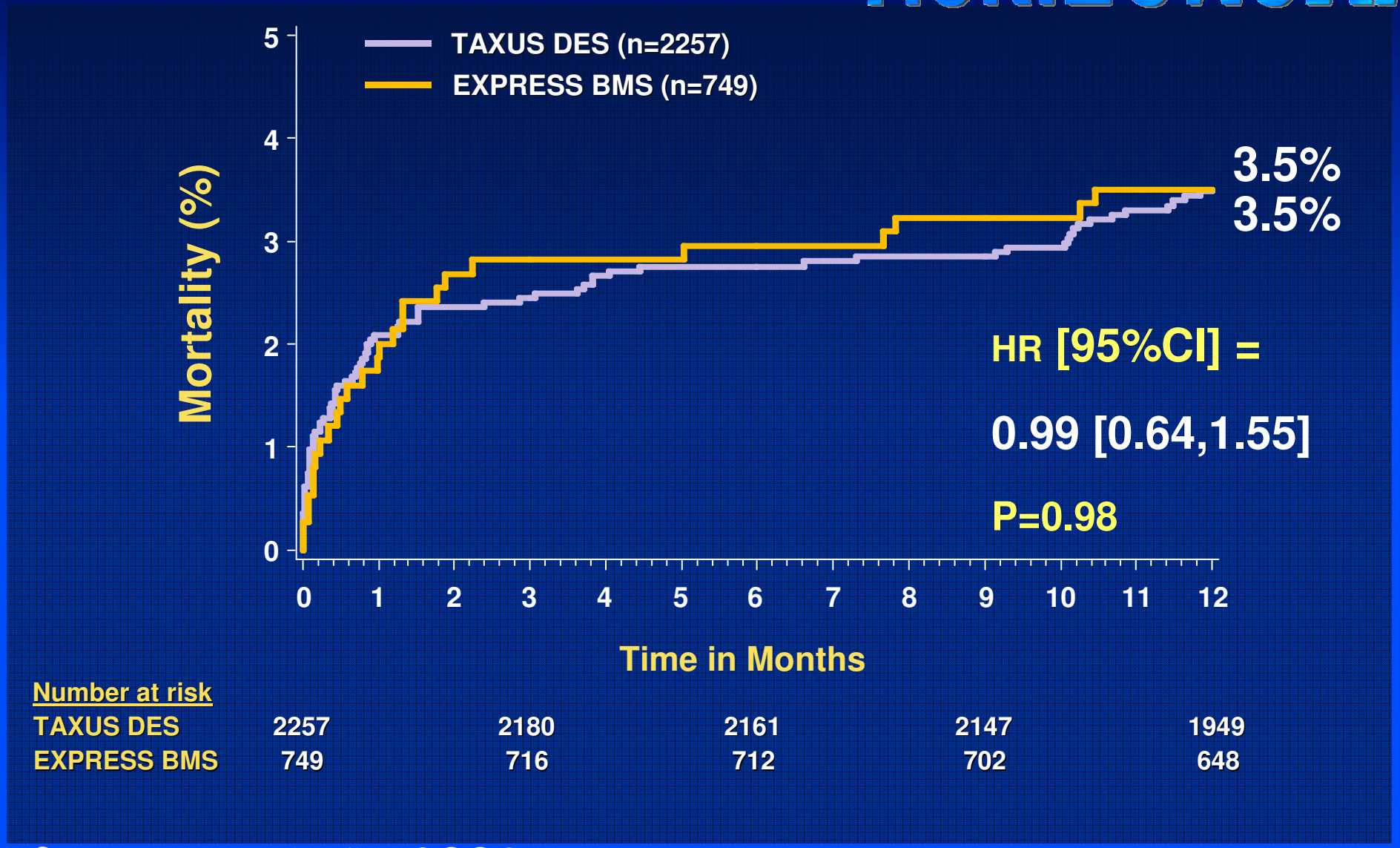


* Safety MACE = death, reinfarction, stroke, or stent thrombosis

G. Stone - TCT 2008

One-Year All-Cause Mortality

HORIZONS AMI



G. Stone - TCT 2008

Management of Acute MI

- Reperfusion therapy
- Adjunctive antithrombotic therapy
- Adjunctive mechanical therapy
- **Reperfusion Injury**

Reperfusion Injury in Acute MI

Outcomes of Trials of Reperfusion Injury Agents

Agent	No. of Patients	Effect on MI Size	Effect on Clinical Endpoints
Antioxidant Agents			
Trimetazidine	19,725	-	No effect
SOD	120	No effect	-
Reduction of Ca^{+2} Overload or Na^{+}/H^{+} Exchange Inhibitors			
Cariporide	3439	No effect	No effect
Eniporide	1389	No effect	No effect
Diltiazem	874	-	No effect
MCC-135	387	No effect	-
Other Interventions			
Adenosine	2118	Reduced	No effect
GIK	20,201	-	No effect

Yellon D and Hausenloy D. N Engl J Med 2007;357:1121-1135

Reperfusion Injury in Acute MI

Outcomes of Trials of Reperfusion Injury Agents

Agent	No. of Patients	Effect on MI Size	Effect on Clinical Endpoints
Anti-Inflammatory Agents			
Pexilizumab	5745	-	No effect
Pexilizumab	960	No effect	No effect
Pexilizumab	943	No effect	No effect
CD-11, Cd-18 Ab	420	No effect	No effect
CD-18 Ab	394	No effect	-
Other Interventions			
Magnesium	6213	-	No effect
Magnesium	4319	-	No effect
Magnesium	2316	-	Improved death, CHF
Nicorandil	545	No effect	No effect

Yellon D and Hausenloy D. N Engl J Med 2007;357:1121-1135

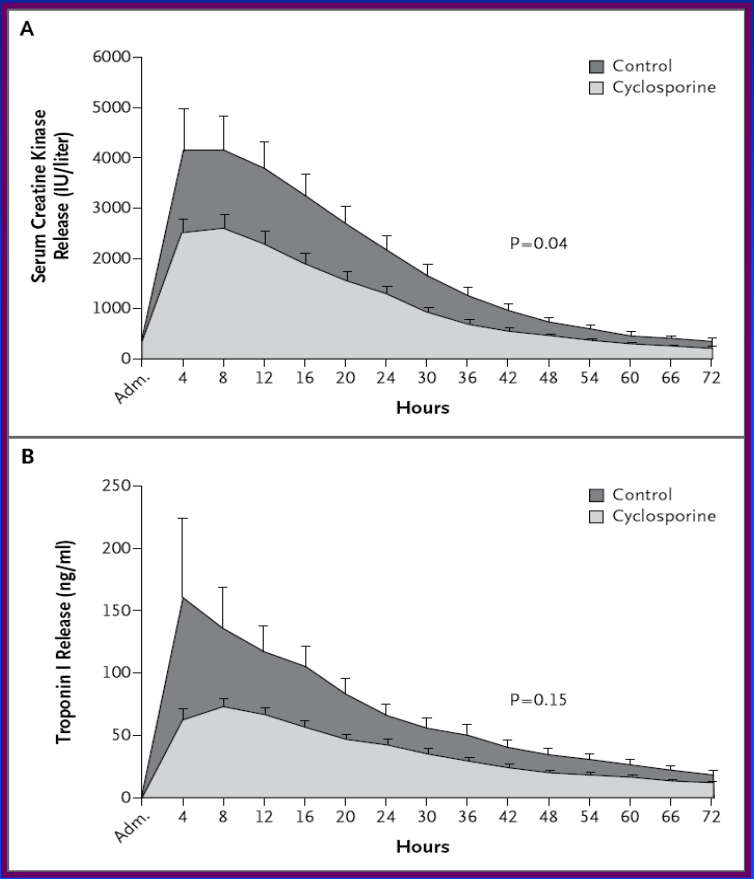
Novel Approaches to Reperfusion Injury

Mitochondrial Permeability Transition Pore (PTP) inhibition

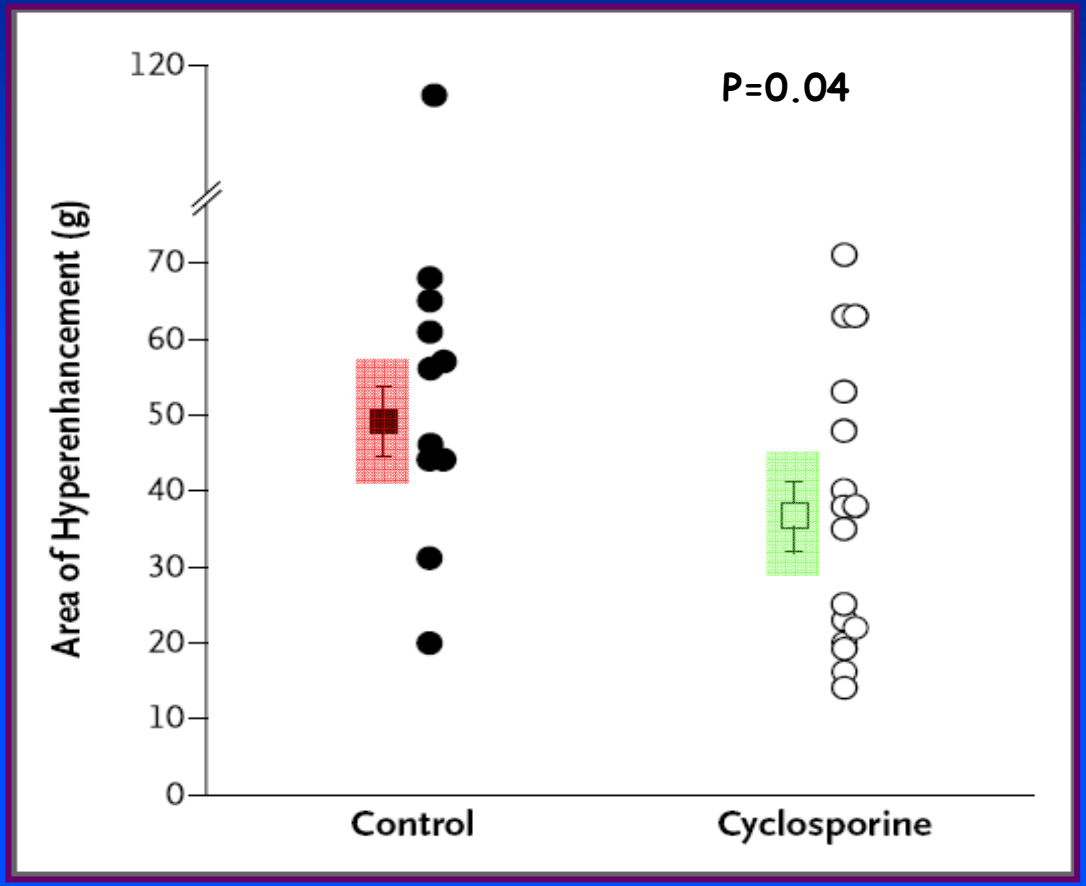
- Reperfusion opens the MPTP via calcium overload and reactive oxygen species
- Opening the MPTP uncouples the respiratory chain leading to release of proapoptotic factors
- Cyclosporine is a potent inhibitor of reperfusion-mediated mitochondrial permeability transision
- Pilot trial (n=58) of intravenous cyclosporine or placebo bolus prior to primary PCI in patients presenting with STEMI

Pre-PCI Cyclosporine and Infarct Size

Enzymatic



MRI



Piot et al. NEJM 2008;359:473

Inhibition of Protein Kinase C

- PROTEin kinase C inhibiTION to reduce infarct size in Acute Myocardial Infarction (PROTECTION-AMI)
- Randomized, placebo controlled investigation of intravenous infusion of KAI-9803 in patients with anterior STEMI (small inferior cohort) begun prior to primary PCI
- Primary endpoint – reduction in infarct size as measured by CK-MB AUC
- Additional clinical endpoints and infarct size by MUGA (small MRI cohort)

Thank You

ESC Guidelines

Doses of Antiplatelet Co-therapies

With Primary PCI

Aspirin:	Oral dose of 150-325 mg or i.v. dose of 250 to 500 mg if oral ingestion is not possible
Clopidogrel:	Oral loading dose of 300 or 600 mg
GPIIb/IIIa inhibitors:	Abciximab: i.v. bolus of 0.25 mg/kg bolus followed by 0.125 µg/kg per min infusion (maximum 10 µg/min for 12 h)

Recommendations for the use of Thienopyridines

MODIFIED Rec

For STEMI patients undergoing *non-primary* PCI, the following regimens are recommended:

If the patient has received fibrinolytic therapy…

I IIa IIb III

C

a. …and has been given clopidogrel, it should be continued as the thienopyridine of choice.

b. …without a thienopyridine, a loading dose of 300-600‡ mg of clopidogrel should be given as the thienopyridine of choice.

If the patient did not receive fibrinolytic therapy…

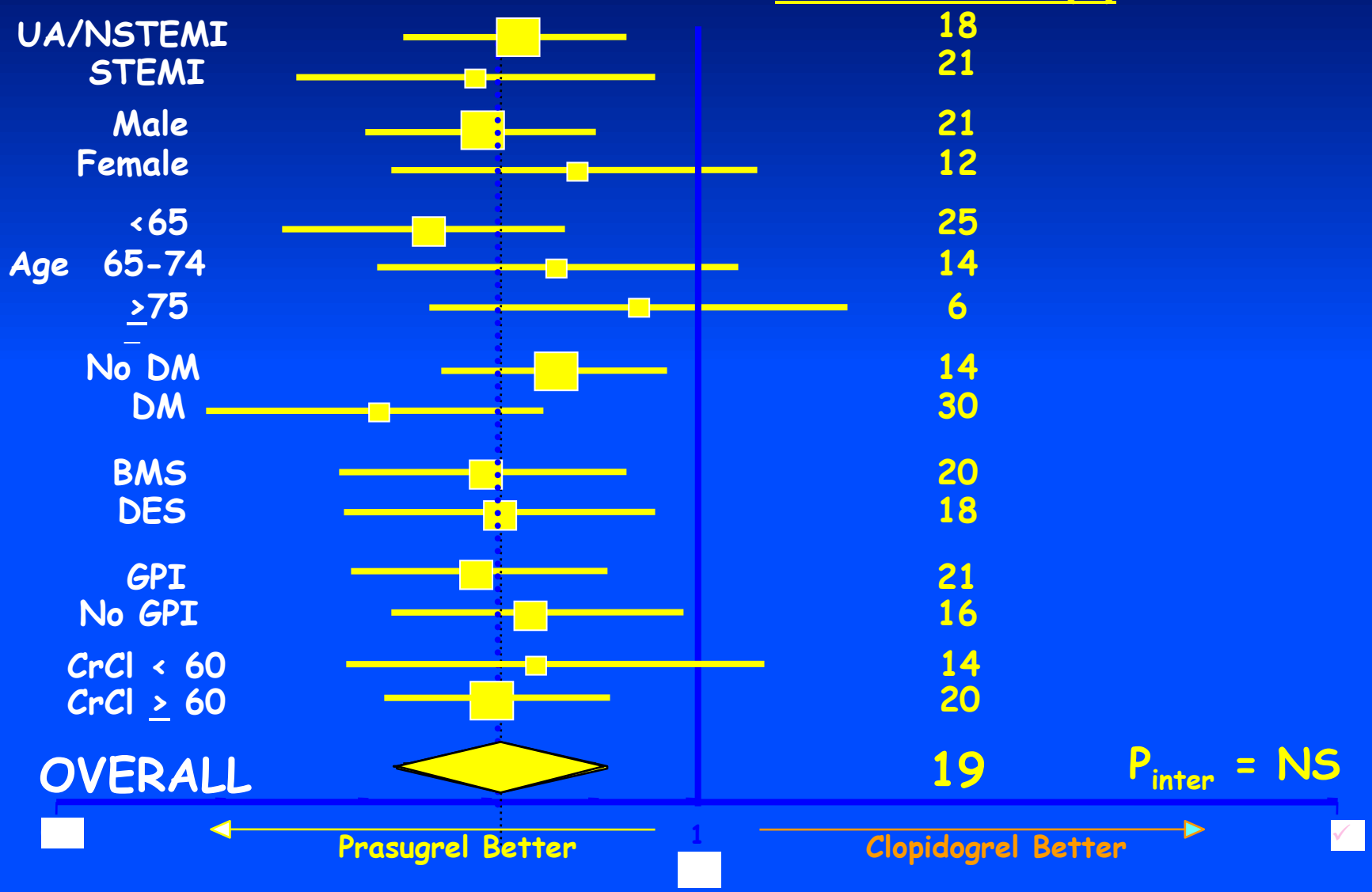
I IIa IIb III

B

c. …either a loading dose of 300-600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after the PCI.

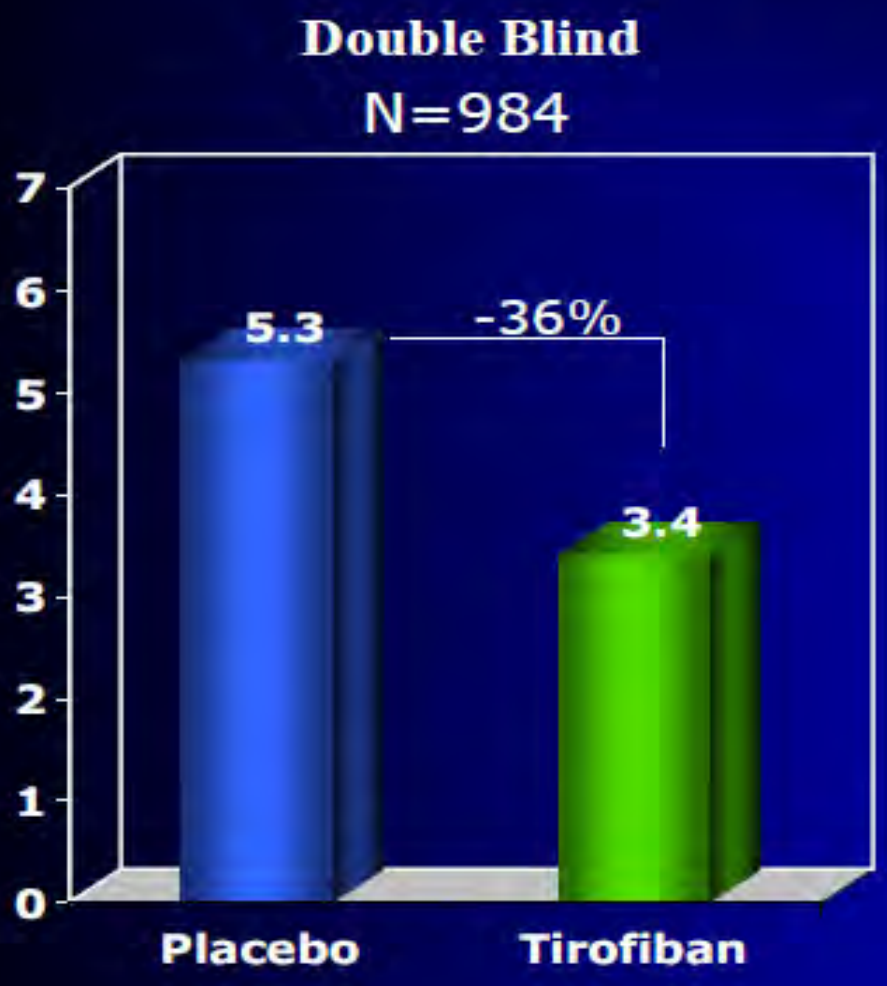
TRITON TIMI-38

CV Death, MI, Stroke
Major Subgroups

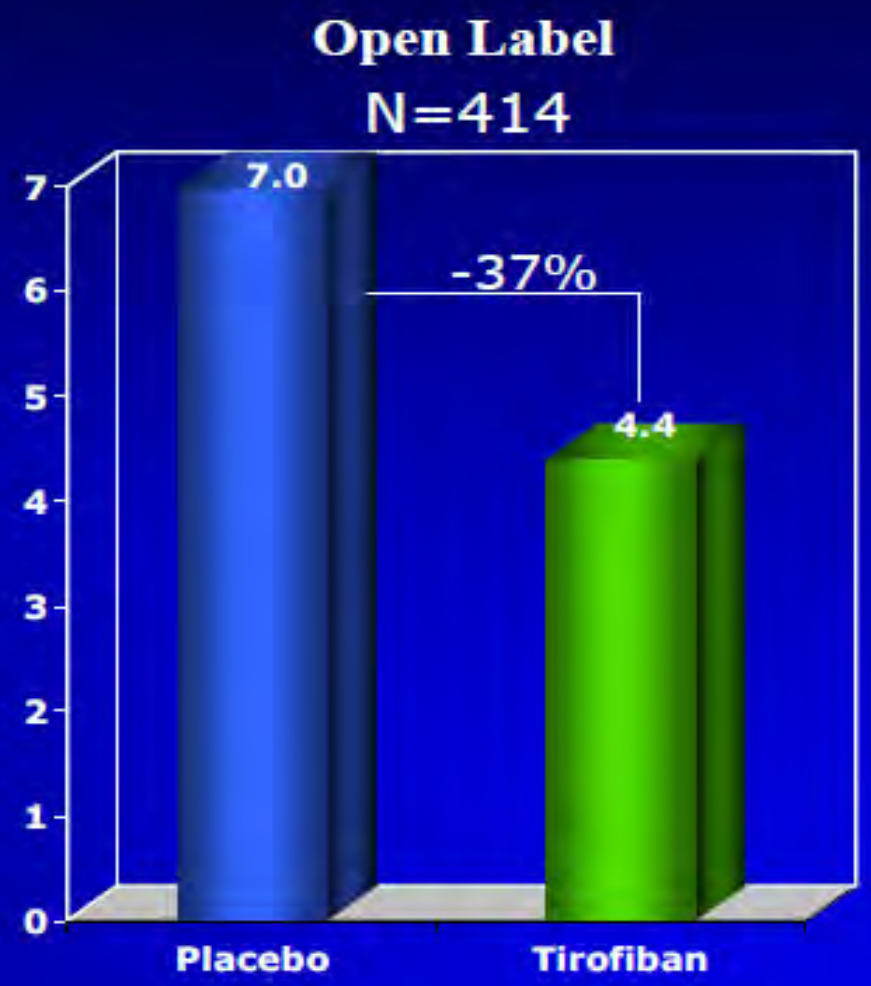


Wiviott SD et al NEJM 357: 2001, 2007

All cause Mortality 1 Year



RR: 0.78 (95% CI: 0.53-1.14, p=0.157)



RR: 0.77 (95% CI: 0.46-1.29, p=0.276)

Outcomes at one year by myocardial blush grade* in TAPAS

End point	Grade 3 (%)	Grade 2 (%)	Grade 0 or 1 (%)	p for trend
Death	3.7	4.7	11.0	0.001
Death/ nonfatal reinfarction	6.1	7.6	14.8	0.001

*0–1=no or minimal myocardial blush

2=moderate blush

3=normal blush

Reflecting no or minimal, moderate, and normal myocardial perfusion.

Svilaas T et al. *N Engl J Med* 2008; 358:557-567.