

ALPIC2012

Advanced Learning on Platelets & Thrombosis International Course

Antithrombotic combinations in PCI. Safety and efficacy.

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1st Cardiology Department

Hippokration Hospital

ENLARGE

THUMBNAILS

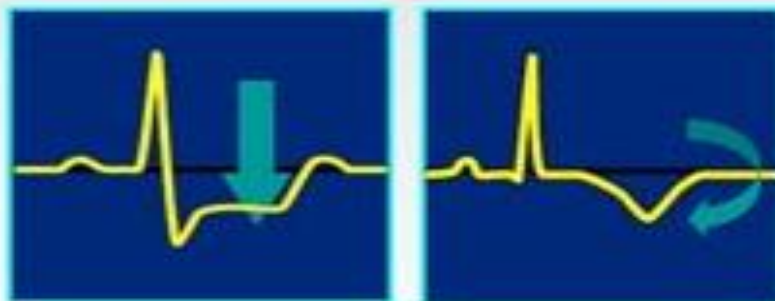


ACS With ST- Elevation STEMI



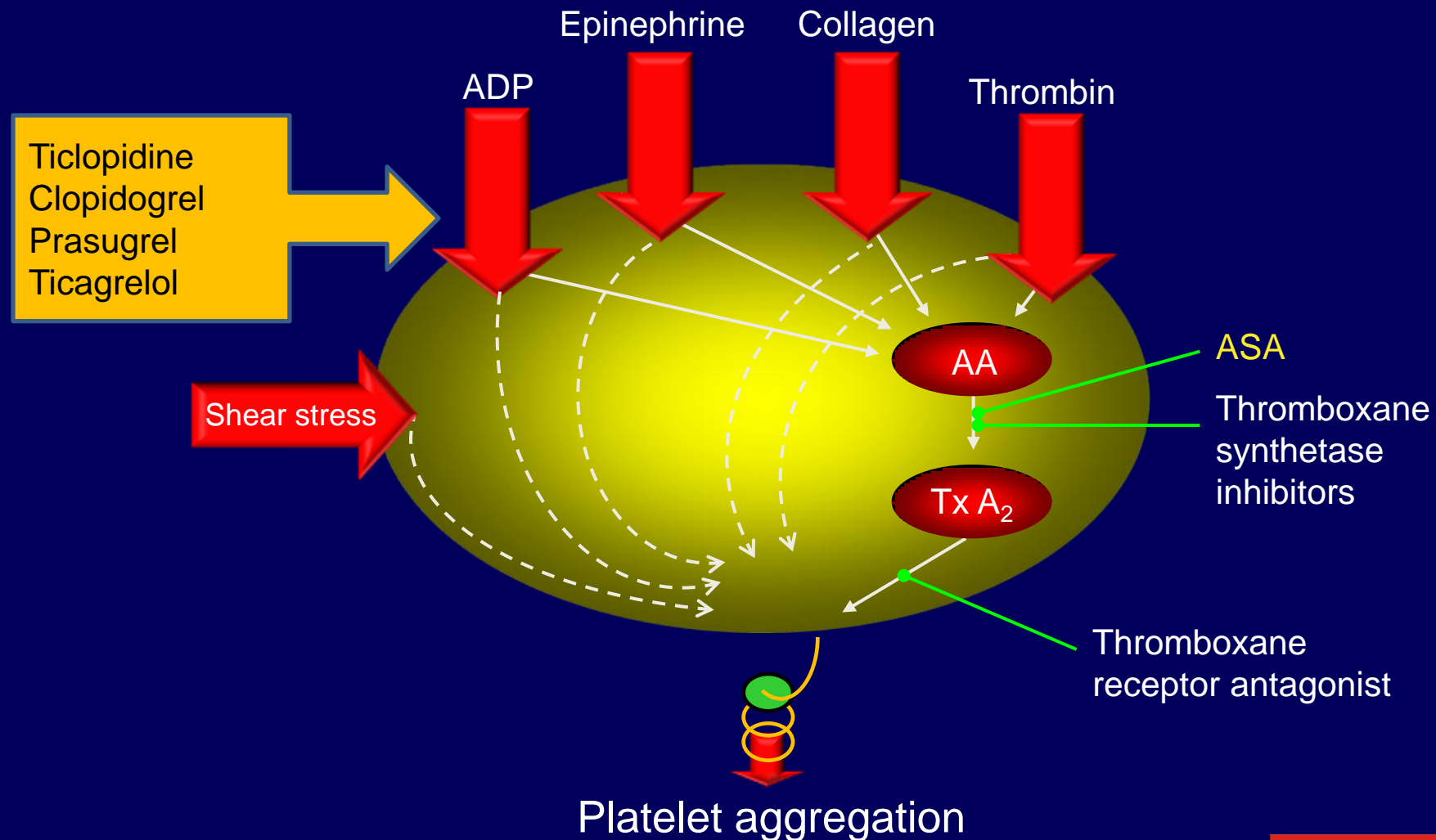
Troponin & creatinine elevated

ACS Without ST- Elevation NSTEMI / Unstable Angina

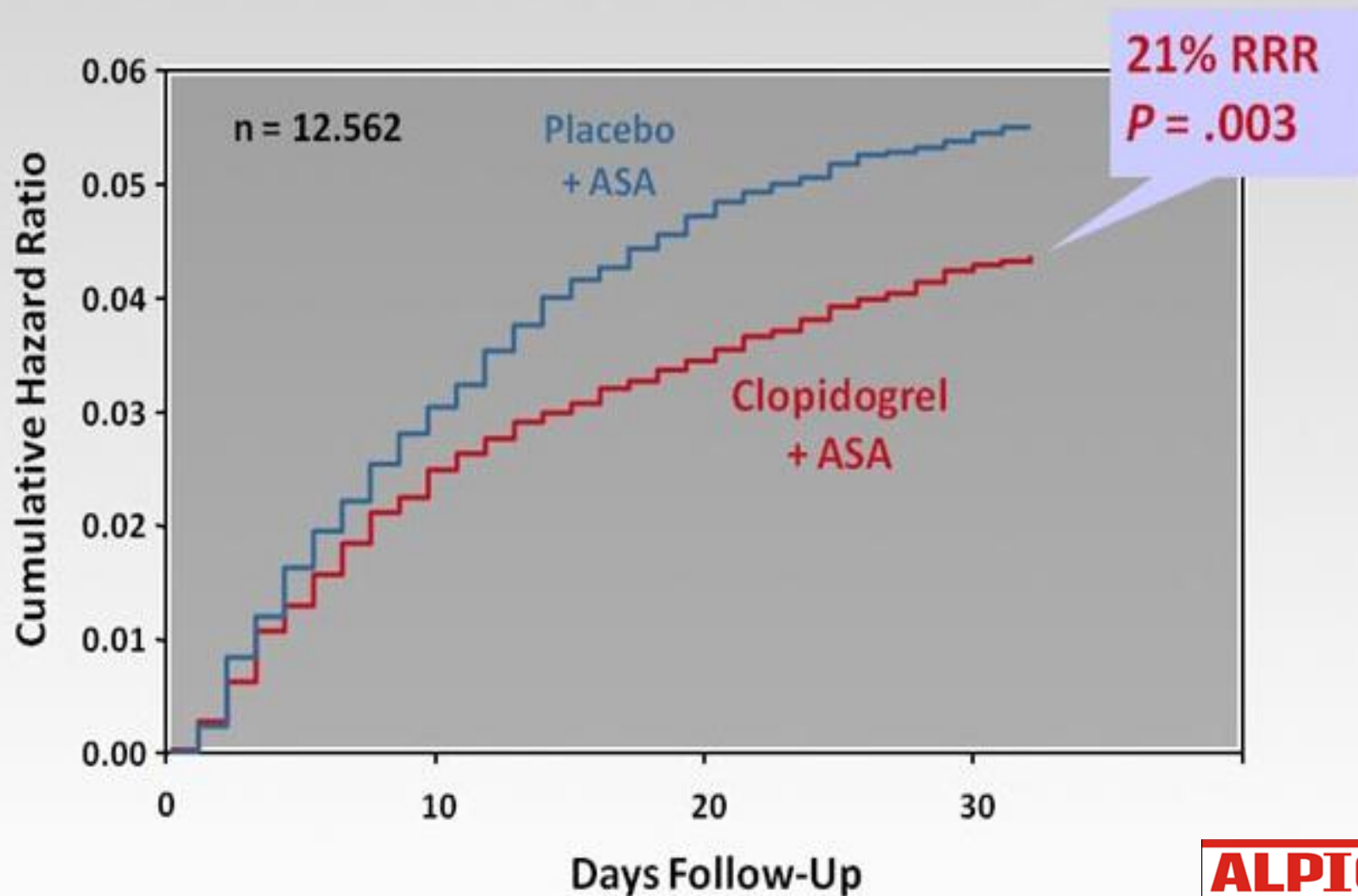


Troponins elevated or not

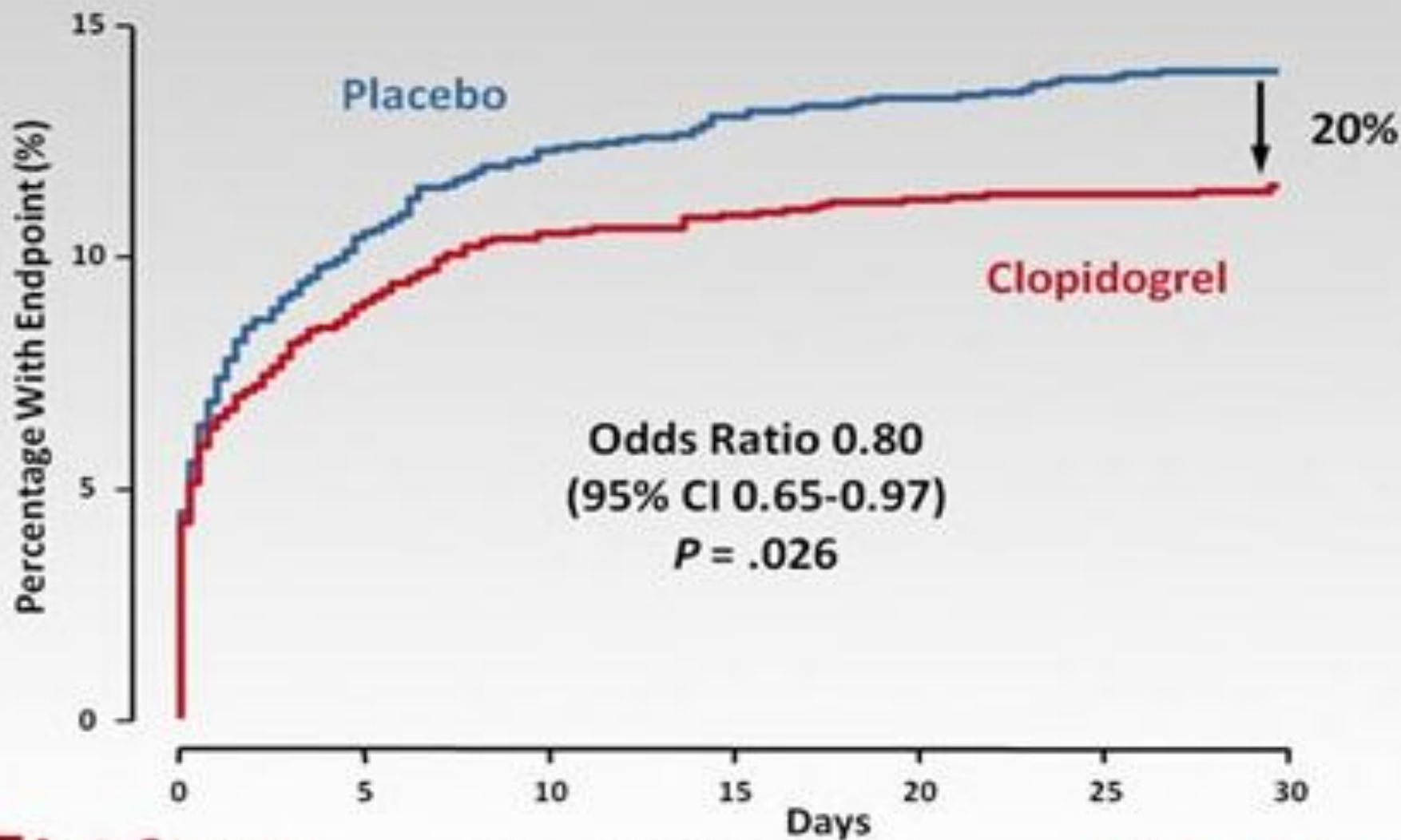
Agents That Inhibit Platelet Activation (dual antiplatelet therapy)



CURE: CV Death / AMI / Stroke in 30 days



CLARITY TIMI-28: CV Death, MI, RI → Urg Revasc





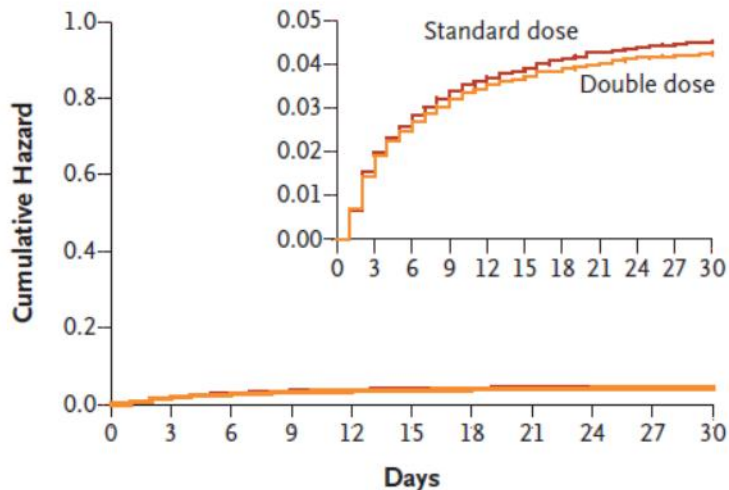
Clopidogrel Weaknesses

- ◆ Clopidogrel limitations:
 1. Prodrug, requiring 2 step metabolic activation
 2. Slow onset of effect
 3. Variability in response
 4. Low level of inhibition in one third of patients (resistance)

OASIS 7

Trial design: Patients presenting with ACS were randomized in a 2 x 2 factorial design to either low-dose or high-dose aspirin, and standard-dose or high-dose clopidogrel. Patients were followed for 30 days

A Clopidogrel



No. at Risk

Double dose	12,520	12,209	12,087	12,032	11,996	11,981
Standard dose	12,566	12,234	12,109	12,045	12,011	11,990

- No significant difference between a 7-day, double-dose clopidogrel regimen and the standard-dose regimen, with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke.
- Bleeding complications were higher with high-dose clopidogrel
- Significant reduction in 30-day events was observed among patients undergoing PCI including a reduction in definite stent thrombosis by 46% .

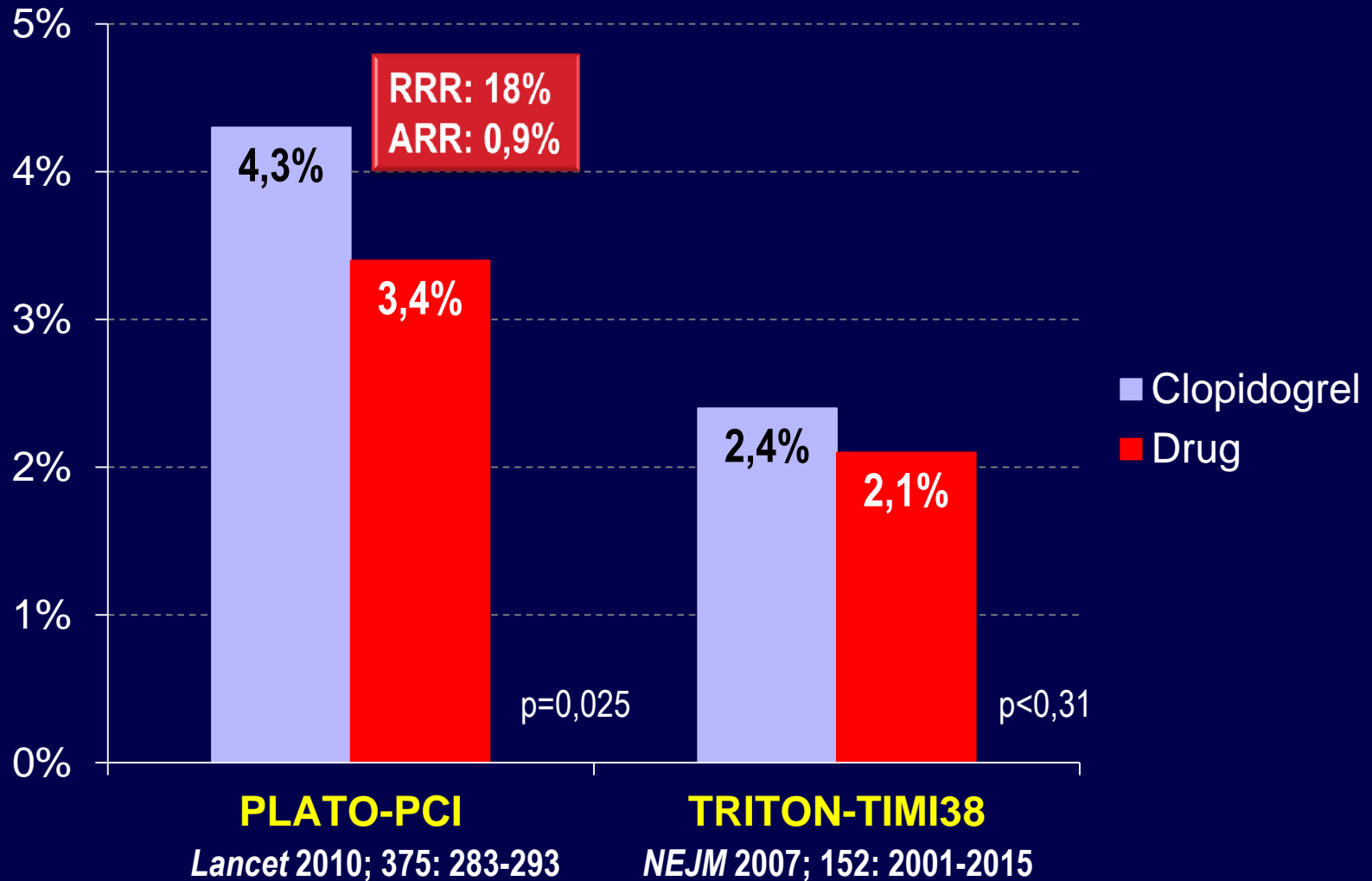
Oral P2Y₁₂ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Drug class	Thienopyridine	Thienopyridine	ATP analogue
Reversibility	irreversible	irreversible	reversible
Route of administration	oral	oral	oral
Time to peak effect	2-3h	1 h	120-240 min
Drug elimination half-life	3 h	3.7 h	12 h
Duration of action	5-8 days	5-10 days	24 h
Trials	CURE CHARISMA	TRITON	PLATO



PCI: Prasugrel & Ticagrelor c/v mortality

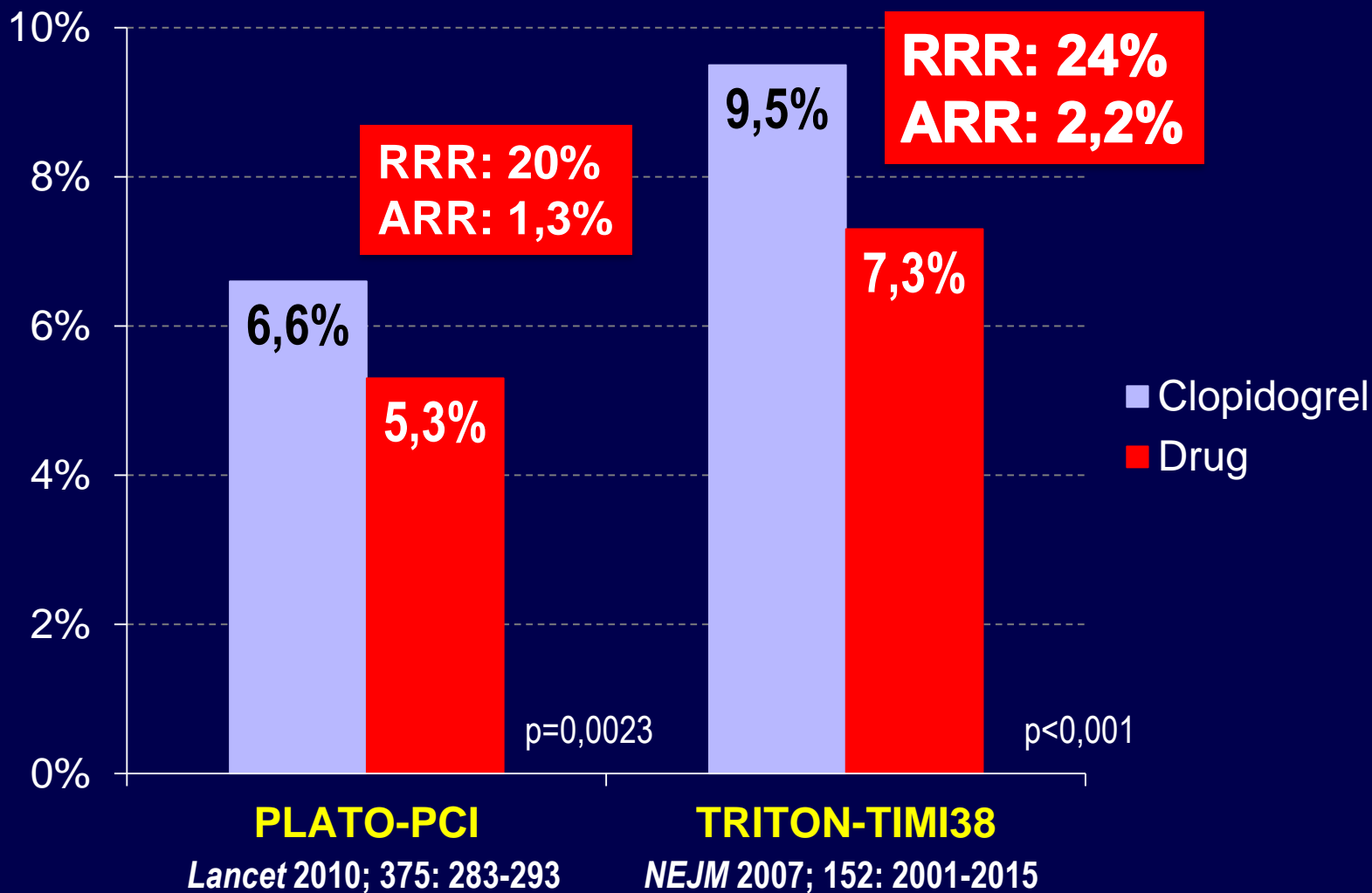
Secondary Endpoint





PCI: Prasugrel & Ticagrelor myocardial infarction

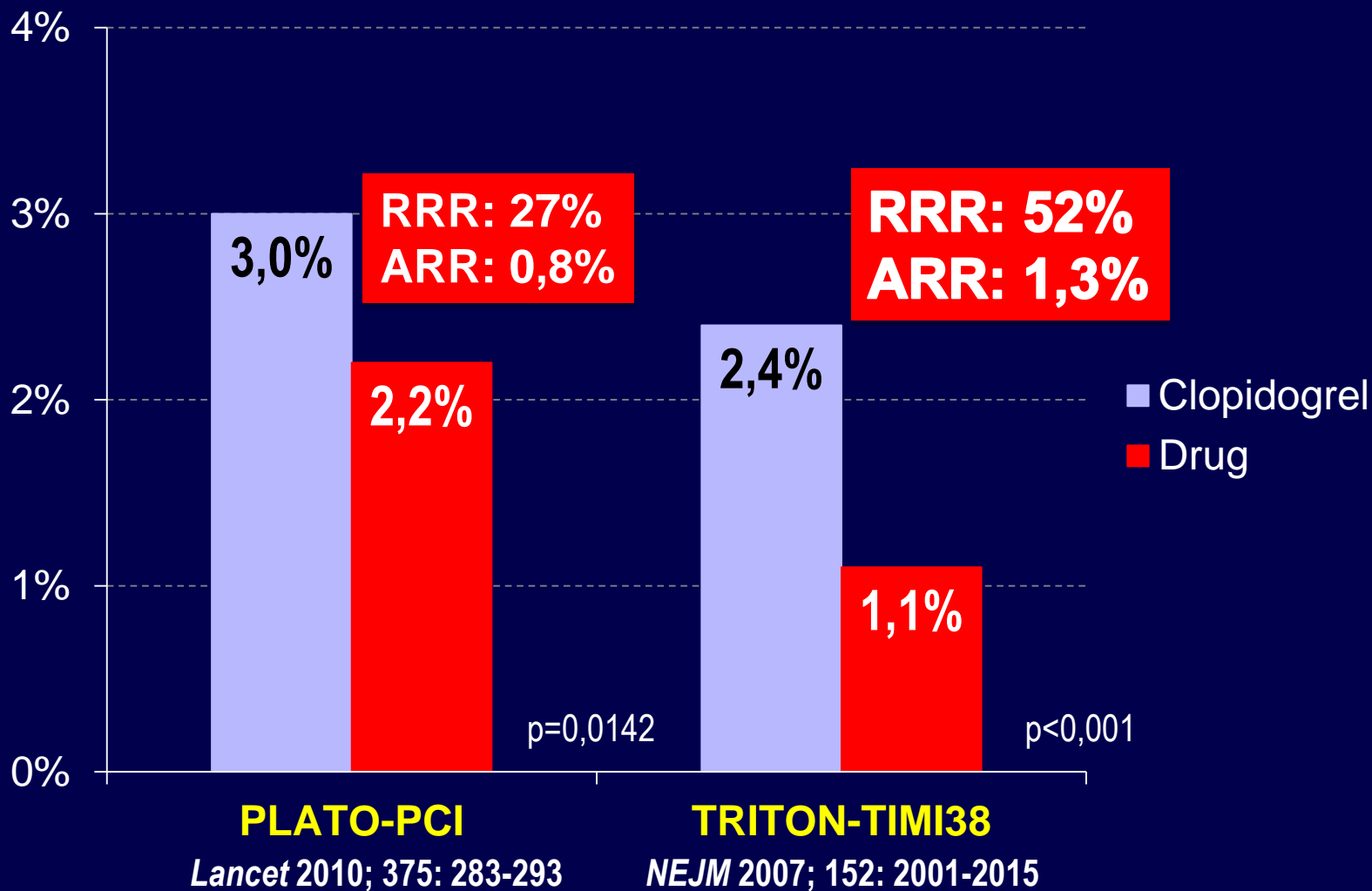
Secondary Endpoint





PCI: Prasugrel & Ticagrelor Stent Thrombosis

Secondary Endpoint



ESC Guidelines for the Management of ACS P₂Y₁₂ Recommendations

Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischemic events (eg, elevated troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is commenced).

Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P₂Y₁₂-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI, unless there is a high risk of life-threatening bleeding or other contraindications.

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.

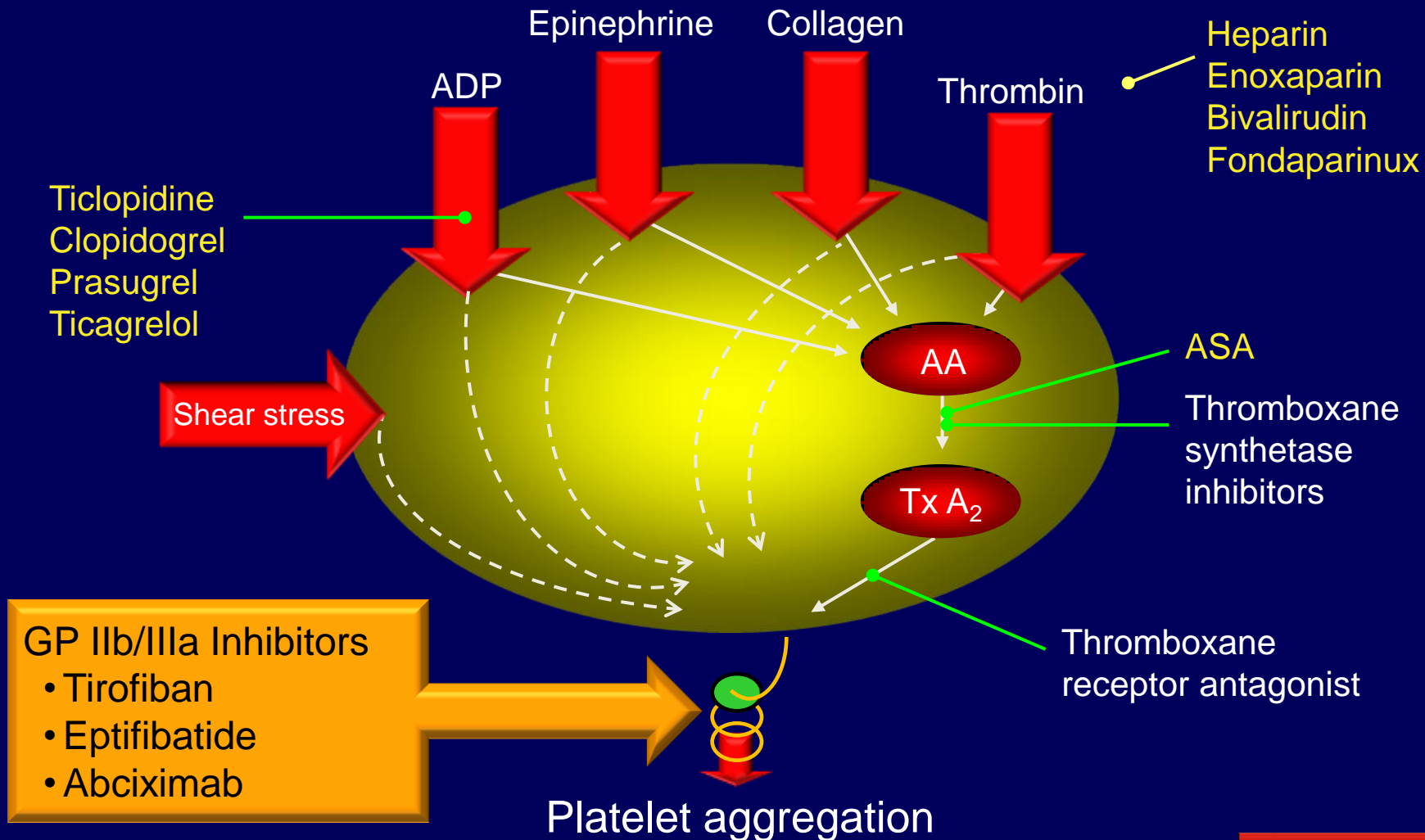
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.



Recommendations for oral antiplatelet agents (2)

Recommendations	Class	Level
Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600 mg loading dose of clopidogrel (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B
In patients pre-treated with P2Y ₁₂ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-)started after CABG surgery as soon as considered safe.	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

Agents That Inhibit Platelet Activation or Aggregation (GP IIb/IIIa Inhibitors)



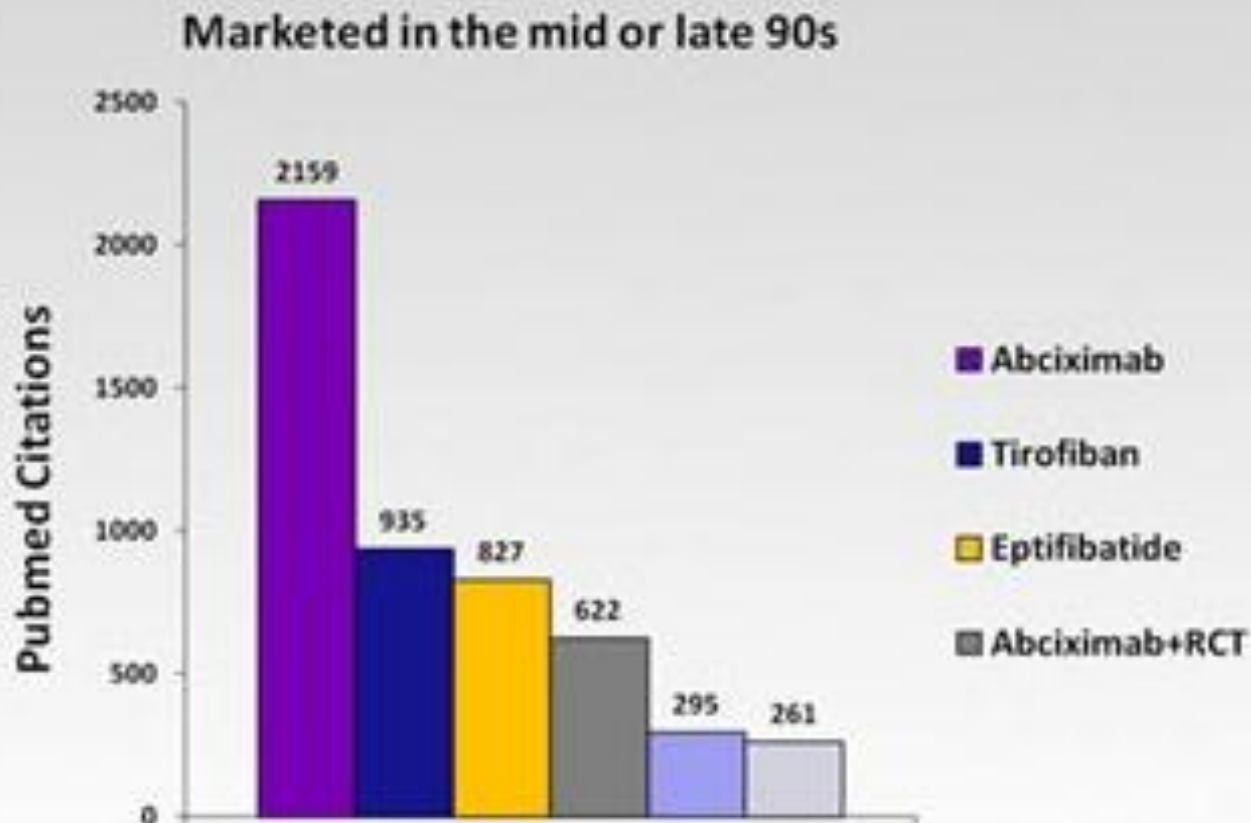
Triple Therapy

15

- Estimation of the risk of stroke,
- stent thrombosis
- and major bleeding
- Assessment of individual patients.

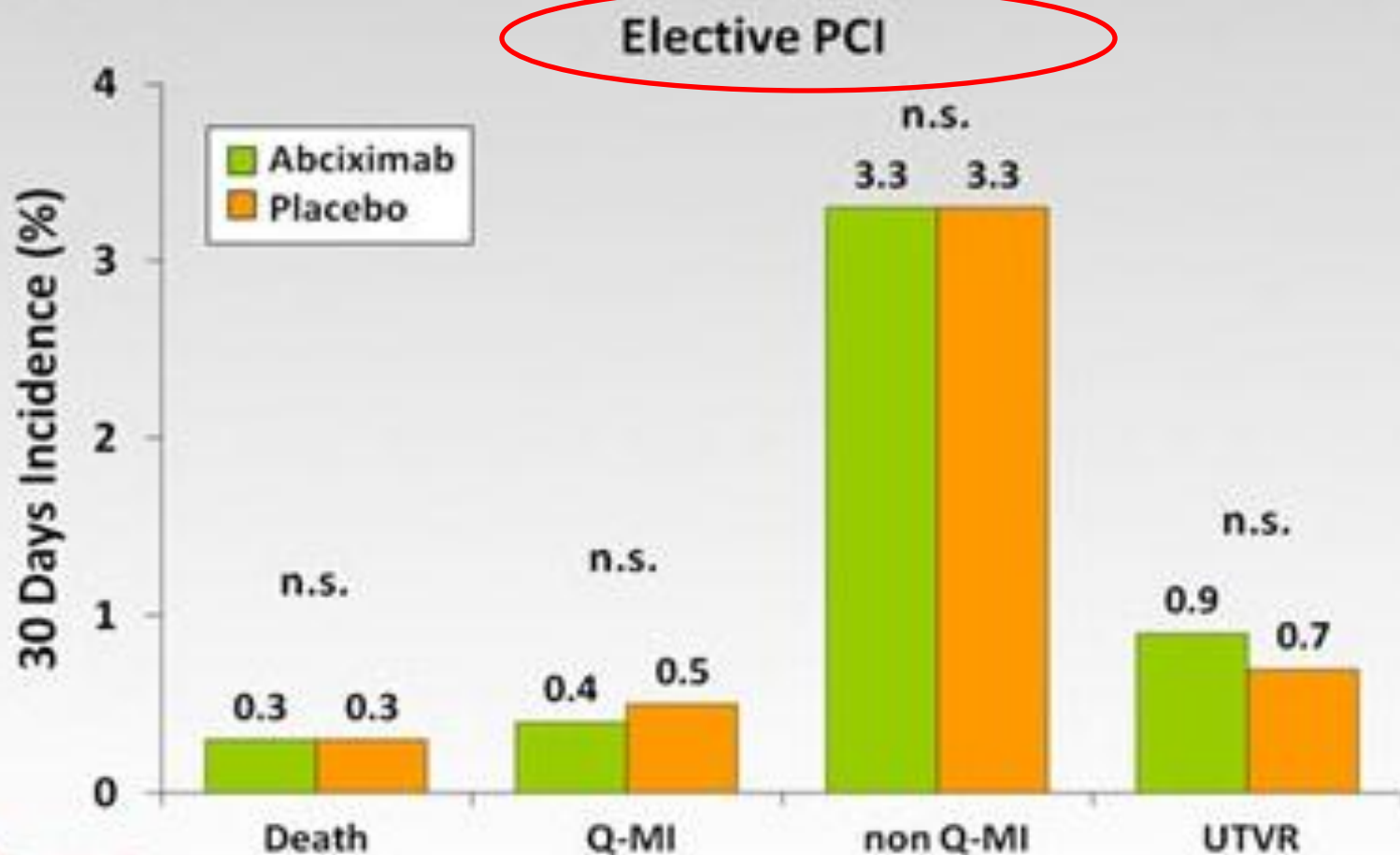
GP IIb/IIIa Antagonists:

A “mature” class of drugs



ISAR REACT Trial

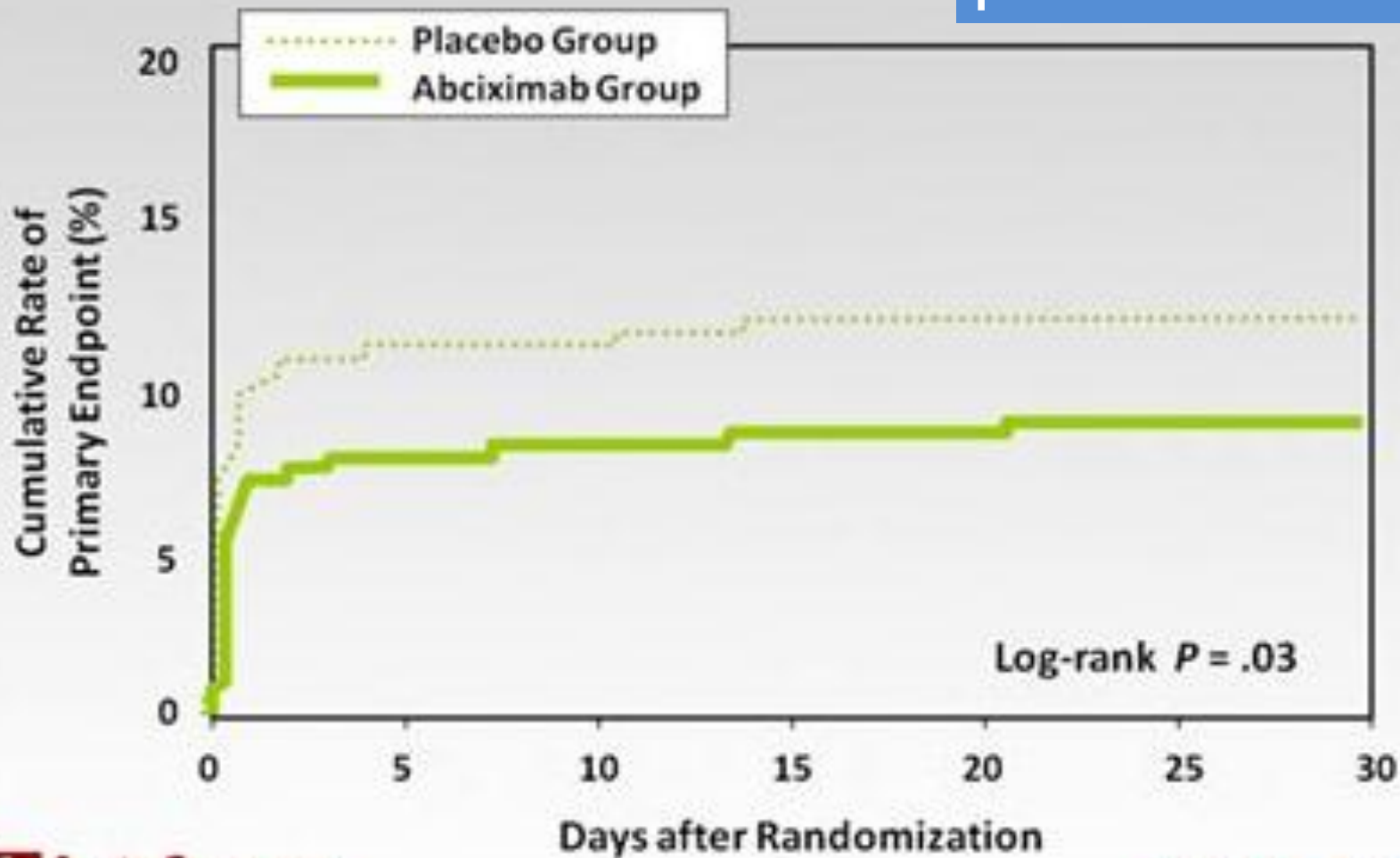
Effect of Abciximab on Top of Clopidogrel 600-mg Loading Dose



ISAR REACT 2 Trial

30-Day Ischemic Events

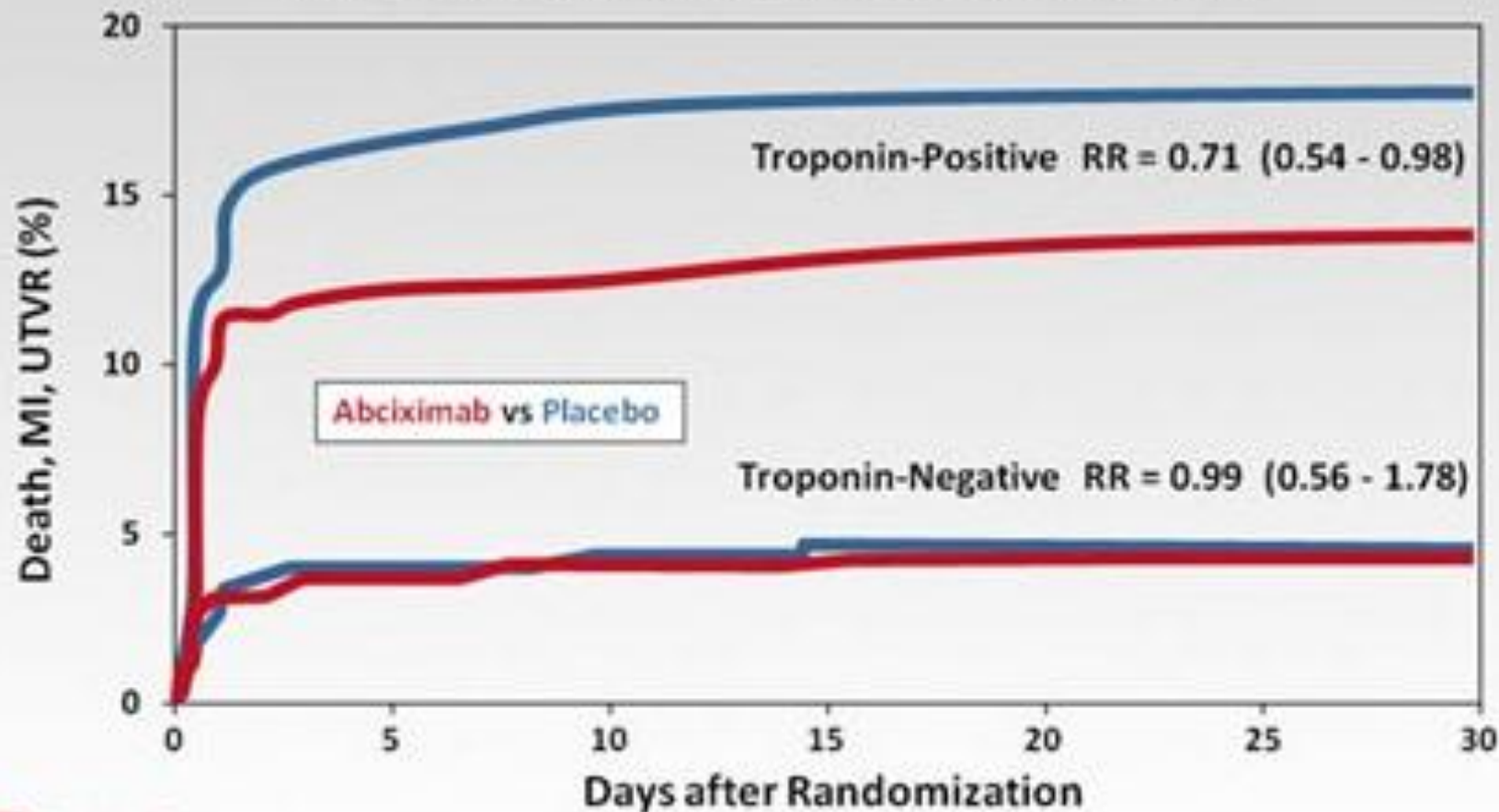
ACS
patients



Double vs Triple Antiplatelet Therapy ? ISAR-REACT-2

ACS

Troponin Level and Benefit of Abciximab

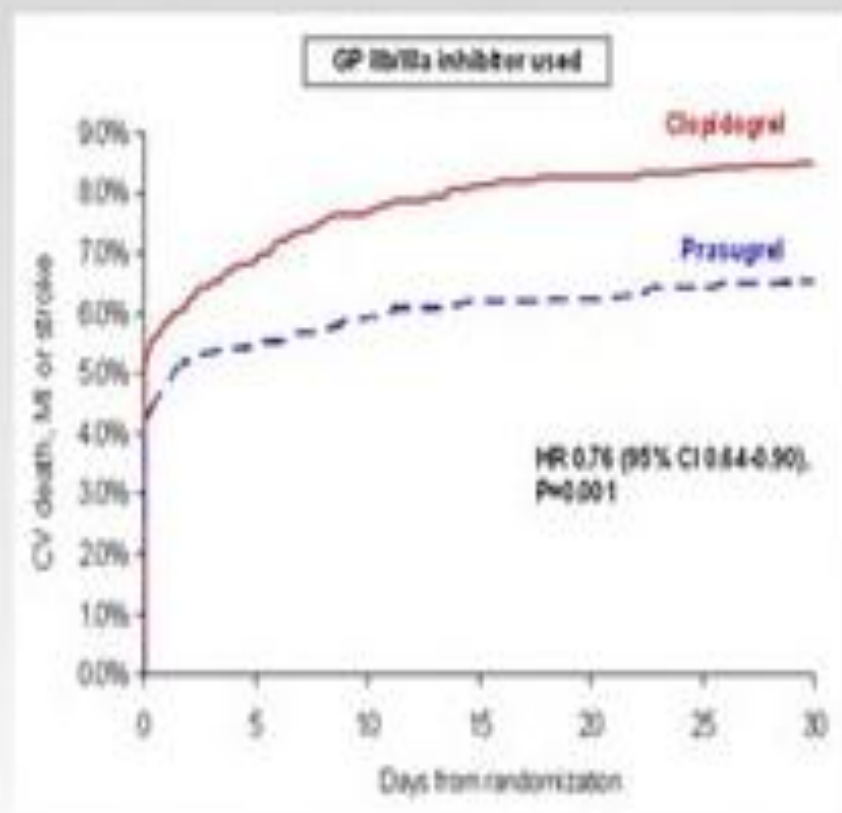
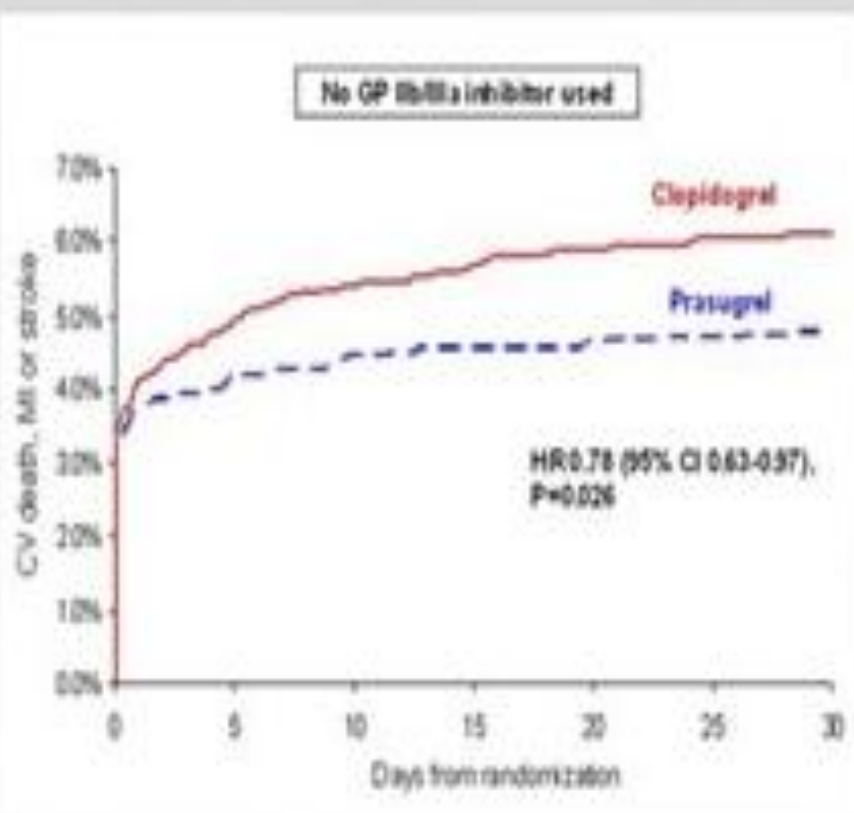


-
- **Triple antiplatelet therapy with the new antiplatelet agents (prasugrel-ticagrelol)**

TRITON TIMI-38: Index Procedure

	Clopidogrel (N = 6795) %	Prasugrel (N = 6813) %
PCI / CABG	99 / 1	99 / 1
Any Stent	95	94
BMS	47	48
DES	47	47
Multivessel PCI	14	14
UFH / LMWH / Bival	65 / 8 / 3	66 / 9 / 3
GP IIb/IIIa	55	54
LD of Study Rx		
Pre PCI	25	26
During PCI	74	73
Post PCI	1	1

The Efficacy and Safety of Prasugrel With and Without GPIs in Patients With ACS Undergoing PCI A TRITON-TIMI 38 Analysis

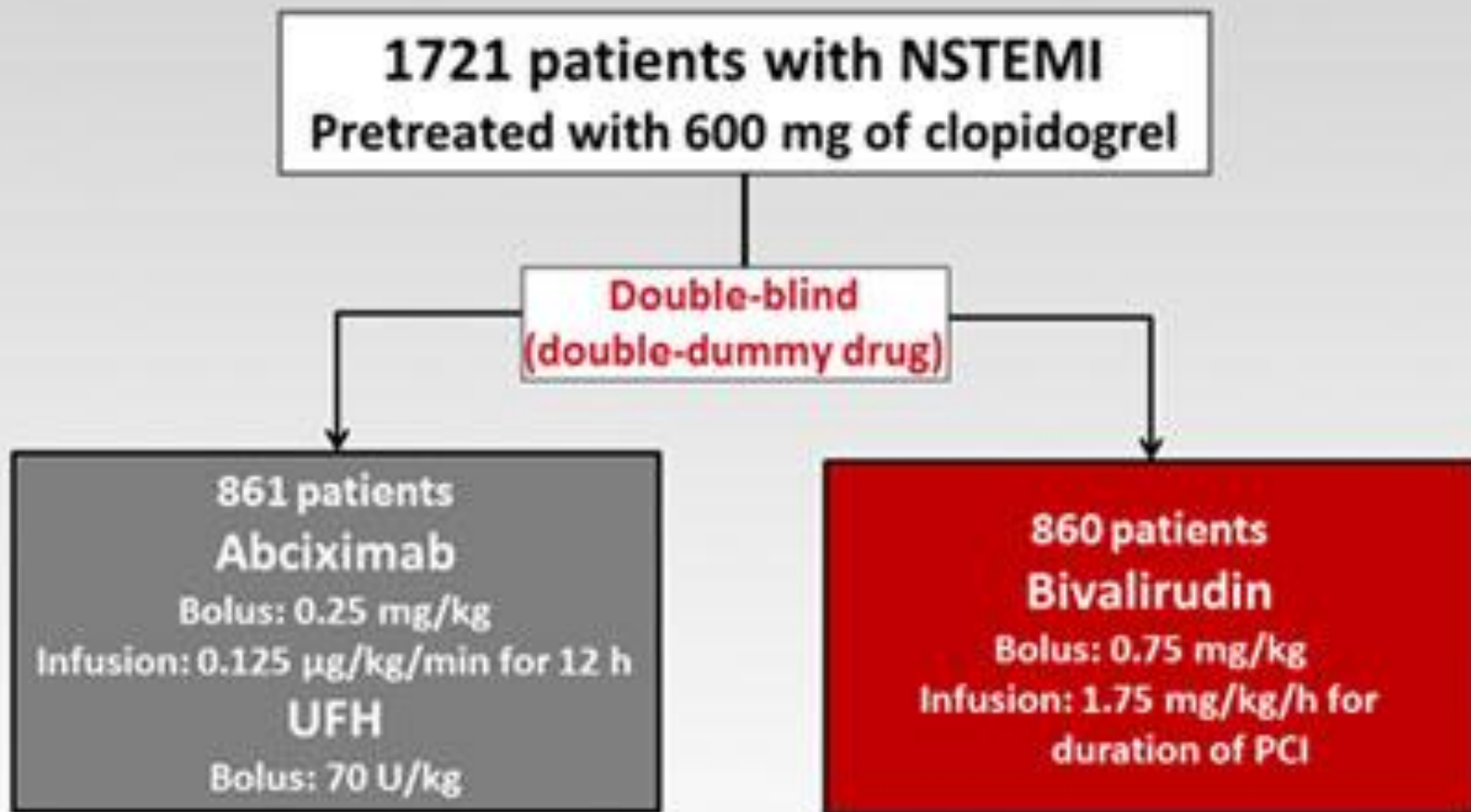


GPI used in 55% of recruited patients

PLATO STEMI: Co-medication

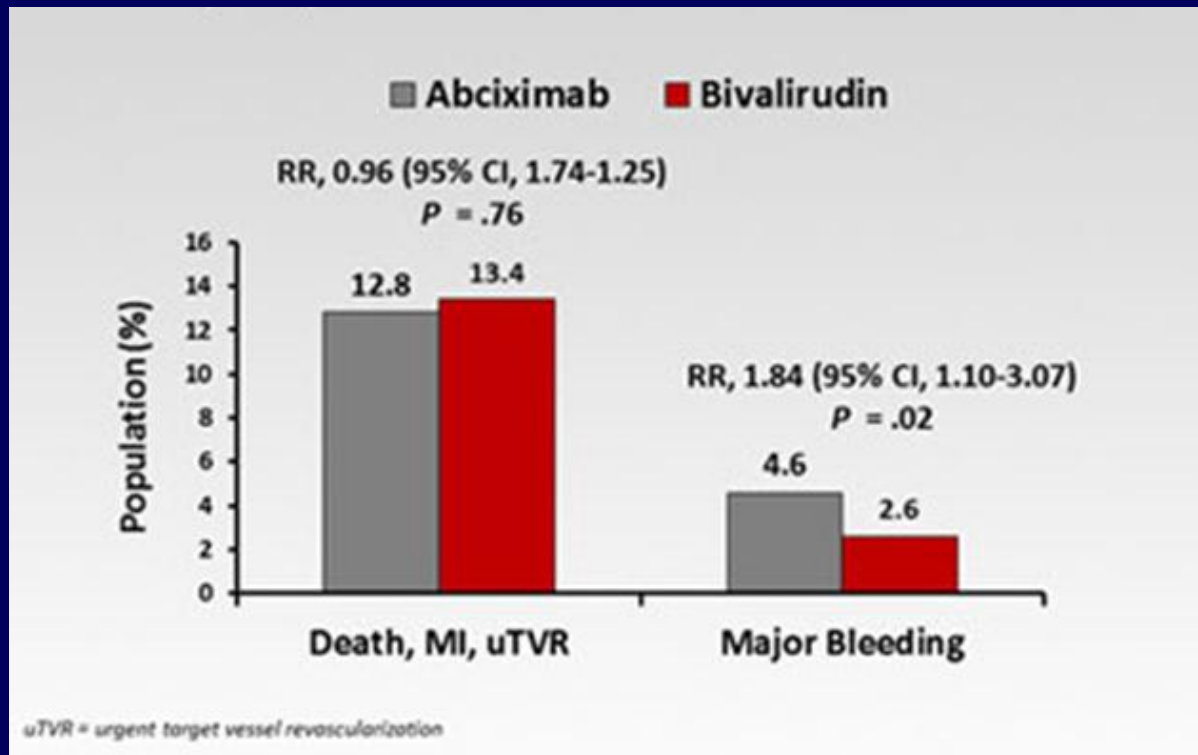
Medication	Ticagrelor (n = 4201)	Clopidogrel (n = 4229)
Antithrombotic treatment in hospital, %		
Aspirin prior to index event	21.4	20.7
Aspirin from index event to discharge	99.0	98.8
Unfractionated heparin	66.3	65.8
Low-molecular-weight heparin	45.8	46.1
Fondaparinux	1.8	1.7
Bivalirudin	1.3	1.4
GP IIb/IIIa inhibitor from index event to randomization	34.7	35.2
Other medication in hospital or at discharge, %		
Beta-blockade	85.8	86.2
ACE inhibitor and/or angiotensin-II receptor blocker	86.0	85.9
Cholesterol lowering (statin)	94.8	95.1
Calcium channel blocker	17.1	17.1
Diuretic	36.2	35.4
Proton pump inhibitor	49.1	49.1

ISAR-REACT 4: Trial Design



ISAR-REACT 4 trial Results

- The primary end point was not significantly different between the two groups, but bivalirudin was associated with less bleeding.



Recommendations for GPIIb/IIIa receptor inhibitors

Recommendations	Class	Level
The choice of combination of oral antiplatelet agents, a GPIIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischaemic and bleeding events.	I	C
Among patients who are already treated with DAPT, the addition of a GPIIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low.	I	B
Eptifibatide or tirofiban added to aspirin should be considered prior to angiography in high-risk patients not preloaded with P2Y ₁₂ inhibitors.	IIa	C
In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low.	IIb	C
GPIIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy.	III	A
GPIIb/IIIa receptor inhibitors are not recommended for patients on DAPT who are treated conservatively.	III	A

Recommendations for anticoagulants

Recommendations	Class	Level
Anticoagulation is recommended for all patients in addition to antiplatelet therapy.	I	A
The anticoagulation should be selected according to both ischaemic and bleeding risks, and according to the efficacy-safety profile of the chosen agent.	I	C
Fondaparinux (2.5 mg subcutaneously daily) is recommended as having the most favourable efficacy-safety profile with respect to anticoagulation.	I	A
If the initial anticoagulant is fondaparinux, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GPIIb/IIIa receptor inhibitors) should be added at the time of PCI.	I	B
Enoxaparin (1 mg/kg twice daily) is recommended when fondaparinux is not available.	I	B
If fondaparinux or enoxaparin are not available, UFH with a target aPTT of 50-70 s or other LMWHs at the specific recommended doses are indicated.	I	C
Bivalirudin plus provisional GPIIb/IIIa receptor inhibitors are recommended as an alternative to UFH plus GPIIb/IIIa receptor inhibitors in patients with an intended urgent or early invasive strategy, particularly in patients with a high risk of bleeding.	I	B
In a purely conservative strategy, anticoagulation should be maintained up to hospital discharge.	I	A
Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated.	IIa	C
Crossover of heparins (UFH and LMWH) is not recommended.	III	B

Trials evaluated GP IIb/IIIa antagonists as
adjuncts to oral antiplatelet therapy in the
setting of
Primary PCI

Trials evaluated GP IIb/IIIa antagonists as adjuncts to oral antiplatelet therapy in the setting of Primary PCI

- FINESSE (facilitated)
- ON-TIME 2 (facilitated)

- BRAVE-3 study
- HORIZONS-AMI
- MULTISTRATEGY was an open-label, multicenter, randomized European trial with a 2-by-2 factorial design that randomized 745 STEMI patients undergoing primary PCI to high-dose bolus tirofiban versus abciximab infusion and sirolimus-eluting stent versus bare-metal stent (BMS)

FINESSE

. Facilitated PCI in patients with ST-elevation myocardial infarction.

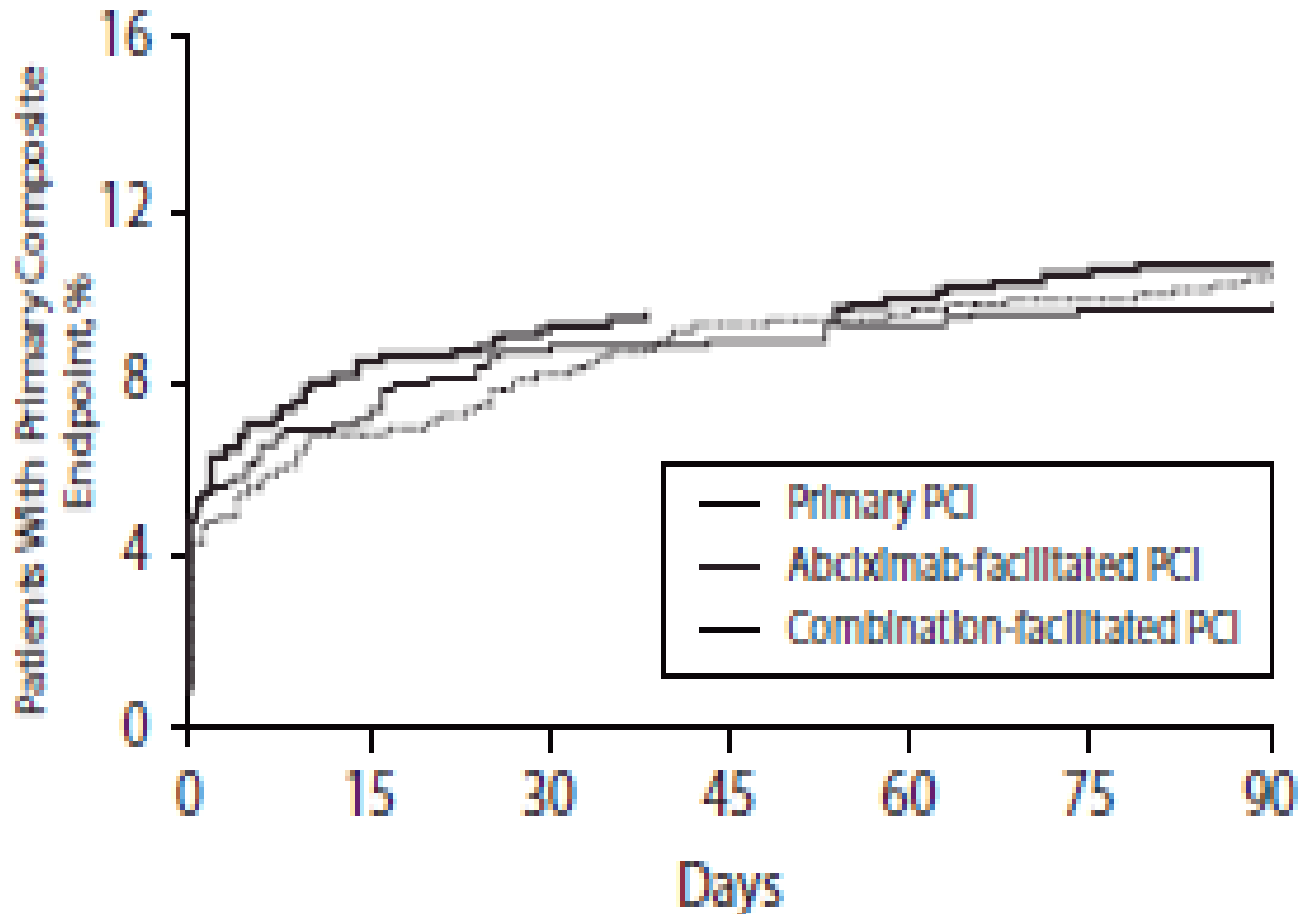
Ellis SG, et al *N Engl J Med*.2008;358(21):2205-2217.

- The hypothesis of this study was that in patients with acute ST segment elevation myocardial infarction (**STEMI**), percutaneous coronary intervention (**PCI**) preceded by
- early treatment with abciximab plus half-dose reteplase (**combination-facilitated PCI**)
or
- with abciximab alone (**abciximab-facilitated PCI**)
as compared with
- abciximab administered immediately before the procedure (**primary**
- **PCI** [PPCI])

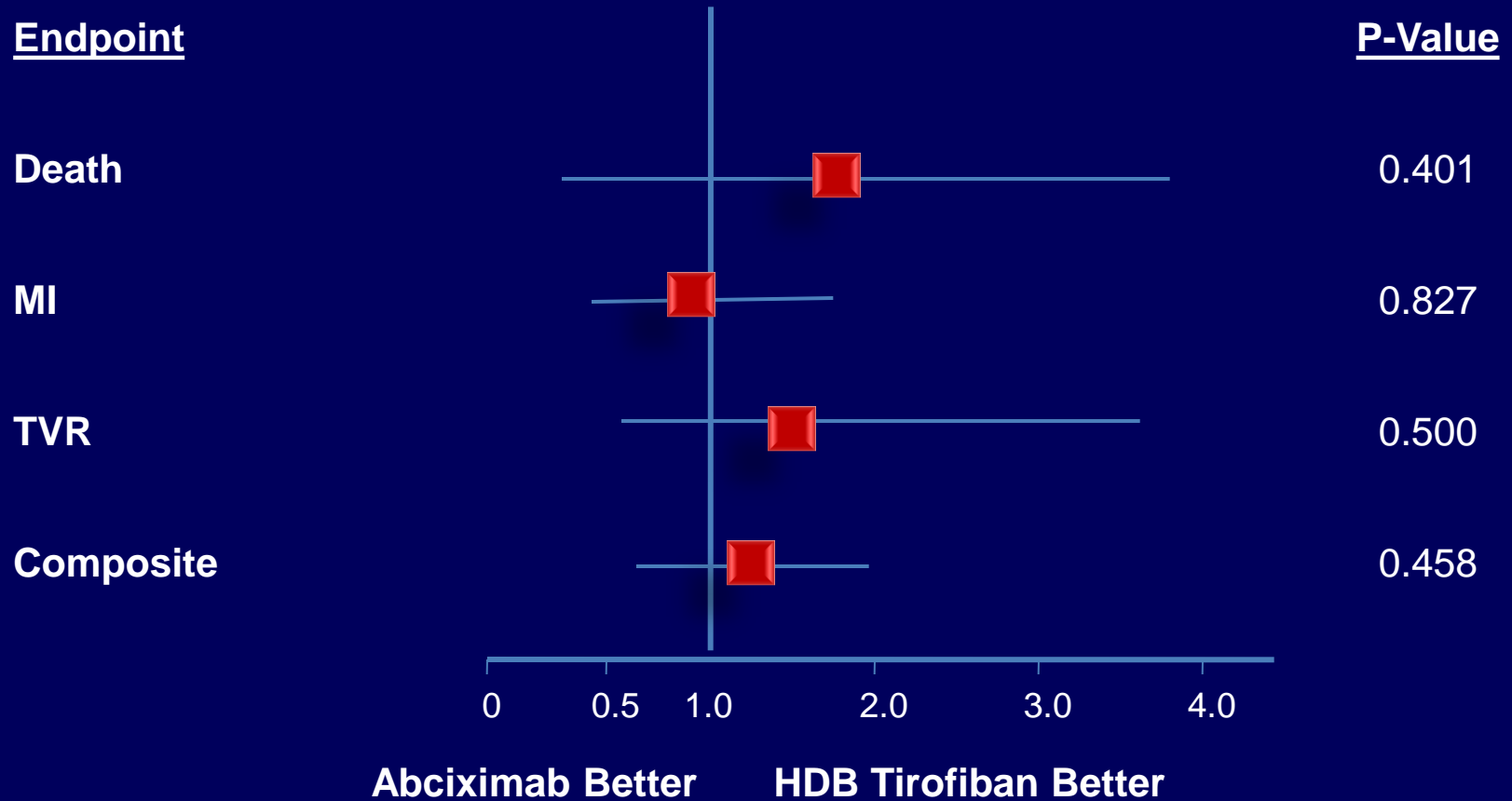
would result in improved outcomes.

The primary endpoint was the

composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomisation, cardiogenic shock, and congestive heart failure during the first 90 days after randomisation

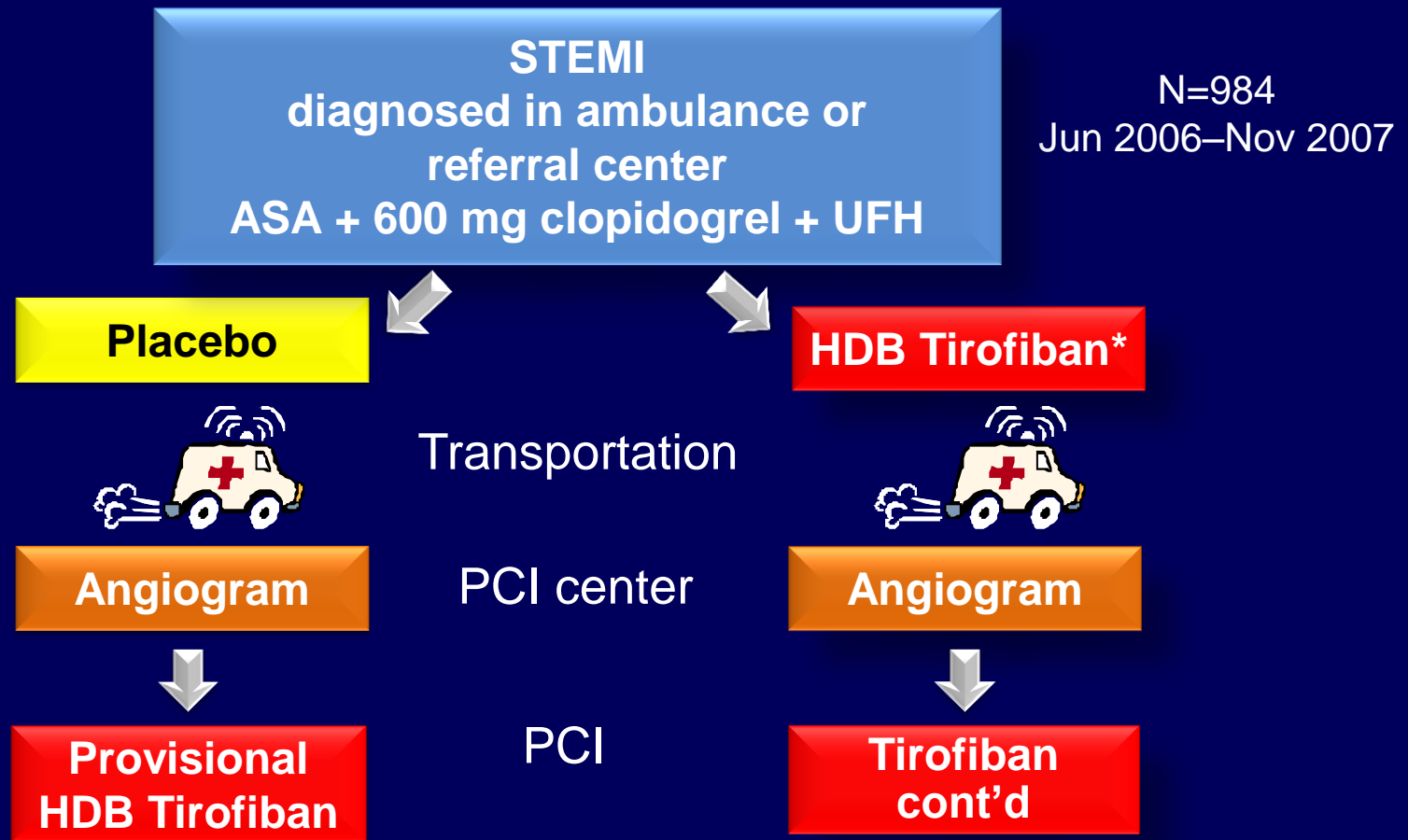


HDB AGGRASTAT Meta-Analysis: 30-Day Outcomes



Dawson CB, et al. *Circulation*. 2006;114:II_647.

On-TIME 2: Study Design



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

On-TIME 2: Inclusion Site

- Ambulance 95%
- Referral Center 3%
- PCI Center (ER) 2%

On-TIME 2: Endpoints

Primary:

- Residual ST segment deviation (>3 mm) 1 hour after PCI

Key Secondary:

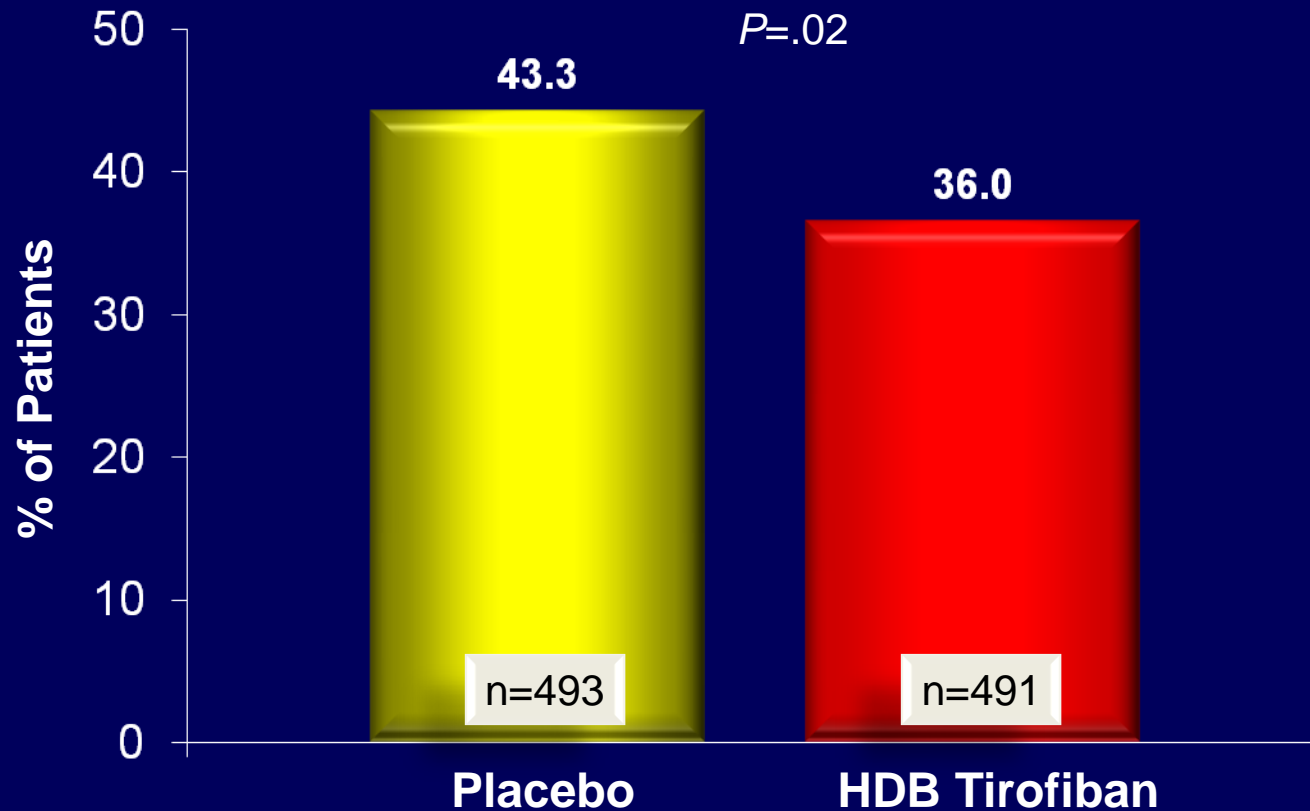
- Combined occurrence of death, recurrent MI, urgent TVR, or thrombotic bailout at 30 days follow-up
- Safety (major bleeding)

On-TIME 2: Drug Regimens

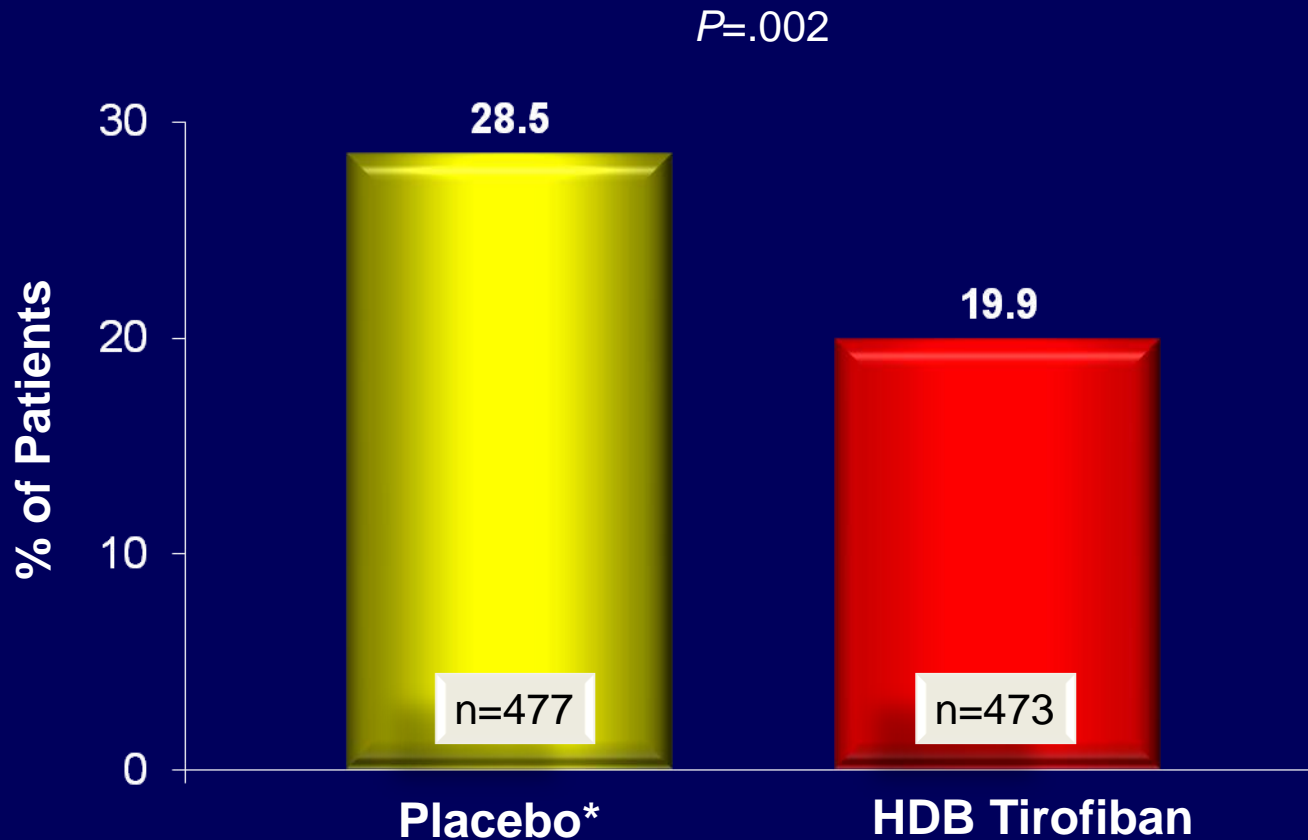
Regimen	Study Drug Dose	Heparin Dose	ASA Dose	Clopidogrel
HDB Tirofiban	Bolus: 25 µg/kg for 3 min Infusion: 0.15 µg/kg/min	5000 U with additional heparin given to keep ACT at 200 s	500 mg IV	600 mg loading dose
Placebo	N/A	5000 U with additional heparin given to keep ACT at 200 s	500 mg IV	600 mg loading dose

van 't Hof AWJ, et al. *Lancet* 2008 Aug 16;372(9638):537-46

On-TIME 2: ST-Segment >3 mm Deviation 1 Hour Post-PCI

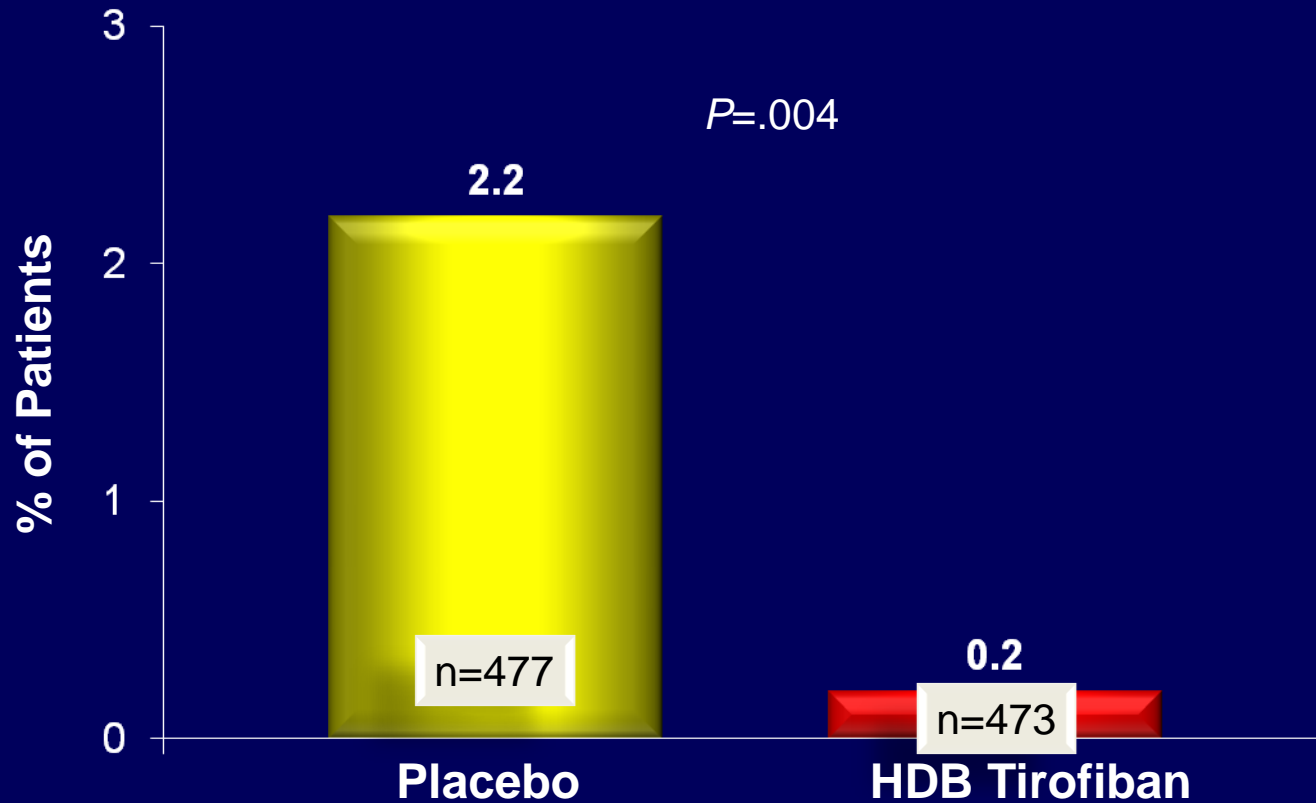


On-TIME 2: Thrombotic Bailout



van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

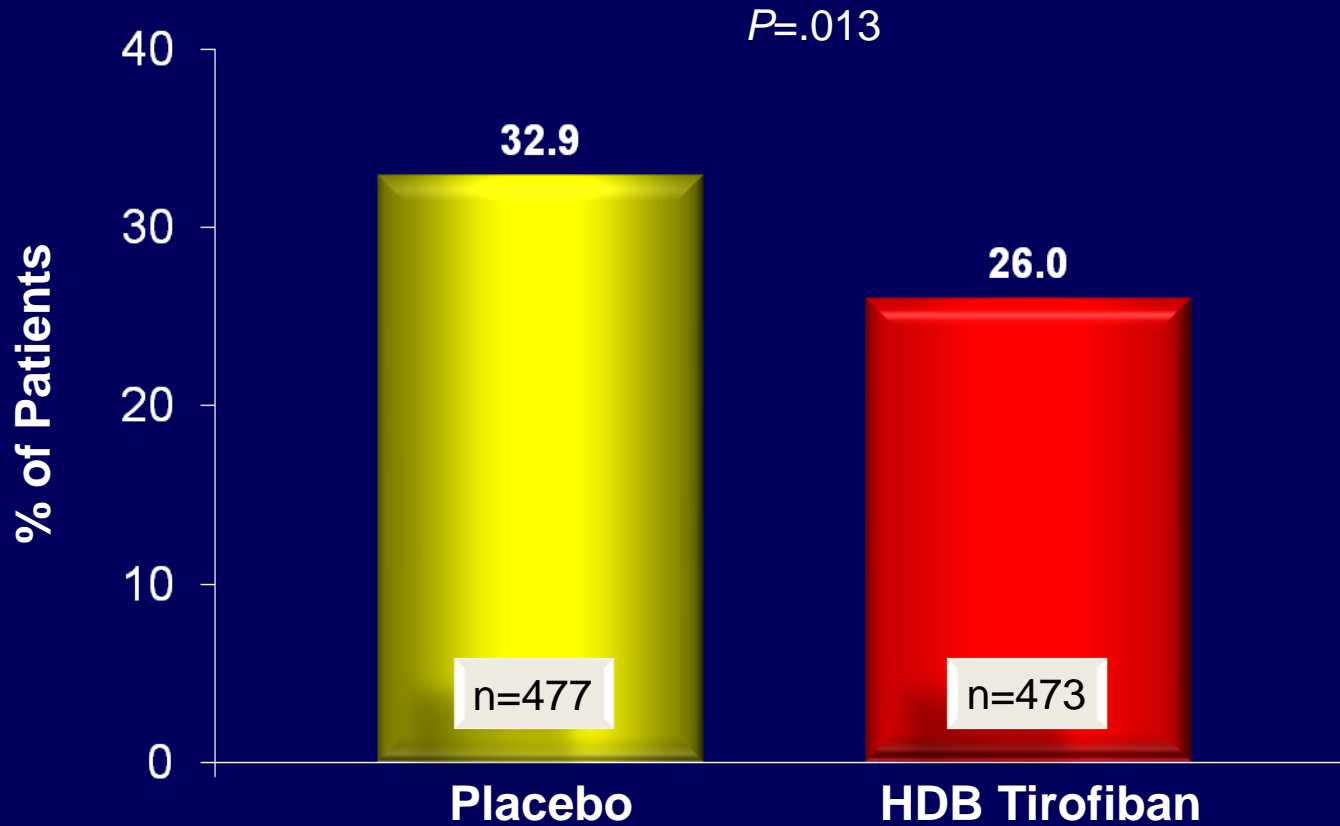
On-TIME 2: Abrupt Closure



van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

On-TIME 2: Combined Endpoint at 30 Days

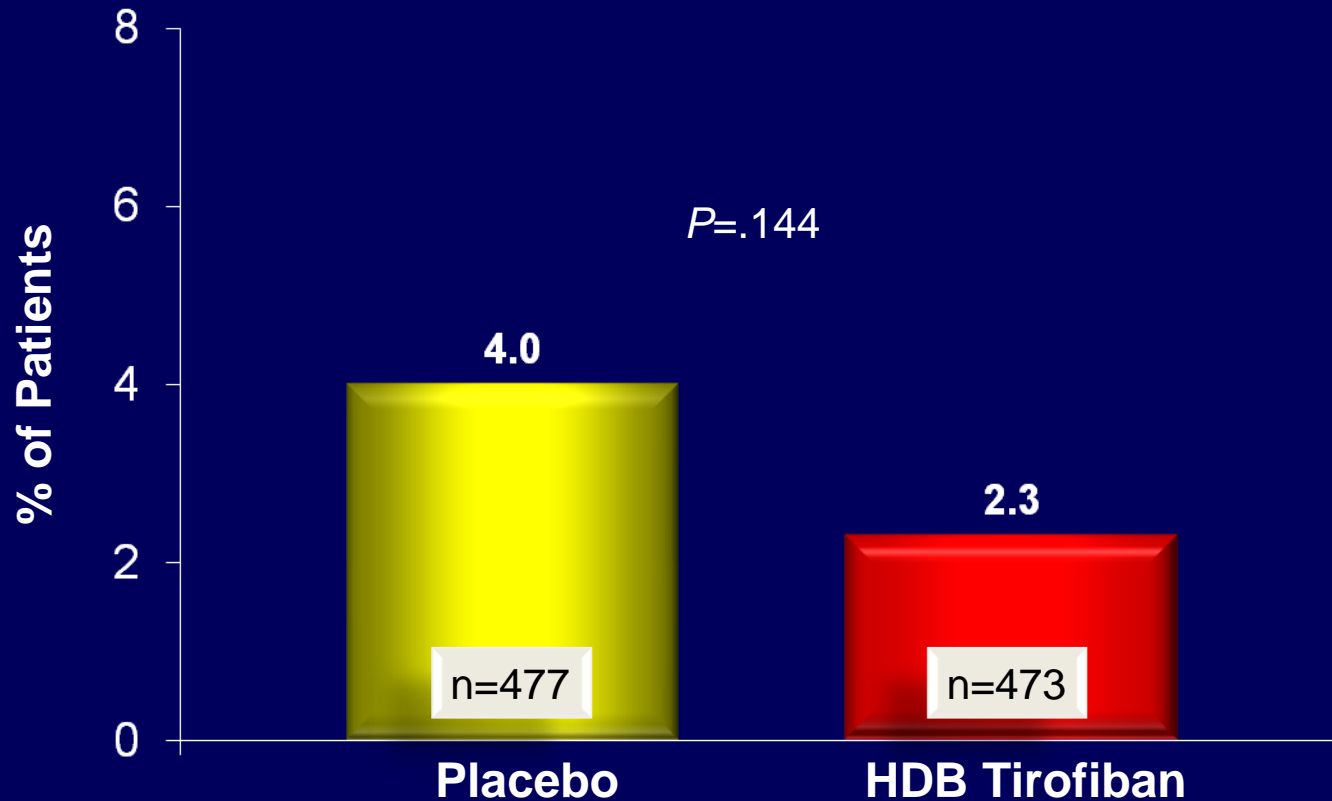
Death, recurring MI, urgent TVR, and thrombotic bailout



van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

On-TIME 2: Death at 30 Days ITT Population

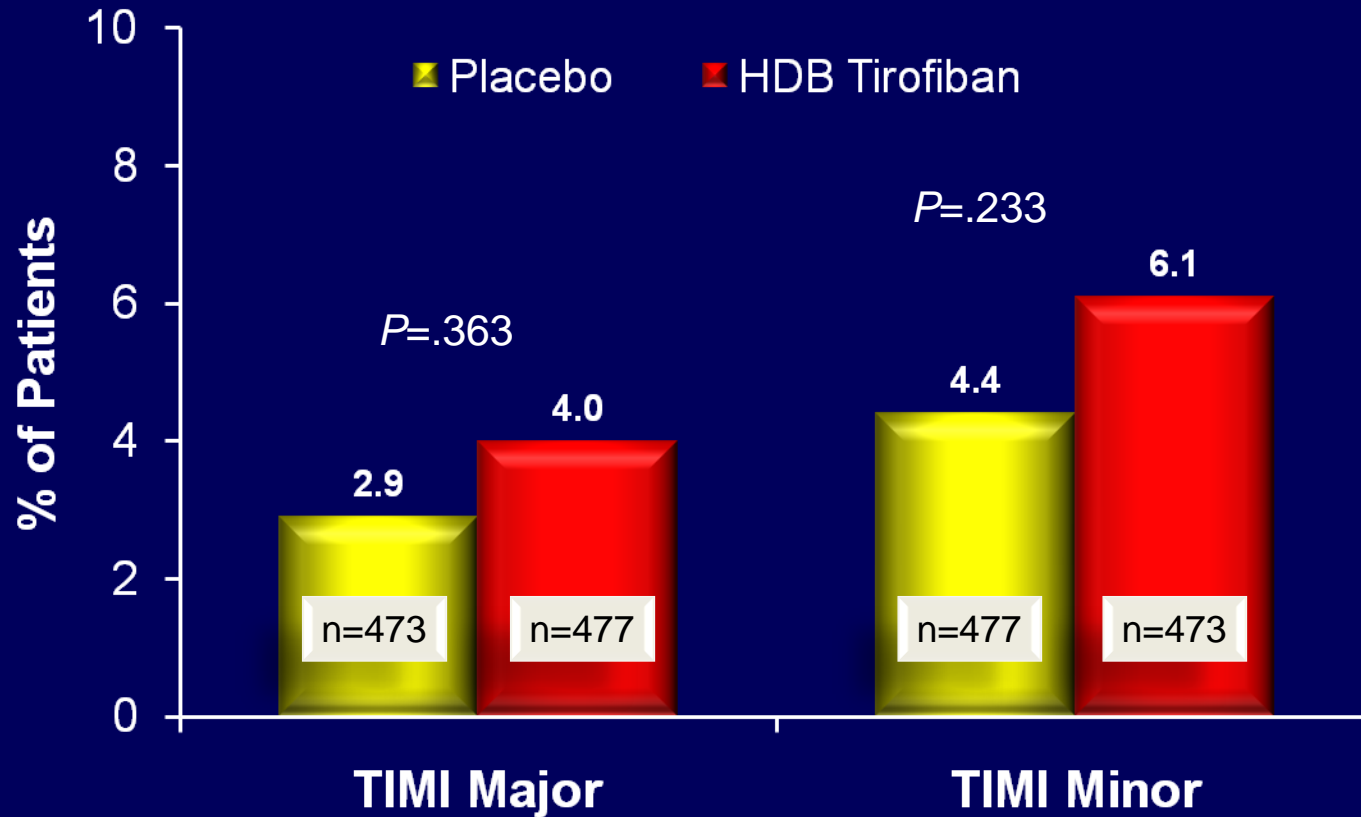
All-cause mortality at 30 days



van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

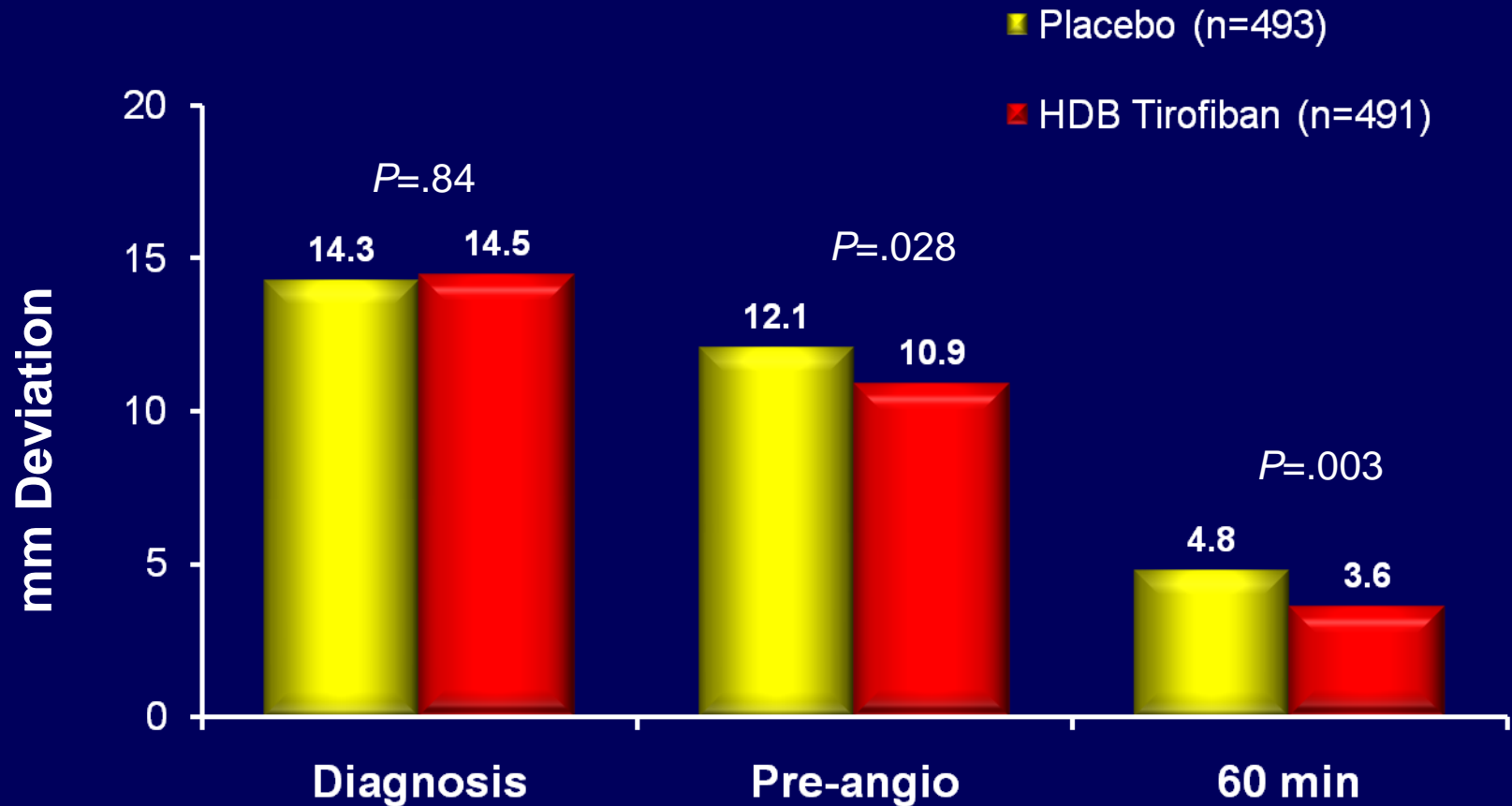
On-TIME 2: Safety

Bleeding at 30 Days



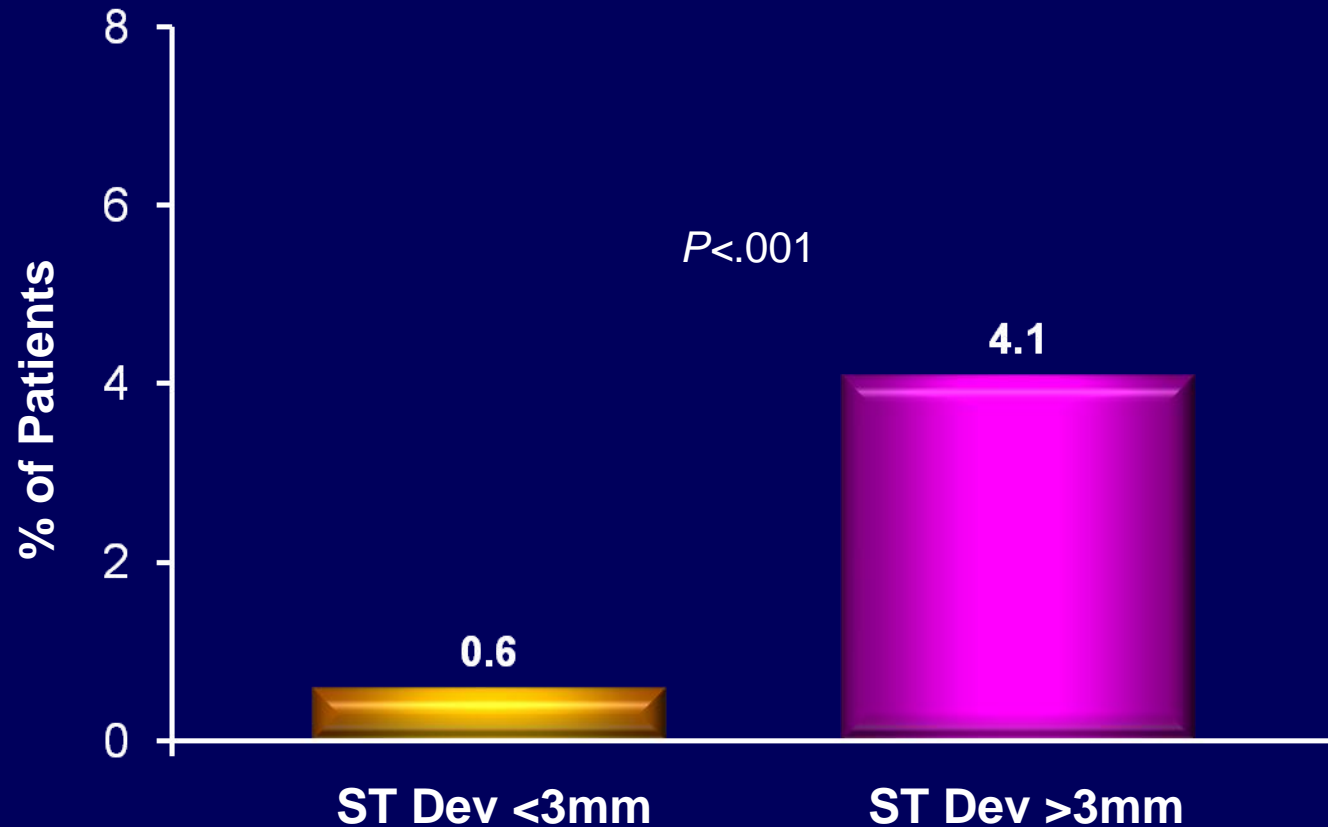
van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

On-TIME 2: ST Deviation Over Time



van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

On-TIME 2: Mortality at 30 Days by Residual ST-Deviation



Hamm C, et al. Presented at: SCAI Annual Scientific Sessions/ACC i2 Summit; April 1, 2008; Chicago, IL. Presentation 413-5.

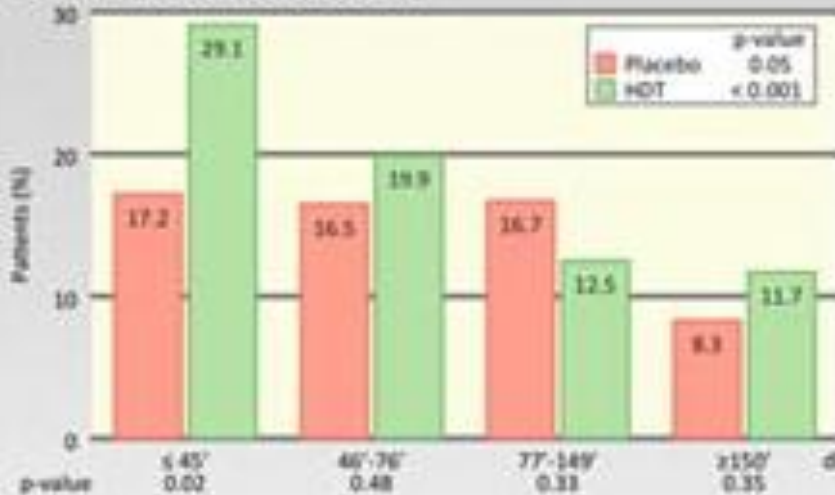
ON TIME 2: Prehospital Tirofiban

STEMI

Better ST resolution

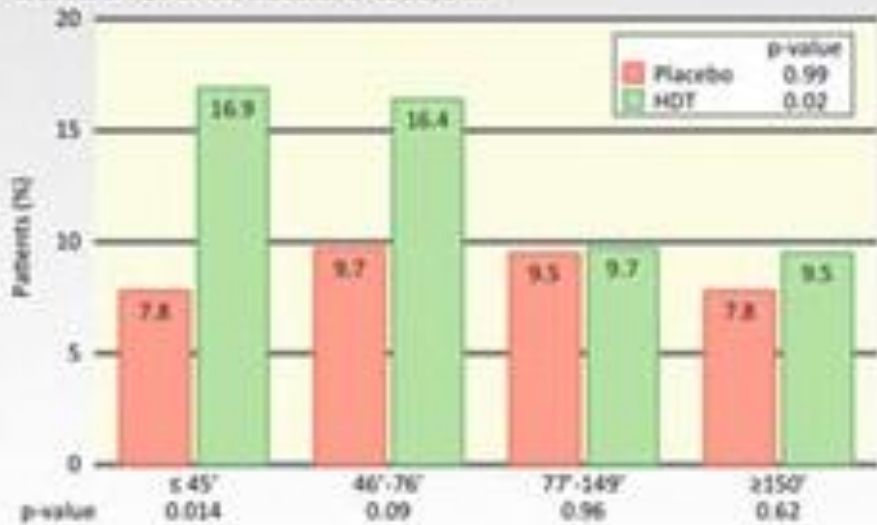
IN EARLY PRESENTATION PATIENTS

a. Effect of HDT on ST resolution before PCI



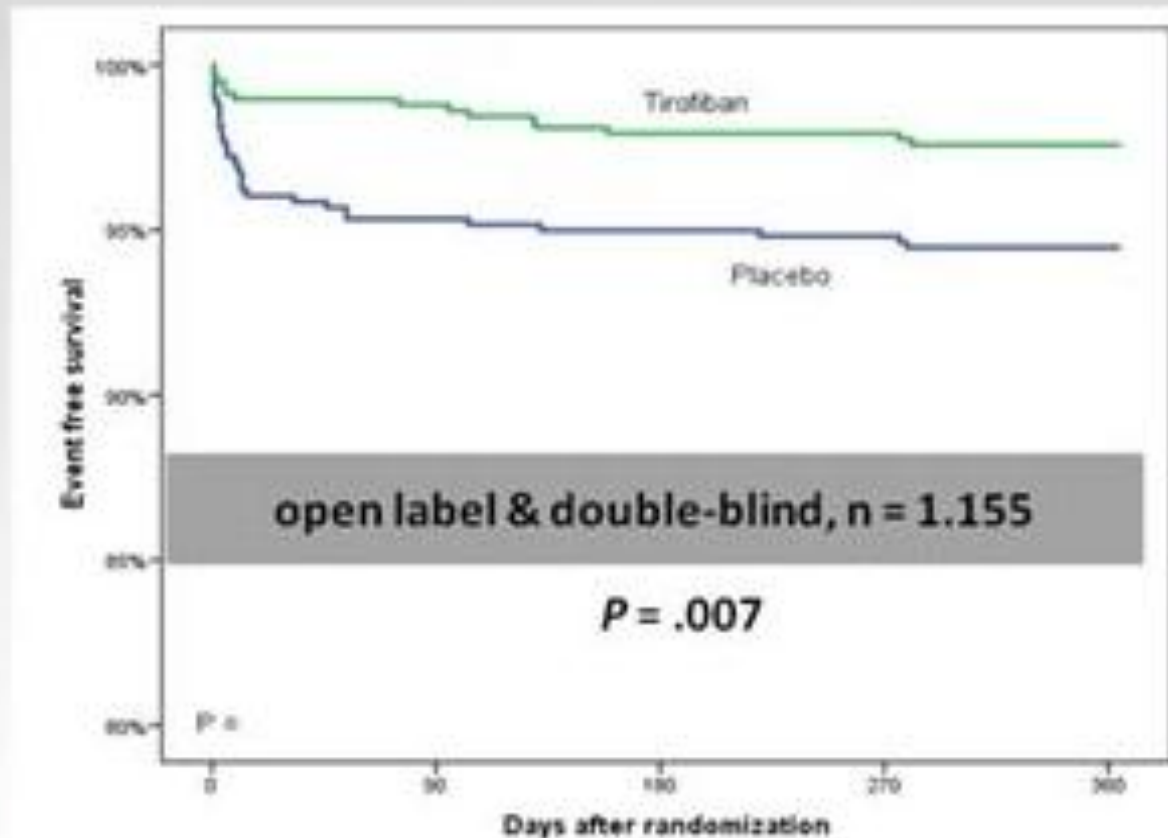
More aborted AMI

d. Effect of HDT on the incidence of aborted MI



1-Year Survival: Patients With Primary PCI

Mortality Reduction at one year by early upstream tirofiban (ON-TIME 2)

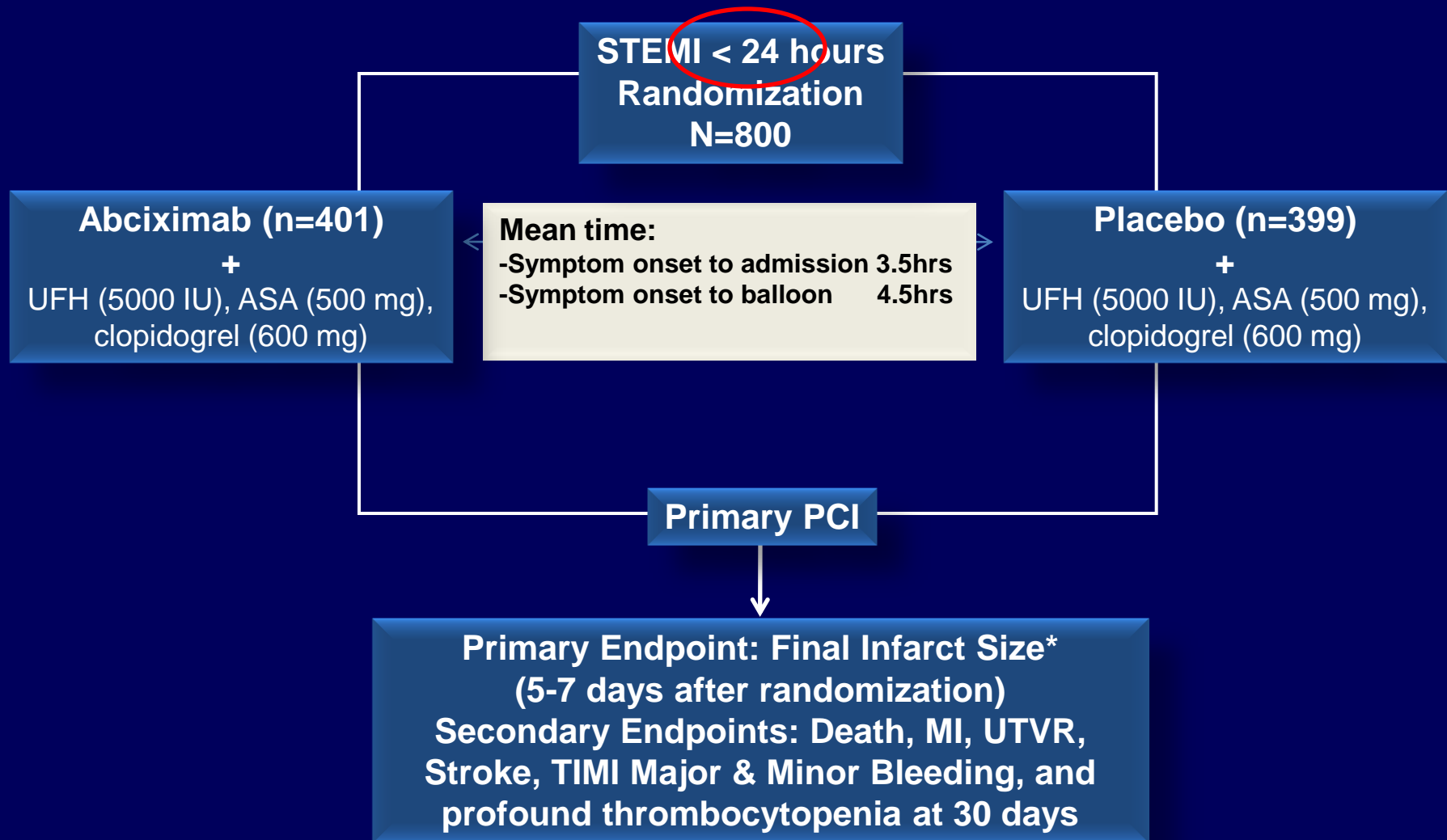


Trials evaluated GP IIb/IIIa antagonists as adjuncts to oral antiplatelet therapy in the setting of Primary PCI

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BRAVE 3: Study Design



* expressed as a percentage of the left ventricle and measured with single photon emission computed tomography (S

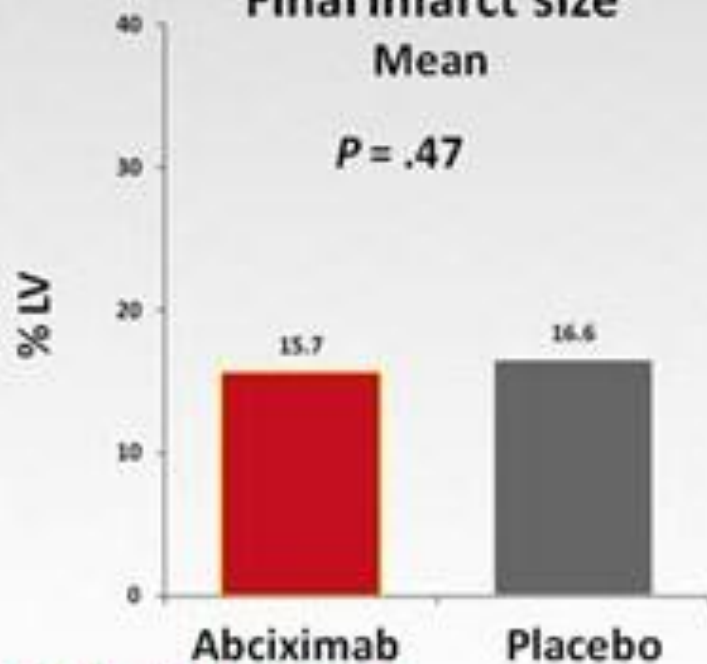
BRAVE-3: Abciximab on top of 600-mg Clopidogrel

800 Patients Recruited Within 24 hours From Symptom Onset

Primary Endpoint

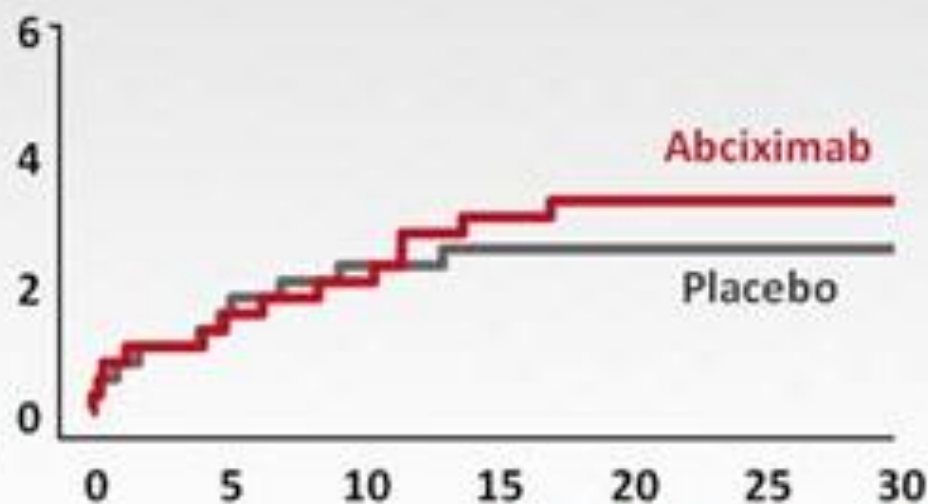
Final infarct size
Mean

$P = .47$

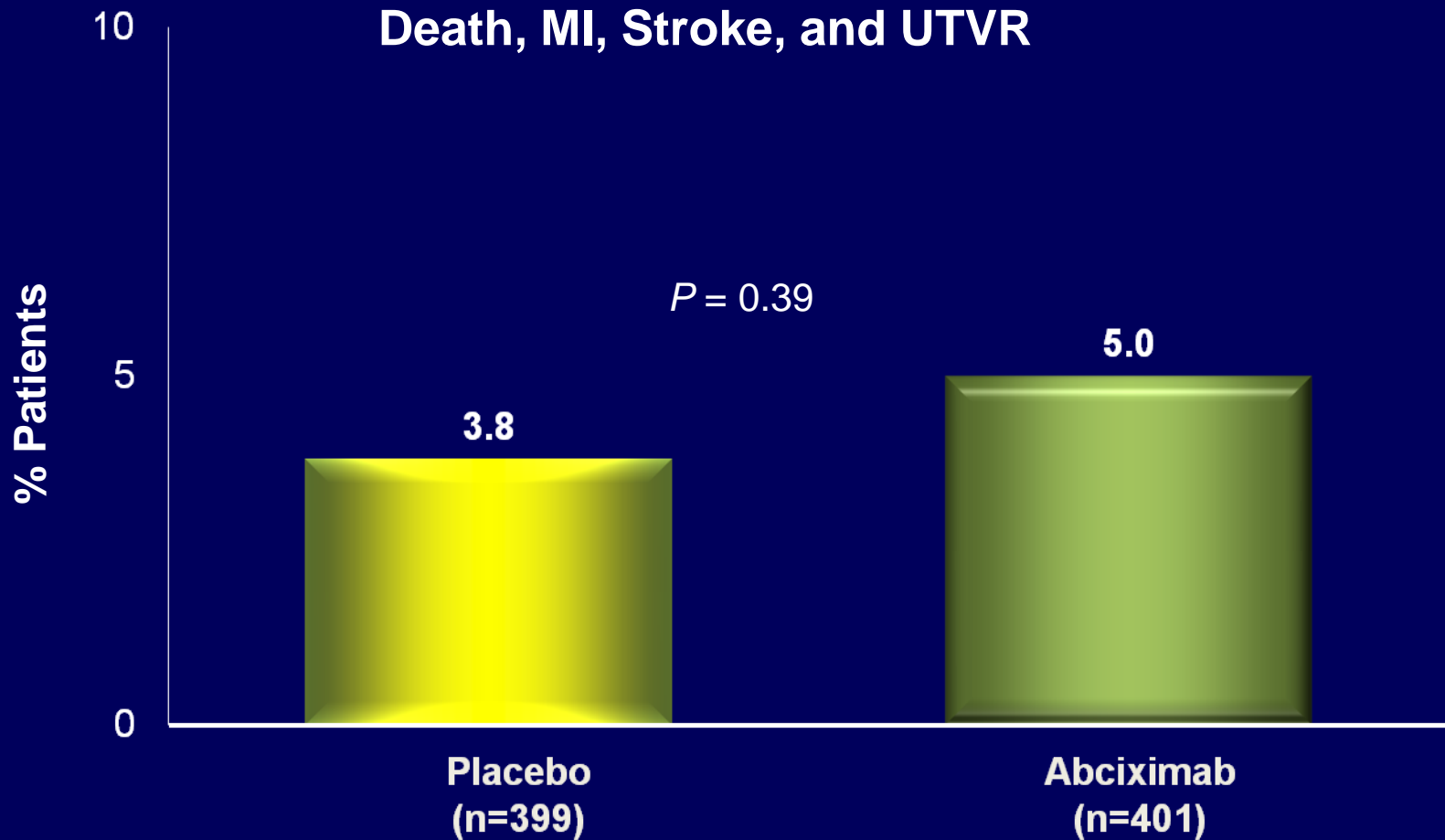


Secondary Endpoint

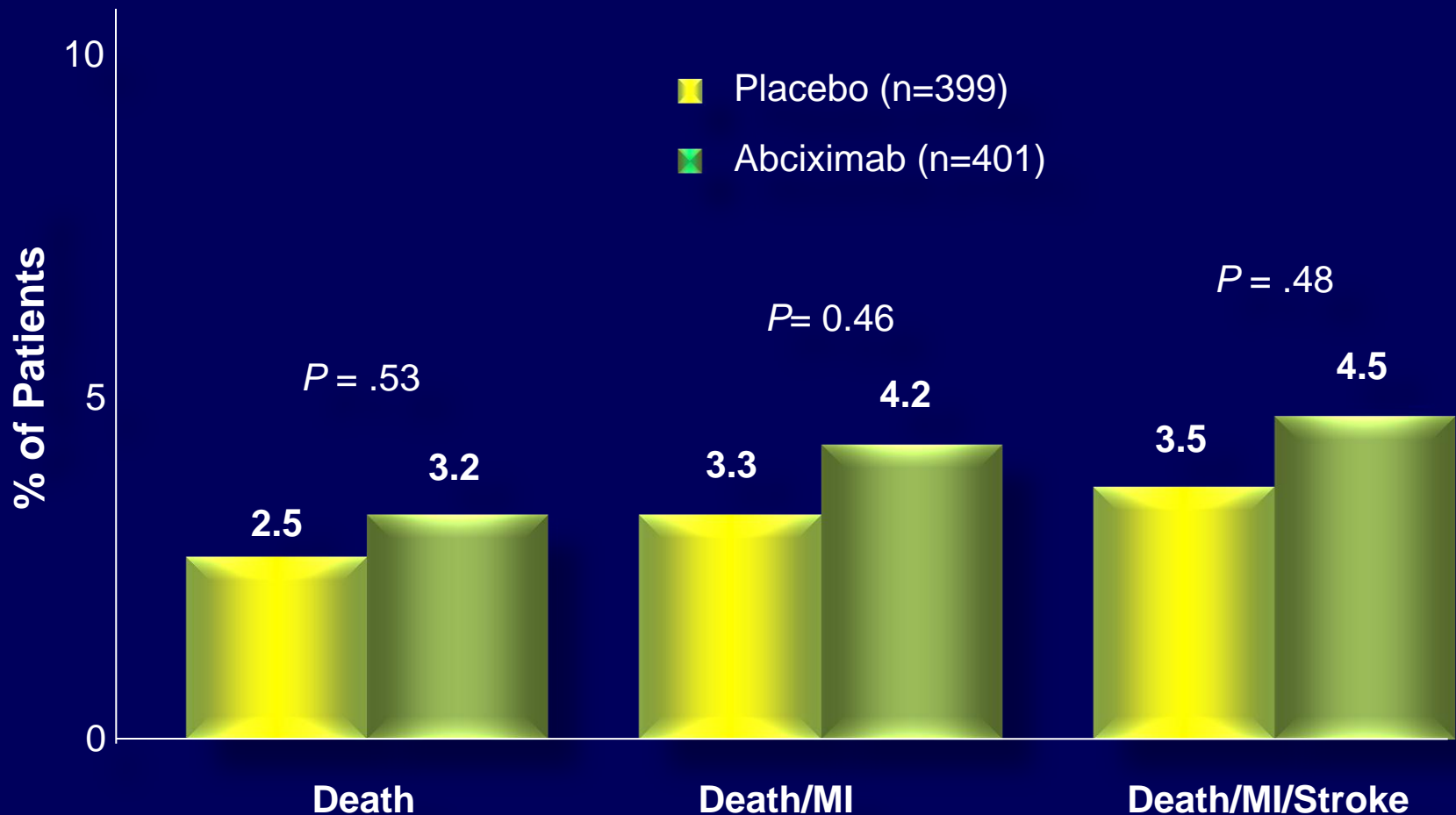
Death at 30 days



BRAVE 3: MACE (30 days)

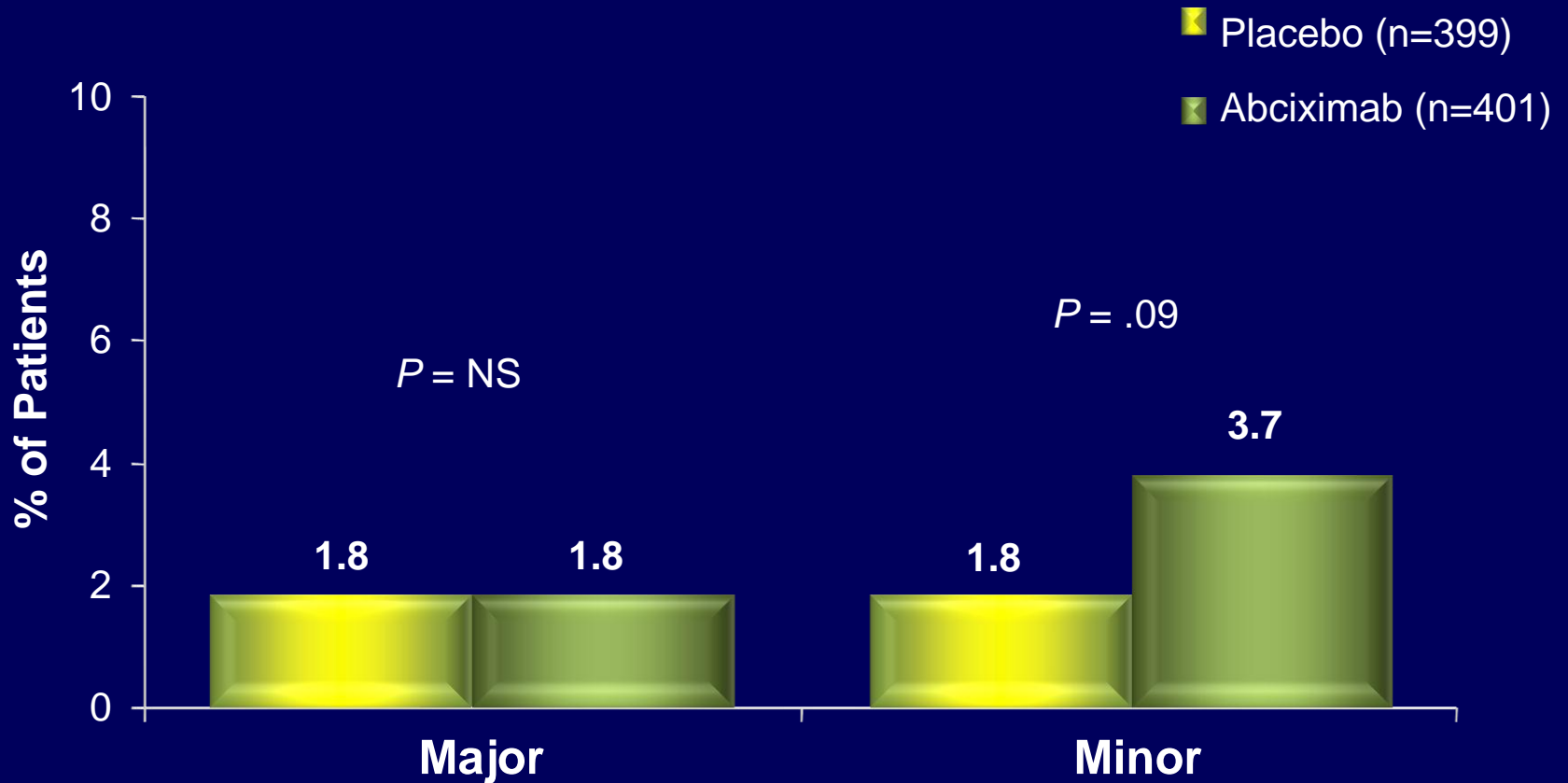


BRAVE 3: Secondary Endpoints (30 days)



BRAVE 3: Safety

TIMI Bleeding

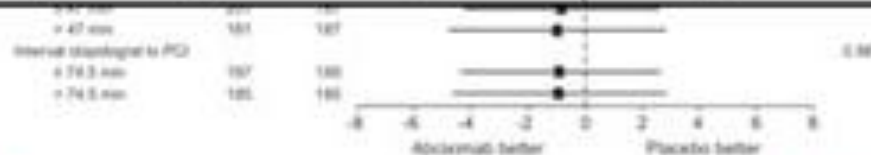
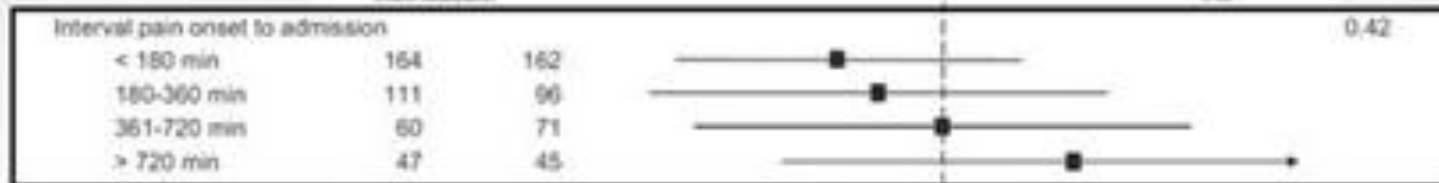
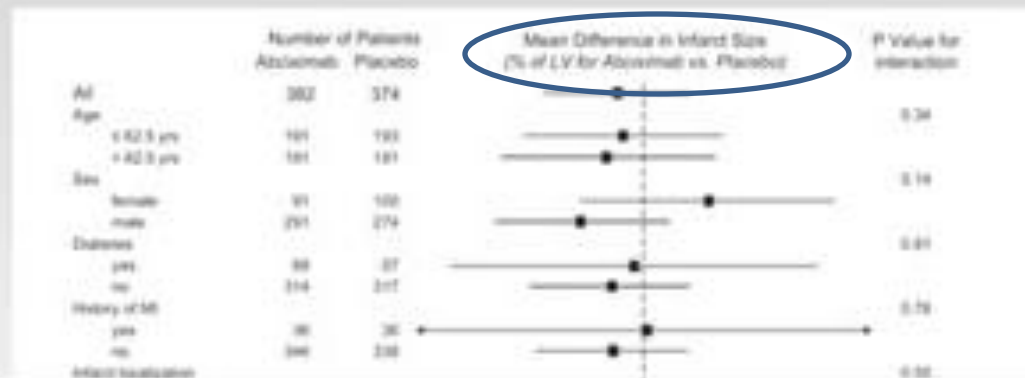


BRAVE-3: Abciximab on Top of 600 mg Clopidogrel

Time Intervals*	Median (Interquartile Range), min	
	Abciximab (n=401)	Placebo (n=399)
Symptom onset to hospital admission	210 (110–420)	216 (110–468)
Symptom onset to study drug	255 (140–465)	260 (135–515)
>50% pts received drug >4 hour delay		
Symptom onset to PPCI	302 (190–540)	315 (189–585)
Hospital admr >50% pts received PCI >5 hour delay		
Clopidogrel loading to PPCI	73 (54–104)	75 (53–105)
Clopidogrel loading to study drug	23 (13–41)	21 (12–38)

BRAVE-3: Abciximab on Top of 600-mg Clopidogrel

TIME Matters Even in Munich



**What about intracoronary IIb/IIIa
administration?**

CICERO trial

Effects on measures of myocardial perfusion and salvage and coronary patency, IC vs IV abciximab bolusing in primary PCI

CICERO: Major results

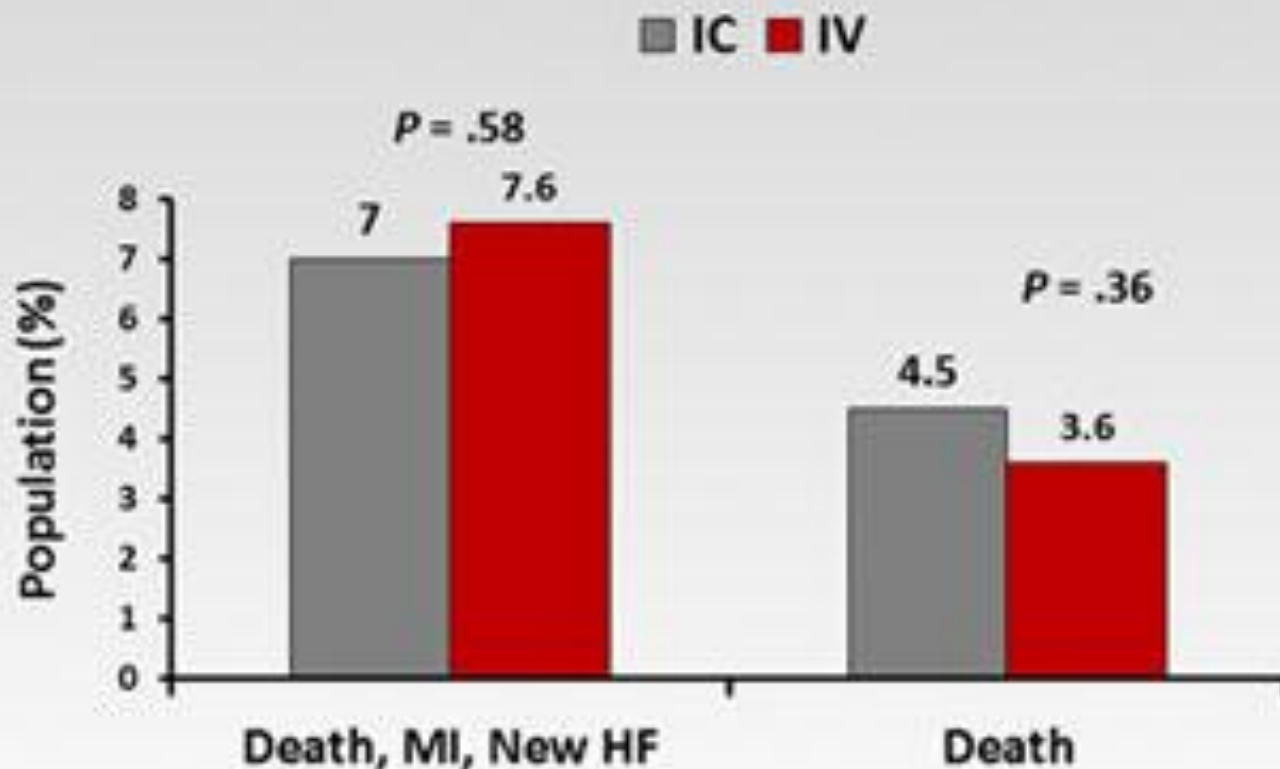
Outcome	Intracoronary abciximab	Intravenous abciximab	p
Complete ST-segment resolution (%)	64	62	0.56
Myocardial blush grade 2/3 (%)	76	67	0.02
Mean enzymatic infarct size (creatine kinase levels in U/L)	1214	1746	0.008
Major adverse cardiac events (%)	5.5	6.1	0.79

CICERO: Mixed results for intracoronary abciximab in STEMI

- when the patients with blush grade 2/3 were separated out into grade 2 and grade 3, it showed that the grade 3 results were almost identical (34% for intracoronary vs 33% for IV),
- "it is only really grade 3 that predicts outcomes.
- cardiac enzymes were reported in only 46% of patients.

AIDA STEMI:

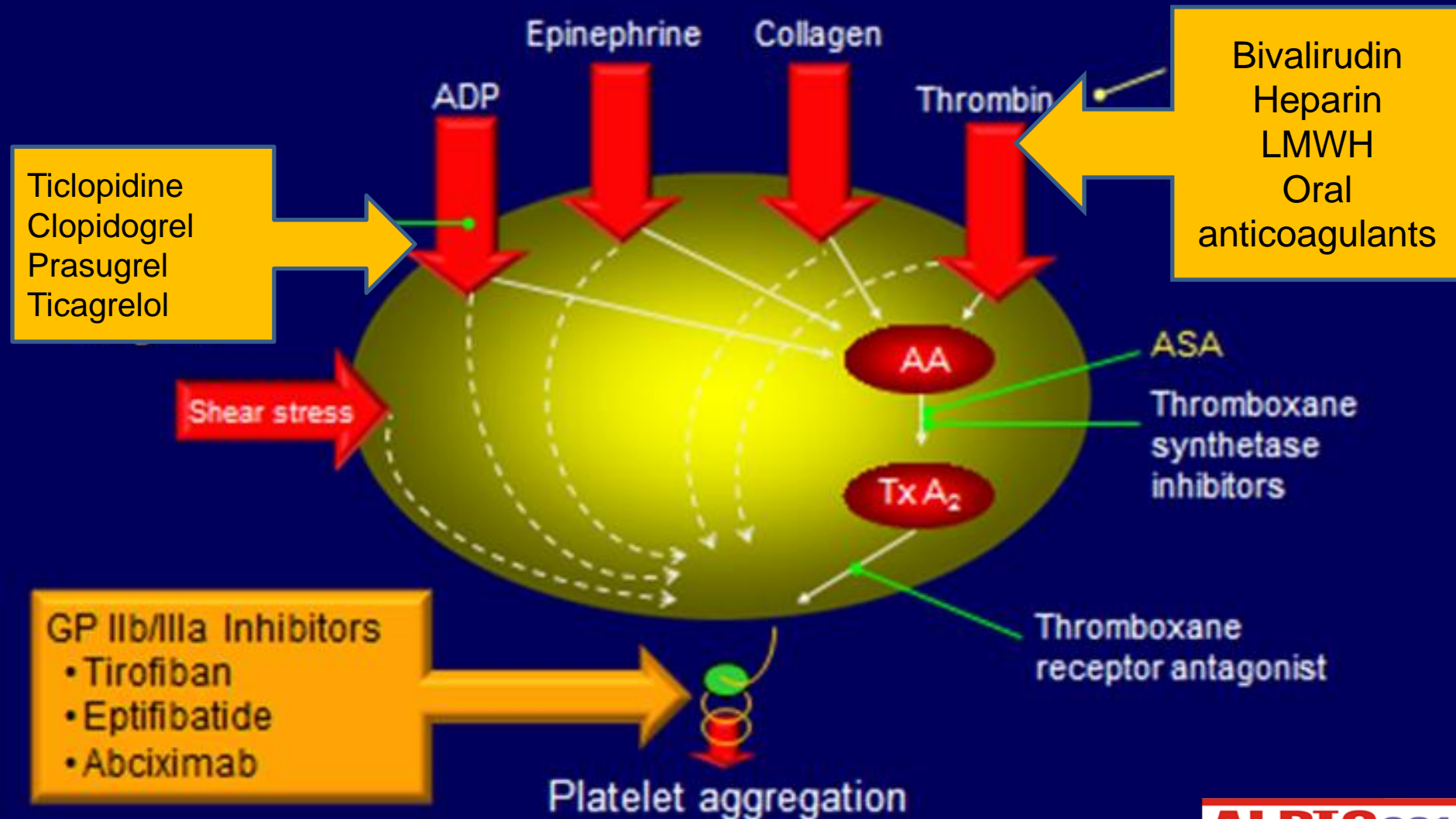
No Difference for Intracoronary vs Intravenous Abciximab



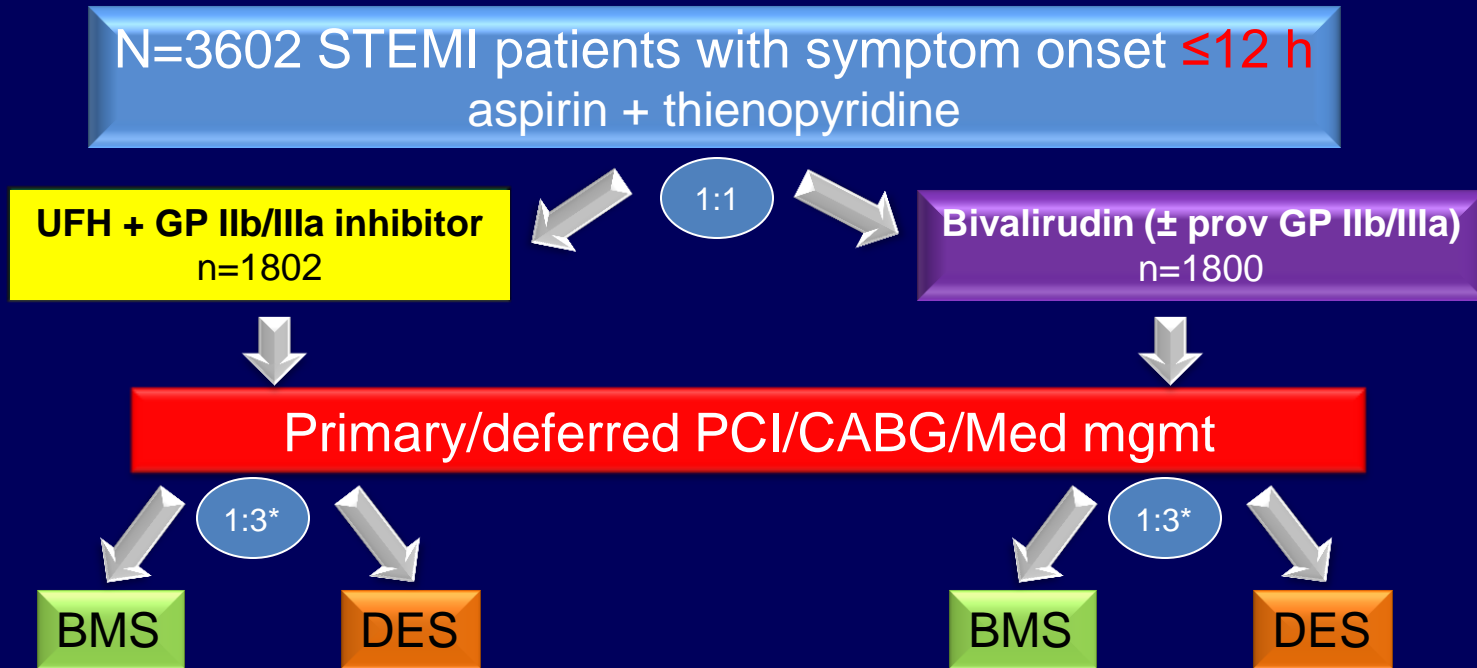
N = 2065 STEMI < 12 hours and planned PCI

Antiplatelet-anticoagulant combinations

What's new?



HORIZONS AMI: Study Design



Endpoints at 30 days: ITT population, PCI population

- Primary: Net adverse clinical events (death/reinfarct/uTVR + major bleeding)
Major bleeding (TIMI/GUSTO/CABG/non-CABG/thrombocytopenia)
- Secondary: MACE (death/reinfarction/uTVR/stroke)

*Stent population: stent thrombosis (definite, probable, acute, subacute)

*All stent randomization results are still blinded.

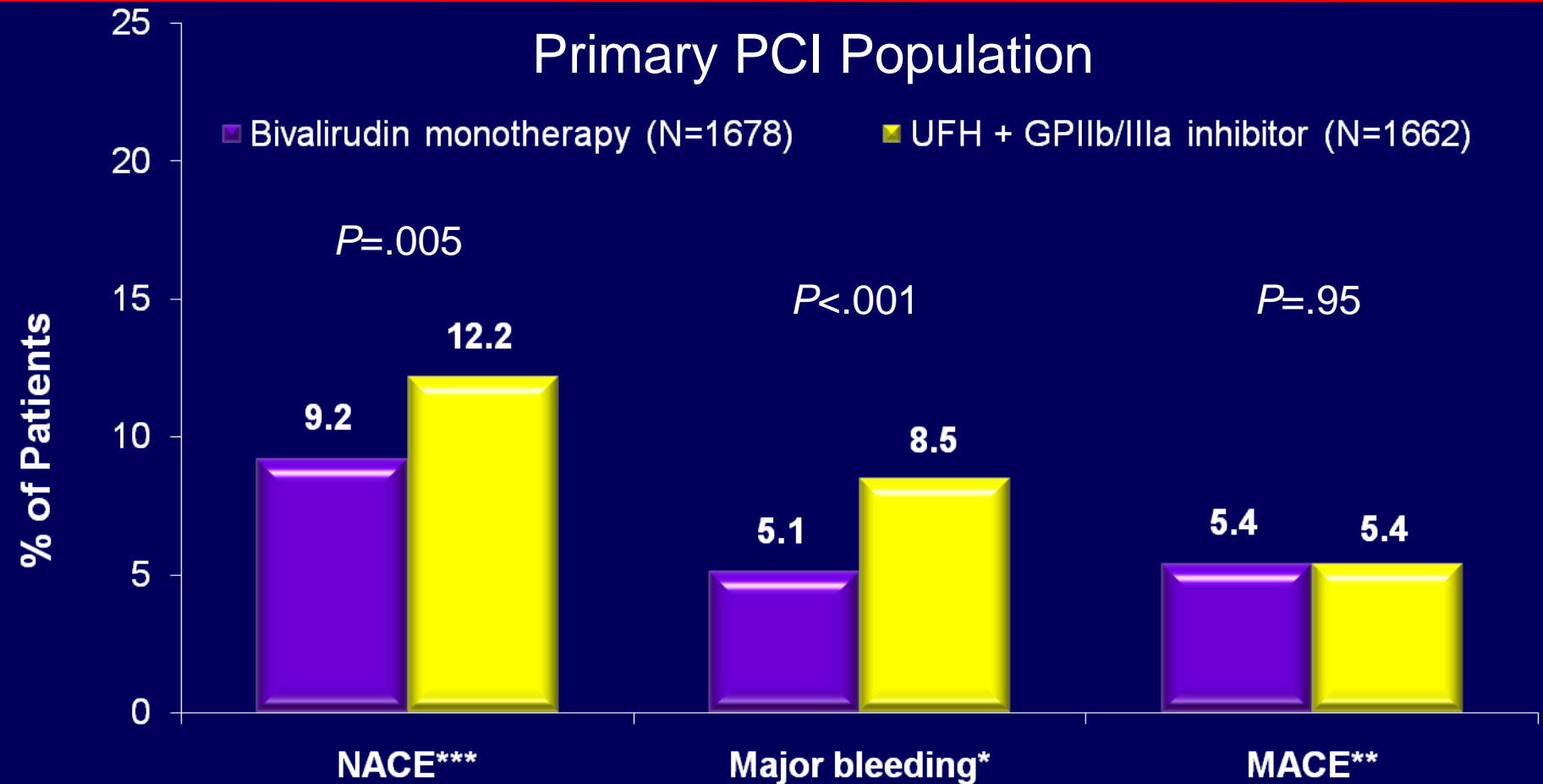
Stone GW, et al. *N Engl J Med.* 2008;358(21):2218-2230.

HORIZONS AMI: Drug Regimens

61

Regimen	Study Drug Dose	ASA Dose	Clopidogrel/Ticlopidine Dose
Bivalirudin	<p>Bivalirudin: Bolus of 0.75 mg/kg bolus followed by infusion of 1.75 mg/kg/hour</p> <p>If heparin was administered prior to randomization, bivalirudin was started 30 minutes later but in all cases before PCI.</p> <p>GP IIb/IIIa Inhibitor: Only in patients with no reflow or with giant thrombus after PCI</p>	<p>324 mg orally or 500 mg IV given in ED</p> <p>300 to 325 mg orally QD during hospitalization</p> <p>75-81 mg QD thereafter indefinitely</p>	<p>Loading dose administered before catheterization:</p> <p>300 mg or 600 mg loading dose at the discretion of the investigator, or</p> <p>Ticlopidine 500 mg in the case of clopidogrel allergy</p> <p>Clopidogrel 75 mg orally every day for at least 6 months (1 year or longer recommended)</p>
Heparin + GP IIb/IIIa Inhibitor	<p>Heparin: IV bolus of 60 U/kg with subsequent boluses to target an ACT of 200 to 250 s</p> <p>GP IIb/IIIa inhibitor: Administered before PCI</p> <p>Abciximab: Bolus of 0.25 mg/kg/ followed by infusion of 0.125 µg/kg/min (max. dose, 10 µg /min) continued for 12 hours</p> <p>Eptifibatide: Double Bolus Regimen - Bolus of 180 µg /kg followed by infusion of 2.0 µg /kg/min, with second bolus after 10 minutes. Infusion continued for 12 – 18 hours. Adjustment for renal impairment according to the label, was permitted investigator’s discretion</p>	<p>324 mg orally or 500 mg IV given in ED</p> <p>300 to 325 mg orally QD during hospitalization</p> <p>75-81 mg QD thereafter indefinitely</p>	<p>Loading dose administered before catheterization:</p> <p>300 mg or 600 mg loading dose at the discretion of the investigator, or</p> <p>Ticlopidine 500 mg in the case of clopidogrel allergy</p> <p>Clopidogrel 75 mg orally every day for at least 6 months (1 year or longer recommended)</p>

HORIZONS-AMI: Primary PCI Outcome Measures at 30 Days



*Not related to CABG

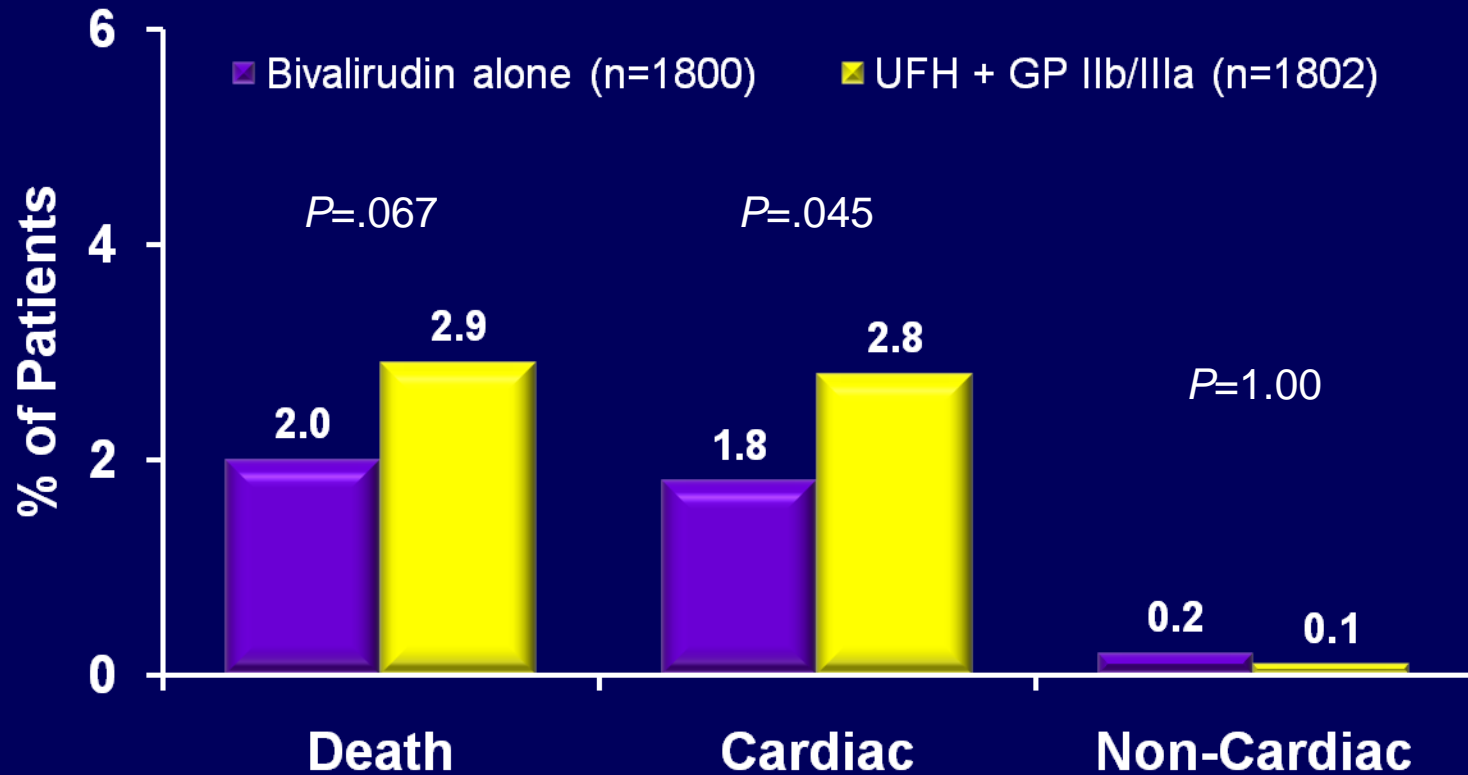
**MACE = All cause death, reinfarction, ischemic TVR or stroke

***NACE = MACE or major bleeding

Stone GW, et al. *N Engl J Med.* 2008;358(21):2218-2230.C

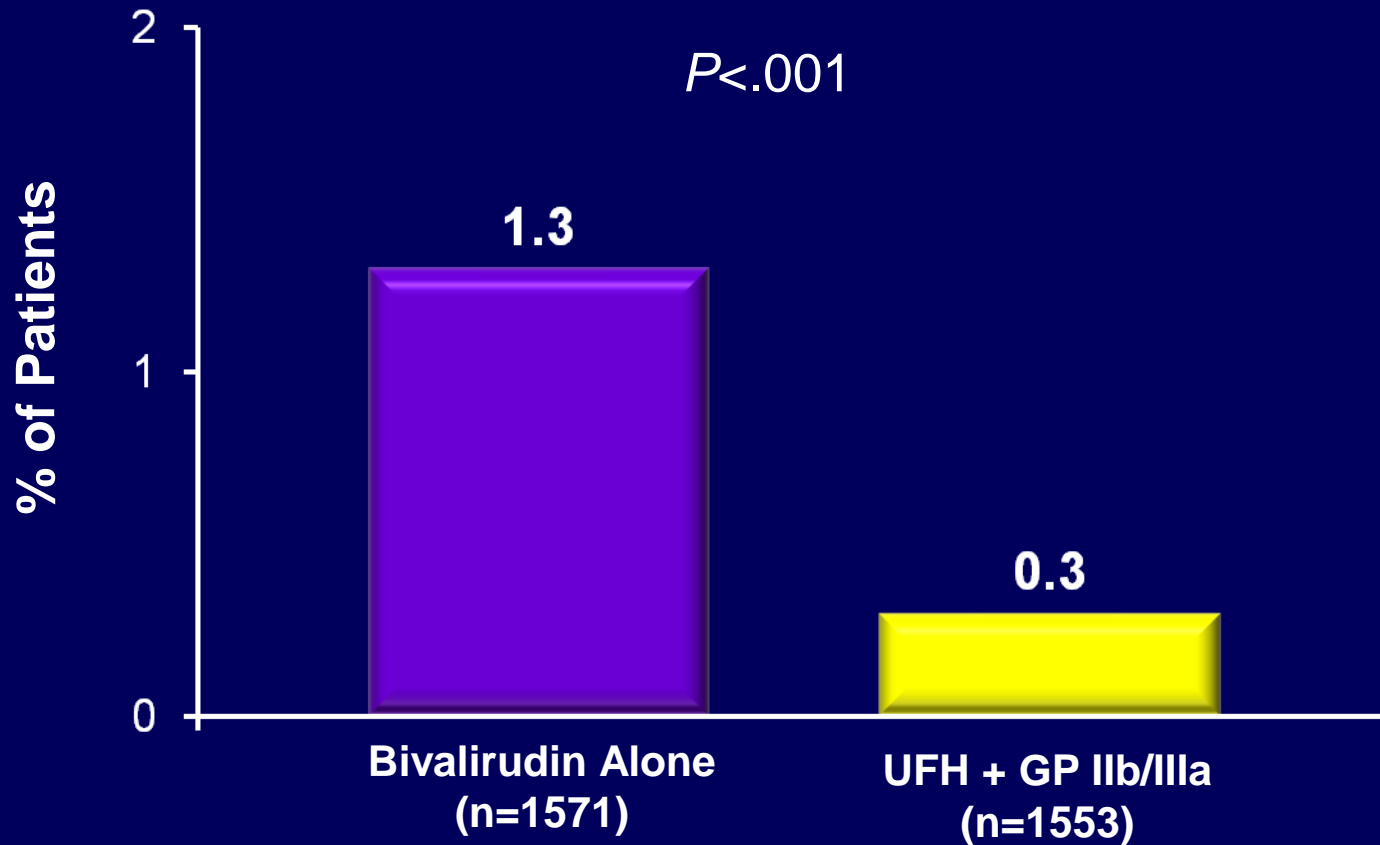
HORIZONS AMI: Mortality at 30 Days

Primary PCI Population



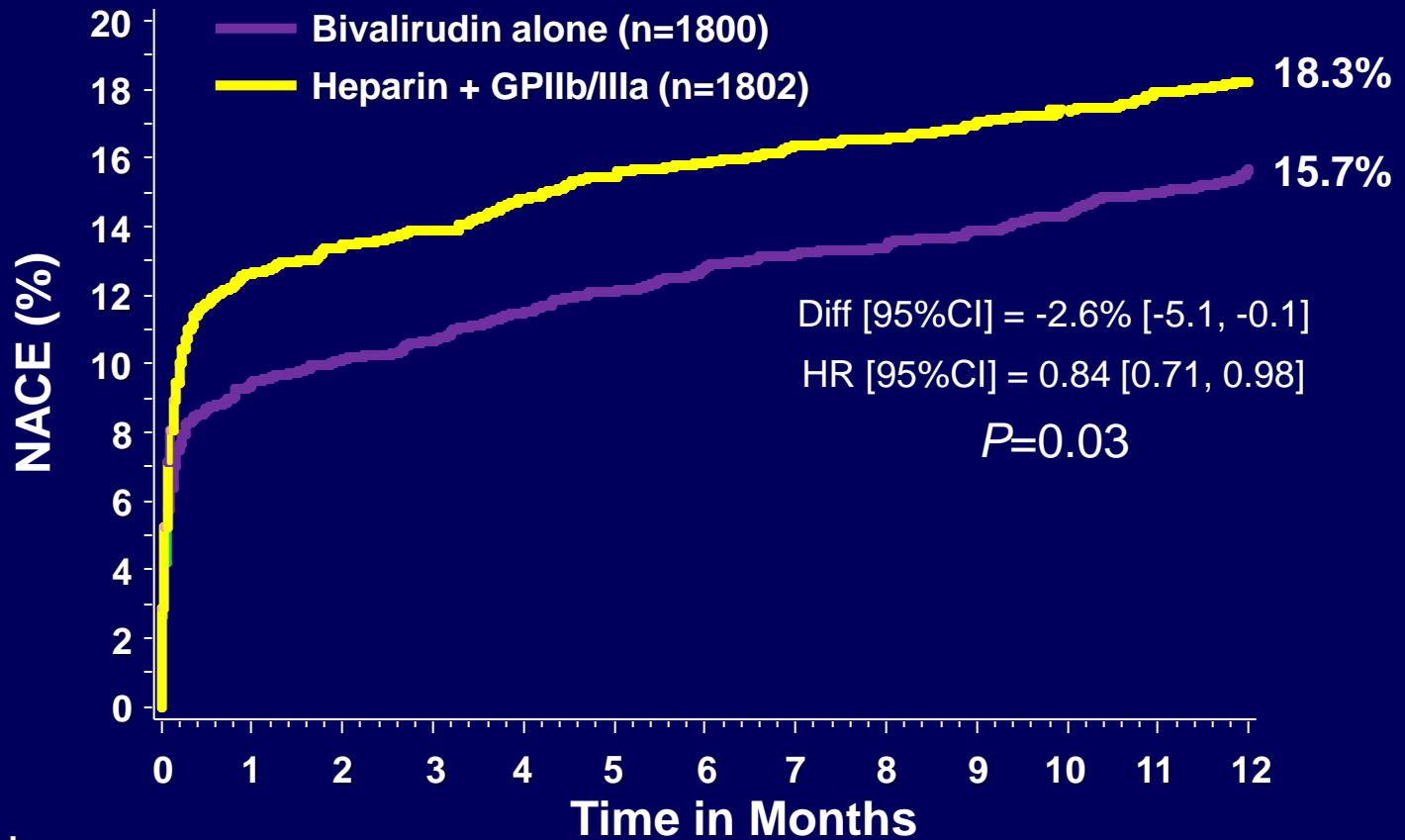
HORIZONS AMI: Stent Thrombosis

Acute (≤ 24 h)



Stone GW, et al. *N Engl J Med.* 2008;358(21):2218-2230.

HORIZONS-AMI: 1-Year Net Adverse Clinical Events*

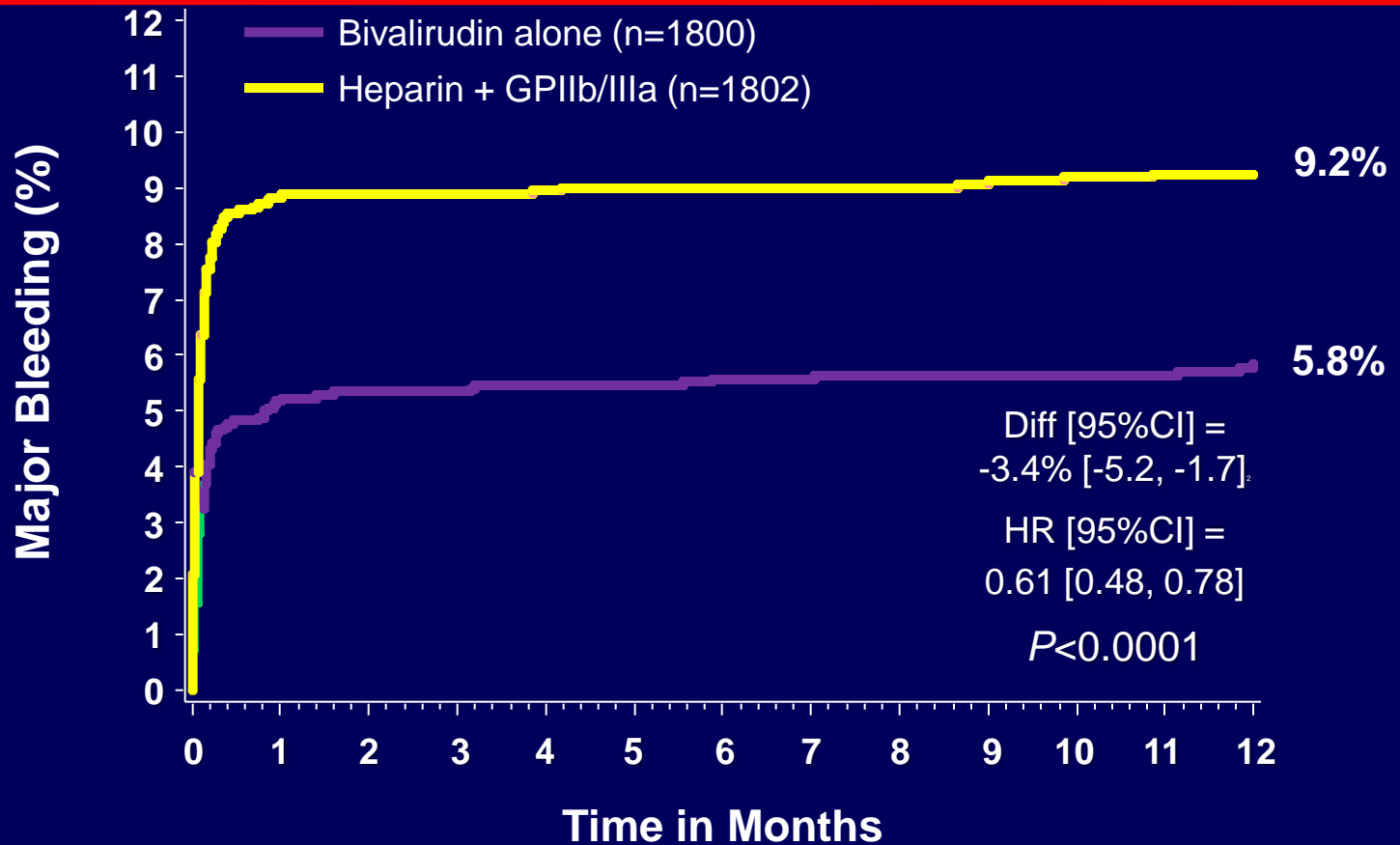


Number at risk

Time (Months)	0	1	2	3	4	5	6	7	8	9	10	11	12
Heparin+GPIIb/IIIa	1800	1559	1514	1483	1459	1427	1343						
Bivalirudin alone	1802	1499	1459	1427	1281								

*MACE or major bleeding (non CABG)

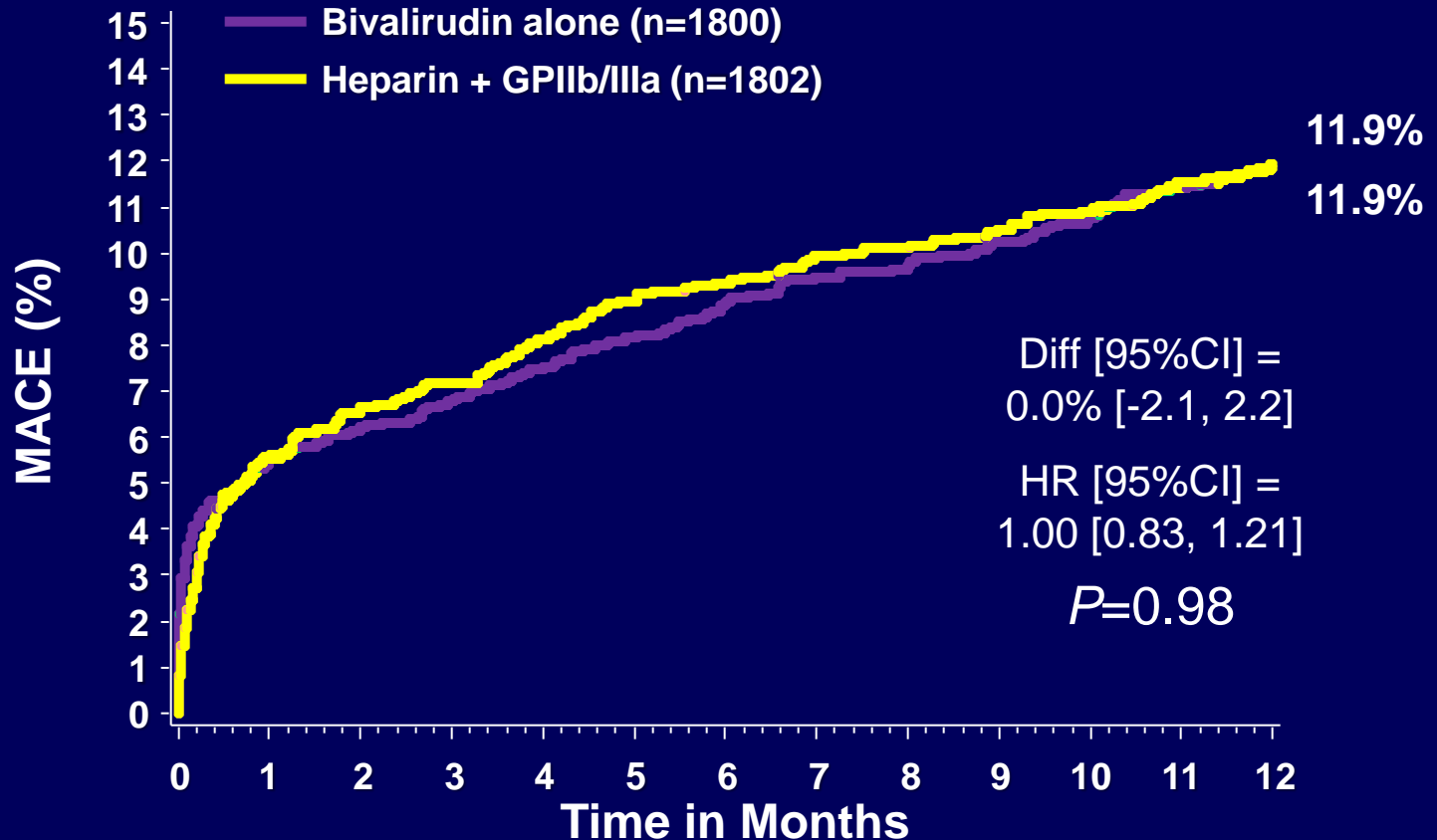
HORIZONS-AMI: 1-Year Major Bleeding (non-CABG)



Number at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12
Bivalirudin alone	1800	1621	1601	1586	1586	1586	1586	1586	1586	1586	1586	1586	1448
Heparin+GPIIb/IIIa	1802	1544	1532	1515	1515	1515	1515	1515	1515	1515	1515	1515	1368

HORIZONS-AMI: 1-Year Major Adverse CV Events*



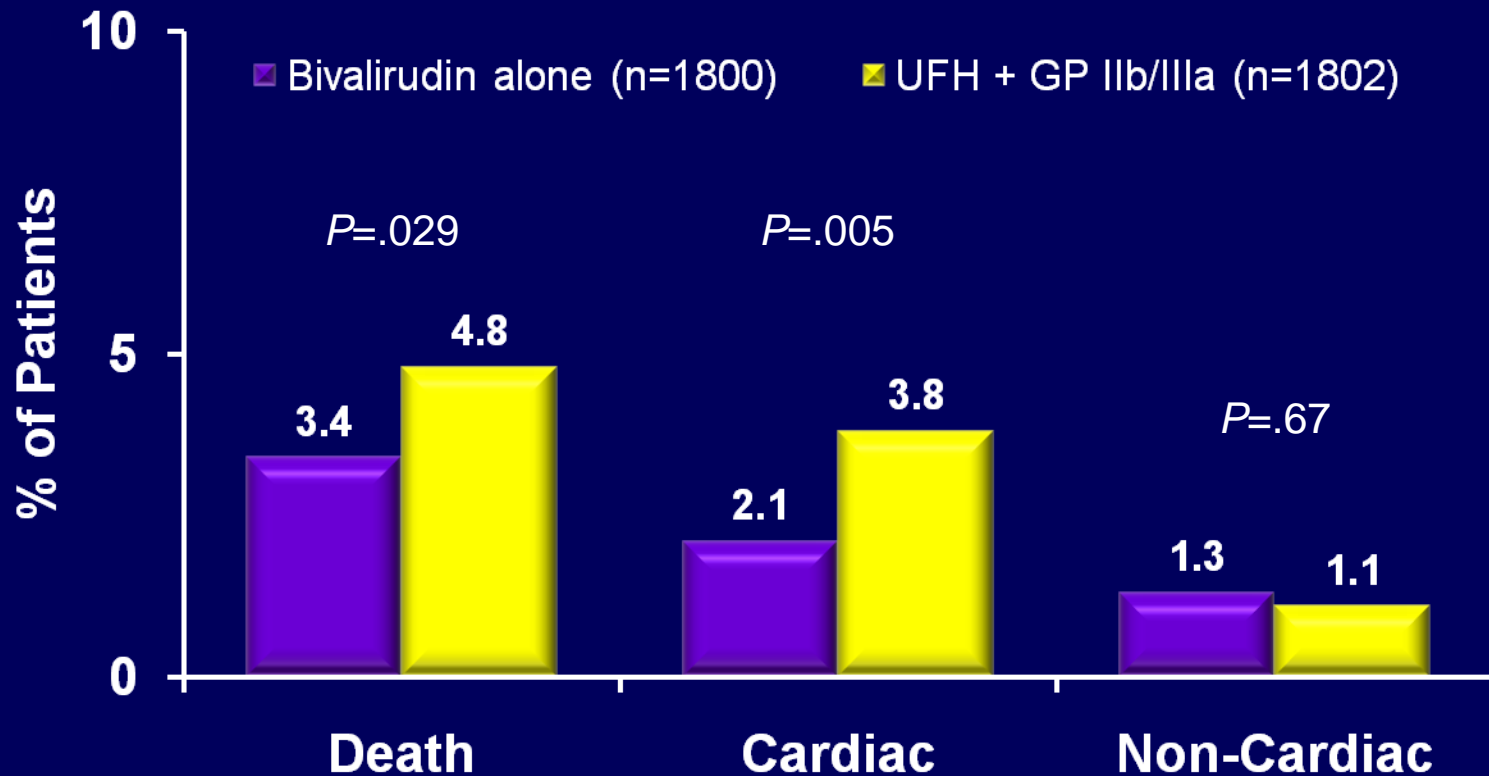
Number at risk

Time (Months)	0	1	2	3	4	5	6	7	8	9	10	11	12
Bivalirudin alone	1800	1627	1579	1544	1394								
Heparin+GPIIb/IIIa	1802	1619	1573	1540	1380								

*MACE = All cause death, reinfarction, ischemic TVR or stroke

HORIZONS AMI: Mortality* at 1 Year

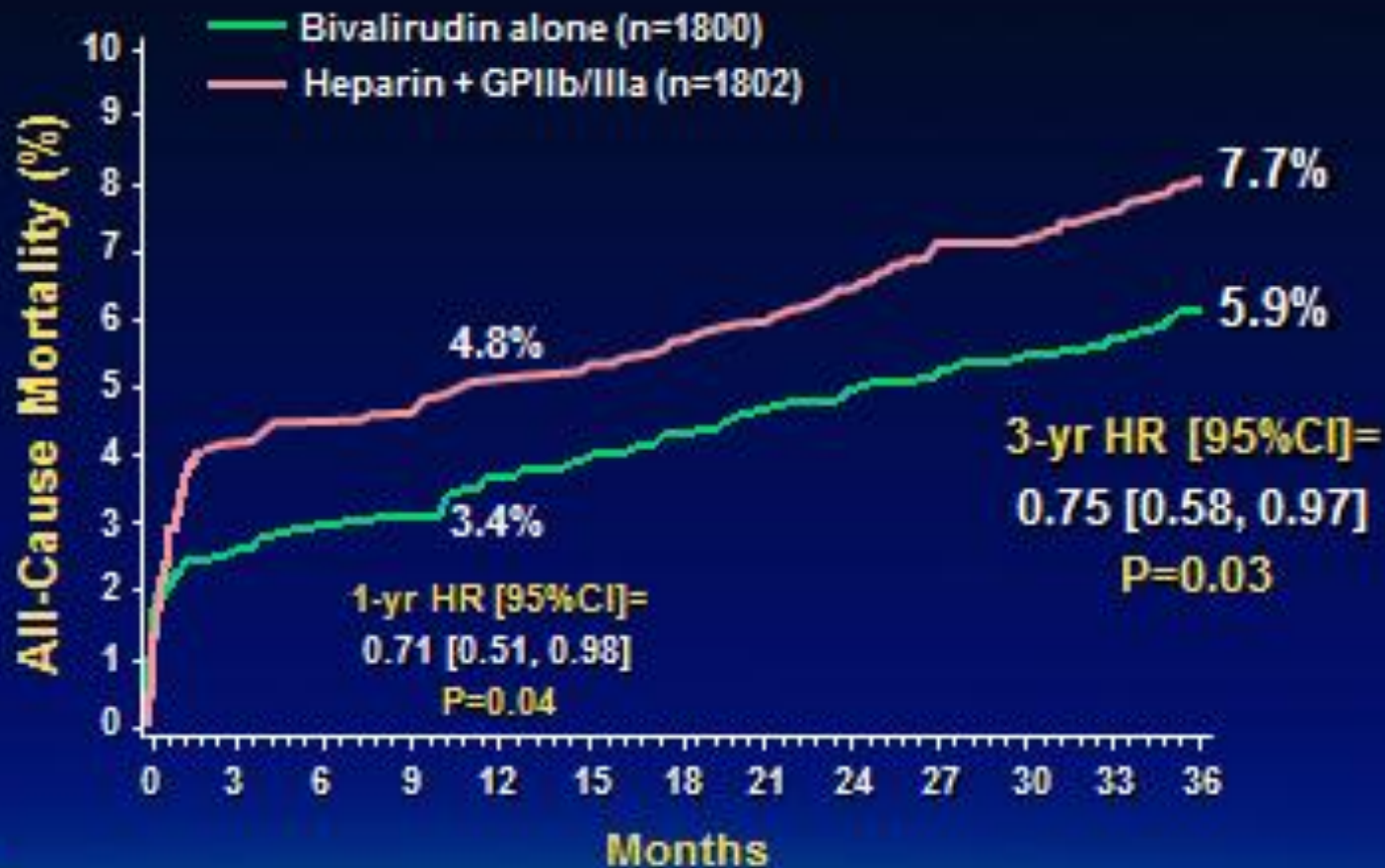
Intent-to-Treat (ITT) Population



*All Kaplan-Meier estimates; all CEC adjudicated

Mehran R et al. Presented at Transcatheter Cardiovascular Therapeutics. October, 2008; Washington, DC.

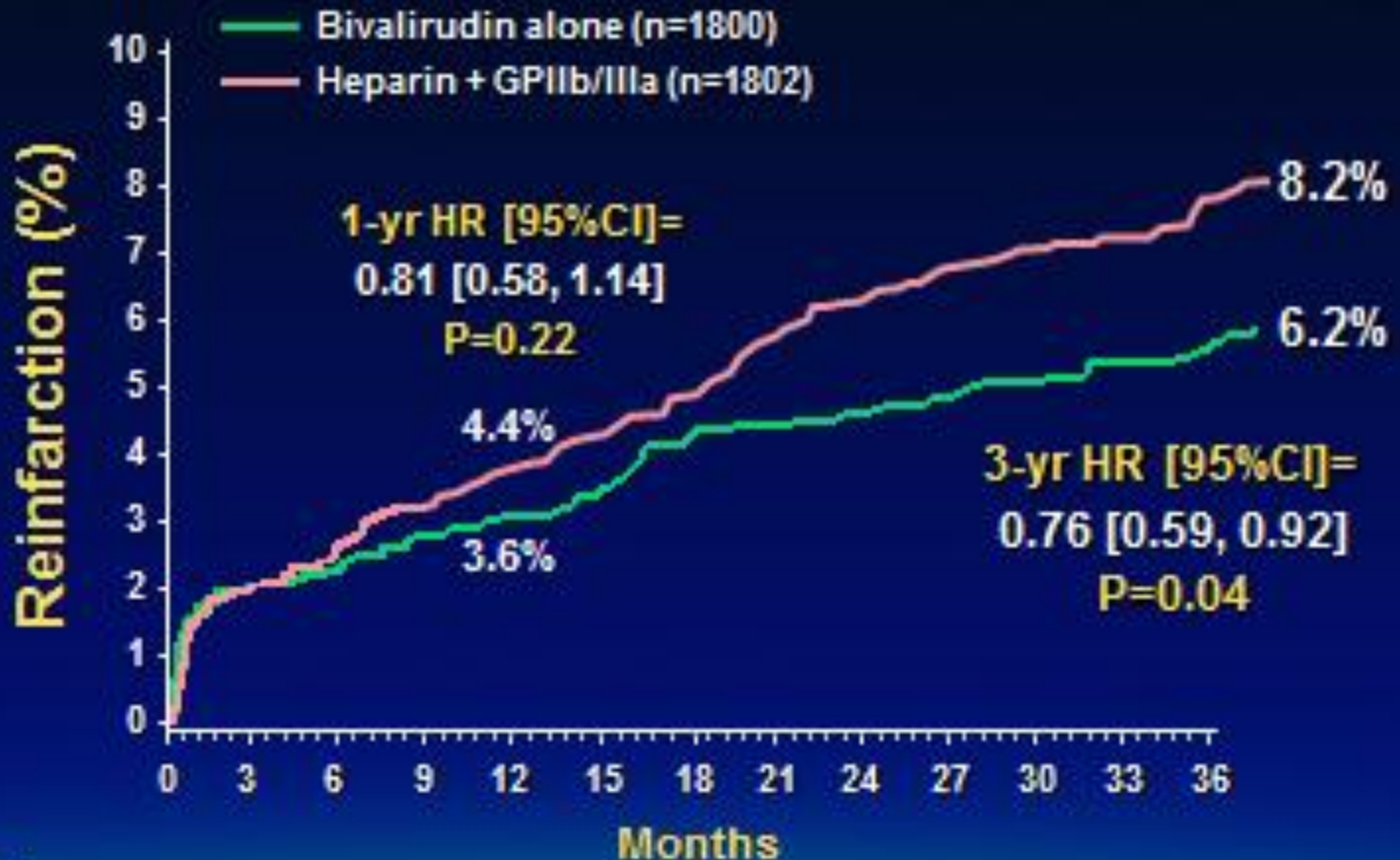
Three-Year All-Cause Mortality



Number at risk

Bivalirudin alone	1800	1689	1660	1633	1611	1574	1098
Heparin+GPIIb/IIIa	1802	1670	1643	1593	1568	1525	1043

Three-Year Reinfarction



Number at risk

Bivalirudin alone	1800	1643	1605	1560	1536	1494	1032
Heparin+GPIIb/IIIa	1802	1623	1581	1513	1474	1425	965

HORIZONS AMI: MAJOR CLINICAL OUTCOMES, BIVALIRUDIN VS UFH/GP IIB/IIIA

End point	Bivalirudin (%)	Heparin+GP IIb/IIIa (%)	HR (95% CI)	p
Major bleeding	6.9	10.5	0.64 (0.51–0.80)	<0.001
All-cause mortality	5.9	7.7	0.75 (0.58–0.97)	0.03
Cardiac mortality	2.9	5.1	0.56 (0.40–0.80)	0.001
Reinfarction	6.2	8.2	0.76 (0.59–0.92)	0.04

MULTISTRATEGY

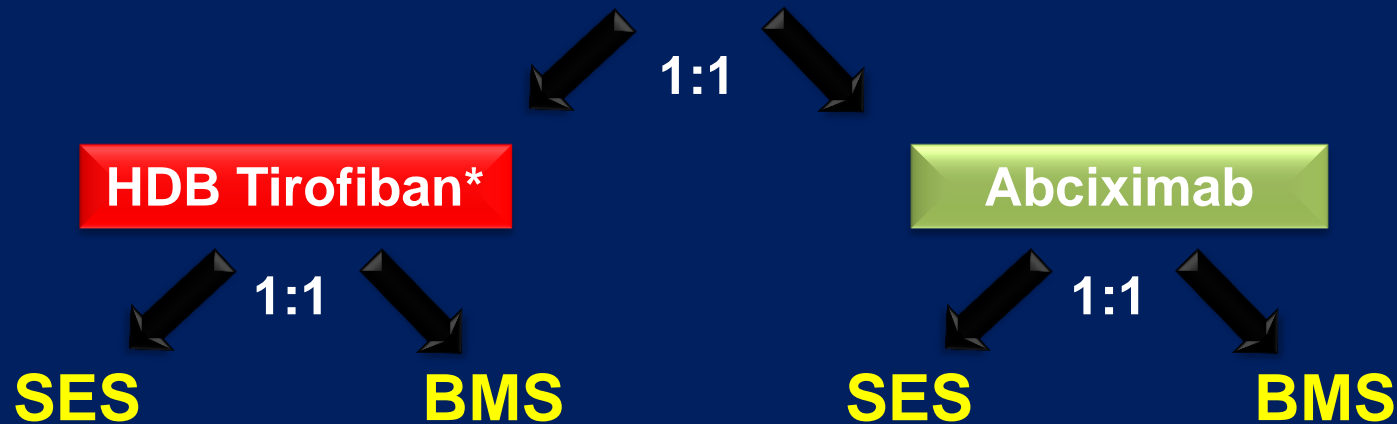
Multicentre Evaluation of
Single High-Dose Bolus Tirofiban vs. Abciximab
With Sirolimus-Eluting Stent or Bare Metal Stent in
Acute Myocardial Infarction

MULTISTRATEGY: Study Design

73

STEMI “all-comer” patients

- Aspirin + clopidogrel + UFH before arterial sheath insertion
- Coronary angiography ± PCI
- Stenting was the default strategy in patients with RVD ≥ 2.5 mm at visual estimation



*Given as a bolus of 25 $\mu\text{g}/\text{kg}$, followed by an 18- to 24-hour infusion at 0.15 $\mu\text{g}/\text{kg}/\text{min}$.

Clinical follow-up at 1, 4, and 8 months; 1 to 5 years

MULTI-STRATEGY: Drug Regimens

74

Regimen	Study Drug Dose	Heparin Dose	ASA Dose	Clopidogrel/Ticlopidine
HDB Tirofiban	Bolus: 25 µg/kg for 3 min Infusion: 0.15 µg/kg/min	40 to 70 U/kg, targeting ACT of 200 s	160-325 mg orally or 250 mg IV, followed by 80-125 mg/d orally indefinitely	300 mg orally and then 75 mg/d for at least 3 months
Abciximab	Bolus: 0.25 mg/kg Infusion: 0.125 µg/kg/min	40 to 70U/kg, targeting ACT of 200 s	160-325 mg orally or 250 mg IV, followed by 80-125 mg/d orally indefinitely	300 mg orally and then 75 mg/d for at least 3 months

Valgimigli M, et al. *JAMA*. 2008;299(15):1788-1799.

MULTISTRATEGY: Primary Endpoints

75

□ Pharmacology Arm

Noninferiority basis

- $\geq 50\%$ Σ ST-segment elevation resolution within 90 min after last balloon inflation @ tt-EKG

□ Stent Arm

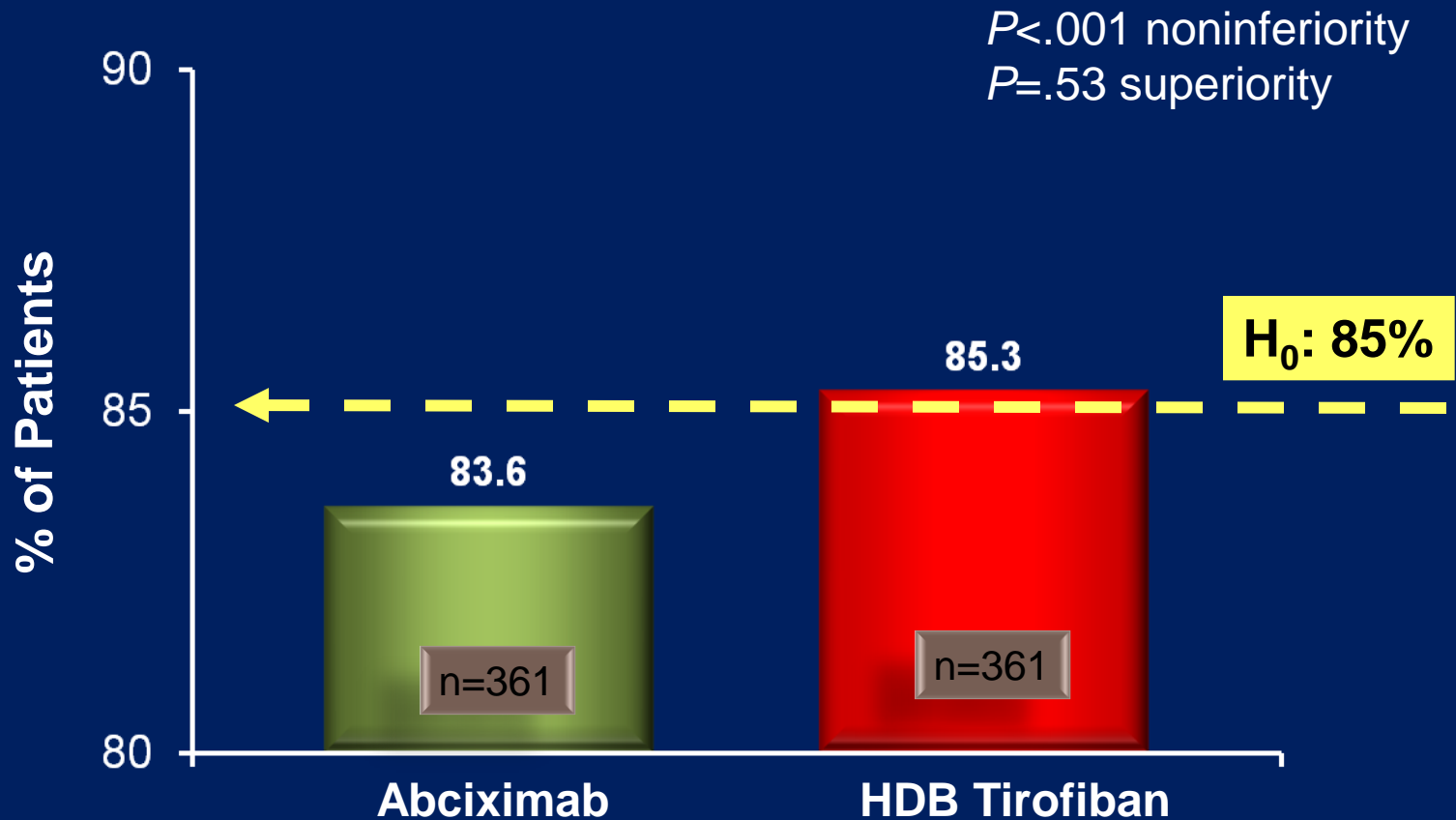
Superiority basis

- Cumulative rate of MACE, defined as overall death, reinfarction, or TVR within 8 months

MULTISTRATEGY: Primary Endpoint

76

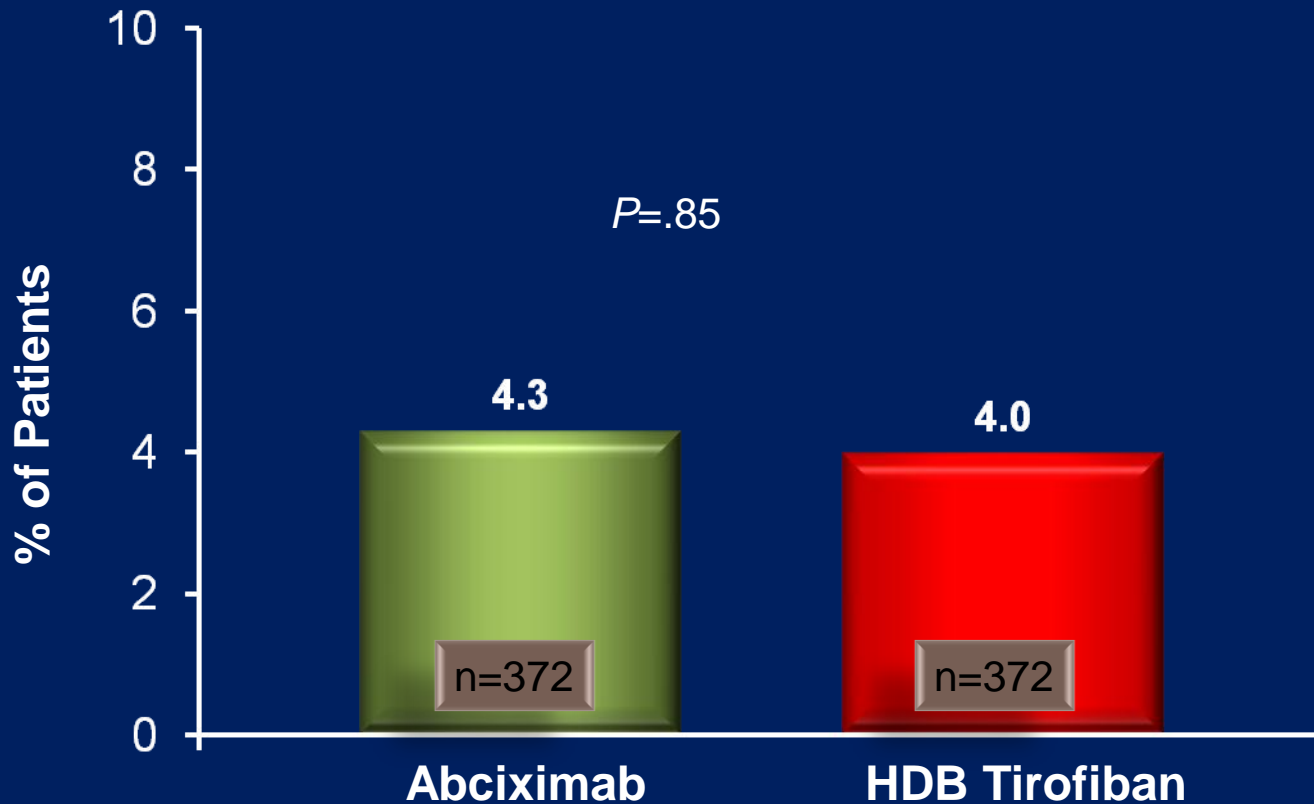
$\geq 50\% \Sigma$ ST segment resolution



MULTISTRATEGY: 30-Day Outcomes (Pharmacology)

77

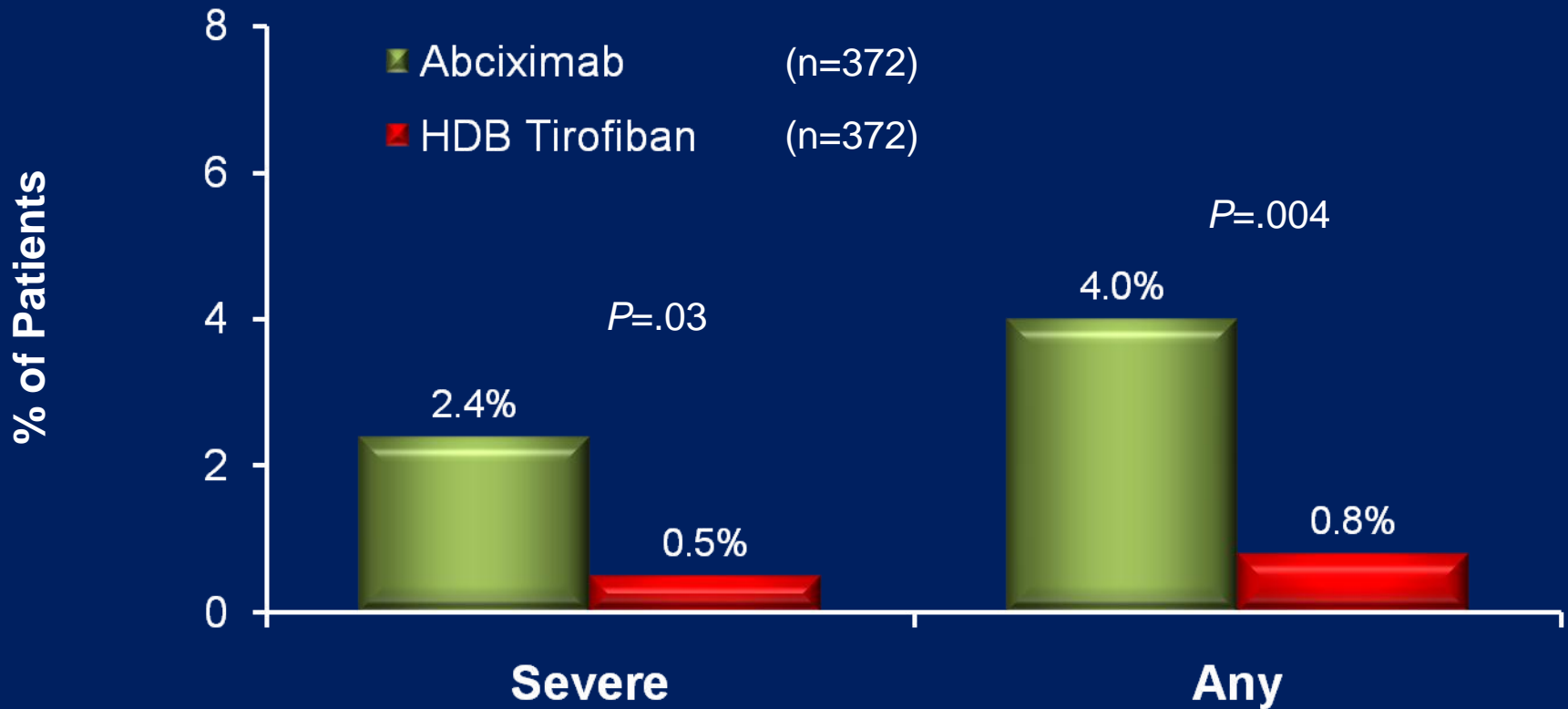
MACE (death, reinfarction, and TVR)



MULTISTRATEGY: Safety Endpoint

78

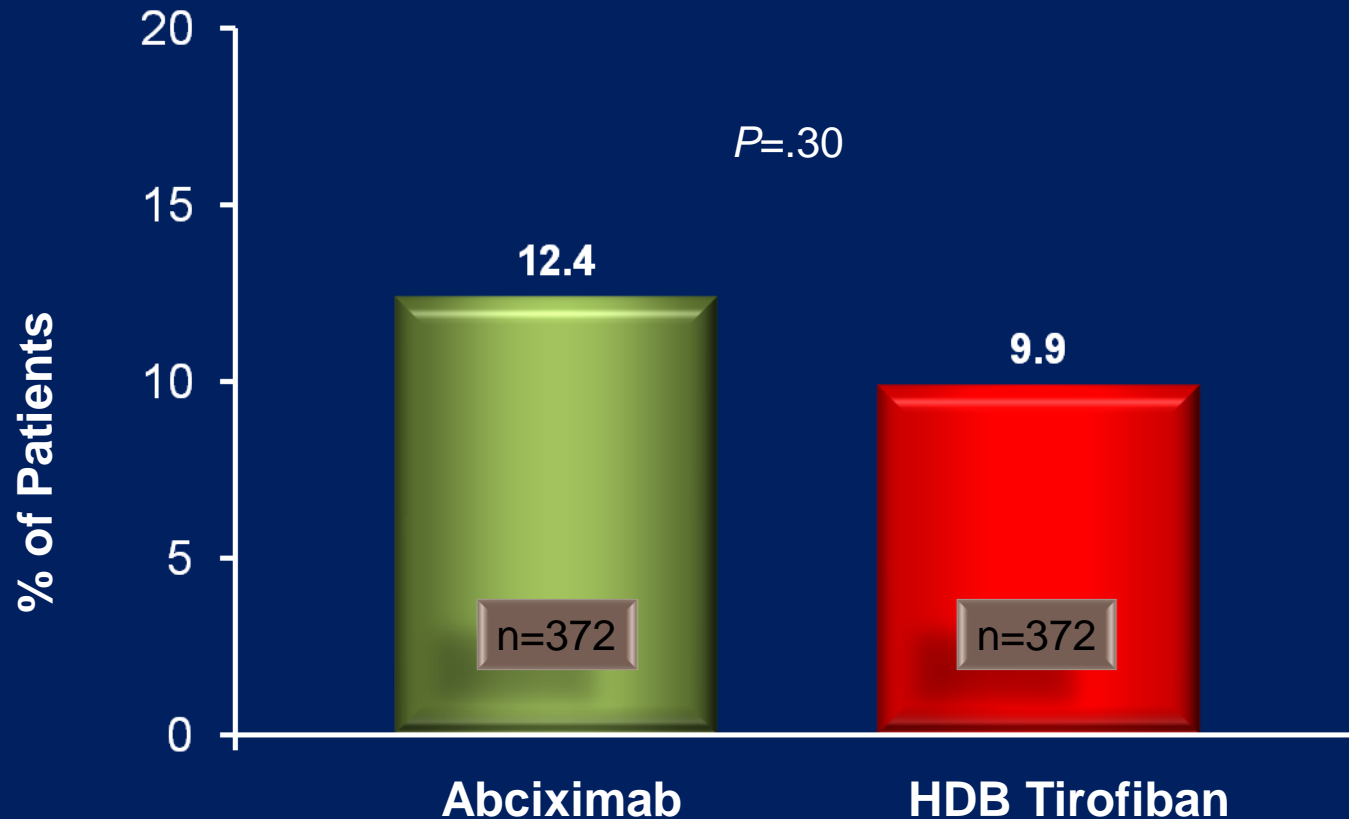
Thrombocytopenia at 30 days



MULTISTRATEGY: 8-Month Outcomes Pharmacology

79

MACE (death, reinfarction, and TVR)



Valgimigli M, et al. *JAMA*. 2008;299(15):1788-1799.

2004/2005/2007 Recommendations:
2004 STEMI Guideline Section 6.3.1.6.8.2.3;
Also 2005 PCI Guideline Section 6.2.2

2009 Joint STEMI/PCI Focused Update Recommendations

Comments

Class IIa

1. It is reasonable to start treatment with abciximab as early as possible before primary PCI (with or without stenting) in patients with STEMI. (*Level of Evidence: B*)

1. It is reasonable to start treatment with glycoprotein IIb/IIIa receptor antagonists (abciximab (9,11) [*Level of Evidence: A*], tirofiban (11,12) [*Level of Evidence: B*] or eptifibatid (6,7,9) [*Level of Evidence: B*]) at the time of primary PCI (with or without stenting) in selected patients with STEMI.

Modified recommendation (class of recommendation changed from IIb to IIa for tirofiban and eptifibatid).

Class IIb

1. Treatment with tirofiban or eptifibatid may be considered before primary PCI (with or without stenting) in patients with STEMI. (*Level of Evidence: C*)

1. The usefulness of glycoprotein IIb/IIIa receptor antagonists (as part of a preparatory pharmacological strategy for patients with STEMI before their arrival in the cardiac catheterization laboratory for angiography and PCI) is uncertain (8,10). (*Level of Evidence: B*)

Modified recommendation (text modified; level of evidence changed from C to B).

A Randomized, Double-Blind, Multicenter Comparison Study of Triple Antiplatelet Therapy With Dual Antiplatelet Therapy to Reduce Restenosis After Drug-Eluting Stent Implantation in Long Coronary Lesions

Results From the DECLARE-LONG II (Drug-Eluting Stenting Followed by Cilostazol Treatment Reduces Late Restenosis in Patients with Long Coronary Lesions) Trial

Seung-Whan Lee, MD,* Seong-Wook Park, MD,* Young-Hak Kim, MD,* Sung-Cheol Yun, PHD,* Duk-Woo Park, MD,* Cheol Whan Lee, MD,* Soo-Jin Kang, MD,* Seung-Jung Park, MD,* Jae-Hwan Lee, MD,† Si Wan Choi, MD,† In-Whan Seong, MD,† Nae-Hee Lee, MD,‡ Yoon Haeng Cho, MD,‡ Won-Yong Shin, MD,§ Seung-Jin Lee, MD,§ Se-Whan Lee, MD,§ Min-Su Hyon, MD,|| Duk-Won Bang, MD,|| Young-Jin Choi, MD,¶ Hyun-Sook Kim, MD,¶ Bong-Ki Lee, MD,# Keun Lee, MD,*** Hoon-Ki Park, MD,*** Chang-Bum Park, MD,*** Sang-Gon Lee, MD,†† Min-Kyu Kim, MD,‡‡ Kyoung-Ha Park, MD,‡‡ Woo-Jung Park, MD,‡‡ for the DECLARE-LONG II Study Investigators

Seoul, Daejeon, Bucheon, Cheonan, Pyeongchon, Chuncheon, and Ulsan, Korea

Objectives

The purpose of this study was to determine whether cilostazol reduces intimal hyperplasia in patients undergoing long zotarolimus-eluting stent implantation (stent length: ≥ 30 mm) for native long coronary lesions (length: ≥ 25 mm).

Background

Restenosis after drug-eluting stent implantation remains a significant clinical problem in long coronary lesions.

Methods

Patients (n = 499) were assigned randomly to triple (aspirin, clopidogrel, and cilostazol, triple group: n = 250) or dual antiplatelet therapy (aspirin and clopidogrel and placebo, dual group: n = 249) for 8 months after long zotarolimus-eluting stent implantation. The primary end point was in-stent late loss at the 8-month angiography according to the intention-to-treat principle.

Results

The 2 groups had similar baseline characteristics. The in-stent (0.56 ± 0.55 mm vs. 0.68 ± 0.59 mm, p = 0.045) and in-segment (0.32 ± 0.54 mm vs. 0.47 ± 0.54 mm, p = 0.006) late loss were significantly lower in the triple versus dual group, as were 8-month in-stent restenosis (10.8% vs. 19.1%, p = 0.016), in-segment restenosis (12.2% vs. 20.0%, p = 0.028), and 12-month ischemic-driven target lesion revascularization (5.2% vs. 10.0%, p = 0.042) rates. At 12 months, major adverse cardiac events including death, myocardial infarction, and ischemic-driven target lesion revascularization tended to be lower in the triple group than the dual group (7.2% vs. 12.0%, p = 0.07). Percent intimal hyperplasia volume by volumetric intravascular ultrasound analysis was reduced from $27.1 \pm 13.2\%$ for the dual group to $22.1 \pm 9.9\%$ for the triple group (p = 0.017).

Conclusions

Patients receiving triple antiplatelet therapy after long zotarolimus-eluting stent implantation had decreased extent of late luminal loss, percent intimal hyperplasia volume, and angiographic restenosis, resulting in a reduced risk of 12-month target lesion revascularization compared with patients receiving dual antiplatelet therapy.

(Triple Versus Dual Antiplatelet Therapy after ABT578-Eluting Stent; NCT00589927) (J Am Coll Cardiol 2011; 57:1264-70) © 2011 by the American College of Cardiology Foundation

From the *Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; †Chungnam National University Hospital, Daejeon, Korea; ‡Soon Chun Hyang University Bucheon Hospital, Bucheon, Korea; §Soon Chun Hyang Univer-

sity Cheonan Hospital, Cheonan, Korea; ||Soon Chun Hyang University Hospital, Seoul, Korea; ¶Hallym University Sacred Heart Hospital, Pyeongchon, Korea; #Kangwon National University Hospital, Chuncheon, Korea; **Seoul Veterans

DECLARE-LONG II (RESULTS)

Table 3 Quantitative Angiographic Measurements

Variable	Triple (n = 250)	Dual (n = 249)	p Value
Reference diameter, mm	2.79 ± 0.48	2.78 ± 0.51	0.758
Lesion length, mm	33.6 ± 13.2	34.7 ± 12.9	0.339
Minimum lumen diameter, mm			
In-segment			
Before procedure	0.94 ± 0.49	0.94 ± 0.45	0.972
After procedure	2.35 ± 0.46	2.32 ± 0.53	0.604
At follow-up	2.01 ± 0.55	1.90 ± 0.62	0.031
In-stent			
After procedure	2.68 ± 0.40	2.67 ± 0.46	0.639
At follow-up	2.12 ± 0.61	1.99 ± 0.68	0.041
Diameter stenosis, %			
In-segment			
Before procedure	69.1 ± 15.5	68.7 ± 15.3	0.793
After procedure	15.9 ± 9.4	16.8 ± 9.6	0.360
At follow-up	29.6 ± 17.9	33.8 ± 19.5	0.019
In-stent			
After procedure	8.2 ± 7.9	8.4 ± 8.5	0.791
At follow-up	28.1 ± 18.3	32.4 ± 19.9	0.021
Acute gain, mm			
In-segment	1.41 ± 0.64	1.38 ± 0.73	0.699
In-stent	1.75 ± 0.60	1.73 ± 0.68	0.725
Late loss, mm			
In-segment	0.32 ± 0.54	0.47 ± 0.54	0.006
In-stent	0.56 ± 0.55	0.68 ± 0.59	0.045
Binary angiographic restenosis			
In-segment	26 (12.2%)	43 (20.0%)	0.028
In-stent	23 (10.8%)	41 (19.1%)	0.016

Values are mean ± SD or n (%).

Table 5 Intravascular Ultrasound Measurements

	Triple (n = 65)	Dual (n = 57)	p Value
EEM volume index, mm ³ /m			
After procedure	14.47 ± 3.79	14.91 ± 3.23	0.490
At follow-up	14.93 ± 4.11	15.34 ± 3.33	0.555
Narrowest EEM, mm ³			
After procedure	11.26 ± 4.78	11.58 ± 3.57	0.678
At follow-up	13.08 ± 4.98	13.64 ± 4.25	0.503
Stent volume index, mm ³ /m			
After procedure	7.12 ± 1.68	7.49 ± 1.61	0.218
At follow-up	7.30 ± 1.76	7.61 ± 1.62	0.237
Lumen volume index, mm ³ /m			
After procedure	7.12 ± 1.68	7.49 ± 1.61	0.218
At follow-up	5.70 ± 1.57	5.53 ± 1.49	0.540
Intimal hyperplasia volume index, mm ³ /m			
After procedure	0	0	
At follow-up	1.60 ± 0.87	2.09 ± 1.17	0.010
Minimal lumen area, mm ²			
After procedure	5.37 ± 1.65	5.58 ± 1.53	0.479
At follow-up	3.79 ± 1.39	3.74 ± 1.38	0.853
Percent intimal hyperplasia volume, %			
After procedure	0	0	
At follow-up	22.1 ± 9.9	27.1 ± 13.2	0.017

EEM = external elastic membrane.

DECLARE-LONG II (RESULTS)

Table 6		Clinical Outcomes at 12 Months		
Variable	Triple (n = 250)	Dual (n = 249)	p Value	
Death	6 (2.4%)	3 (1.2%)	0.51	
Cardiac	4 (1.6%)	1 (0.4%)		
Noncardiac	2 (0.8%)	2 (0.8%)		
MI	4 (1.6%)	4 (1.6%)	0.99	
Q-wave	2 (0.8%)	1 (0.4%)		
Non-Q-wave	2 (0.8%)	3 (1.2%)		
Ischemic-driven TLR	13 (5.2%)	25 (10.0%)	0.04	
Cutting balloon	6 (2.4%)	12 (4.8%)		
Drug-eluting stent	6 (2.4%)	12 (4.8%)		
Bypass surgery	1 (0.4%)	1 (0.4%)		
Stent thrombosis	4 (1.6%)	1 (0.4%)	0.18	
Acute	1 (0.4%)	0		
Subacute	2 (0.8%)	1 (0.4%)		
Late	1 (0.4%)	0		
Ischemic-driven TVR	13 (5.2%)	26 (10.4%)	0.03	
Death/MI/ischemic-driven TVR	18 (7.2%)	31 (12.4%)	0.05	
MACE (death/MI/ischemic-driven TLR)	18 (7.2%)	30 (12.0%)	0.07	

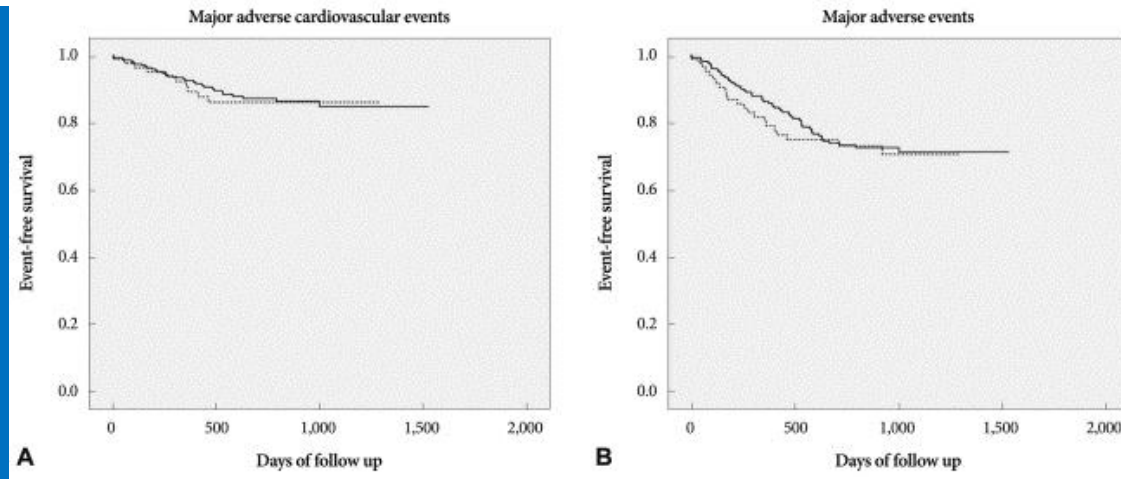
MACE – major adverse cardiac event(s); MI – myocardial infarction; TLR – target lesion revascularization; TVR – target vessel revascularization.

Triple Antithrombotic Therapy

(aspirin, thienopyridine + vitamin K antagonist [VKA])

Atrial Fibrillation After PCI

- Three hundred sixty-two patients (68.0% men, mean age: 68.3±7.8 years) with AF, who had undergone PCI with stent implantation



Event, n (%)	Not anticoagulated (n=278)	Anticoagulated (n=84)	p
Death	23 (8.3)	3 (3.6)	0.144
AMI	4 (1.4)	3 (3.6)	0.206
TLR	12 (4.3)	1 (1.2)	0.132
Stent thrombosis	4 (1.4)	3 (3.6)	0.206
Major bleeding	6 (2.2)	9 (10.7)	0.002
Minor bleeding	3 (1.1)	2 (2.4)	0.329
Stroke	12 (4.3)	1 (1.2)	0.314
MACE	43 (15.5)	10 (11.9)	0.849
MAE	64 (23.0)	22 (26.2)	0.550

Outcomes of Patients Treated With Triple Antithrombotic Therapy

After PCI for STEMI (HORIZONS-AMI Trial)

- Among the 3,320 patients triaged to primary PCI, 126 (3.8%) were prescribed triple therapy (aspirin, thienopyridine and vitamin K antagonist [VKA]) and 3,194 (96.2%) were prescribed dual antiplatelet therapy.
- Most frequent indications for VKA treatment were a severely reduced left ventricular ejection fraction with a large akinetic area, atrial fibrillation (23.8% each), and mural thrombus (23.0%).

Results

Comparable short- and long-term ischemic outcomes but significantly increased rates of major bleeding.

Table 1: SCAI survey (168 respondents, conducted on 2/21/2011).

1. How often do you use a drug eluting stent in patients with AF on warfarin?

- a. Never 1.8%
- b. Rarely 32.9%
- c. Sometimes 35.3%
- d. Often 30.6%

2. What is your preferred regimen in a patient with chronic AF on warfarin and requiring a DES?

- a. ASA, clopidogrel and warfarin for one month then ASA + warfarin 5.3%
- b. ASA, clopidogrel and warfarin for one month then clopidogrel + warfarin 19.3%
- c. ASA, clopidogrel and warfarin for 6 months or more 47.5%
- d. ASA and clopidogrel for 6 months or more 8.8%
- e. Clopidogrel and warfarin for 6 months or more 9.6%

3. What is your preferred regimen in a patient with chronic AF on warfarin and requiring a BMS?

- a. ASA, clopidogrel and warfarin for one month then ASA + warfarin 86.5%
- b. ASA, clopidogrel and warfarin for one month then clopidogrel + warfarin 7.6%
- c. ASA, clopidogrel and warfarin for 6 months or more 3.2%
- d. ASA and clopidogrel for 6 months or more 1.3%
- e. Clopidogrel and warfarin for 6 months or more 0.6%

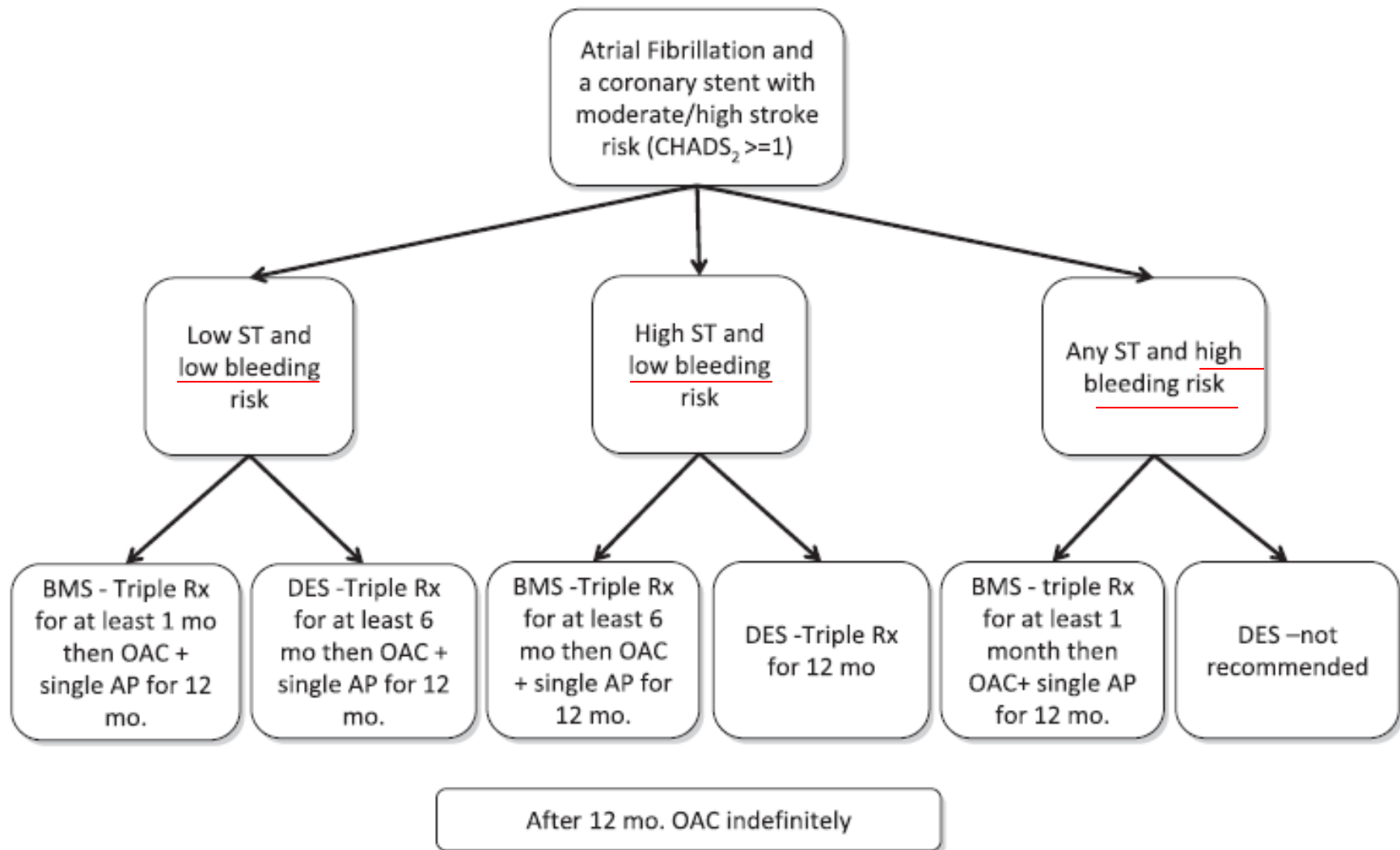


Figure 1: Recommendations for the duration of triple therapy in patients with atrial fibrillation and a coronary stent (BMS or DES) with moderate/high stroke risk (CHADS₂ ≥ 1). BMS, bare metal stent; DES, drug eluting stent; OAC, warfarin; AP, anti-platelet agent; triple therapy, aspirin, clopidogrel and warfarin.

THANK YOU!

- In patients without a prior thromboembolic event, the risk of
- stroke or systemic embolism is relatively constant over time;
- 1.4%/year on warfarin and 2.4%/year on aspirin and clopidogrel as
- reported in the Atrial Fibrillation Clopidogrel Trial with Irbesartan
- for Prevention of Vascular Events—W (ACTIVE- W) trial (18). In
- this study, the benefit of warfarin over aspirin and clopidogrel was
- only seen when the international normalised ratio (INR) was in
- the therapeutic range more than 58% of the time (26)

- This
- should translate into a low risk per month (estimated to be 0.2%)
- on DAPT alone for atrial fibrillation patients at intermediate or
- high-risk of stroke based upon data from ACTIVE W trial (18).

- Additional risk factors for stent thrombosis
- include incomplete stent apposition, significant proximal vessel disease, malignancy, post-procedure Thrombolysis in Myocardial Infarction (TIMI) flow <3, residual dissection, bifurcation stents, low ejection fraction, ACS, renal failure, diabetes mellitus, stent length, and left anterior descending artery location (20, 27, 33).
- Stent thrombosis is also increased in 'off-label' indications and following
- primary angioplasty for STEMI (37, 38)





Triple Antithrombotic Therapy

(aspirin, thienopyridine + vitamin K antagonist [VKA])

RECOMMENDATIONS

Warfarin and one antiplatelet agent

- The use of one antiplatelet agent in combination with warfarin is uncommon after PCI but is almost always prescribed after the initial use of triple therapy for 1–12 months.
- Which antiplatelet agent, aspirin or clopidogrel, should be used is unclear

Specific recommendations

- Clopidogrel is the thienopyridine of choice in combination with aspirin and warfarin. Prasugrel and ticagrelor cannot be recommended with warfarin.
- Warfarin should be dose adjusted and closely monitored to maintain the INR between 2 and 2.5
- Triple therapy use should depend on the balance of risks**

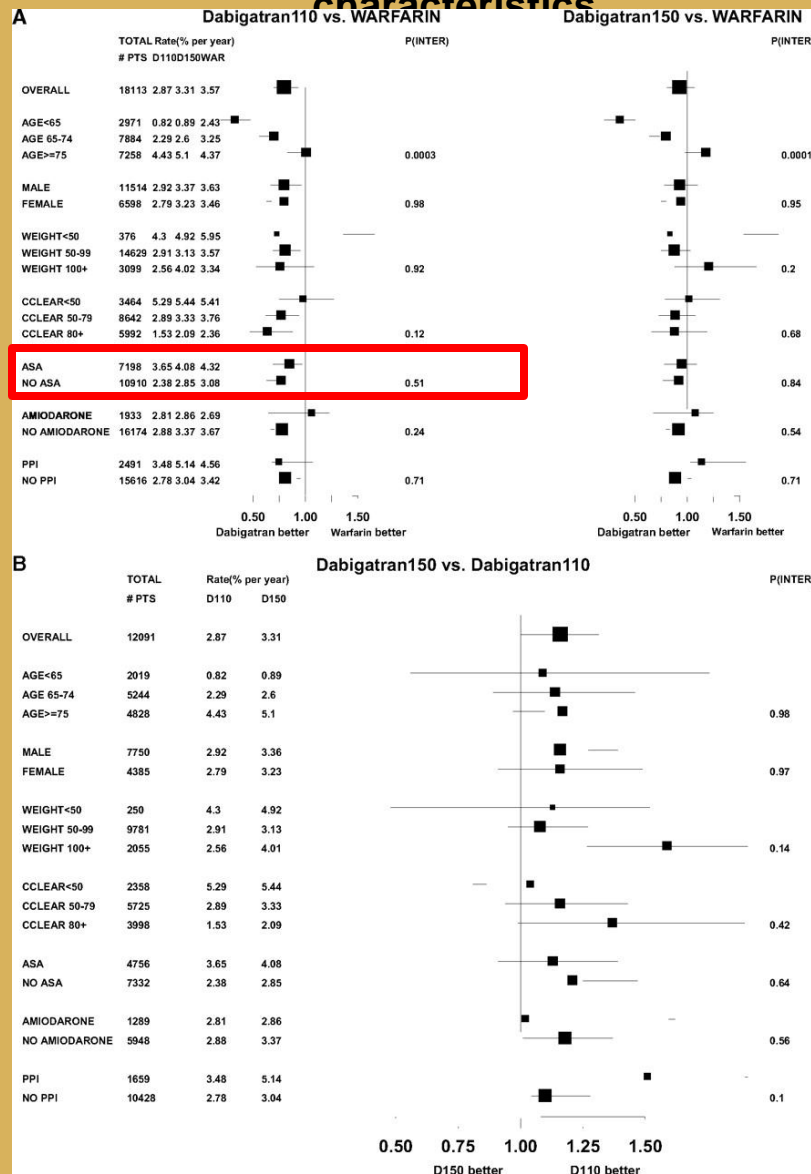
Future randomised trials on triple therapy

Three registered ongoing randomised clinical trials of triple therapy in patients undergoing PCI

- I. **ISAR-TRIPLE**: 600 patients and will compare a short course of triple therapy (6 weeks) to a long course (6 months) followed by aspirin and warfarin. The primary endpoint will be the composite of death, MI, definite stent thrombosis, stroke, or major bleeding at nine months
- II. **WOEST**: will randomise 496 patients to either oral anticoagulation plus clopidogrel or to triple therapy. The primary endpoint will be any bleeding over one year
- III. **MUSICA-2**: will randomise 304 patients with low to moderate stroke risk ($\text{CHADS}_2 \leq 2$) to DAPT or triple therapy. The primary endpoint will be death, MI, stroke, embolisation, or stent thrombosis at 12 months

-
- **Combinations with new oral anticoagulants**

Risk of major bleeding with dabigatran versus warfarin (A) and with dabigatran 150 mg twice a day vs dabigatran 110 mg twice a day (B) in key subgroups according to baseline characteristics



Recent ACS: STEMI, NSTEMI, UA

Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH,
prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Placebo

n=5,176

Rivaroxaban

2.5 mg BID

n=5,174

Rivaroxaban

5.0 mg BID

n=5,176

PRIMARY ENDPOINTS:

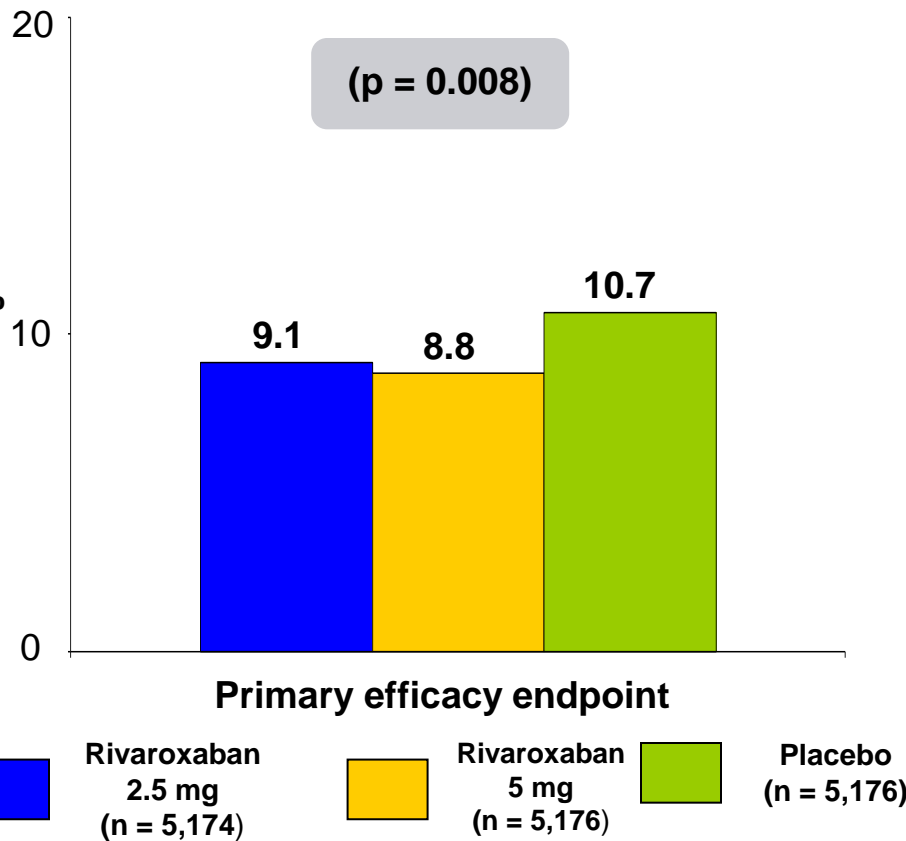
EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

SAFETY: TIMI major bleeding not associated with CABG

Event driven trial with 1,002 primary efficacy events

ATLAS ACS 2-TIMI 51

Trial design: Patients with recent ACS were randomized in a 1:1:1 fashion to rivaroxaban 2.5 mg twice daily, 5 mg twice daily, or placebo, in addition to dual antiplatelet therapy (DAPT) with aspirin and a thienopyridine in 93%. Patients were followed for 2 years.



Results

- Primary endpoint: CV death/MI/stroke for rivaroxaban vs. placebo: 8.9% vs. 10.7%, $p = 0.008$. True for 2.5 mg (9.1%) and 5 mg (8.8%) doses individually. Greatest efficacy for ischemic endpoints with the 2.5 mg daily dose, including mortality (2.9% vs. 4.5%, $p = 0.002$)
- Non-CABG TIMI major bleeding: 2.1% vs. 0.6%, $p < 0.001$. Similar for 2.5 mg (1.8%) and 5 mg (2.4%)

Conclusions

- Addition of very low dose rivaroxaban (2.5 mg twice daily) in patients with a recent ACS (most of whom were on DAPT) ↓ mortality, and ischemic events as compared with placebo. However, bleeding was simultaneously ↑
- First successful large trial with an oral anti-Xa agent in patients with ACS taking antiplatelet agents; use will require assessment of ischemia/bleeding risks

Mega JL, et al. N Engl J Med 2011;Nov 13:





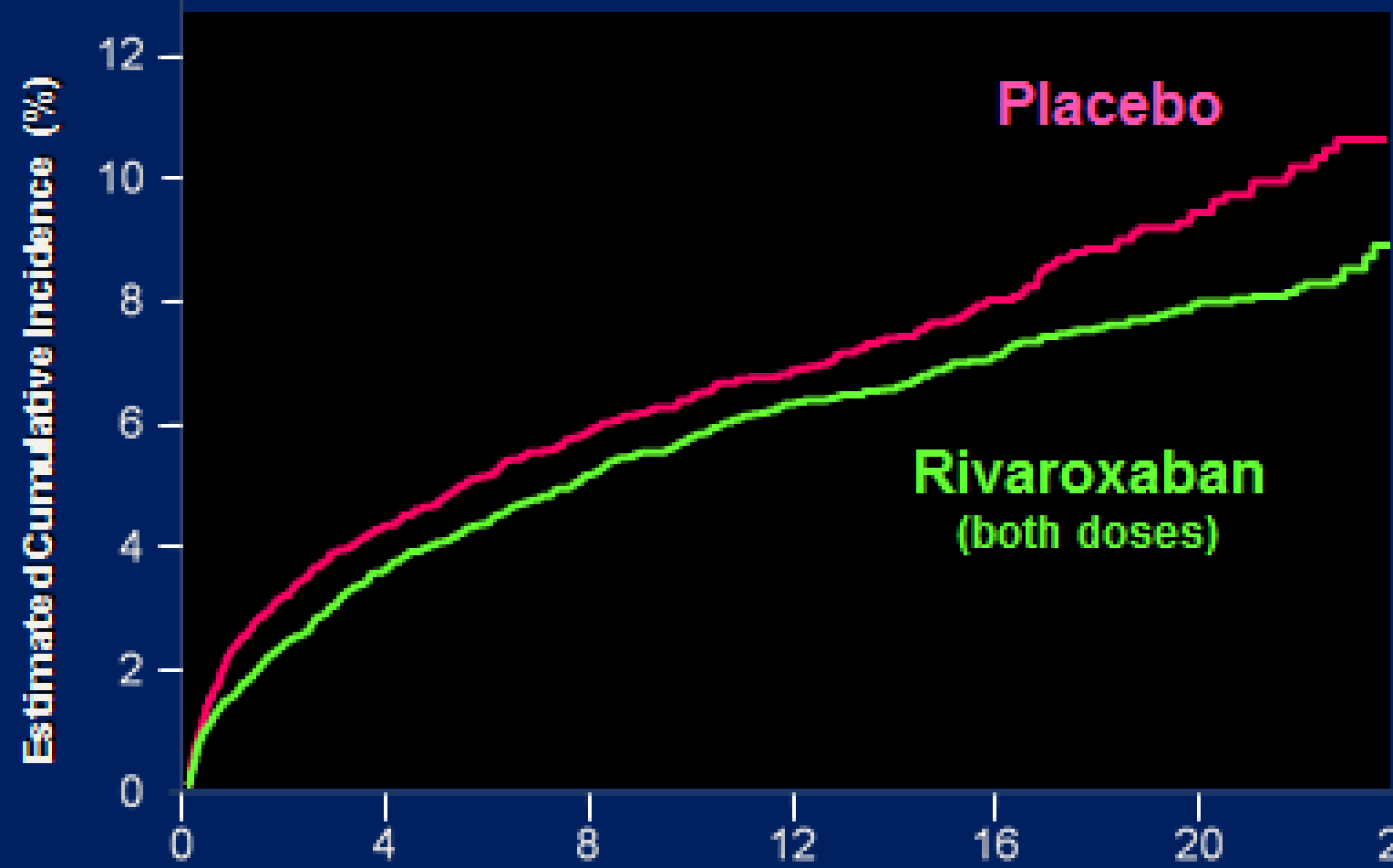






PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke



2 Yr KM Estimate

10.7%

8.9%

HR 0.84
 (0.74-0.96)

mITT p = 0.008
 ITT p = 0.002

ARR 1.8%
 NNT = 56

No. at Risk	Months After Randomization							
	0	4	8	12	16	20	24	
Placebo	5113	4307	3470	2664	1831	1079	421	
Rivaroxaban	10229	8502	6753	5137	3554	2084	831	

HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified logrank p-values are provided for both mITT and ITT approaches.

STENT THROMBOSIS

ARC Definite / Probable / Possible

2 Yr KM Estimate

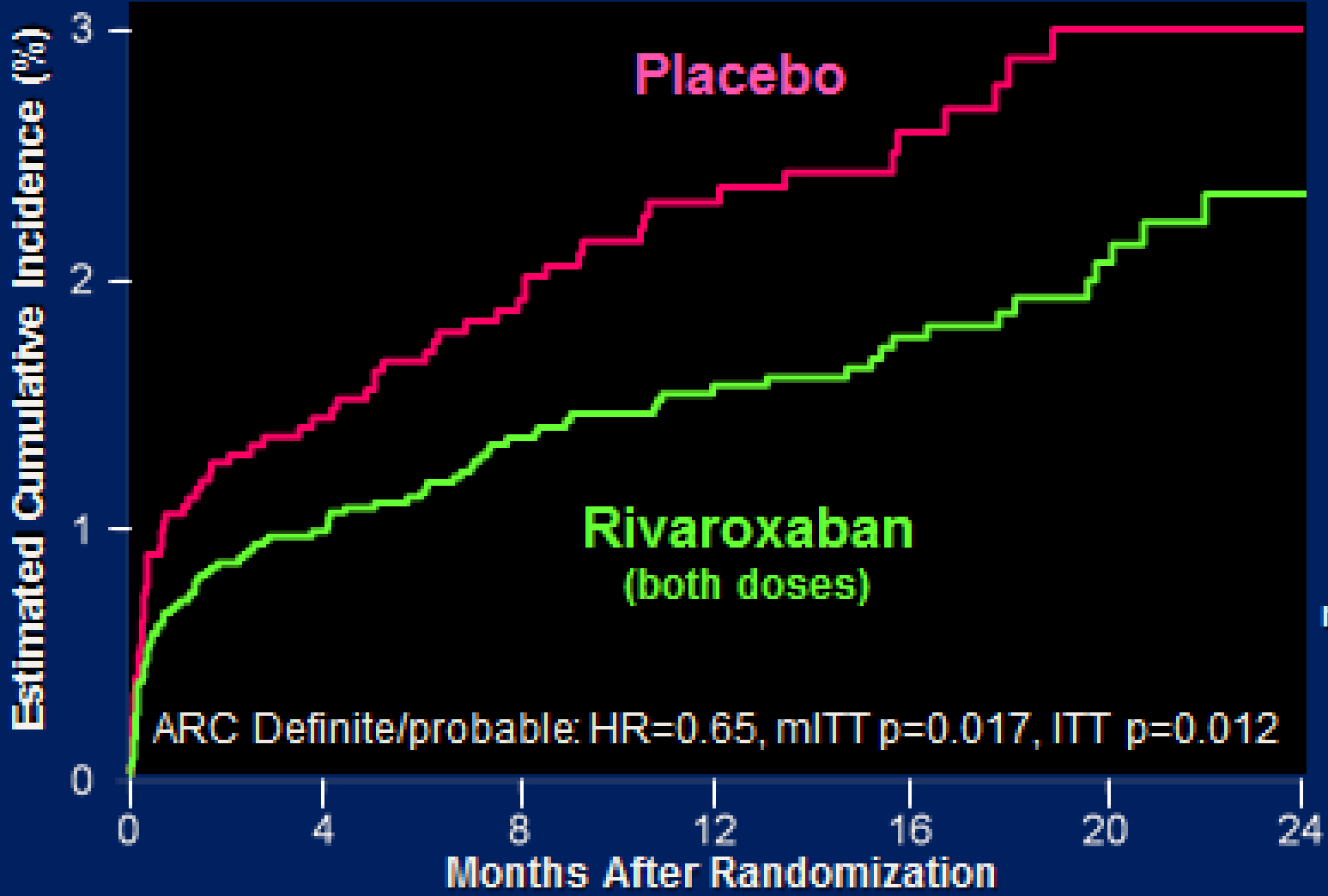
2.9%

2.3%

HR 0.69
(0.51- 0.93)

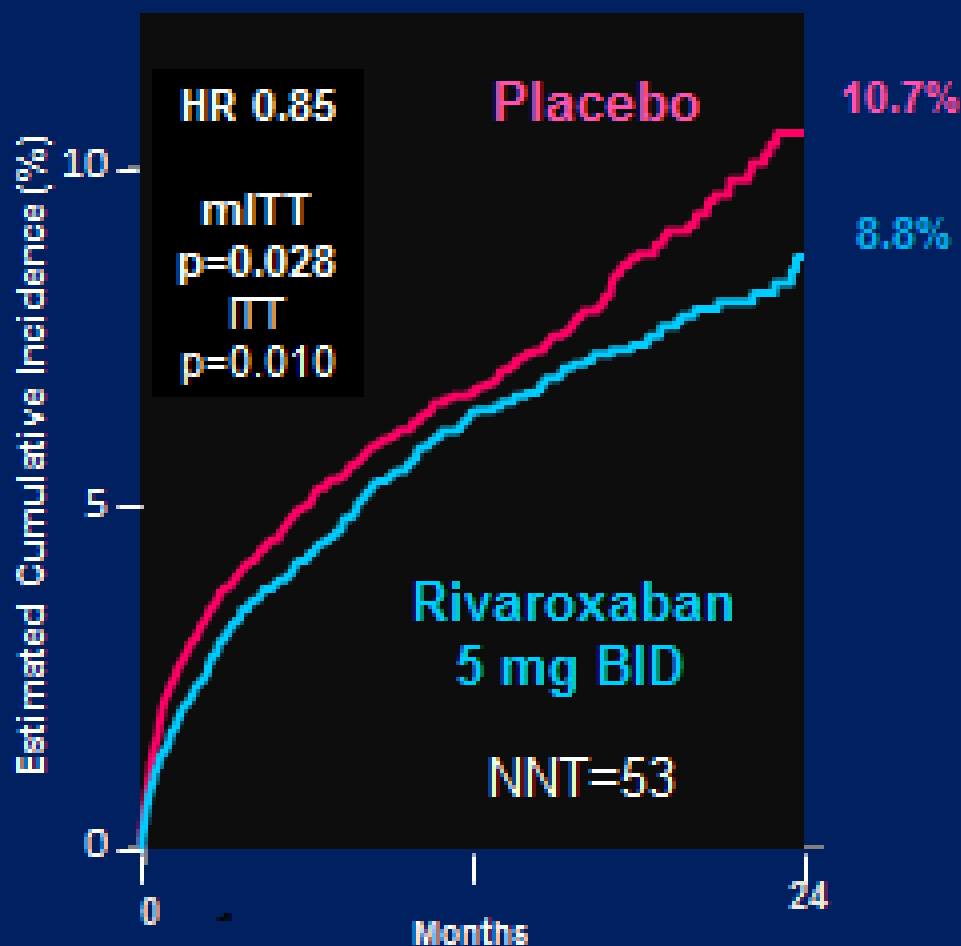
mITT **p= 0.016**

ITT **p= 0.008**

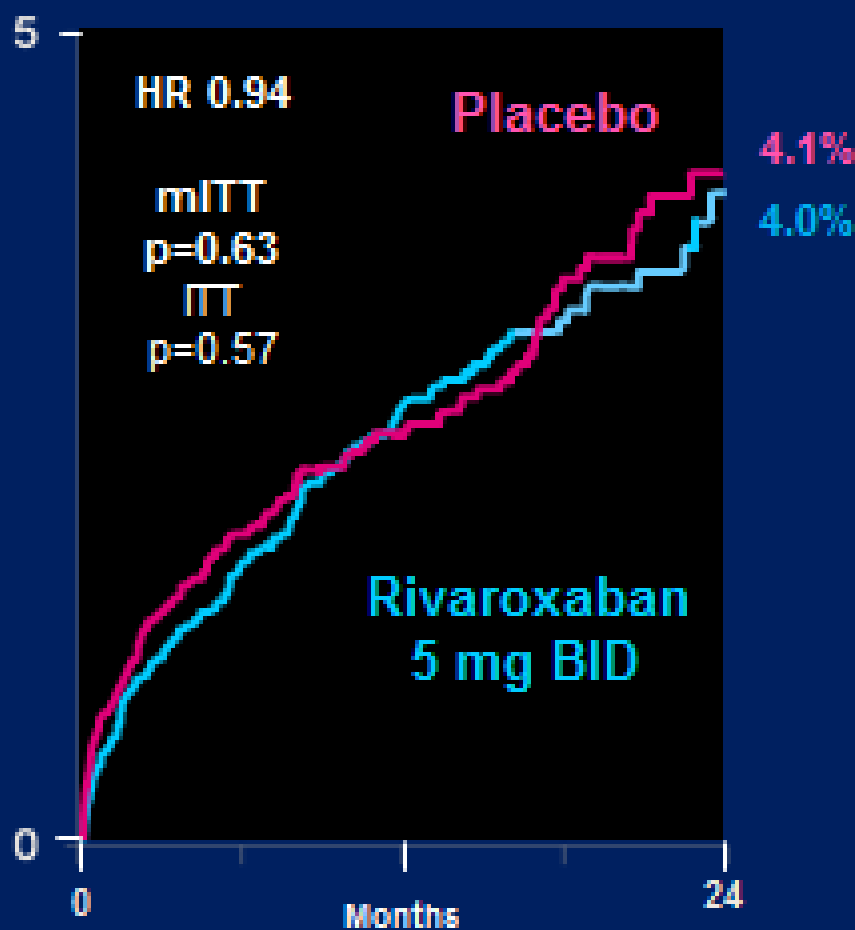


EFFICACY ENDPOINTS: Low Dose 5.0 mg BID

CV Death / MI / Stroke



Cardiovascular Death

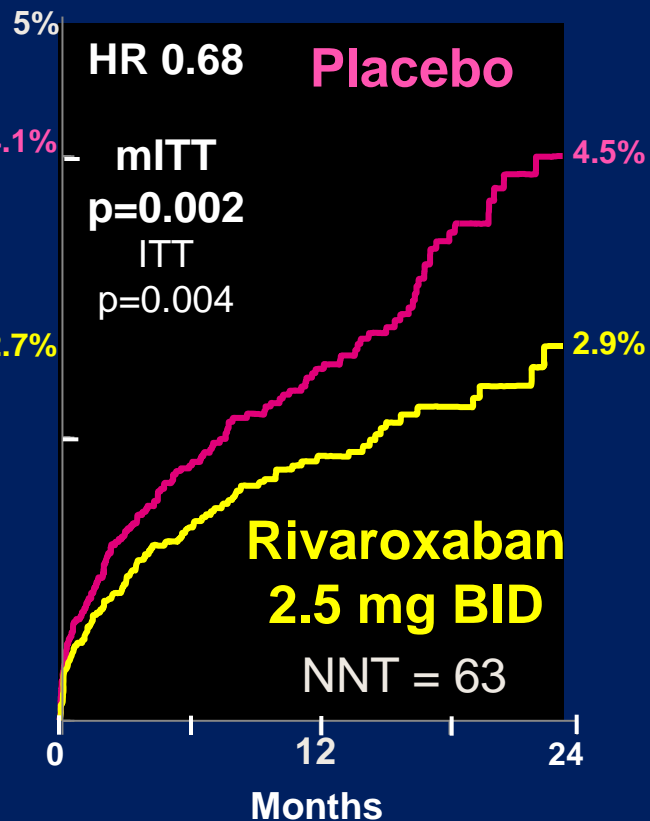
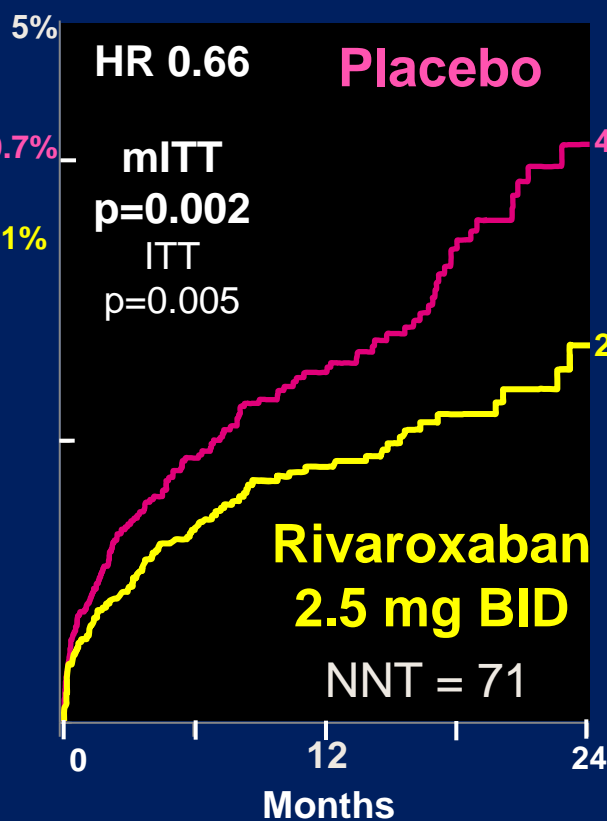
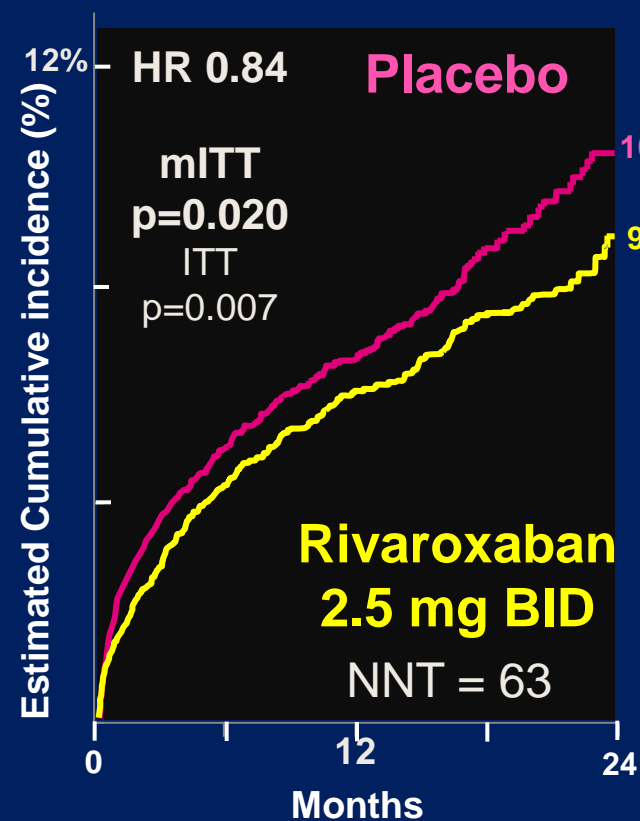


EFFICACY ENDPOINTS: Very Low Dose 2.5 mg BID

CV Death / MI / Stroke

Cardiovascular Death

All Cause Death

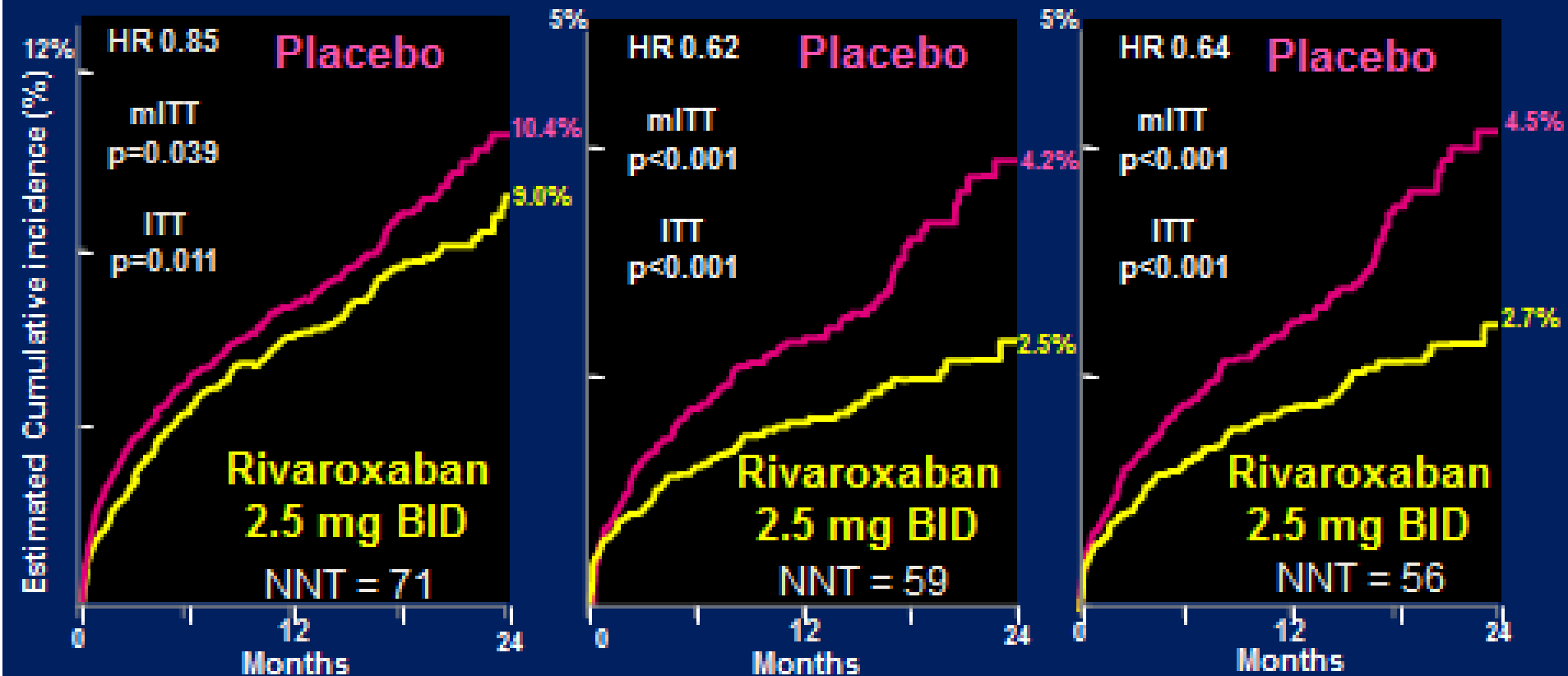


EFFICACY ENDPOINTS: Very Low Dose 2.5 mg BID Patients Treated with ASA + Thienopyridine

CV Death / MI / Stroke

Cardiovascular Death

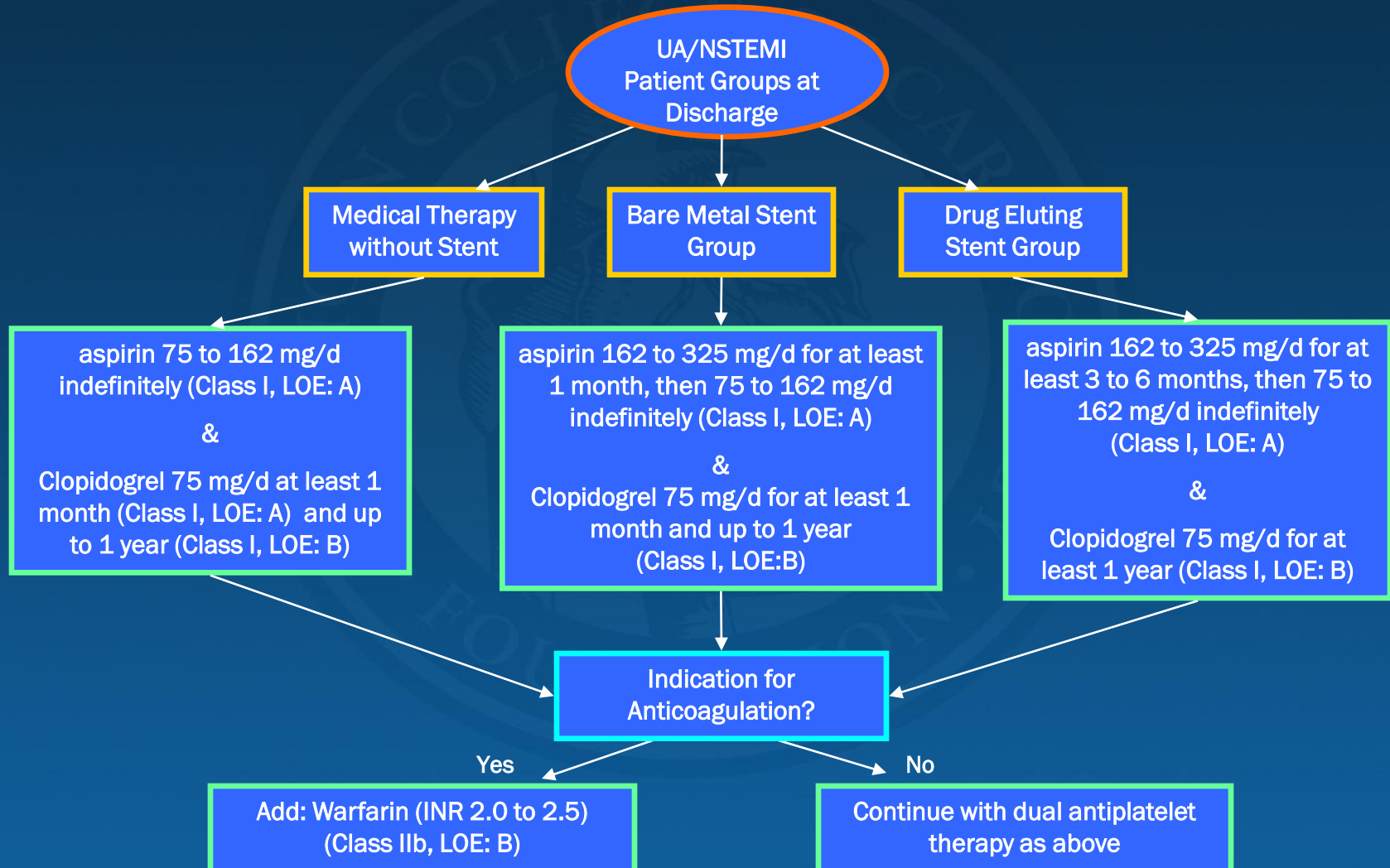
All Cause Death



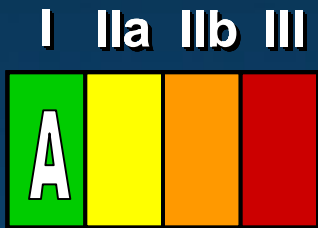
Triple Antithrombotic Therapy

(aspirin, thienopyridine + cilostazol)

Long-Term Antithrombotic Therapy at Hospital Discharge after UA/NSTEMI



Warfarin Therapy

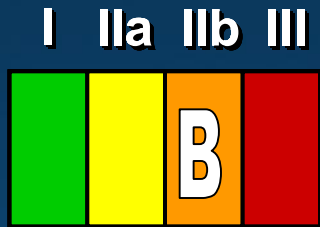


*Modified
2011*

Use of warfarin in conjunction with aspirin and/or a thienopyridine agent is associated with an increased risk of bleeding, and patients and clinicians should watch for bleeding, especially gastrointestinal, and seek medical evaluation for evidence of bleeding.

Recommendation was modified, updated to include a choice of thienopyridine.

Warfarin Therapy



Warfarin either without (INR 2.5 to 3.5) or with low-dose aspirin (75 to 81 mg per day; INR 2.0 to 2.5) may be reasonable for patients at high CAD risk and low bleeding risk who do not require or are intolerant of clopidogrel.

2008 ESC GUIDELINES:
Management of acute
myocardial infarction in
patients presenting with
persistent ST-segment
elevation (STEMI)

Primary PCI: Adjunctive Therapies

Recommendations	Class	LOE
<ul style="list-style-type: none"> ■ Antiplatelet co-therapy <ul style="list-style-type: none"> □ aspirin □ NSAID and COX-2 selective inhibitors □ clopidogrel loading dose □ GPIIb/IIIa antagonist <ul style="list-style-type: none"> ▪ abciximab ▪ tirofiban ▪ eptifibatide ■ Antithrombin co-therapy <ul style="list-style-type: none"> □ heparin □ bivalirudin □ fondaparinux ■ Adjunctive devices <ul style="list-style-type: none"> □ thrombus aspiration 	<ul style="list-style-type: none"> I III I IIa IIb IIb I IIa III IIb 	<ul style="list-style-type: none"> B B C A B C C B B B

Long-Term Medical Treatment

Recommendations	Class	LOE
<u>Anticoagulants</u>		
<ul style="list-style-type: none"> Oral anticoagulant at INR 2-3 in patients who do not tolerate aspirin or clopidogrel 	IIa	B
<ul style="list-style-type: none"> Oral anticoagulant at recommended INR when clinically indicated (e.g. atrial fibrillation, LV thrombus, mechanical valve) 	I	A
<ul style="list-style-type: none"> Oral anticoagulant (at INR 2-3) in addition to low-dose aspirin (75-100 mg) in patients at high risk of thromboembolic events 	IIa	B
<ul style="list-style-type: none"> Oral anticoagulant in addition to aspirin and clopidogrel (recent stent placement plus indication for oral anticoagulation)* 	IIb	C
<ul style="list-style-type: none"> Oral anticoagulant in addition to clopidogrel or aspirin (recent stent placement plus indication for oral anticoagulation and increased risk of bleeding) 	IIb	C

*If long-term oral anticoagulation is required use of a bare metal stent rather than a drug-eluting stent will expose the patient to a shorter duration of triple therapy and hence a lower bleeding risk

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Christian W. Hamm (Chairperson) (Germany)*, Jean-Pierre Bassand (Co-Chairperson)*, (France), Stefan Agewall (Norway), Jeroen Bax (The Netherlands), Eric Boersma (The Netherlands), Hector Bueno (Spain), Pio Caso (Italy), Dariusz Dudek (Poland), Stephan Gielen (Germany), Kurt Huber (Austria), Magnus Ohman (USA), Mark C. Petrie (UK), Frank Sonntag (Germany), Miguel Sousa Uva (Portugal), Robert F. Storey (UK), William Wijns (Belgium), Doron Zahger (Israel).

ESC Committee for Practice Guidelines: Jeroen J. Bax (Chairperson) (The Netherlands), Angelo Auricchio (Switzerland), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The Netherlands), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), Don Poldermans (The Netherlands), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker (Switzerland).

Recommendations for oral antiplatelet agents (1)

Recommendations	Class	Level
Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg, and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy.	I	A
A P2Y ₁₂ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (<i>H. elicobacter pylori</i> infection, age ≥ 65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of P2Y ₁₂ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for P2Y ₁₂ -inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.	I	B

Recommendations for oral antiplatelet agents (2)

Recommendations	Class	Level
Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600 mg loading dose of clopidogrel (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B
In patients pre-treated with P2Y ₁₂ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-)started after CABG surgery as soon as considered safe.	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

Recommendations for GPIIb/IIIa receptor inhibitors

Recommendations	Class	Level
The choice of combination of oral antiplatelet agents, a GPIIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischaemic and bleeding events.	I	C
Among patients who are already treated with DAPT, the addition of a GPIIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low.	I	B
Eptifibatide or tirofiban added to aspirin should be considered prior to angiography in high-risk patients not preloaded with P2Y ₁₂ inhibitors.	IIa	C
In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low.	IIb	C
GPIIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy.	III	A
GPIIb/IIIa receptor inhibitors are not recommended for patients on DAPT who are treated conservatively.	III	A

Recommendations for anticoagulants

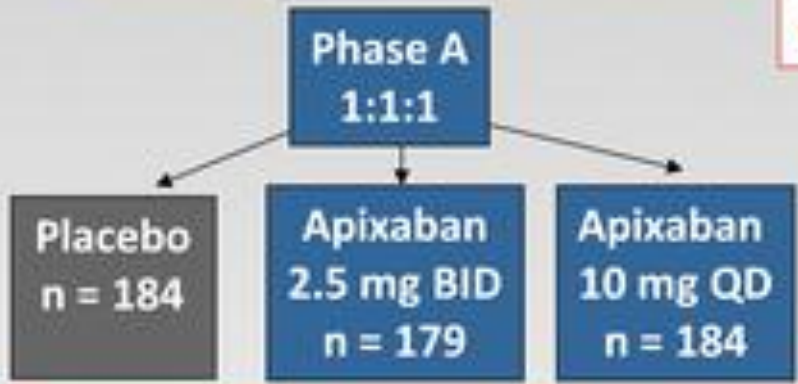
Recommendations	Class	Level
Anticoagulation is recommended for all patients in addition to antiplatelet therapy.	I	A
The anticoagulation should be selected according to both ischaemic and bleeding risks, and according to the efficacy-safety profile of the chosen agent.	I	C
Fondaparinux (2.5 mg subcutaneously daily) is recommended as having the most favourable efficacy-safety profile with respect to anticoagulation.	I	A
If the initial anticoagulant is fondaparinux, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GPIIb/IIIa receptor inhibitors) should be added at the time of PCI.	I	B
Enoxaparin (1 mg/kg twice daily) is recommended when fondaparinux is not available.	I	B
If fondaparinux or enoxaparin are not available, UFH with a target aPTT of 50-70 s or other LMWHs at the specific recommended doses are indicated.	I	C
Bivalirudin plus provisional GPIIb/IIIa receptor inhibitors are recommended as an alternative to UFH plus GPIIb/IIIa receptor inhibitors in patients with an intended urgent or early invasive strategy, particularly in patients with a high risk of bleeding.	I	B
In a purely conservative strategy, anticoagulation should be maintained up to hospital discharge.	I	A
Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated.	IIa	C
Crossover of heparins (UFH and LMWH) is not recommended.	III	B

APPRAISE: Study Design

- Randomized, double-blind
- Study drug for 6 months
- Aspirin \leq 165 mg/d
- Clopidogrel per investigator discretion
- 151 sites/14 countries

Recent (\leq 7 days) ACS + \geq 1 additional risk factor

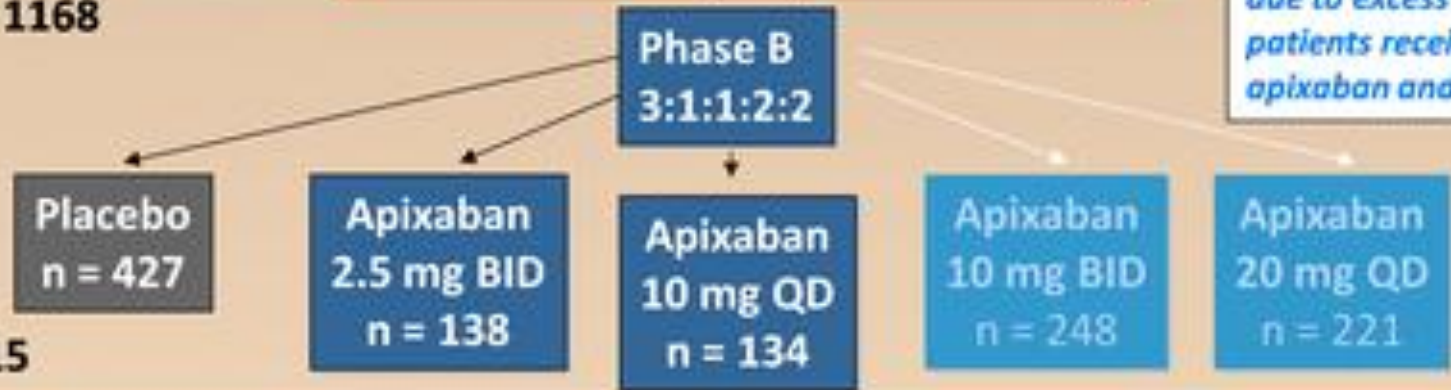
Phase A = 547



Interim analysis (DSMB review)

10 mg BID and 20 mg QD doses discontinued early due to excess bleeding in patients receiving apixaban and DAPT

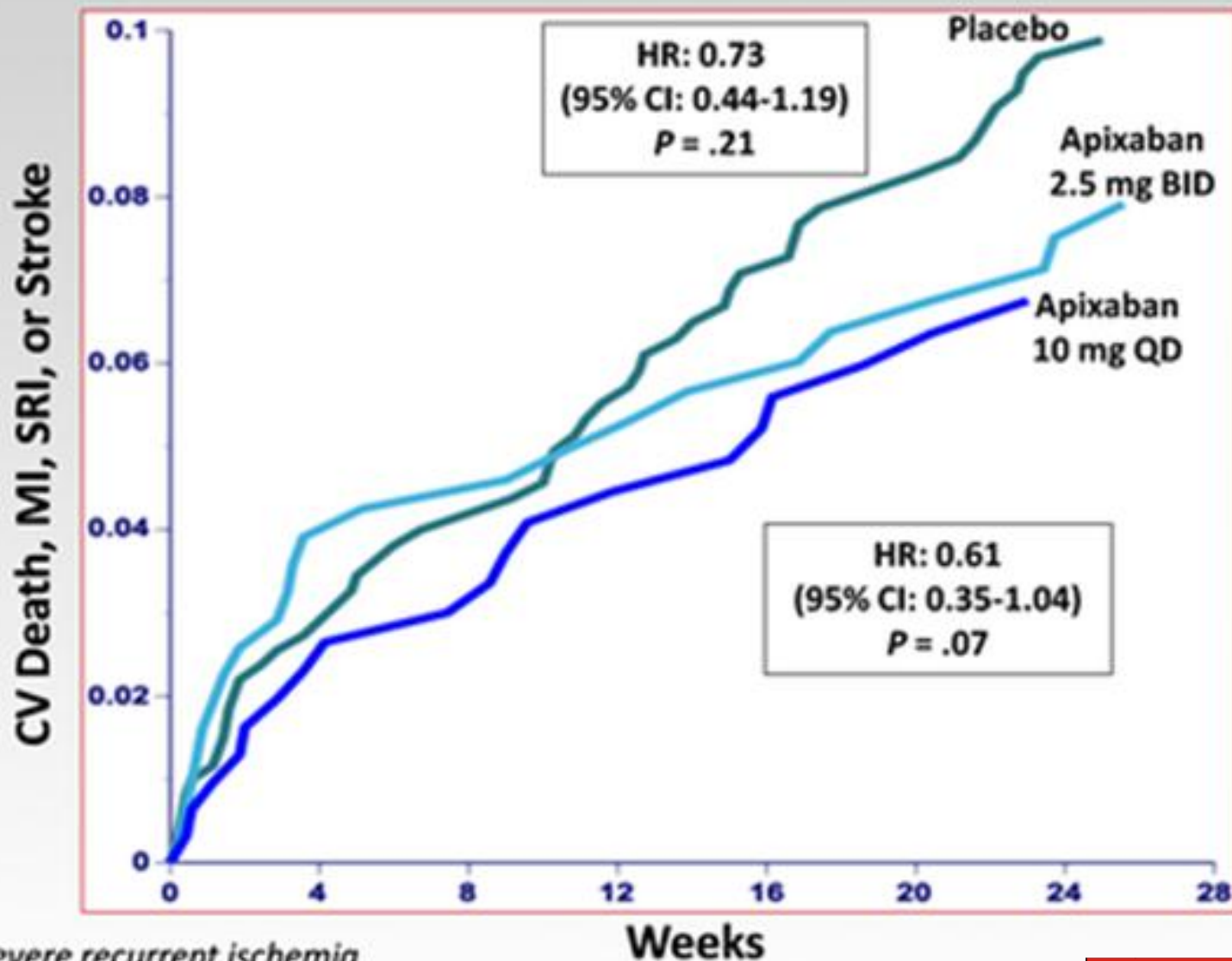
Phase B = 1168



Total = 1715

Primary safety outcome: International Society of Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major bleeding; secondary efficacy outcome: cardiovascular death, MI, severe recurrent ischemia, or ischemic stroke.

APPRAISE: Ischemic Outcome

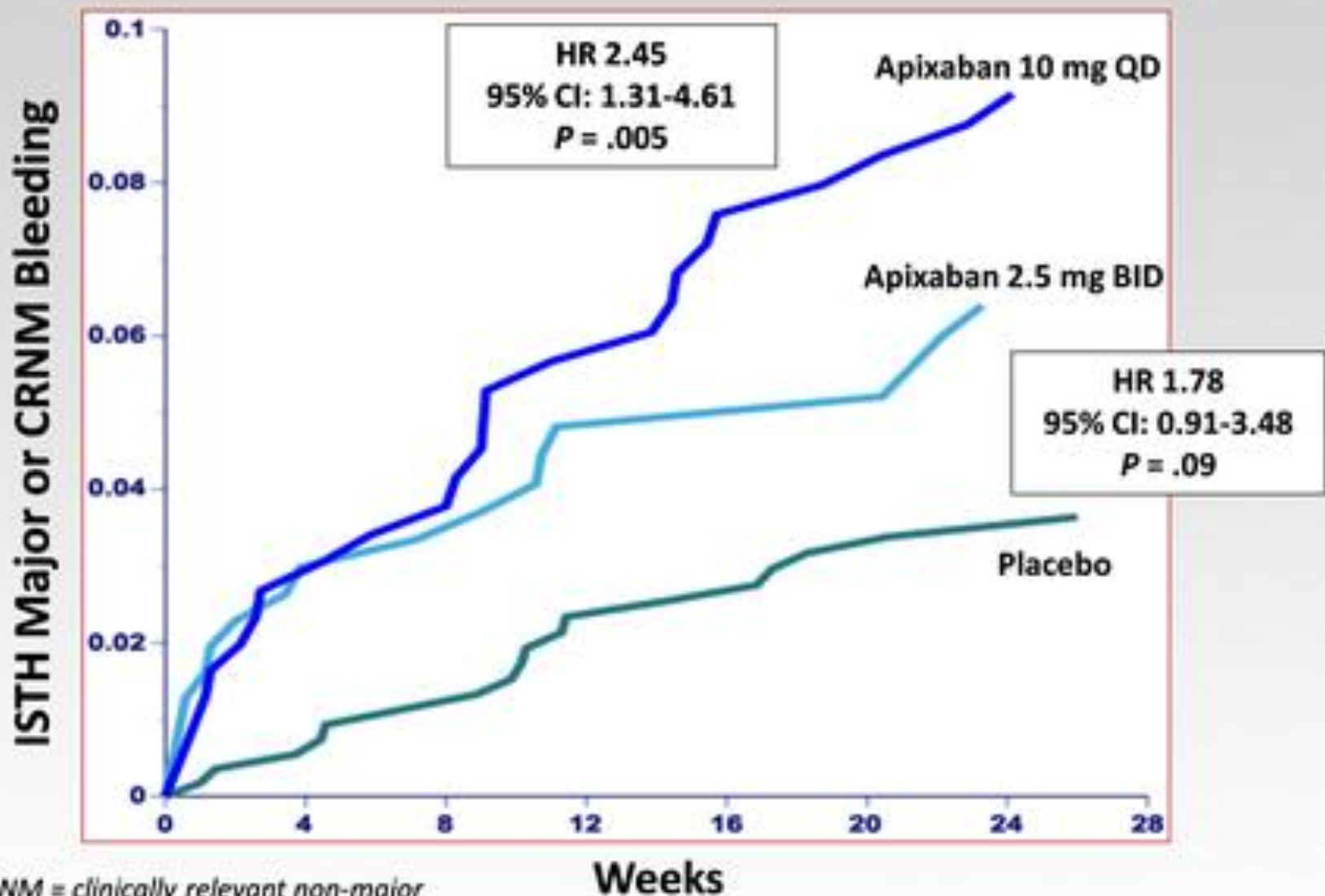


SRI = severe recurrent ischemia

Used with permission:

APPRAISE Investigators. *Circulation*. 2009;119:2877-2885.

APPRAISE: ISTH Major or CRNM Bleeding

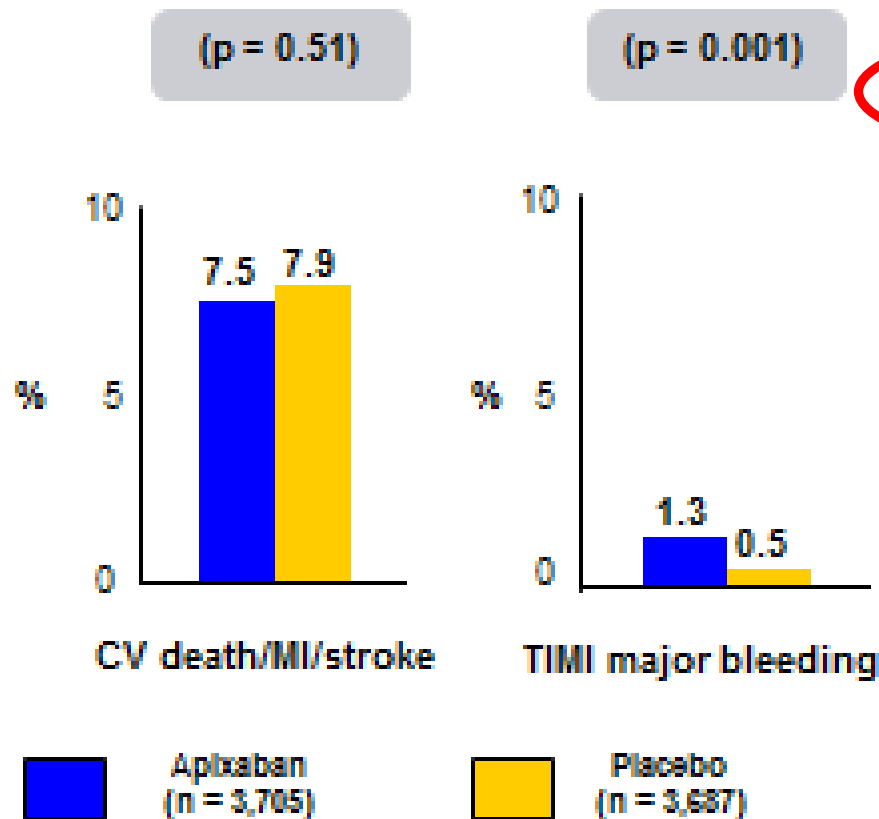


CRNM = clinically relevant non-major

Used with permission: APPRAISE Steering Committee and Investigators. *Circulation*. 2009;119:2877-2885.

APPRAISE-2

Trial design: Patients with recent ACS and at high risk for recurrent ischemic events were randomized to either apixaban 5 mg twice daily or matching placebo, in addition to dual antiplatelet therapy. Patients were followed for 8 months.



Results

- Trial was terminated early due to excessive bleeding
- CV death/MI/stroke for apixaban vs. placebo: 7.5% vs. 7.9%, $p = 0.51$; all-cause mortality: 4.2% vs. 3.9%, $p = 0.51$; stent thrombosis: 0.9% vs. 1.3%, $p = 0.15$
- TIMI major bleeding: 1.3% vs. 0.5%, $p = 0.001$; TIMI major/minor bleeding: 2.2% vs. 0.8%, $p < 0.001$; intracranial bleed: 0.3% vs. 0.1%, $p = 0.03$

Conclusions

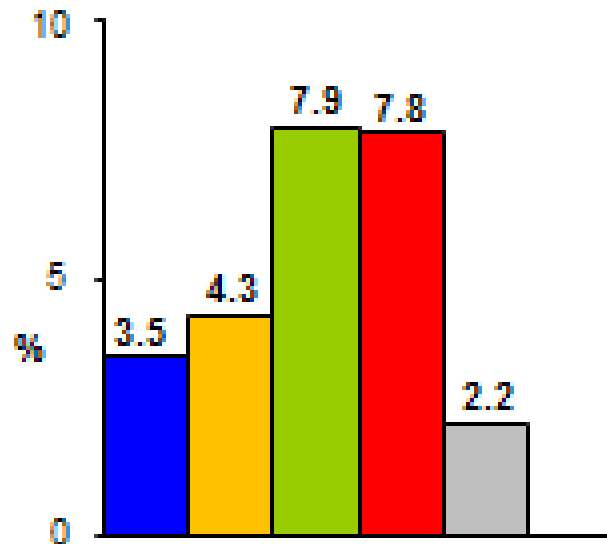
- Apixaban in addition to dual antiplatelet therapy associated with increased bleeding, as compared with placebo, without significant improvement in ischemic outcomes over a median follow-up of 8 months
- First oral anti Xa agent to undergo phase III trial; results from phase III trials with similar agents awaited

Alexander JH, et al. N Engl J Med 2011;365:689-703

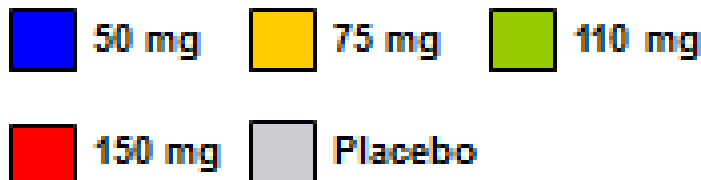
RE-DEEM

Trial design: After STEMI or NSTEMI, patients on dual antiplatelet therapy were randomized to dabigatran twice daily: 50 mg (n = 369), 75 mg (n = 368), 110 mg (n = 406), 150 mg (n = 347), or placebo (n = 371). Follow-up was 6 months.

(p < 0.001)



Major or clinically significant minor bleeding



Results

- Major or clinically significant minor bleeding: 3.5% of the 50 mg group, 4.3% of the 75 mg group, 7.9% of the 110 mg group, 7.8% of the 150 mg group, and 2.2% with placebo
- TIMI major bleeding: 0.3%, 0%, 1.2%, 0.3%, 0.3%, respectively
- Cardiovascular death, MI, or stroke: 4.6%, 4.9%, 3.0%, 3.5%, and 3.8% (p = NS), respectively

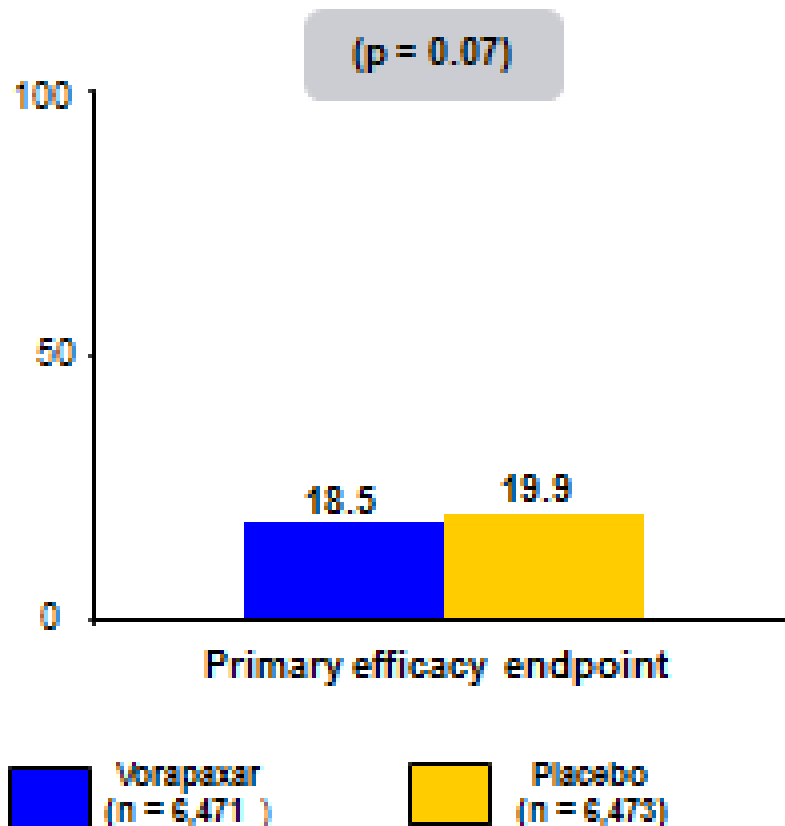
Conclusions

- In this phase II trial of patients with STEMI or NSTEMI, the addition of dabigatran to dual antiplatelet therapy increased the risk of bleeding in a dose-dependent manner
- Phase III trials are awaited

Oldgren J, et al. Eur Heart J 2011;May 7:[Epub]

TRACER

Trial design: Patients with acute coronary syndromes (ACS) were randomized to either vorapaxar 40 mg loading dose/2.5 mg daily or placebo, in addition to dual antiplatelet therapy (DAPT) with aspirin and a thienopyridine. Patients were followed for 2 years.



Results

- Trial was terminated early after safety review. Primary efficacy endpoint: CV death/MI/stroke/recurrent ischemia/coronary revascularization for vorapaxar vs. placebo: 18.5% vs. 19.9%, p = 0.07
- Death: 6.5% vs. 6.1%; stroke: 1.9% vs. 2.1%, stent thrombosis: 1.7% vs. 1.5% (p > 0.05)
- Moderate to severe GUSTO bleeding: 7.2% vs. 5.2%; intracranial bleeding: 1.1% vs. 0.2%, p < 0.001

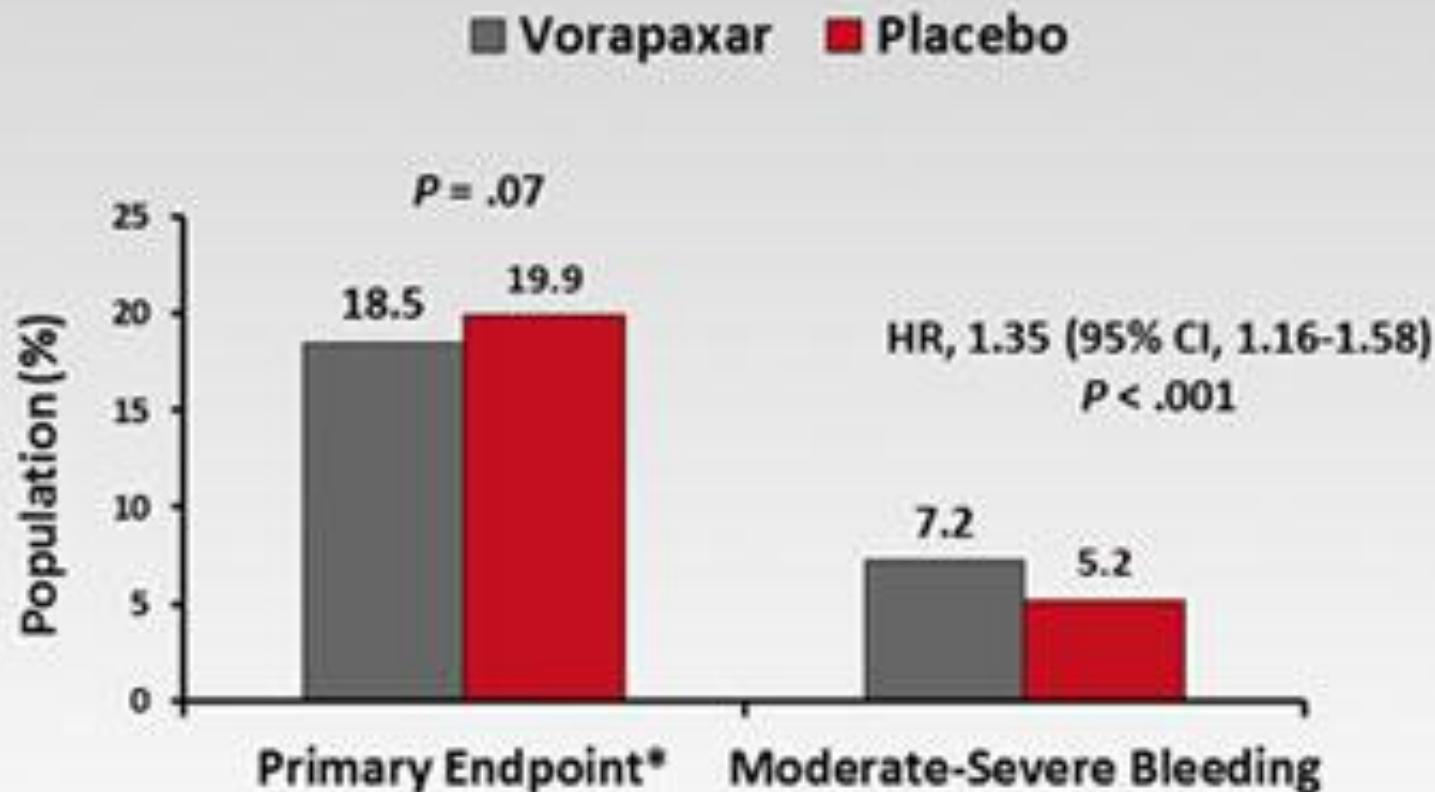
Conclusions

- Addition of vorapaxar to DAPT in patients with a recent ACS was not associated with a reduction in ischemic events, but an increase in bleeding events as compared with placebo
- Novel antiplatelet agent; inhibits PAR-1 receptor on platelets

Tricoci P, et al. N Engl J Med 2011;Nov 13:[Epub]

TRACER:

No Ischemic Benefit and Increased Bleeding With Vorapaxar



*CV death, MI, stroke, urgent revascularization, hospitalization for ischemia

N = 12,944 NSTEMI patients on standard therapies