MedStar Heart Institute

Cleveland Clinic
Heart and Vascular Institute

Highlights of Recent Clinical Trials from ACC I2 2013
Cangrelor for PCI
Statins for CIN
PE Treatment

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CHAMPION PHOENIX

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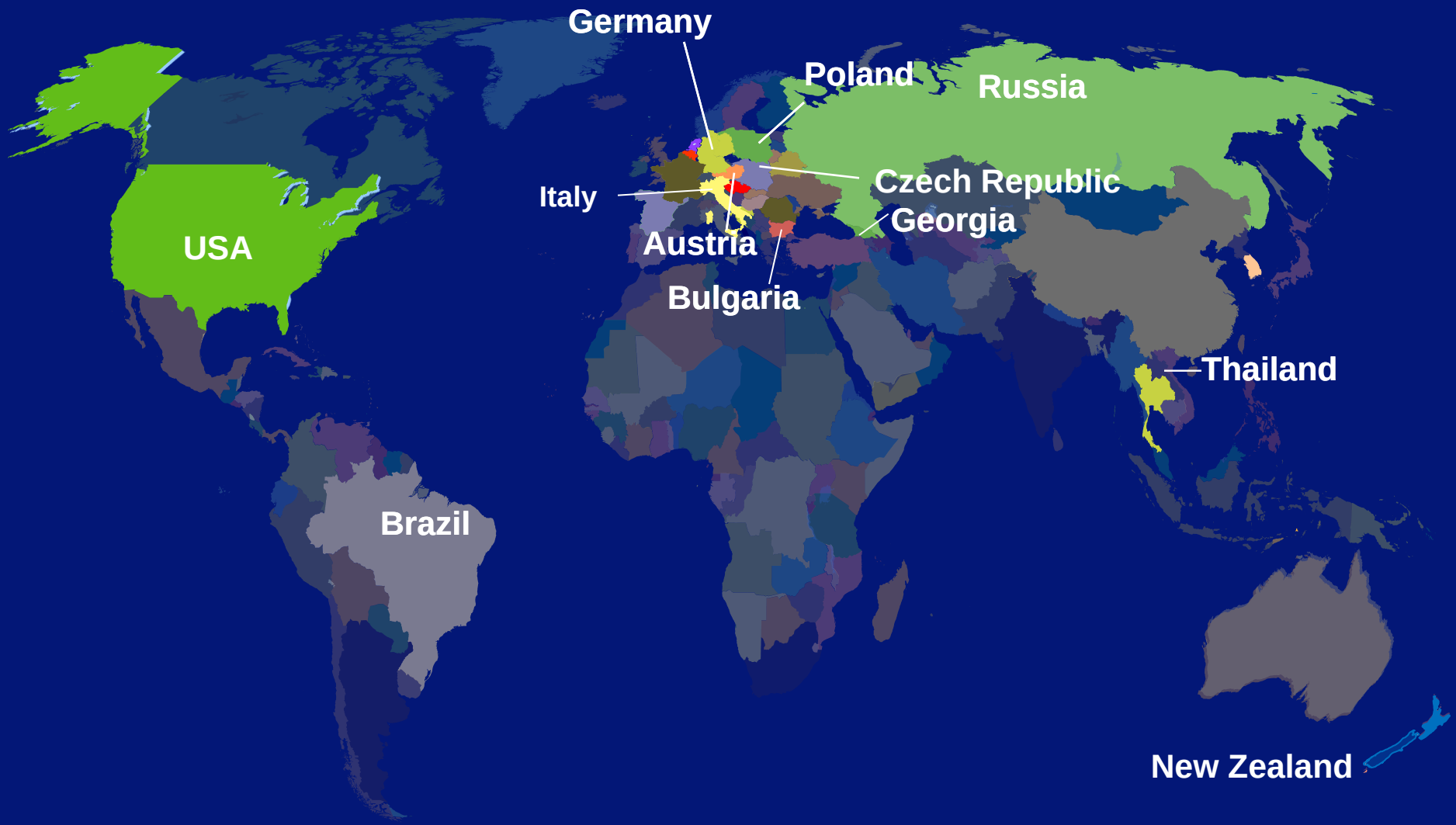
Cangrelor

- Cangrelor is an intravenous ADP receptor antagonist that is rapidly acting, potent, and reversible, with return of normal platelet function within an hour.
- Cangrelor was studied previously in two large Phase 3 PCI trials, CHAMPION PCI and CHAMPION PLATFORM. Neither study met its primary endpoint, but the secondary endpoint of stent thrombosis at 48 hours was significantly reduced in CHAMPION PLATFORM and in a prespecified pooled analysis of the two trials. There was no excess in severe bleeding.
- The potential efficacy signal prompted us to launch the CHAMPION PHOENIX trial.

Harrington RA, et al. CHAMPION PCI. NEJM 2009
Bhatt DL, et al. CHAMPION PLATFORM. NEJM 2009
White HD, et al. Meta-Analysis of CHAMPION PCI and PLATFORM. AHJ 2012

CHAMPION PHOENIX – A Global Trial

12 Countries | 153 Sites



CHAMPION PHOENIX Study Design

- Randomized, double-blind, double-dummy, superiority
- Primary efficacy endpoint: **Death/MI/IDR/ST at 48 hours**
  - Adjusted for 600 mg versus 300 mg clopidogrel use
  - Modified Intent-to-Treat (MITT) analysis (patients actually got study drug and PCI)
- Key secondary endpoint: Stent Thrombosis at 48 hours
- Efficacy endpoints also examined at 30 days
- Primary safety endpoint: GUSTO Severe Bleeding at 48 hours

Harrington RA, et al. CHAMPION PCI. NEJM 2009
Bhatt DL, et al. CHAMPION PLATFORM. NEJM 2009
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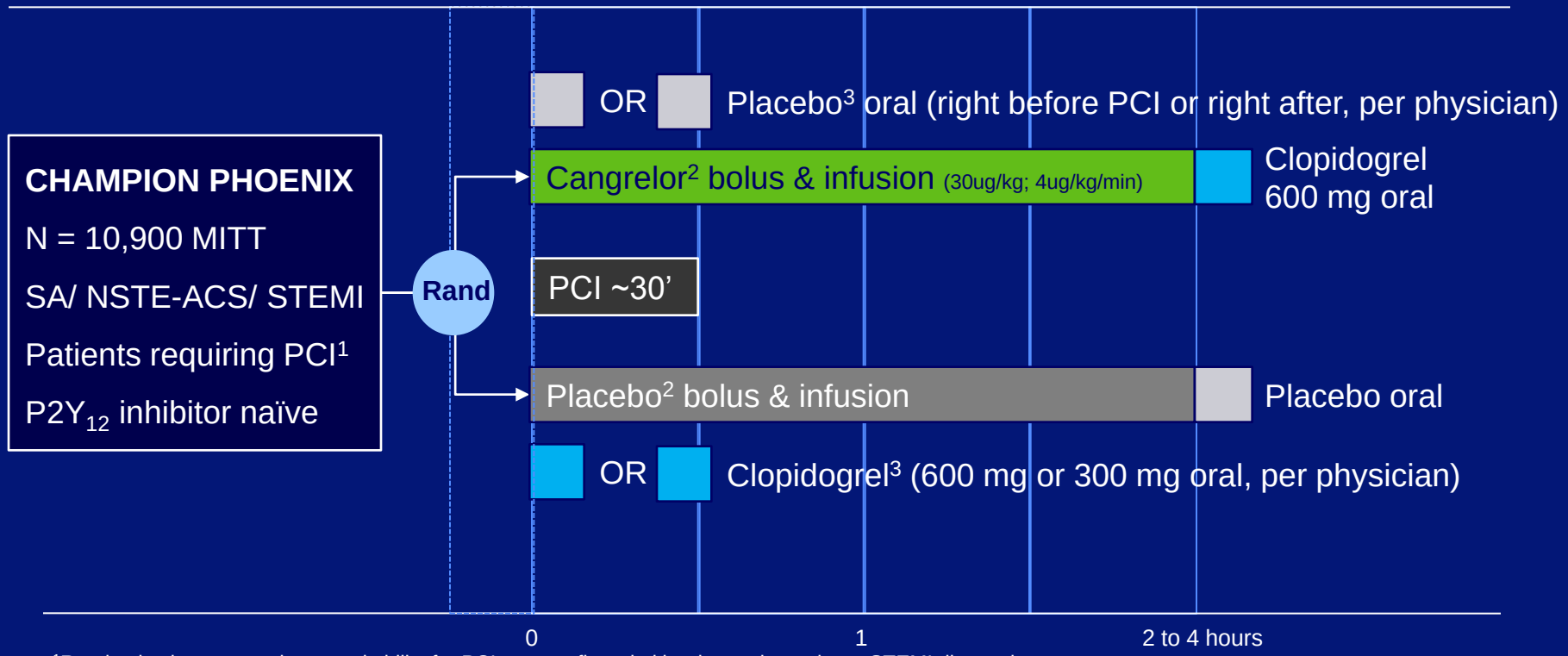
CHAMPION PHOENIX Study Design



[1]Randomization occurred once suitability for PCI was confirmed either by angiography or STEMI diagnosis. Double blind study medication was administered as soon as possible following randomization.

[2]Study drug Infusion (cangrelor or matching placebo) was continued for 2-4 hours at the discretion of the treating physician. At the end of the infusion patients received a loading dose of clopidogrel or matching placebo and were transitioned to maintenance clopidogrel therapy.

[3]Clopidogrel loading dose (or matching placebo) was administered as directed by the investigator. At the time of patient randomization, a clopidogrel loading dose of 600 mg or 300 mg was specified by the investigator.

MITT=modified intent-to-treat; NSTE-ACS=non-ST-elevation acute coronary syndrome; PCI=percutaneous coronary intervention; SA=stable angina; STEMI=ST-elevation MI.

Primary Efficacy Outcomes at 48 Hours, MITT

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR (95% CI)	P-value
Primary Analysis Adjusted[1]				
Death/MI/IDR/ST	257/5470 (4.7%)	322/5469 (5.9%)	0.78 (0.66, 0.93)	0.005

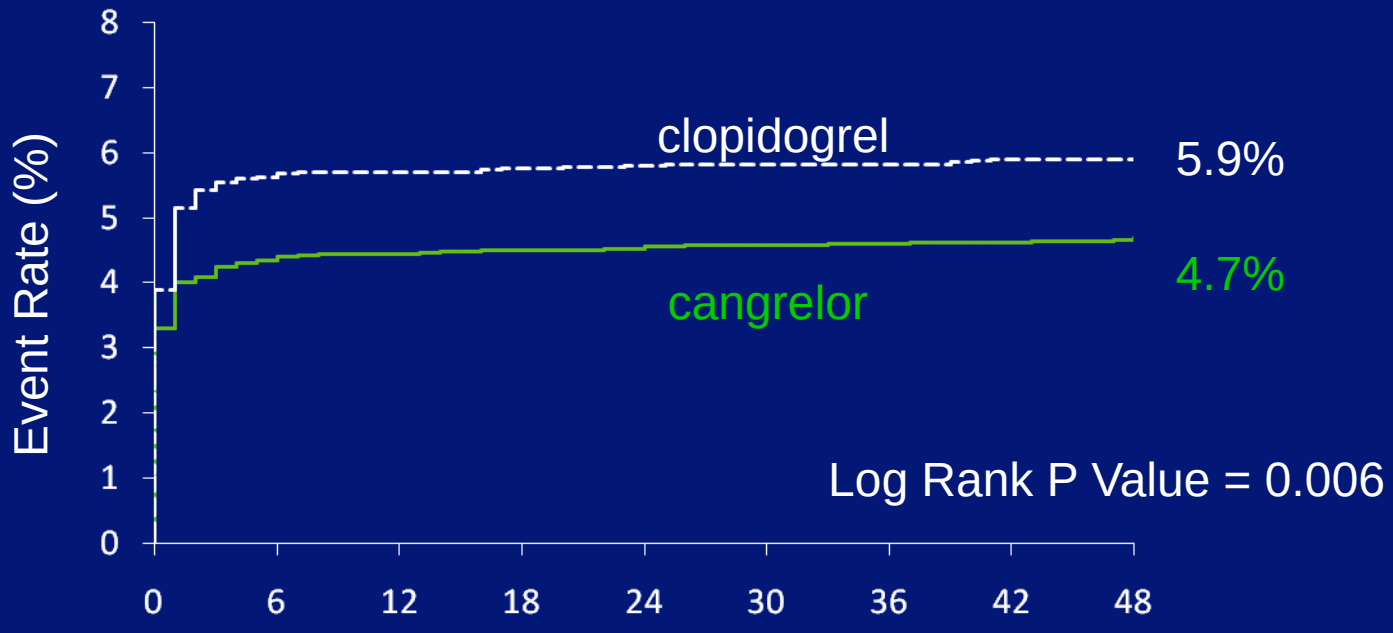
Secondary Efficacy Outcomes at 48 Hours, MITT

Stent thrombosis (key secondary endpoint)	46/5470 (0.8%)	74/5469 (1.4%)	0.62 (0.43,0.90)	0.01
MI	207/5470 (3.8)	255/5469 (4.7)	0.80 (0.67,0.97)	0.02
Q-wave MI	11/5470 (0.2)	18/5469 (0.3)	0.61 (0.29,1.29)	0.19
IDR	28/5470 (0.5)	38/5469 (0.7)	0.74 (0.45,1.20)	0.22
Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52,1.92)	>0.99
CV Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52,1.92)	>0.99

[1] The logistic model was adjusted for baseline status and clopidogrel dose. P value of 0.006 shown on the KM curve is log rank p value.

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

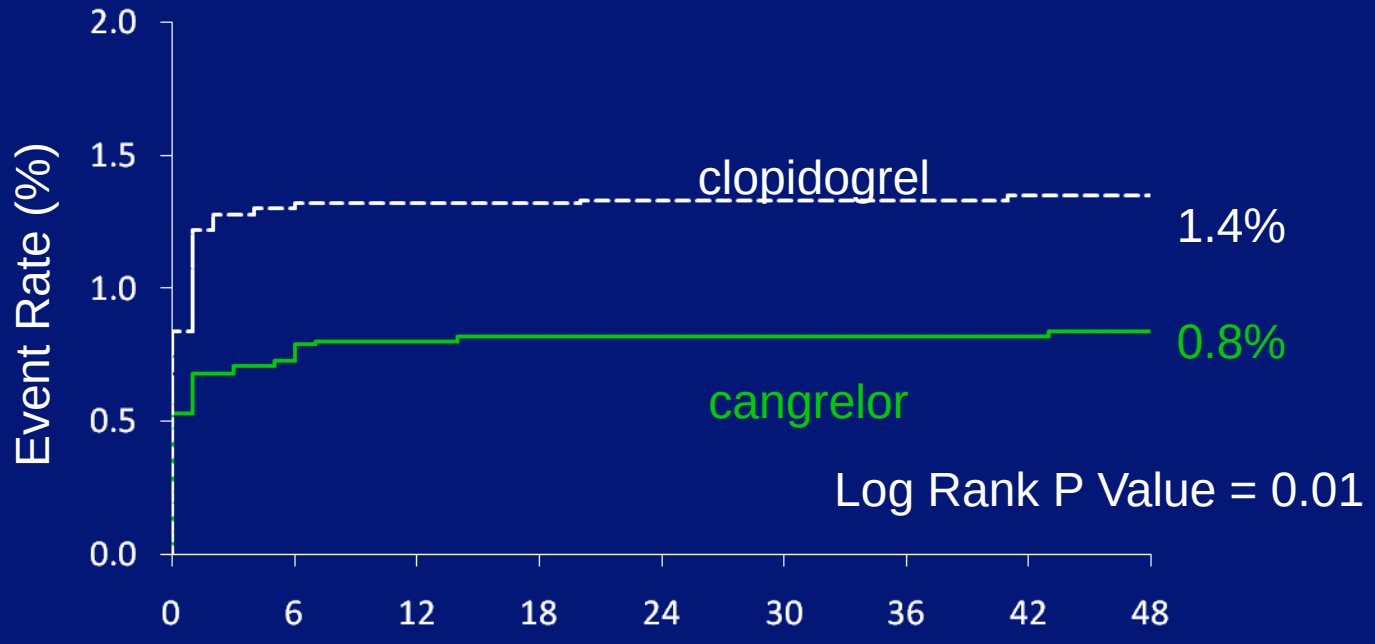
Death/ MI/ IDR/ Stent Thrombosis within 48 Hours



Patient at Risk									
Cangrelor:	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel:	5470	5162	5159	5155	5152	5151	5151	5147	5147

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Stent Thrombosis within 48 Hours



Patient at Risk									
Cangrelor:	5472	5426	5421	5419	5419	5418	5417	5416	5414
Clopidogrel:	5470	5392	5389	5388	5386	5385	5385	5383	5383

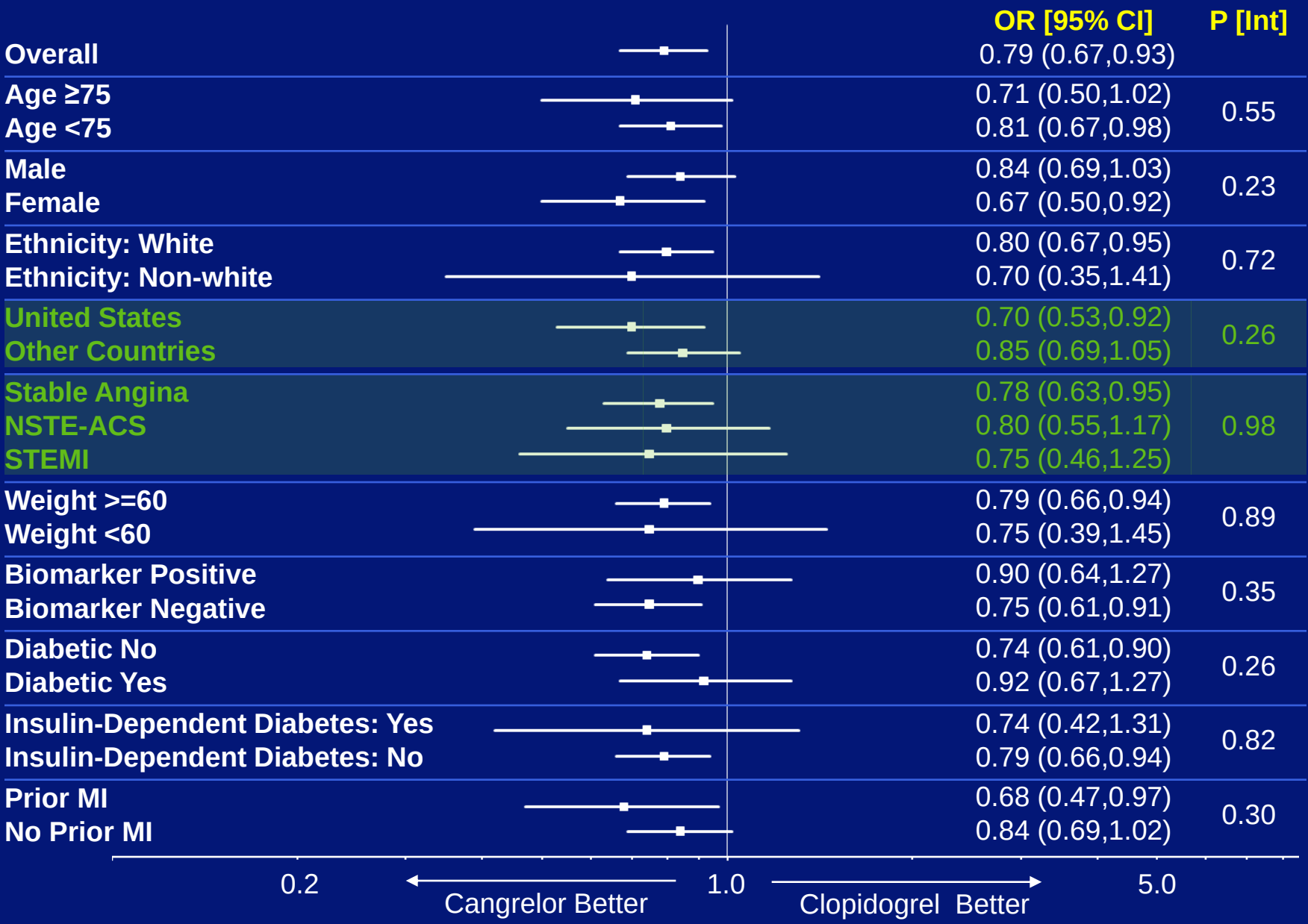
Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Efficacy Outcomes at 30 Days, MITT

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR (95% CI)	P Value
Death/MI/IDR/ST (primary endpoint, adjusted)	326/5462 (6.0%)	380/5457 (7.0%)	0.85 (0.73,0.99)	0.03
Stent thrombosis	71/5462 (1.3%)	104/5457 (1.9%)	0.68 (0.50,0.92)	0.01
MI	225/5462 (4.1%)	272/5457 (5.0%)	0.82 (0.68,0.98)	0.03
Q-wave MI	14/5462 (0.3%)	22/5457 (0.4%)	0.63 (0.32,1.24)	0.18
IDR	56/5462 (1.0%)	66/5457 (1.2%)	0.85 (0.59,1.21)	0.36
Death	60/5462 (1.1%)	55/5457 (1.0%)	1.09 (0.76,1.58)	0.64
CV Death	48/5462 (0.9%)	46/5457 (0.8%)	1.04 (0.69,1.57)	0.84

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Subgroups: Death/MI/IDR/ST at 48 Hours



Non-CABG Bleeding at 48 Hours, Safety

Bleeding Scale	Cangrelor (N=5529)	Clopidogrel (N=5527)	OR (95% CI)	P Value
GUSTO Severe	9 (0.16%)	6 (0.11%)	1.50 (0.53,4.22)	0.44
GUSTO Moderate	22 (0.4%)	13 (0.2%)	1.69 (0.85,3.37)	0.13
GUSTO Severe + Moderate	31 (0.6%)	19 (0.3%)	1.63 (0.92,2.90)	0.09
TIMI Major	5 (0.1%)	5 (0.1%)	1.00 (0.29,3.45)	>0.999
TIMI Minor	9 (0.2%)	3 (0.1%)	3.00 (0.81,11.10)	0.08
TIMI Major + Minor	14 (0.3%)	8 (0.1%)	1.75 (0.73,4.18)	0.2
Any Blood Transfusion	25 (0.5%)	16 (0.3%)	1.56 (0.83,2.93)	0.16
ACUITY Major	235 (4.3%)	139 (2.5%)	1.72 (1.39,2.13)	<0.001
ACUITY w/out hematoma	42 (0.8%)	26 (0.5%)	1.62 (0.99,2.64)	0.05

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Summary of Treatment Emergent Adverse Events

Adverse Event	Cangrelor (N=5529)	Clopidogrel (N=5527)	P Value
Patients with at least one AE	20.2%	19.1%	0.13
Patients with at least one AE causing study drug discontinuation	0.5%	0.4%	0.21
Transient dyspnea	1.2%	0.3%	<0.001

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Limitations

- A loading dose of 600 mg has become more common than 300 mg
  - However, in the three quarters of patients who received 600 mg, the benefit of cangrelor remained statistically significant and was not attenuated.
- It is possible the benefits we saw here would have been attenuated with a longer duration of pretreatment.
  - Of note, the clopidogrel pretreatment was given “on the table” as is consistent with many practices around the world and in particular in the United States.
  - Importantly, prospective randomized clinical trials, namely CREDO and PRAGUE-8, did not find a significant benefit for clopidogrel pretreatment.
- The benefits seen here may also have been attenuated had prasugrel or ticagrelor been used in the control arm.
  - However, to date, the largest trial of prasugrel pretreatment, ACCOAST, was terminated by the DSMB for lack of efficacy and excess bleeding.
  - Thus, oral pretreatment, while biologically appealing and intuitive, remains unproven in prospective randomized clinical trials.

Conclusions

- In CHAMPION PHOENIX, intravenous ADP receptor antagonism with cangrelor significantly (p=0.005) reduced the composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours, with a 22% odds reduction.
- The key secondary endpoint of stent thrombosis was also significantly reduced, with a 38% odds reduction.
- The benefit was sustained through 30 days.
- There was no excess in severe bleeding or transfusions.
- Intravenous cangrelor may be an attractive option across the full spectrum of PCI, including stable angina, NSTEMI, and STEMI.

Early high-dose Rosuvastatin for Contrast-Induced Nephropathy Prevention in Acute Coronary Syndrome

The PRATO-ACS (Protective effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome) Study

Anna Toso, MD

on behalf of the *PRATO-ACS* investigators

Study Hypothesis

On-admission high-dose statins
for CI-AKI prevention in ACS patients

Does early high-dose hydrophilic statin rosuvastatin -in addition to standard preventive measures (hydration and N-acetylcystein)- exert beneficial effects against CI-AKI in statin-naïve patients with NSTE-ACS scheduled for early invasive strategy?

Methods

Inclusion criteria

All consecutive statin-naïve NSTE-ACS patients admitted to CCU and scheduled for early invasive strategy

Study period: July 2010-August 2012

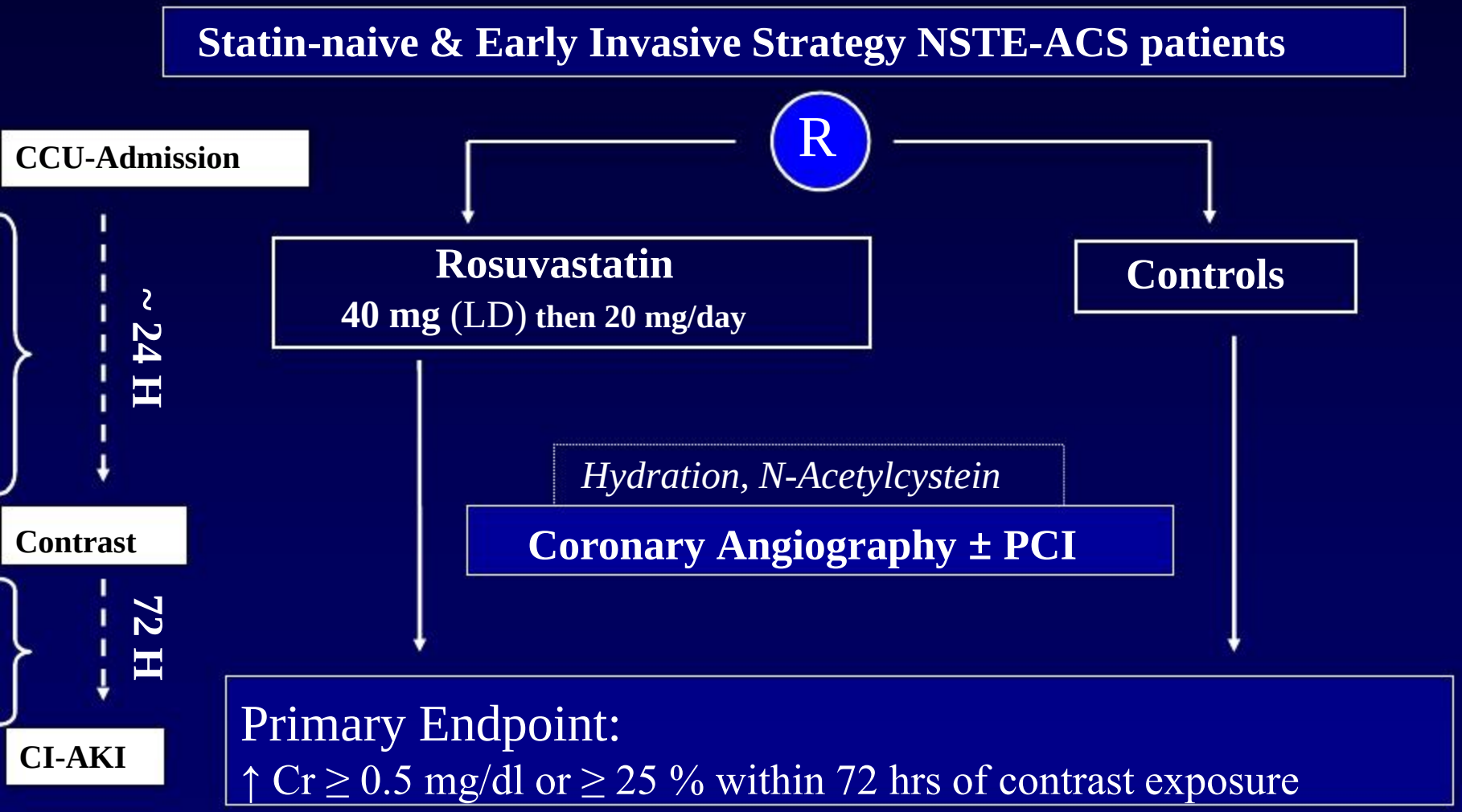
Methods

Exclusion criteria

- Emergency (within 2 hrs) angiography
- Acute renal failure or ESRD requiring dialysis
- Baseline serum creatinine ≥ 3 mg/dl
- Contraindications to statin treatment
- Contrast administration within the last 10 days
- Refusal to consent

Methods

Study Design



Sample size: assumed 18% CI-AKI in control and 50% reduction in treatment. With a 80% statistical power and 2-sided type 1 error of 5%; 15% drop out → ~ 540 pts

Methods

Additional End-points

3. Adverse Clinical Events (30 days):

Acute renal failure requiring dialysis

Persistent renal damage*

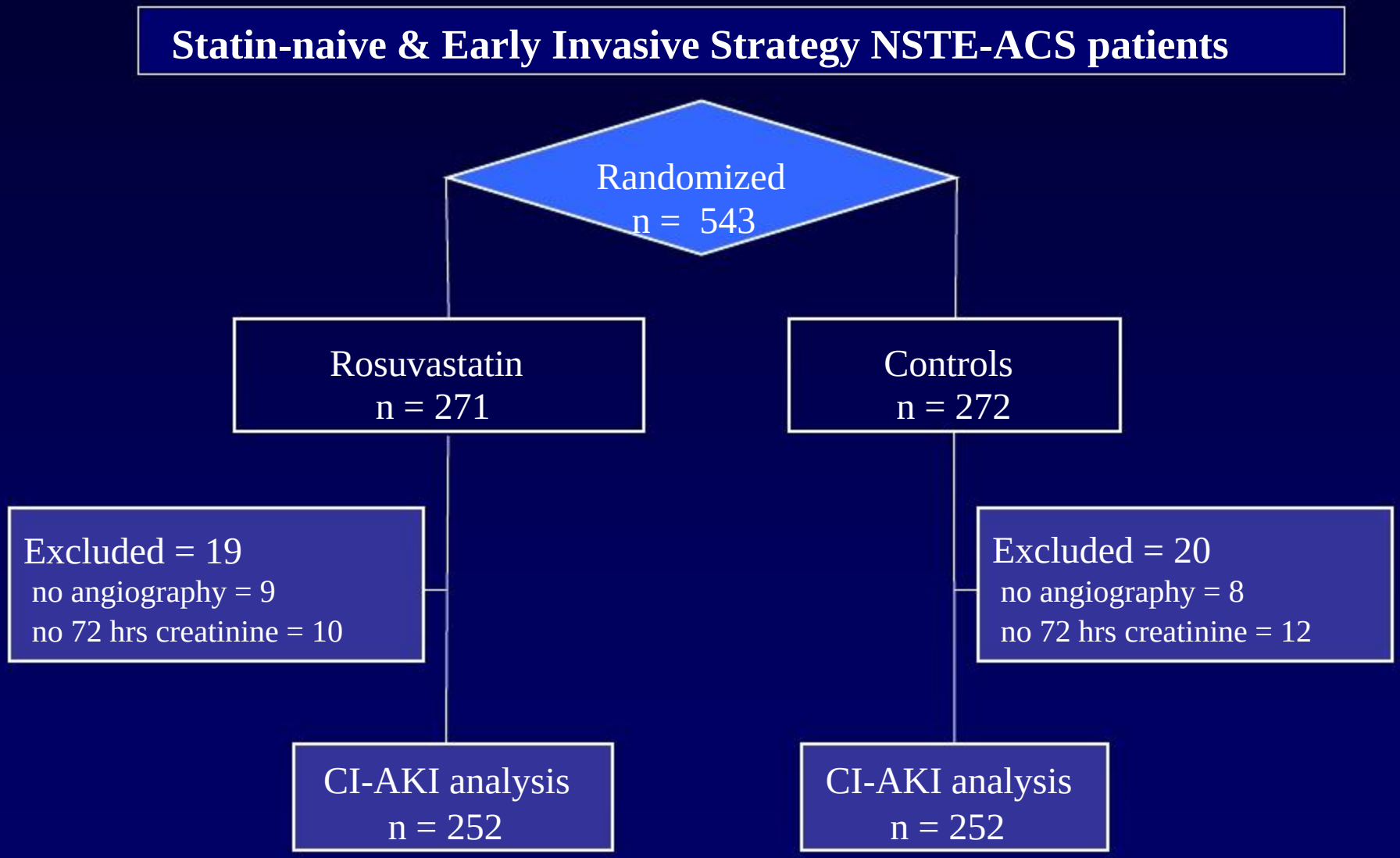
All-causes mortality

Myocardial infarction

Stroke

**↓ eGFR ≥ 25% within 1 month in CI-AKI pts*

Study Flow


Statin-naive & Early Invasive Strategy NSTE-ACS patients
Randomized
n = 543
Rosuvastatin
n = 271
Controls
n = 272
Excluded = 19
no angiography = 9
no 72 hrs creatinine = 10
Excluded = 20
no angiography = 8
no 72 hrs creatinine = 12
CI-AKI analysis
n = 252
CI-AKI analysis
n = 252

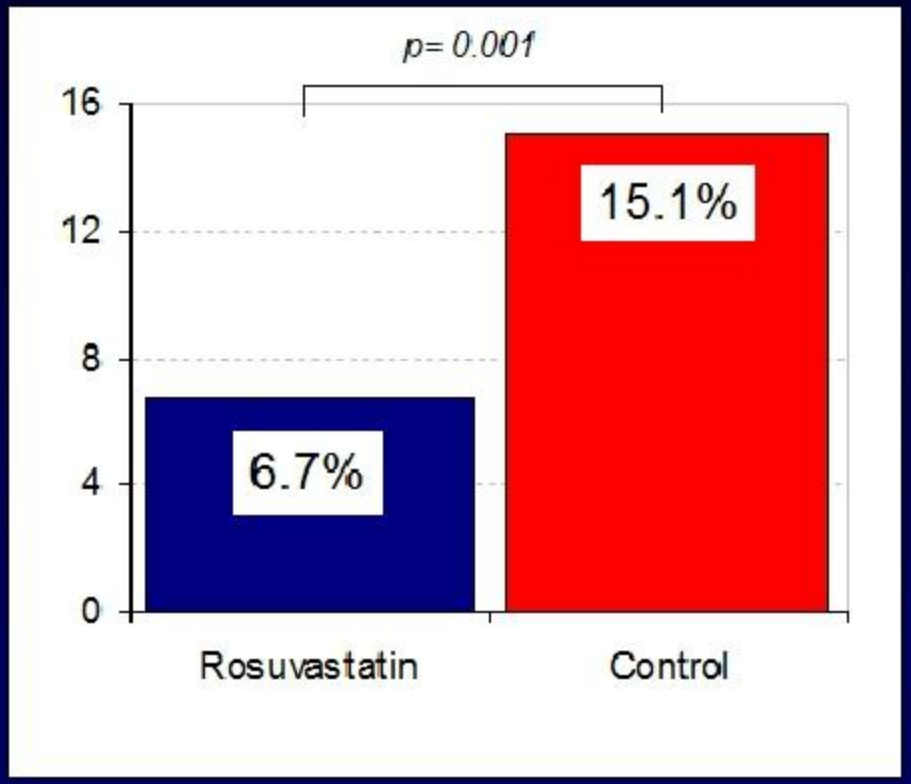
Baseline Characteristics

Clinical and Demographic

	Rosuvastatin	Control	*p value*
Age	66.2 ± 12.4	66.1 ± 13.5	0.91
Age ≥ 70 years.%	46.4	44.8	0.72
Female, %	34	34	0.93
Body Mass Index	26.2 ± 3.7	26.6 ± 4.4	0.35
Clinical presentation, %			
NSTE-MI	92.4	92.1	>0.90
Unstable angina	7.5	7.9	>0.90
Risk factors, %			
Hypertension	56.7	54.8	0.65
Diabetes mellitus	19.8	22.6	0.45
Creatinine clearance < 60ml/min	41.7	41.7	>0.90
Previous MI	9.5	5.9	0.13
Previous PCI or CABG	11.9	7.1	0.07
Baseline LV EF (%)	50 ± 9	50 ± 9	>0.90
EF ≤ 45%	33.3	33.7	0.93
High Clinical Risk Level, %	71.4	67.1	0.29

CI-AKI Primary Endpoint

(≥ 0.5 or ≥ 25% within 72 hrs)



OR$_{crude}$ (95% CI):

0.41 (0.22 - 0.74)

OR$_{adjusted}$ (95% CI):

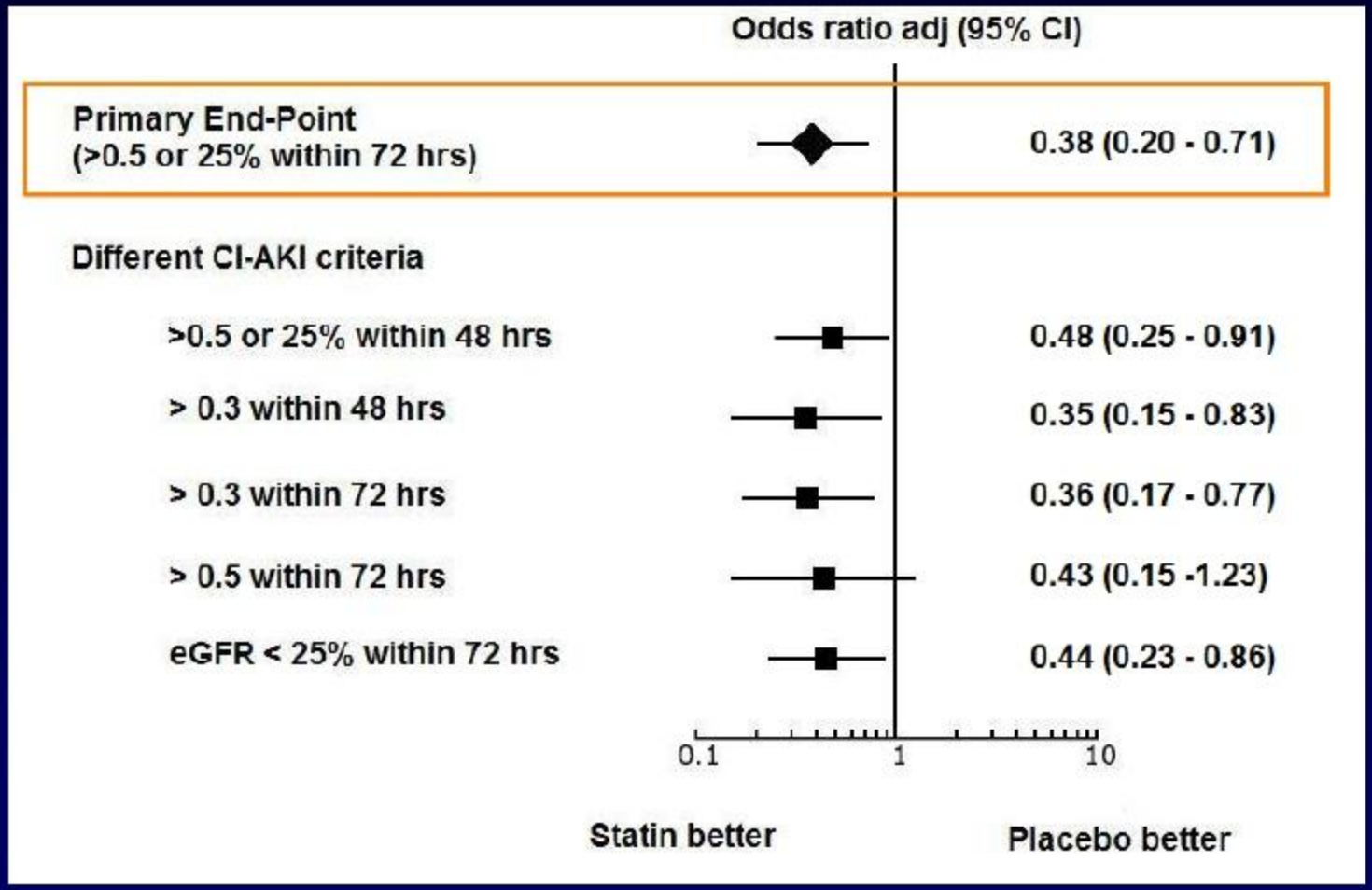
0.38 (0.20 – 0.71)

NNT = 12

**Adjusted for: Sex, Age, Diabetes, Hypertension, LDL-cholesterol, Creatinine Clearance, LV-EF, Contrast Volume, CI-AKI Risk Score*

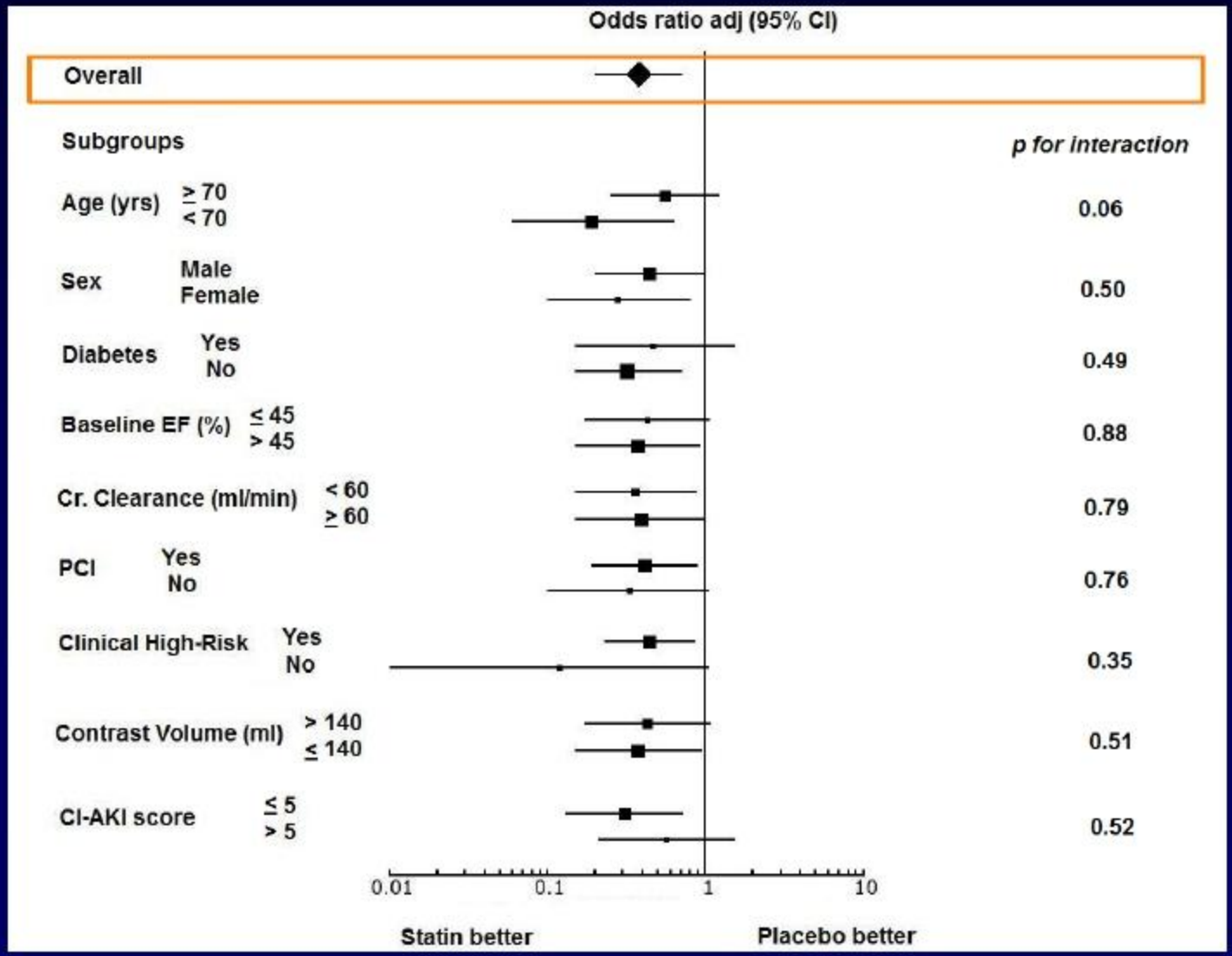
Additional Endpoints:

1.Different CI-AKI criteria



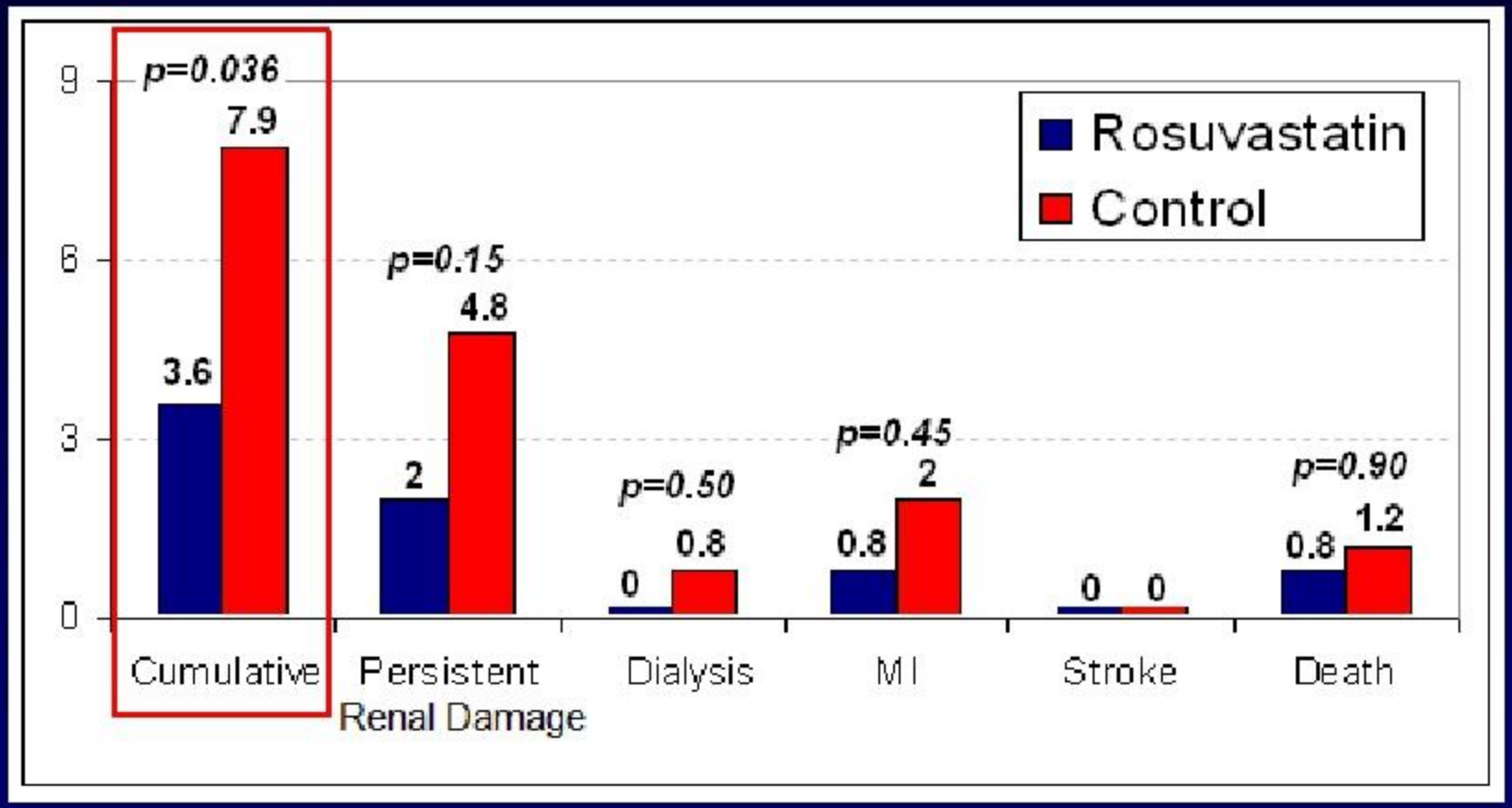
Additional Endpoints:

2.Pre-specified Subgroups



Additional Endpoints:

3. Adverse Clinical Events (30 days)



Conclusions-1

In statin-naïve patients with NSTE-ACS scheduled for early invasive strategy on-admission high-dose rosuvastatin:

•exerts additional preventive effects against CI-AKI (w/ hydration & N-Acetylcystein);

•is associated to better short-term clinical outcome.

Pulmonary Embolism Thrombolysis Study

an investigator-initiated, investigator-sponsored trial

The OPEITHO Investigators

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Bundesministerium für Bildung und Forschung

ClinicalTrials.gov # NCT00639743
EudraCT # 2006-005328-18

PEITHO: Objectives

Primary

To investigate the clinical benefits (efficacy) of thrombolysis with tenecteplase* over placebo in normotensive patients with acute intermediate-risk PE (**both treatment arms receive standard heparin anticoagulation**)

Secondary

To assess the safety of tenecteplase* in patients with intermediate-risk PE

* Tenecteplase is not approved medication for use in pulmonary embolism in the United States or Europe.

PEITHO: Primary outcome

- All-cause mortality *or*
- Hemodynamic collapse

within 7 days of randomization, defined as:

need for cardiopulmonary resuscitation

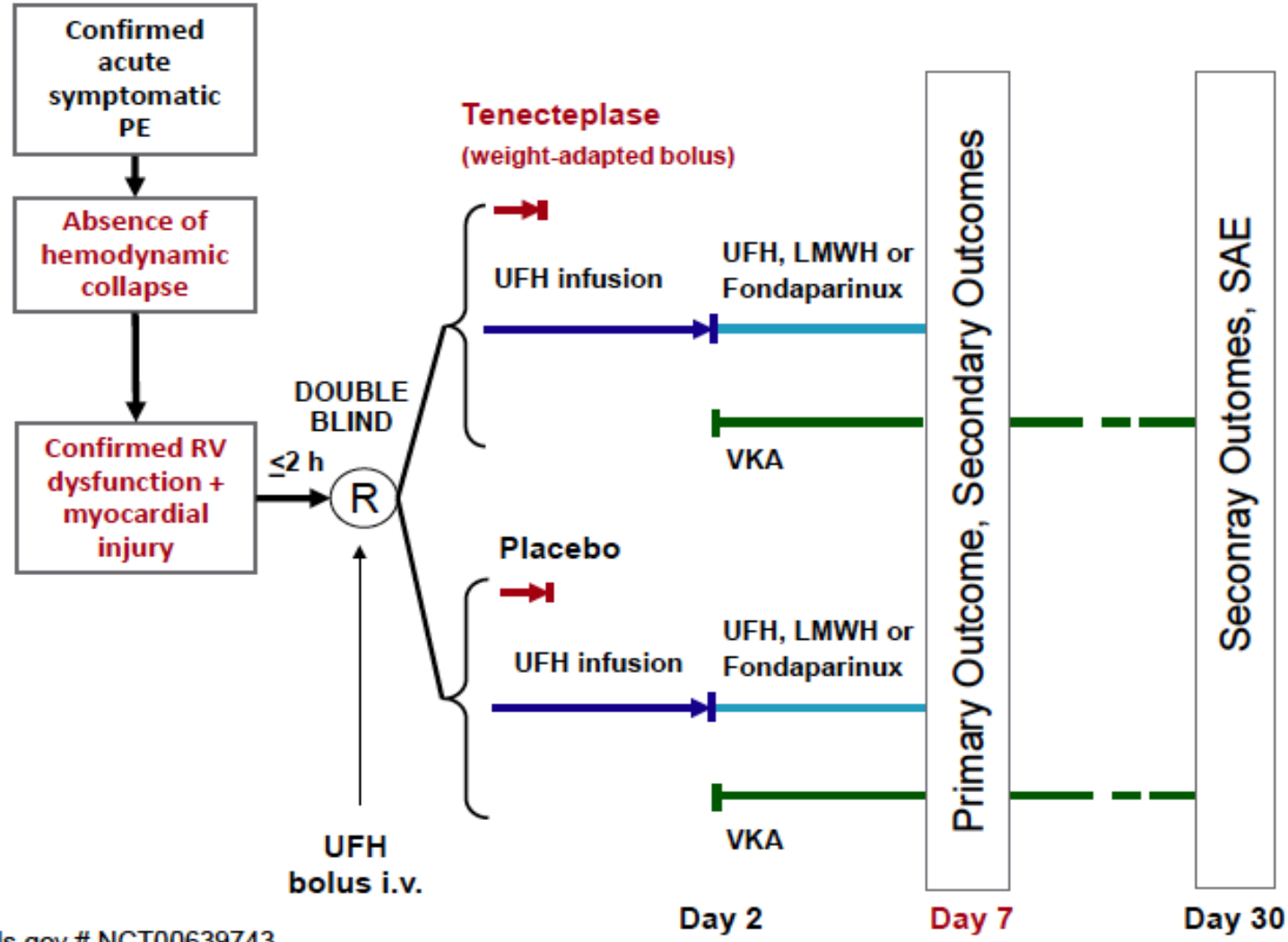
or

systolic BP < 90 mm Hg for ≥15 min ***or*** drop by ≥ 40 mm Hg for ≥15 min with end organ hypoperfusion (cold extremities, urinary output < 30 mL/h, mental confusion)

or

need for catecholamines to maintain adequate organ perfusion and a systolic BP of >90 mm Hg

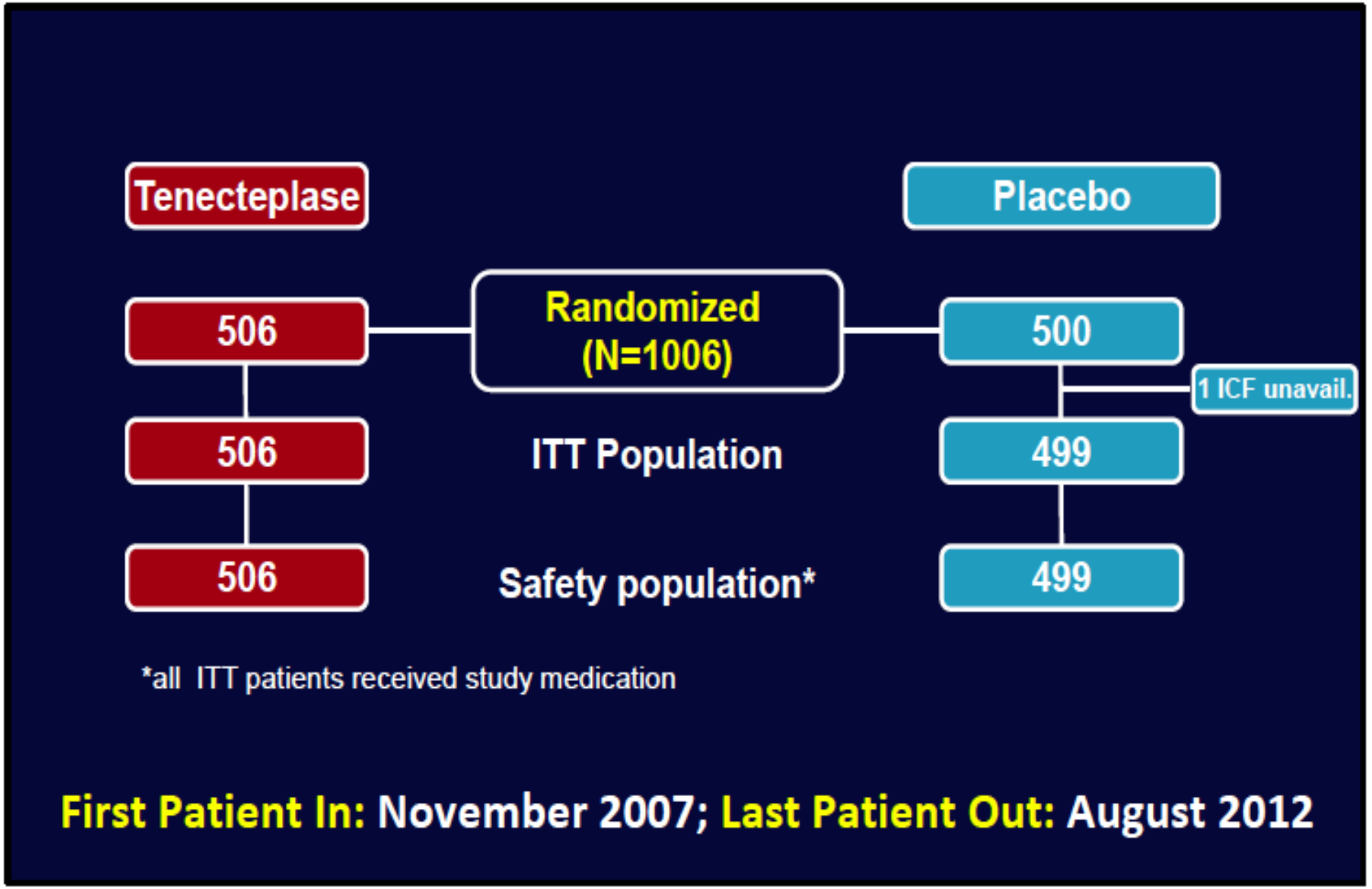
PEITHO: Overview of study design



ClinicalTrials.gov # NCT00639743
EudraCT # 2006-005328-18

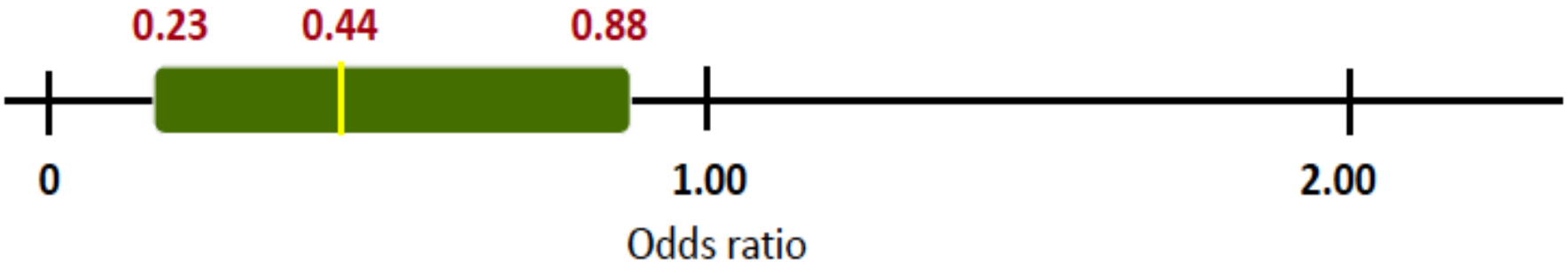
S Konstantinides for the PEITHO Steering Committee. Am Heart J 2012;163:33-38.e1

PEITHO: Analyzed population



PEITHO: Primary efficacy outcome

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality or hemodynamic collapse within 7 days of randomization	13	(2.6)	28	(5.6)	0.015



Thrombolysis superior

PEITHO: Analysis of primary efficacy outcome

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality within 7 days	**6**	**(1.2)**	**9**	**(1.8)**	**0.43**
Hemodynamic collapse within 7 days	**8**	**(1.6)**	**25**	**(5.0)**	**0.002**
Need for CPR	1		5		
Hypotension / blood pressure drop	8		18		
Catecholamines	3		14		
Resulted in death	1		6		

PEITHO: Safety outcomes (within 7 days of randomization)

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
Non-intracranial bleeding					
Major	32	(6.3)	6	(1.5)	<0.001
Minor	165	(32.6)	43	(8.6)	<0.001

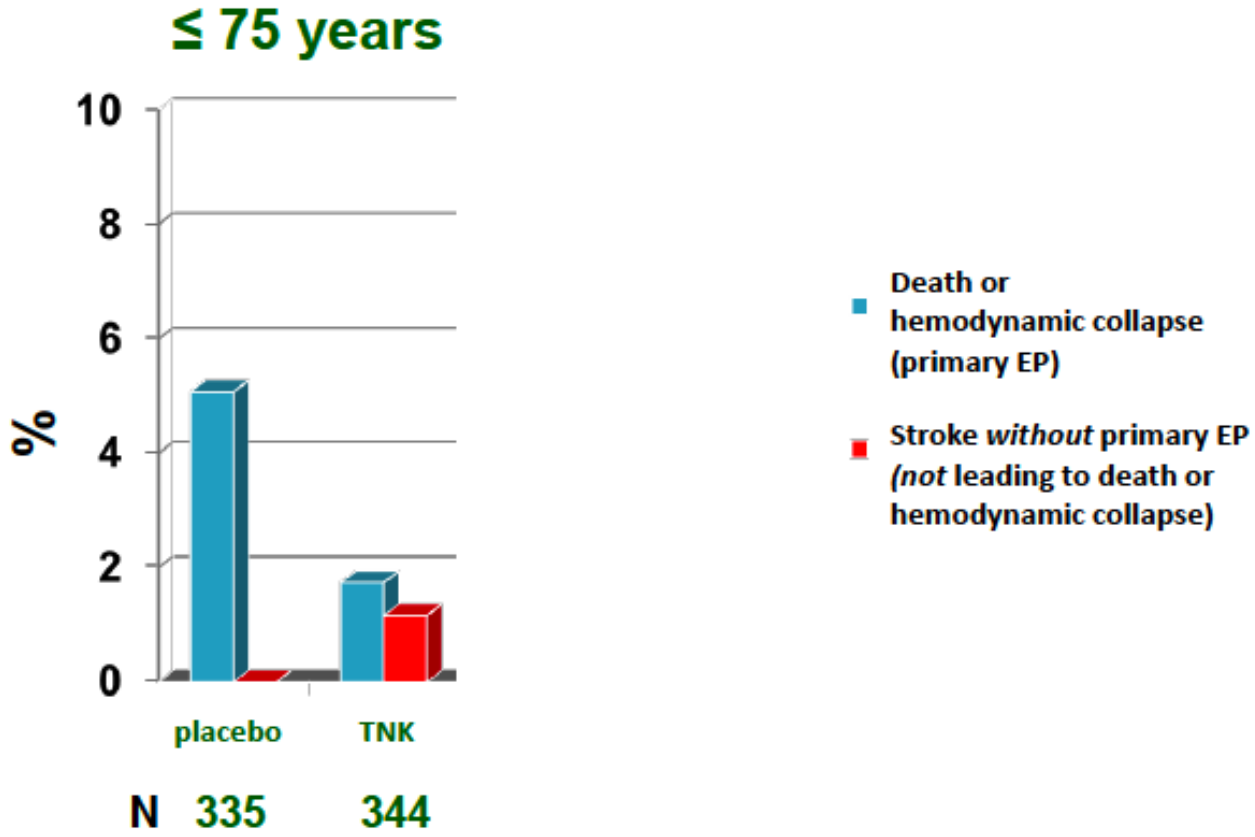
ITT population

PEITHO: Safety outcomes (2)

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All strokes by day 7	**12**	**(2.4)**	**1**	**(0.2)**	**0.003**
Hemorrhagic	10		1		
Ischemic	2		0		
Serious adverse events (SAE)	**29**	**(5.7)**	**39**	**(7.8)**	**0.19**

ITT population

PEITHO: Efficacy versus safety according to age



ITT population

The PEITHO Investigators

PEITHO: Conclusions

- In patients with intermediate-risk pulmonary embolism, intravenous bolus tenecteplase significantly reduced the primary end point of death or hemodynamic collapse within 7 days of randomization.
- The results of PEITHO justify the concept of risk stratification of normotensive patients with acute PE.
- They confirm the notion that early “advanced” (recanalization) treatment prevents clinical deterioration in patients with evidence of right ventricular dysfunction and myocardial injury.
- In PEITHO, the benefits of thrombolysis came at the cost of a significantly increased risk of major, particularly intracranial, hemorrhage.
- The patient’s age should be taken into account when weighing the expected benefits versus risks of systemic thrombolysis in clinical practice.