Statin: For Better outcome in patients with ACS

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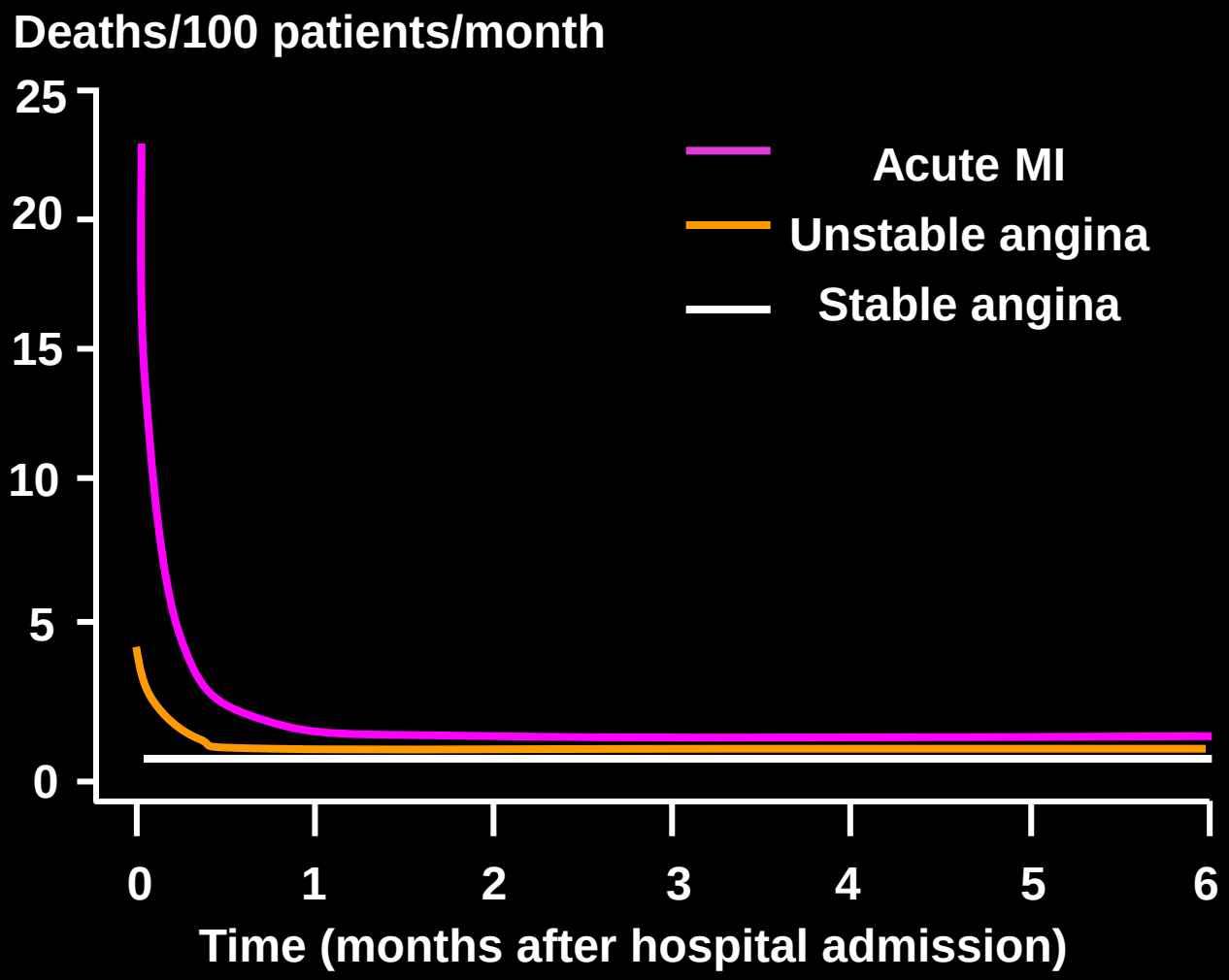
Cardiovascular Center

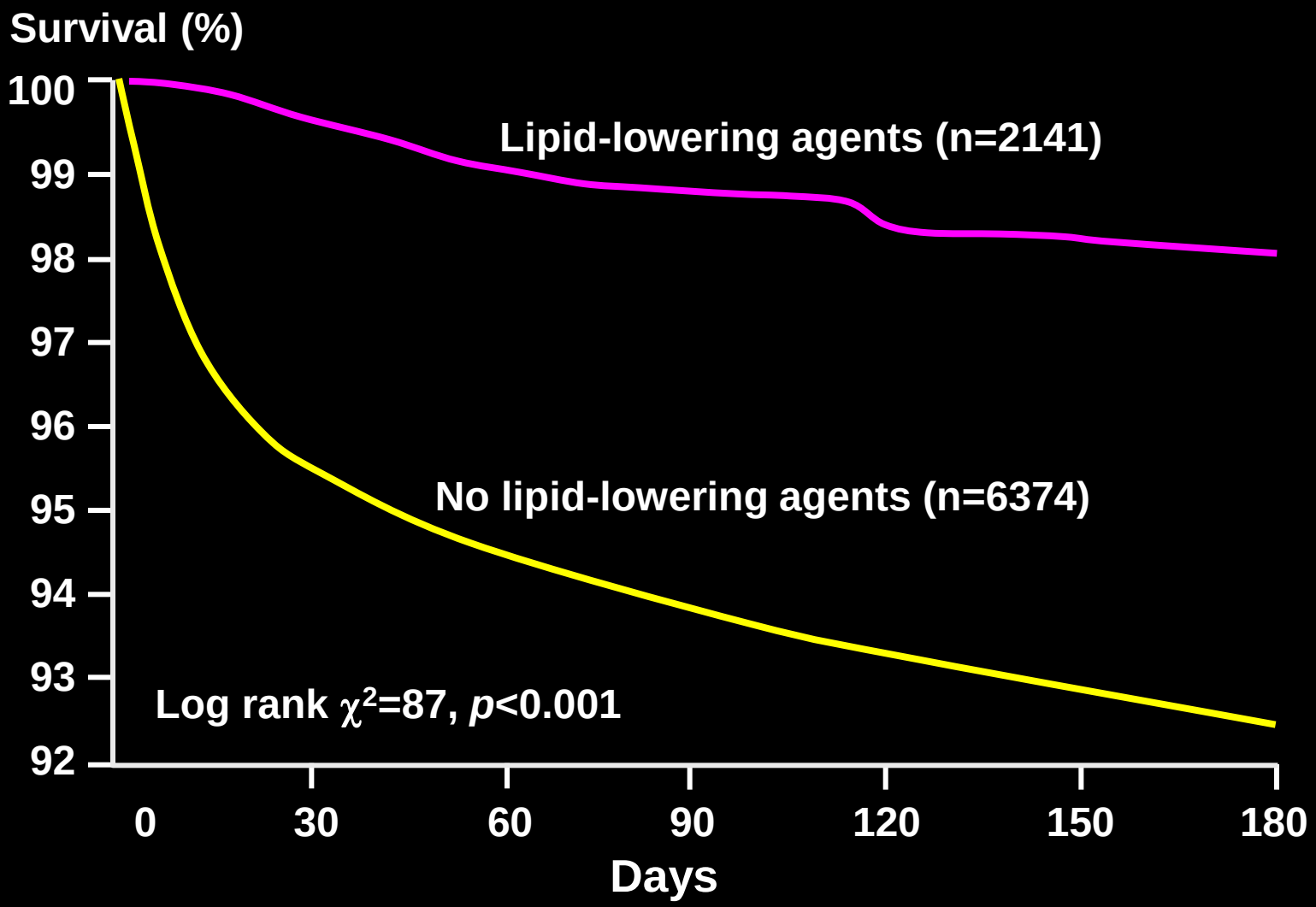
Most fatalities occur within the first 30 days after ACS



Braunwald (1996)

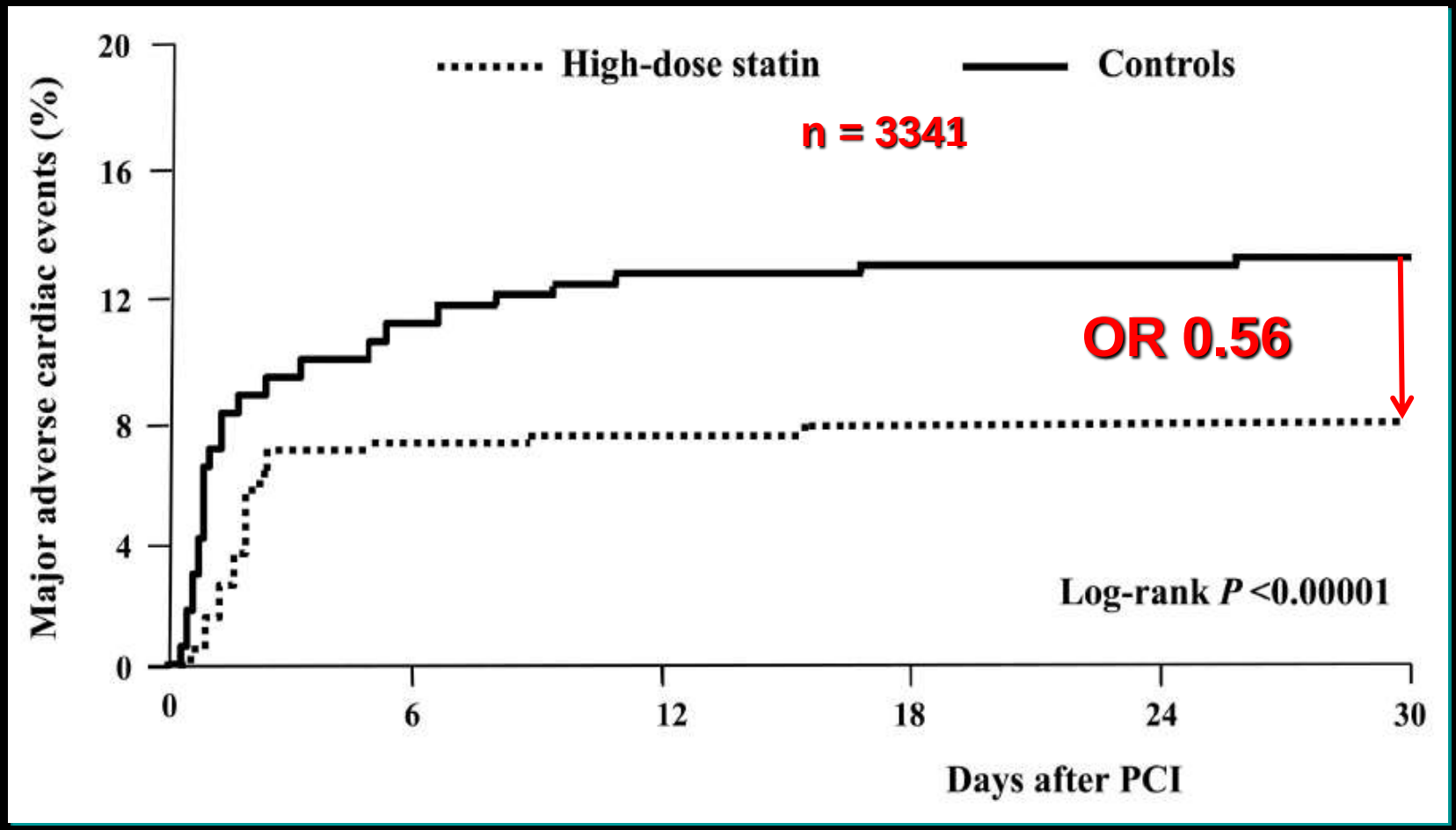
Do Statins play a role in the early management of acute coronary syndrome?

PURSUIT: Retrospective analysis shows early mortality reduction with lipid-lowering therapy



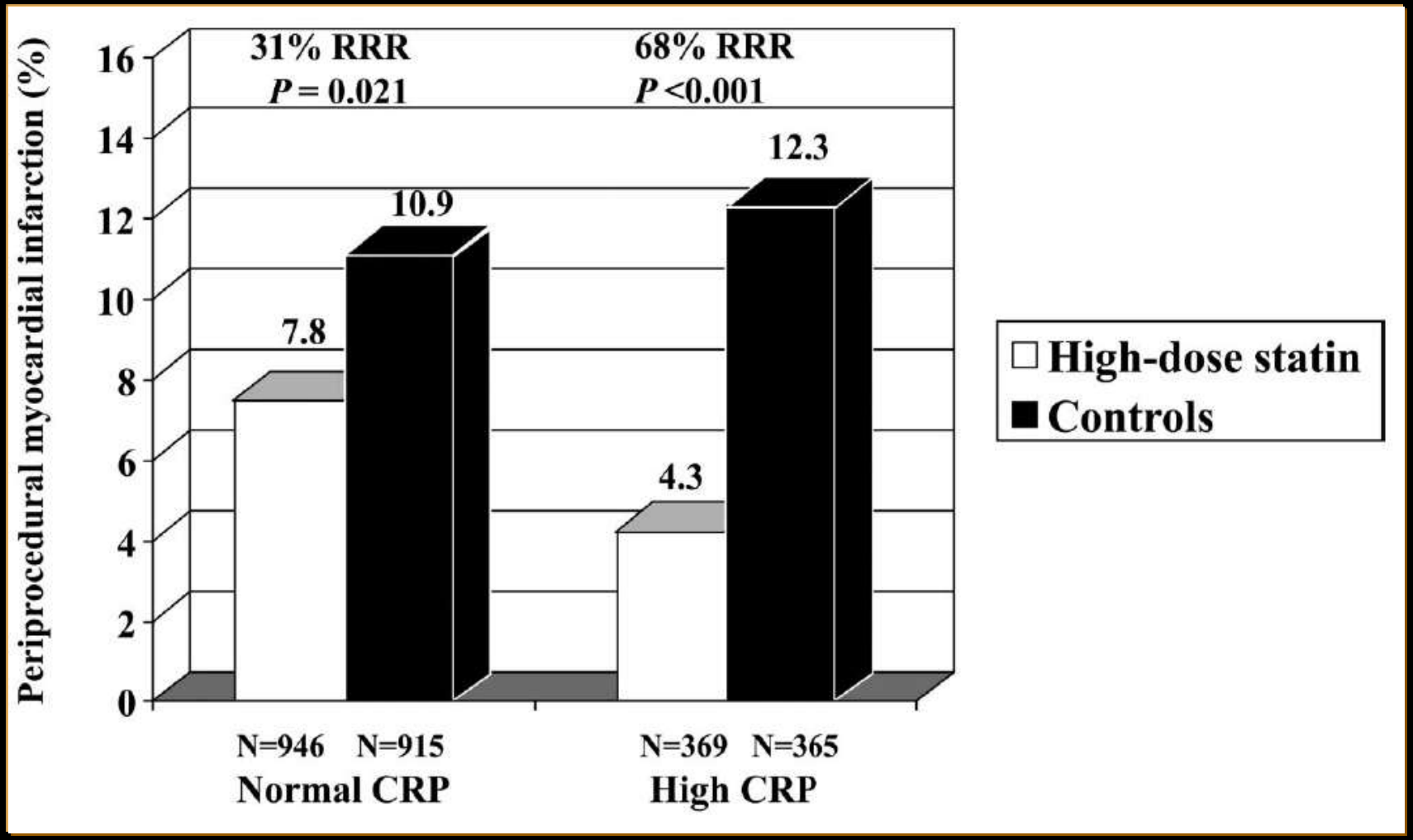
Aronow et al (2000)

Statin Pretreatment in PCI: Meta-analysis
MACE at 30 Days in High Dose Statin vs Control Arms



Patti et al. Circulation 2011;123:1622-32

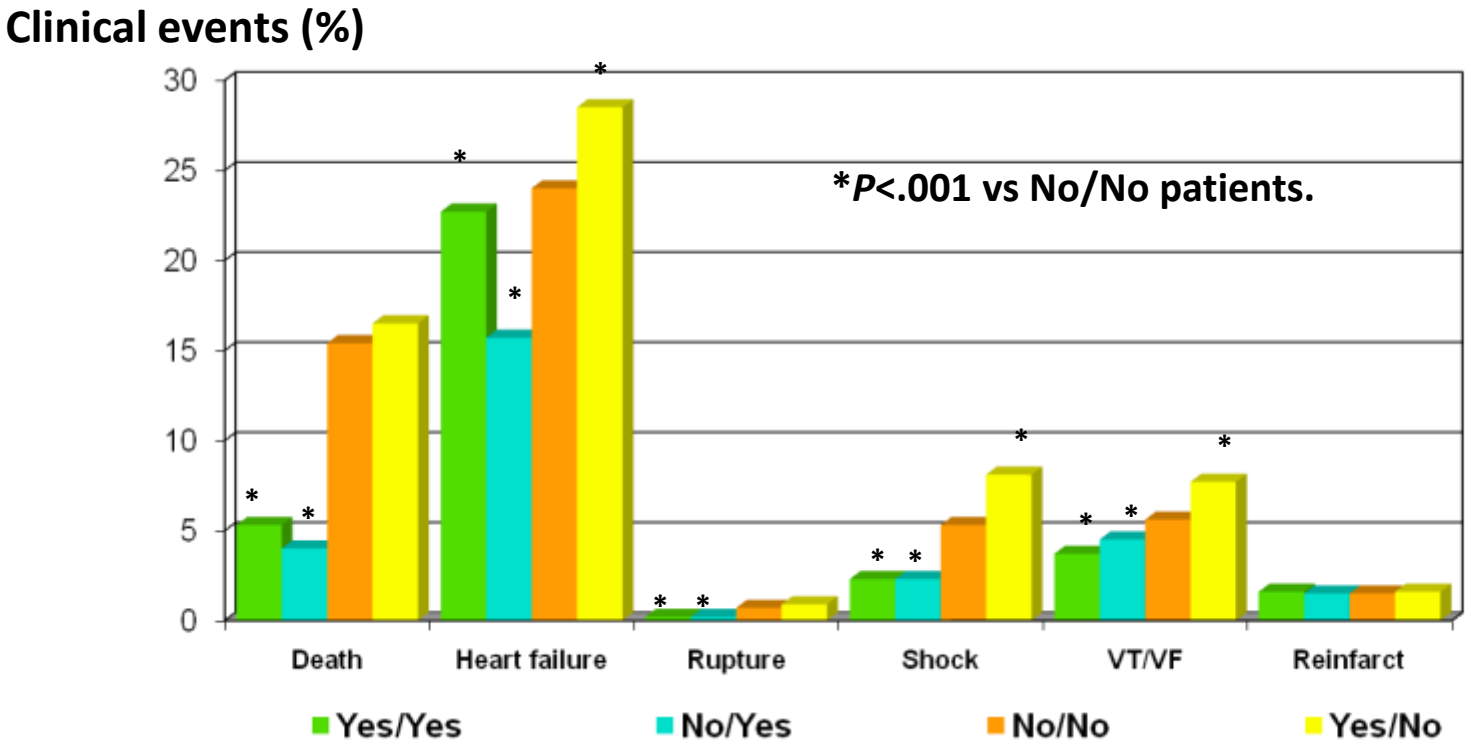
Statin Pretreatment in PCI: Meta-analysis Incidence of Periprocedural MI



Patti et al. Circulation 2011;123:1622-32

National Registry of MI-4:

Statin Use Within 24 Hours of AMI Is Associated With Reduced Early Morbidity and Mortality



yes/yes =patients continued on statin therapy;

no/yes =patients newly started on statin therapy;

no/no =patients who did not receive statin before or within the first 24 h of hospitalization;

yes/no =patients in whom statin therapy was discontinued.

Adapted from Fonarow GC et al. *Am J Cardiol*. 2005;96:611-616.

National Registry of MI 4:

Statin Use Within 24 Hours of AMI Is Associated With Reduced Early Morbidity and Mortality

All Acute Myocardial Infarction

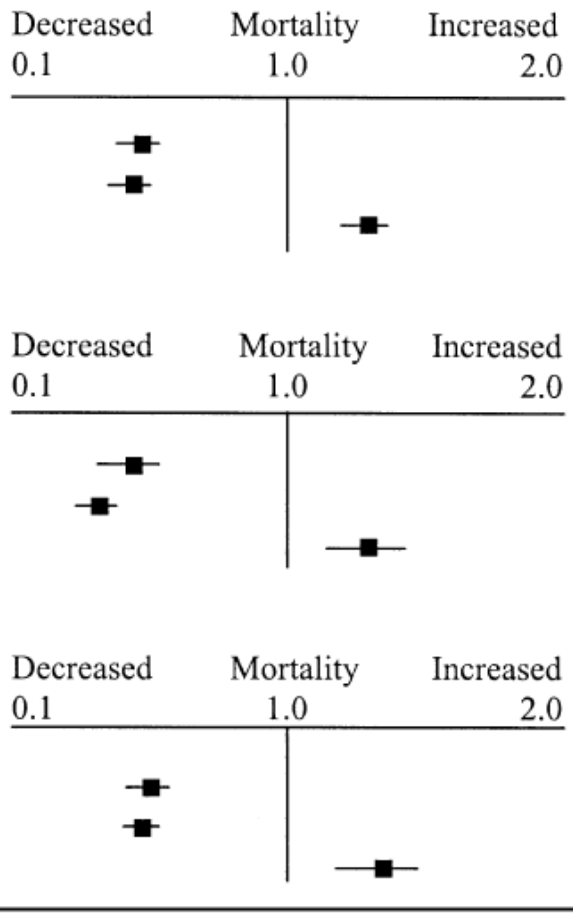
	Odds Ratio (95% CI)
Yes/Yes	0.46 (0.42-0.50)
No/Yes	0.42 (0.38-0.45)
Yes/No	1.25 (1.15-1.36)

ST Segment Elevation Myocardial Infarction

	Odds Ratio (95% CI)
Yes/Yes	0.40 (0.33-0.48)
No/Yes	0.32 (0.27-0.37)
Yes/No	1.25 (1.07-1.45)

Non-ST Segment Elevation Myocardial Infarction

	Odds Ratio (95% CI)
Yes/Yes	0.49 (0.44-0.54)
No/Yes	0.47 (0.42-0.52)
Yes/No	1.30 (1.18-1.45)



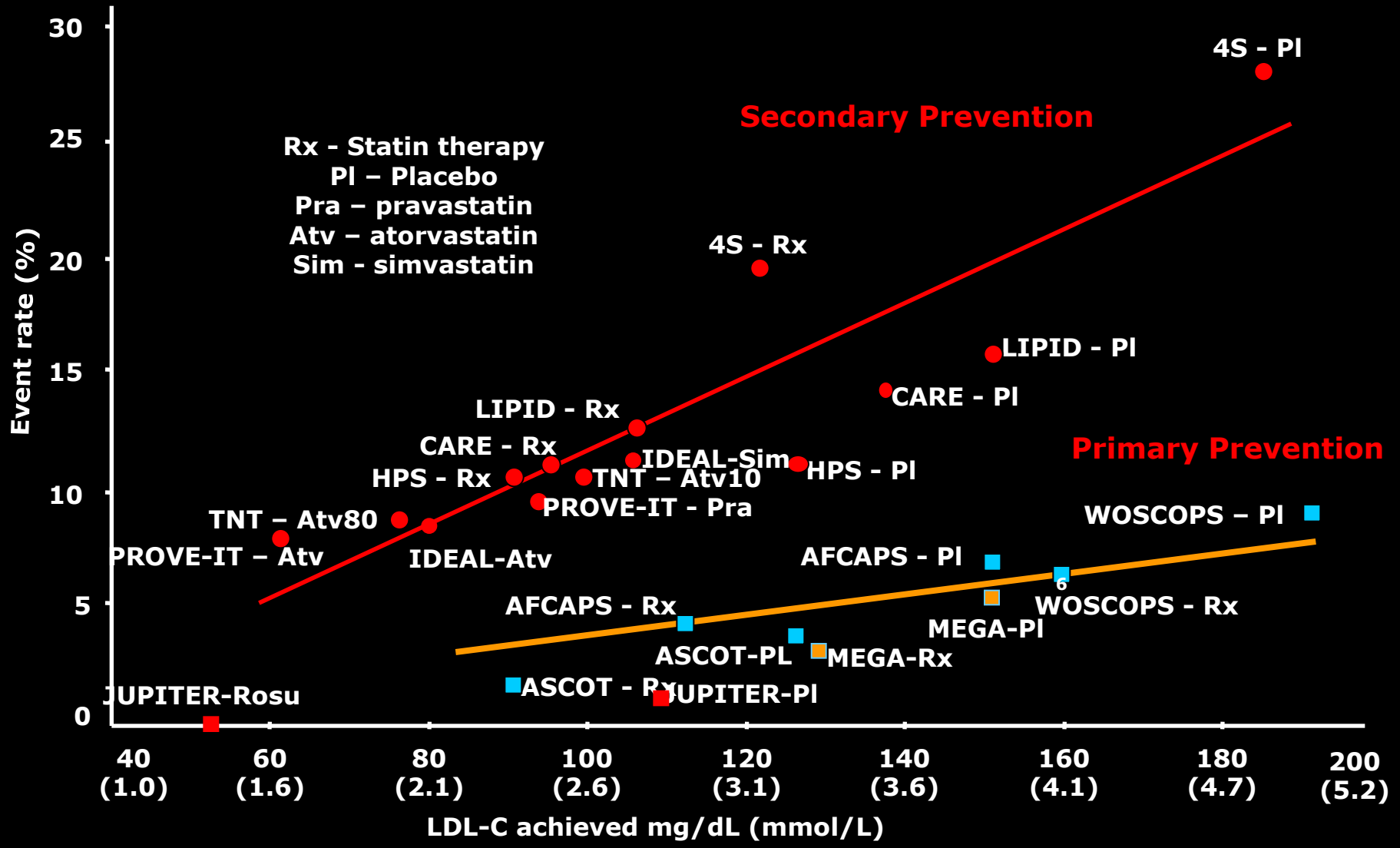
Adapted from Fonarow GC et al. *Am J Cardiol*. 2005;96:611-616.

How does statin therapy optimize the treatment of acute coronary syndrome?

The role of statin in the treatment of acute coronary syndrome

a. Lipid management

Multiple landmark clinical trials have demonstrated beneficial effects of statin therapy for CV prevention



Exp Opin Emerg Drugs 2004;**9**(2):269–279, *N Engl J Med* 2005;**352**:1425–1435. *JAMA* 2005;294:2437; *Lancet* 2006;368:1155

Efficacy and Safety of Rosuvastatin 20 and 40 mg versus Atorvastatin 80 mg in ACS

LUNAR Study Design

Patients (n=825), 18–75 years with:

- **Non-ST or ST segment elevation ACS receiving optimal reperfusion therapy**
- **Evidence of CAD**
- **LDL-C >70mg/dL (~1.8 mmol/L) and fasting triglycerides <500 mg/dL (~5.6 mmol/L)**

Rosuvastatin 20 mg (n=277)

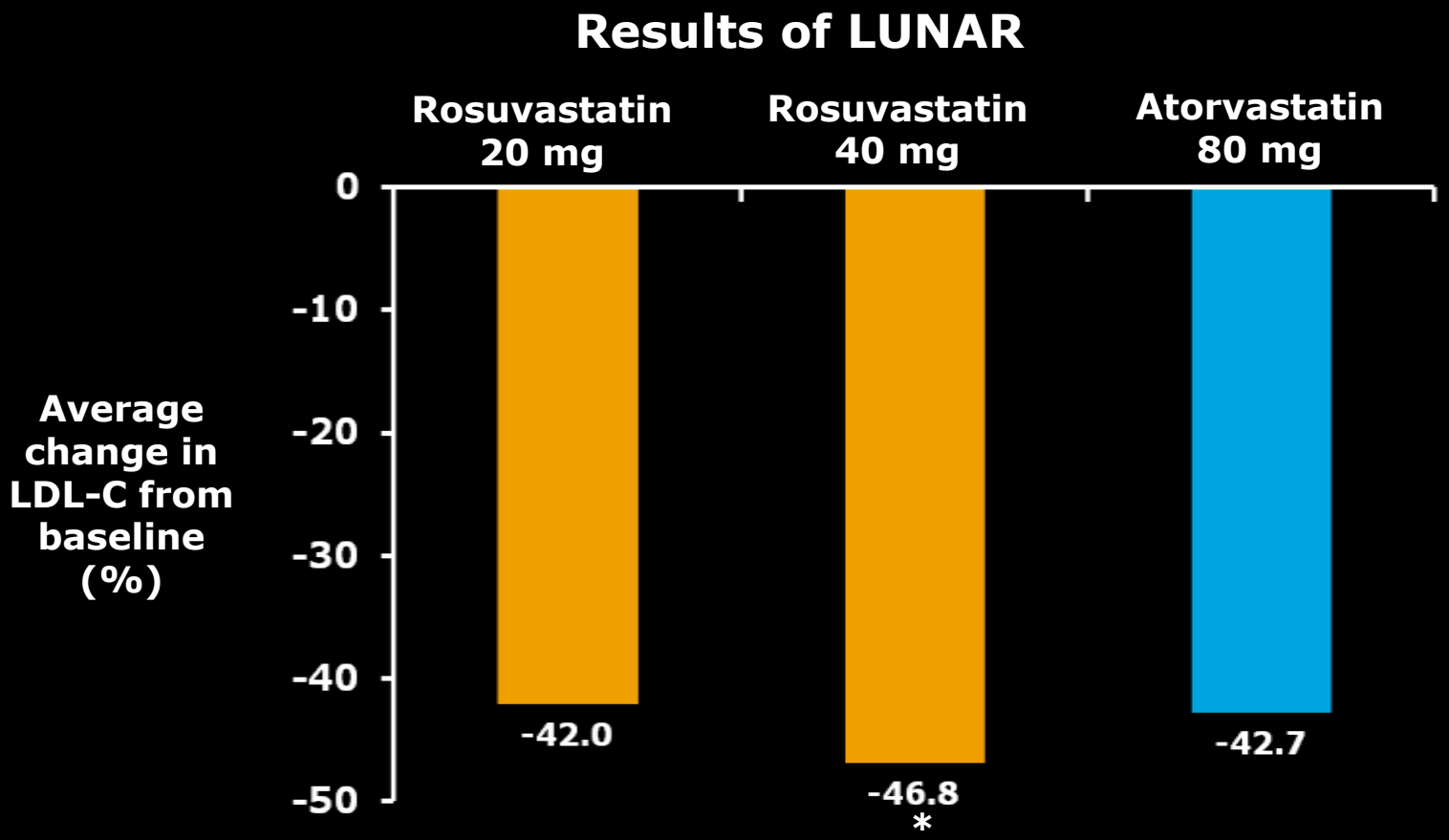
Rosuvastatin 40 mg (n=270)

Atorvastatin 80 mg (n=278)

Visit:	1	2	3	4	5
Week:	−2 to −3 days	1 day	2	6	12
	Dietary run in / eligibility	Lipids CRP Safety	Lipids Safety	Lipids CRP Safety	Lipids CRP Safety

Pitt B et al. Am J Cardiol 2012; 109:1239-46

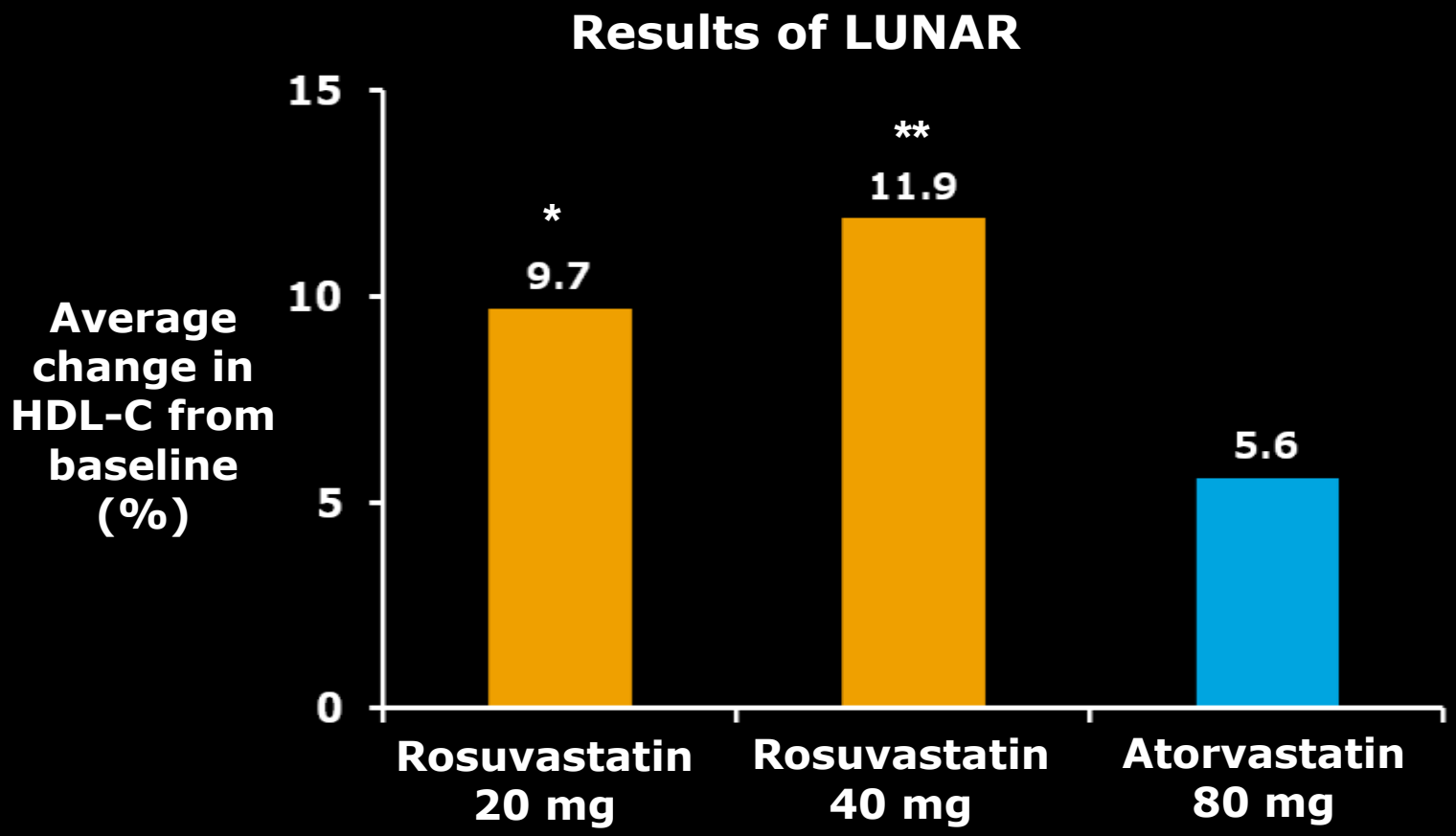
Rosuvastatin 40 mg Reduces LDL-C more than Atorvastatin 80 mg in ACS



*p=0.0219 vs atorvastatin 80 mg

Pitt B et al. Am J Cardiol 2012; 109:1239-46

Rosuvastatin 20 and 40 mg Increases HDL-C more than Atorvastatin 80 mg in ACS



*p<0.01 vs atorvastatin 80 mg; **p<0.001 vs atorvastatin 80 mg

Pitt B et al. Am J Cardiol 2012; 109:1239-46

The role of statin in the treatment of acute coronary syndrome

b. short-term and long-term outcome

Beyond lipid lowering, additive effect of statin may drive more benefit

Statin Evidence beyond Lipid lowering

↓ Lesion initiation
- Restores endothelial dysfunction
- Antioxidant effect
- ↓ endothelial permeability
- ↑ endothelial cell migration

↓ Lesion progression
- ↓ Lipid core
- ↓ Inflammation
- ↓ Foam cell formation
- ↓ SMC transmigration
- ↓ Platelet aggregation

↑ Myocardial perfusion
- ↑ NO production
- ↓ Endothelin-1
- ↓ Blood / plasma viscosity

↓ Coagulation
- ↓ TF expression
- ↓ Thrombin gen

↓ Myocardial damage
- Troponin T
- CK-MB
- ↓ Blood pressure
- ↓ LV hypertrophy
- ↓ Heart failure
- ↓ Aortic stenosis

↑ Myocardial repair
- EPC recruitment

↓ Ischemic burden
- AS regression
- ↑ angiogenesis

↑ Survival post transplantation
- Immunosuppression
- ↓ Inflammation

Rosuvastatin Pre-treatment in Patients Undergoing Elective PCI to Reduce the Incidence of Myocardial Periprocedural Necrosis

Study Hypothesis

Pleiotropic effects of statins may lead to an improvment in micro vessel coronary circulation and endothelial function, with a reduction of thromboembolic events, and consequent myocardial protection form procedural ischemic damage that translates into clinical early and long-term positive outcomes

The risk of subsequent cardiac events is related to the extent of cardiac troponin or creatineine kinase MB isoform(CK-MB) increase

Single high loading dose of statin may be effective in reducing the post procedural elevation of cardiac biomarkers after elective, nonurgent coronary angioplasty

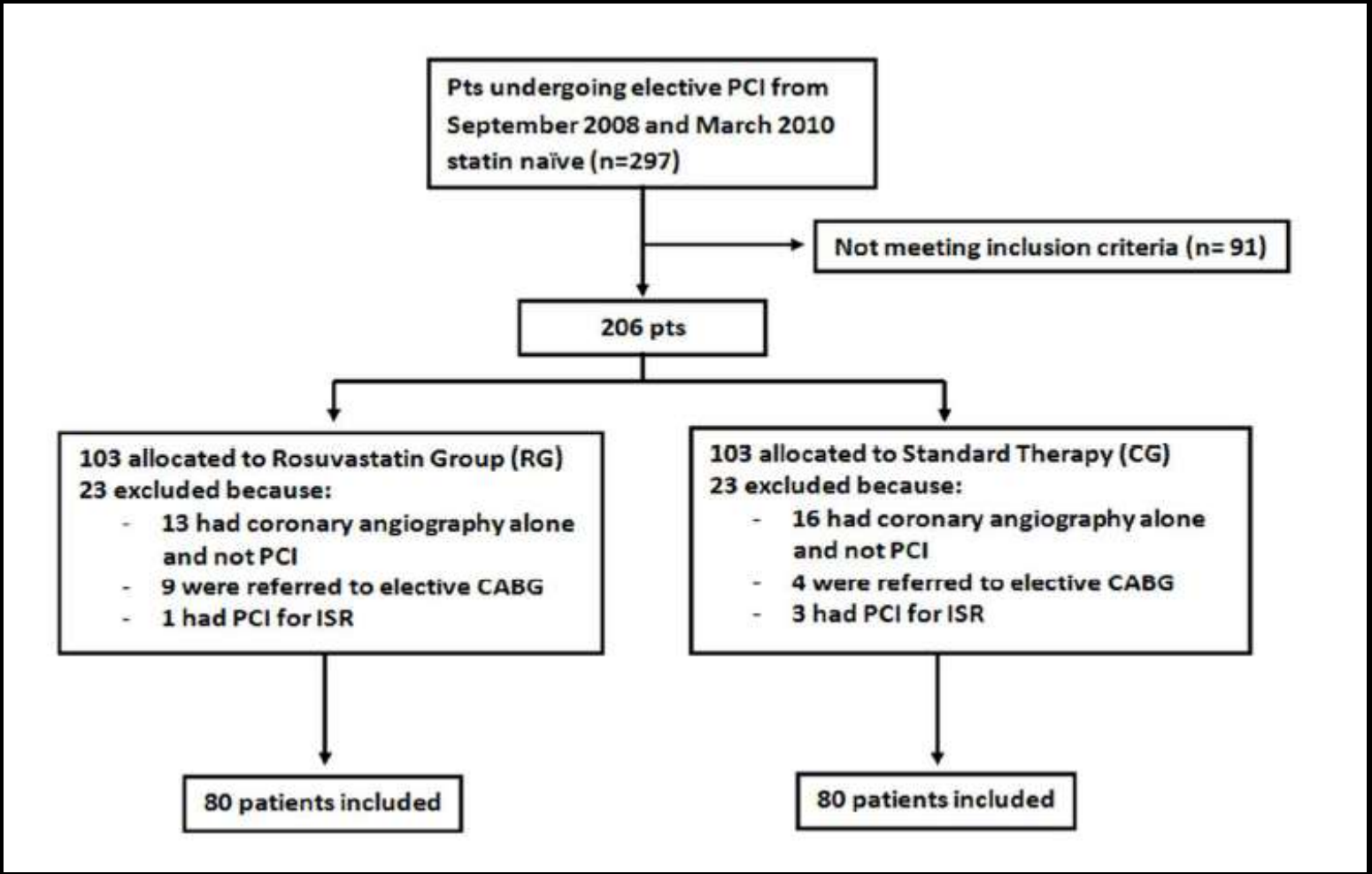
Catheter Cardiovasc Interv. 2012 Apr 19. doi: 10.1002/ccd.24403

ROMA trial

Study Design

CATHETERIZATION & CARDIOVASCULAR INTERVENTIONS ROMA Trial

<Flow chart of the study>



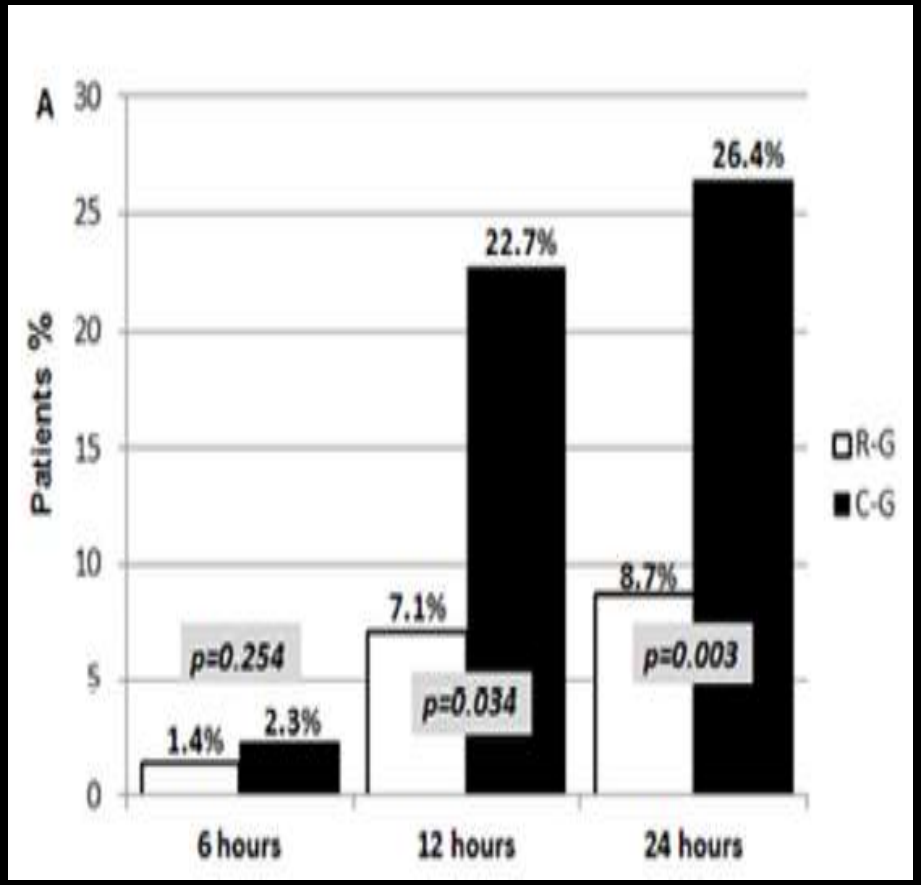
Catheter Cardiovasc Interv. 2012 Apr 19. doi: 10.1002/ccd.24403

12hr and 24hr post PCI myonecrosis occurred more frequently in CG than RG

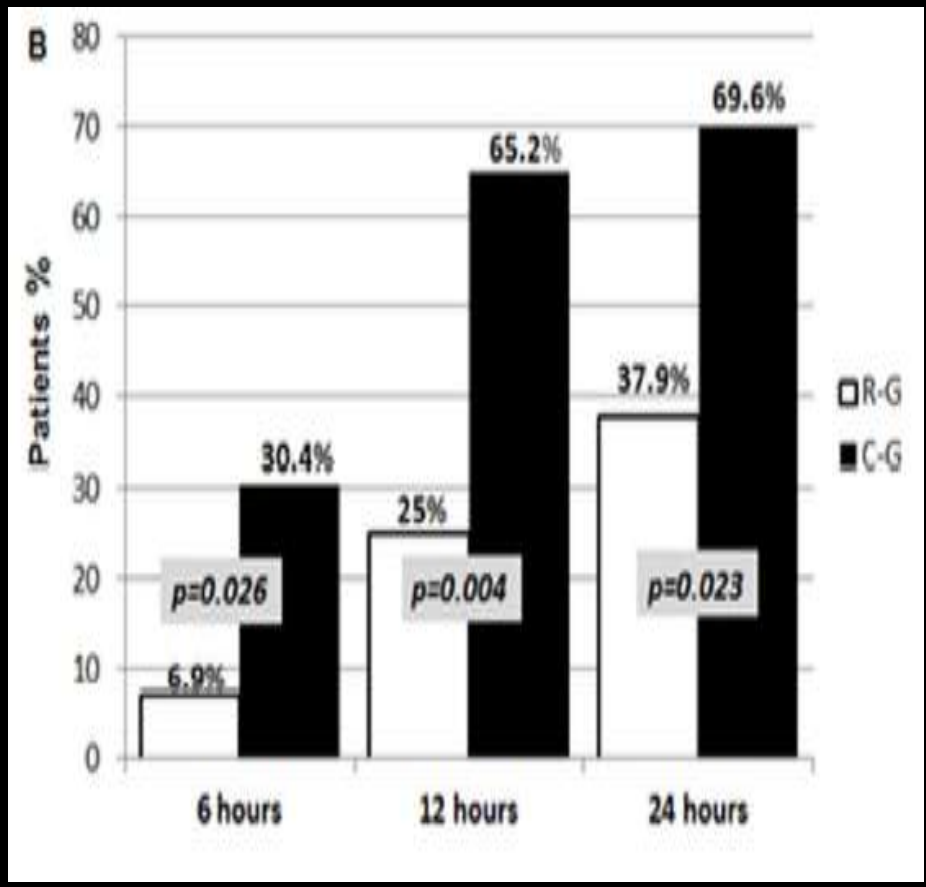
CATHETERIZATION & CARDIOVASCULAR INTERVENTIONS

ROMA Trial

< CK-MB >3*ULN at 6–12 and 24 hr after elective PCI >



< TnT>3* ULN at 6–12 and 24 hr after elective PCI >



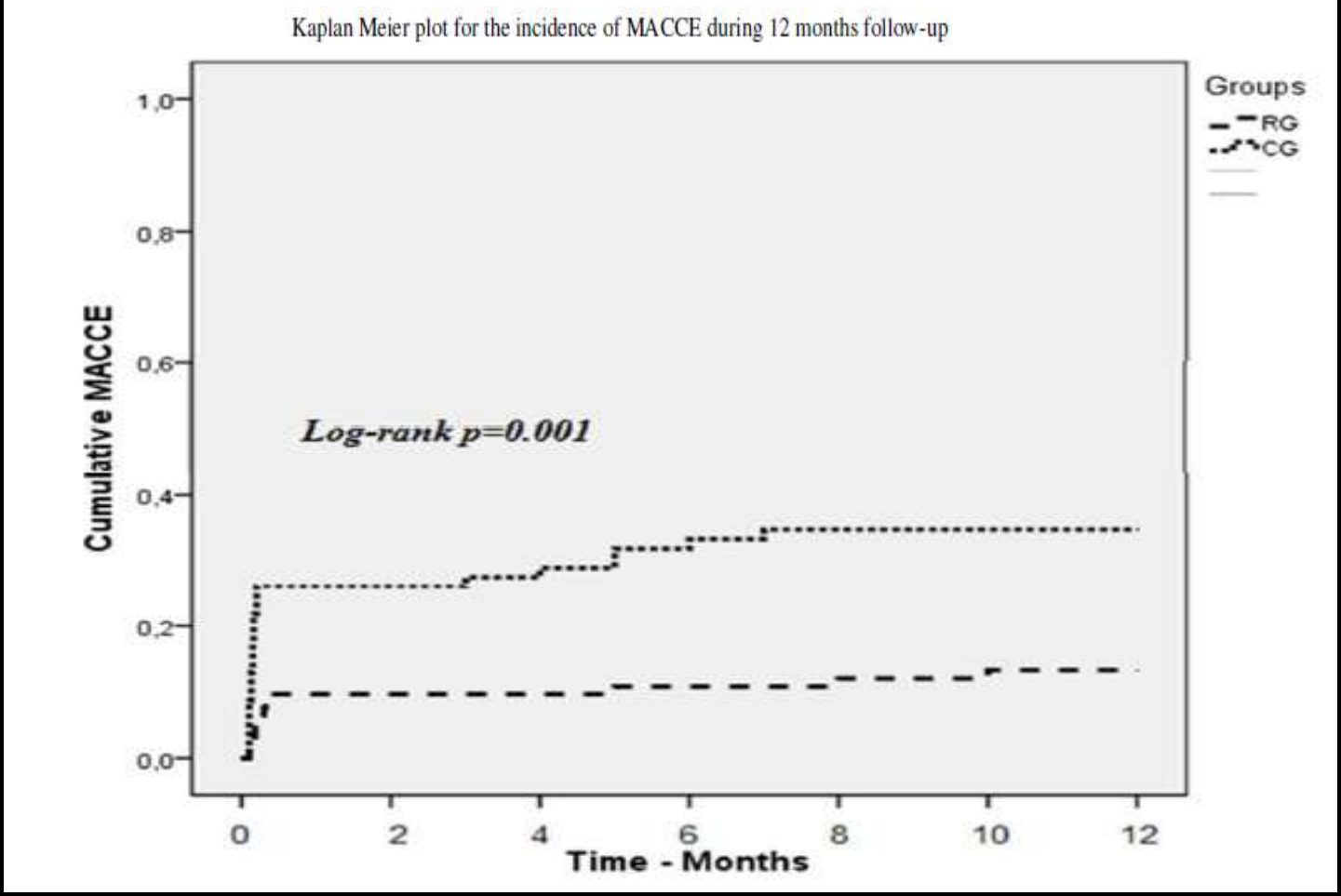
Catheter Cardiovasc Interv. 2012 Apr 19. doi: 10.1002/ccd.24403

The rate of cumulative MACCE was significantly higher in the CG than RG

CATHETERIZATION & CARDIOVASCULAR INTERVENTIONS

ROMA Trial

< Kaplan–Meier plot for the incidence of MACCE during 12 months follow-up >



Catheter Cardiovasc Interv. 2012 Apr 19. doi: 10.1002/ccd.24403

Preloading of rosuvastatin with Korean ACS patients Study Hypothesis

Statin therapy prior to PCI is associated with reduced mortality and the reduction of periprocedural myocardial injury after PCI in patients with or without acute myocardial infarction

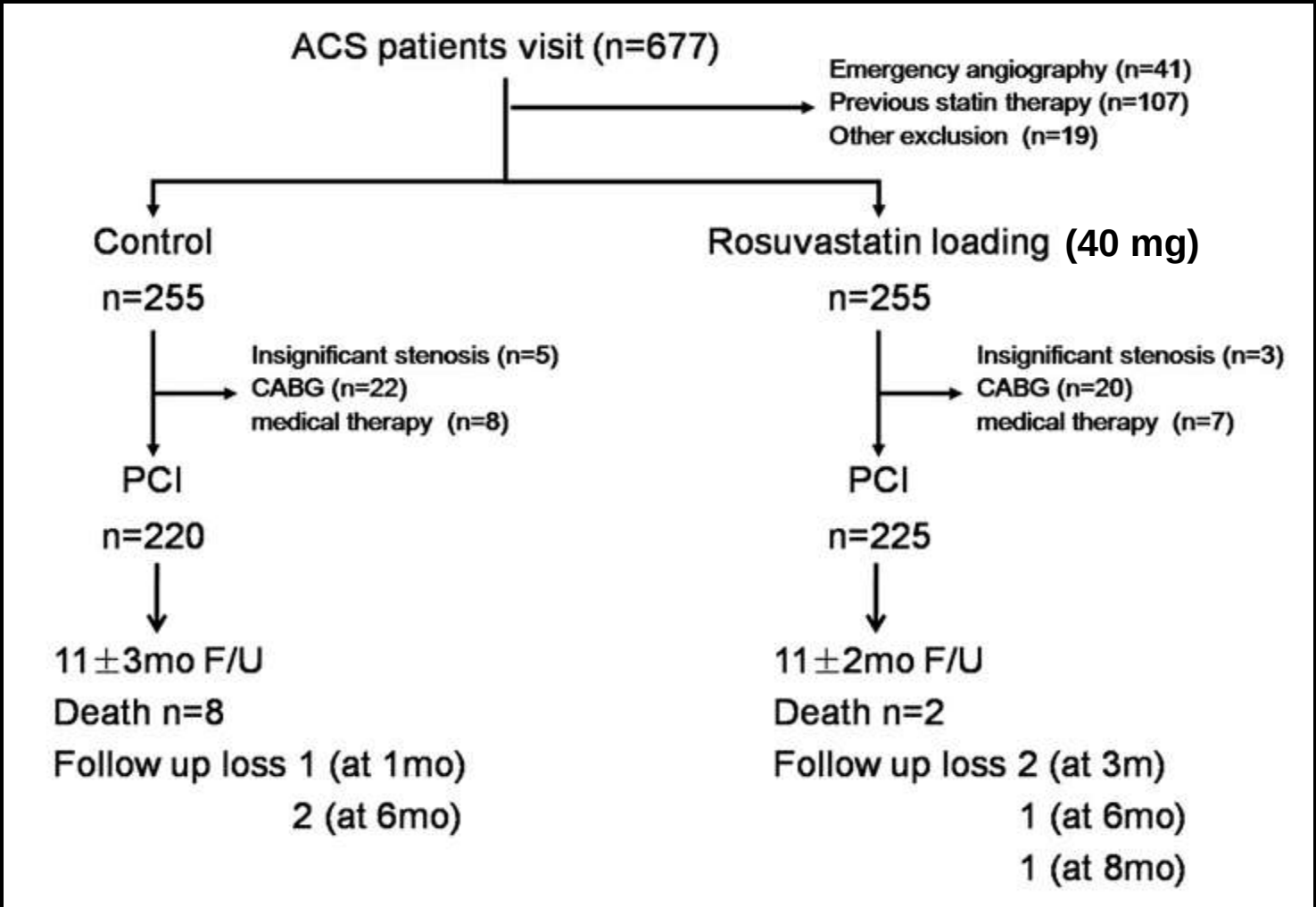
Vascular injury during PCI is associated with a systemically measurable inflammatory response, and the degree of inflammation has been shown to correlate with cardiovascular risk

Single high dose Rosuvastatin loading before PCI may beneficial effects on the long-term clinical outcome

Yun et al. Int J Cardiol. 2009;137:246-251.
Yun et al. Int J Cardiol. 2011;146:68-72.

Study Design

<Flow chart of the study>



Yun et al. Int J Cardiol. 2009;137:246-251.
Yun et al. Int J Cardiol. 2011;146:68-72.

Pre- and post-PCI medication

	Control group ($n=220$)	Rosuvastatin group ($n=225$)	p value
Pre-PCI medication (%)			
ACEI	83 (38)	87 (39)	0.838
ARB	22 (10)	25 (11)	0.703
Beta blocker	83 (38)	96 (43)	0.288
Calcium antagonist	23 (11)	28 (12)	0.510
Post-PCI medication (%)			
Aspirin	217 (98.6)	222 (98.2)	1.000
Clopidogrel	220 (100)	225 (100)	1.000
ACEI or ARB	198 (90.0)	204 (90.7)	0.812
Beta blocker	168 (76.4)	162 (72.0)	0.293
Calcium antagonist	80 (36.4)	82 (36.4)	0.986
Statin therapy (%)			0.499
Continued rosuvastatin 10 mg	191 (86.8)	192 (85.3)	
Discontinued	4 (1.8)	1 (0.4)	
Dose reduction to 5 mg	2 (0.9)	1 (0.4)	
Dose elevation to 20 mg	2 (0.9)	2 (0.9)	
Changed to other statin	21 (9.5)	29 (12.9)	

PCI: percutaneous coronary intervention; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

Yun et al. Int J Cardiol. 2009;137:246-251.
Yun et al. Int J Cardiol. 2011;146:68-72.

incidence of post-procedural elevation of troponin T was higher in CG than in Rosuvastatin group

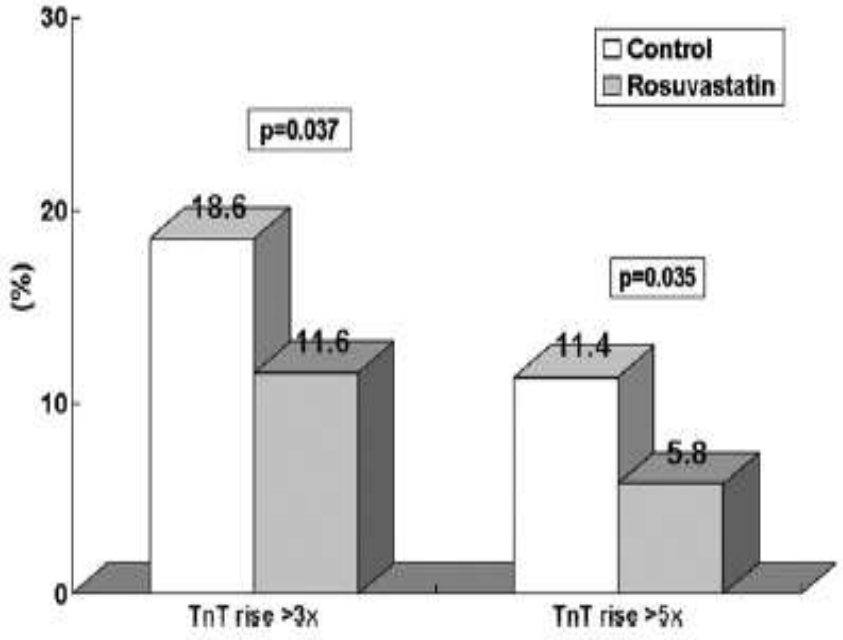


Fig. 3. Incidence of troponin T (TnT) elevation in control group and rosuvastatin loading group.

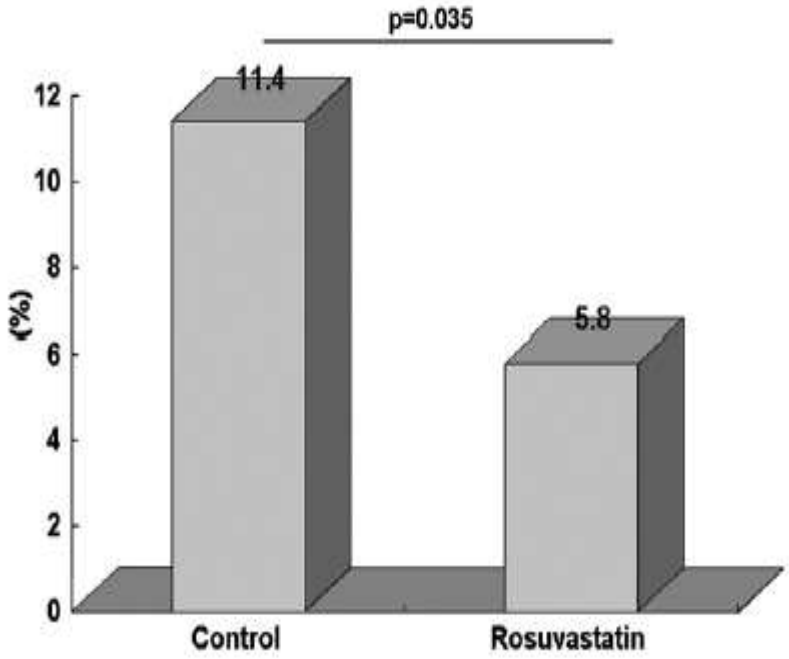


Fig. 2. Incidence of periprocedural myocardial injury, defined by post-procedural increase of creatine kinase-MB >2 times above the upper limit of normal, in the control group and high dose rosuvastatin loading group.

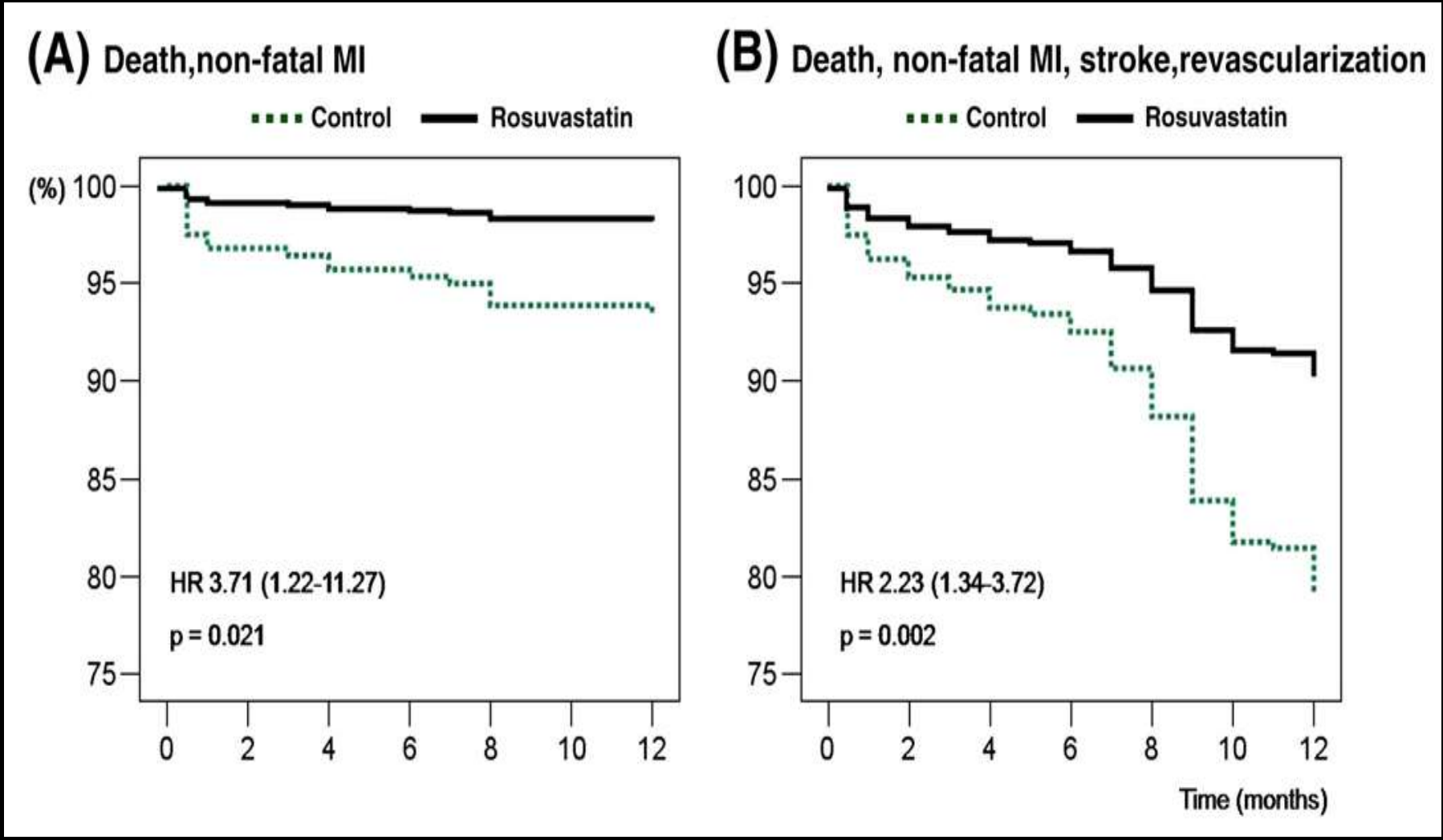
Yun et al. Int J Cardiol. 2009;137:246-251.
Yun et al. Int J Cardiol. 2011;146:68-72.

Significantly better outcome in Rosuvastatin group

	Control group	Rosuvastatin group	*p* value
0–1-month clinical events (%)	*n* = 220	*n* = 225	
Death	3 (1.4)	0 (0.0)	0.120
Non-fatal MI	5 (2.3)	2 (0.9)	0.280
Non-fatal stroke	2 (0.9)	1 (0.4)	0.620
Revascularization	3 (1.4)	0 (0.0)	0.120
Any of the above	13 (5.9)	3 (1.3)	0.010
1–12-month clinical events (%)[a]	*n* = 206	*n* = 222	
Death	5 (2.4)	2 (0.9)	0.269
Non-fatal MI	1 (0.5)	0 (0.0)	0.481
Non-fatal stroke	4 (1.9)	3 (1.4)	0.715
Revascularization	22 (10.7)	14 (6.3)	0.103
Any of the above	32 (15.5)	19 (8.6)	0.026
Total clinical events (%)	*n* = 220	*n* = 225	
Death	8 (3.6)	2 (0.9)	0.060
Non-fatal MI	6 (2.7)	2 (0.9)	0.171
Non-fatal stroke	6 (2.7)	4 (1.8)	0.540
Revascularization	25 (11.4)	14 (6.2)	0.055
Any of the above	45 (20.5)	22 (9.8)	0.002

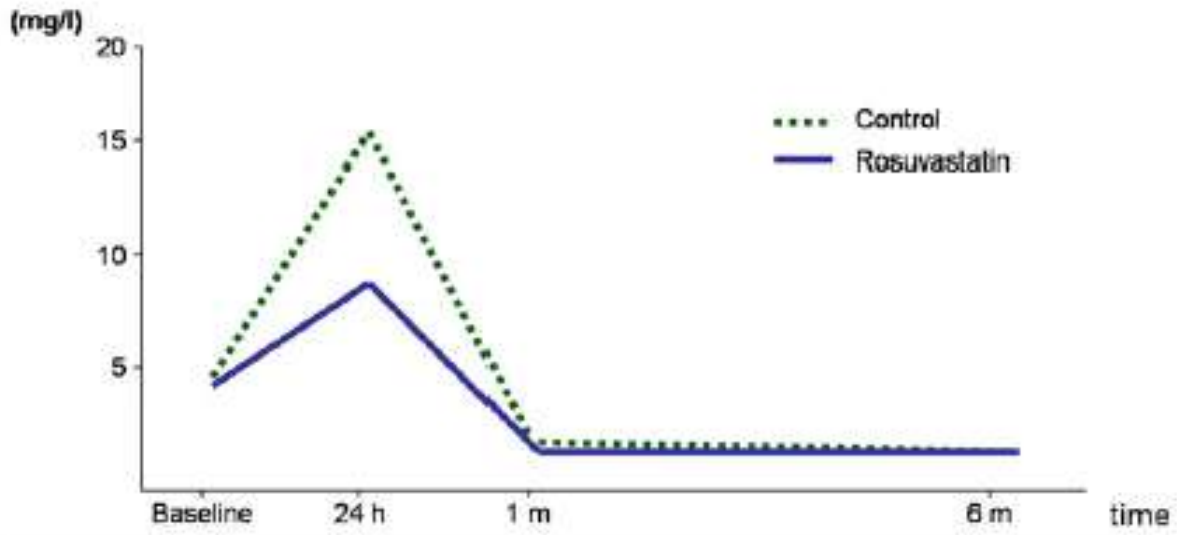
Yun et al. Int J Cardiol. 2009;137:246-251.
Yun et al. Int J Cardiol. 2011;146:68-72.

Rosuvastatin group shows a significant reduction of incidence of death and non-fatal MI up to 12 mths



Yun et al. Int J Cardiol. 2009;137:246-251.
Yun et al. Int J Cardiol. 2011;146:68-72.

hsCRP peak after stenting was significantly lower in the rosuvastatin group



	Baseline	24h after PCI	1 month	6 months
No. of patients	445	434	355	308
Control group (mg/l)	4.9 ± 8.7	15.9 ± 27.7	1.7 ± 2.8	1.4 ± 2.1
Rosuvastatin group (mg/l)	4.6 ± 8.7	9.2 ± 12.5	1.9 ± 3.9	1.7 ± 2.1
p value	0.656	<0.001	0.366	0.133

Fig. 4. The change in high-sensitivity C-reactive protein level over time in patients with acute coronary syndrome who received no rosuvastatin treatment (control group) or high dose (40 mg) rosuvastatin loading (rosuvastatin group) before percutaneous coronary intervention (PCI).

hsCRP peak after stenting was significantly lower in the rosuvastatin group than in the control group, supporting the hypothesis that the anti-inflammatory effects of statins reduce the risk of periprocedural MI and improve clinical outcomes.

Yun et al. Int J Cardiol. 2009;137:246-251.
Yun et al. Int J Cardiol. 2011;146:68-72.

Chinese ACS pts

Wang et al

Effect of Rosuvastatin on Percutaneous Coronary Intervention for Acute Coronary Syndromes

Study Hypothesis

Single and high dose of statin prior to PCI reduces postprocedural myocardial injury in patients with ACS, with a concomitant attenuation of the post procedural increase in hs-CRP and IL-6 levels, suggesting that the anti-inflammatory effect may contribute to the procedural myocardial protection provided by statin

Vascular injury during PCI is associated with a systemically measurable inflammatory response, and the degree of inflammation has been shown to correlate with cardiovascular risk

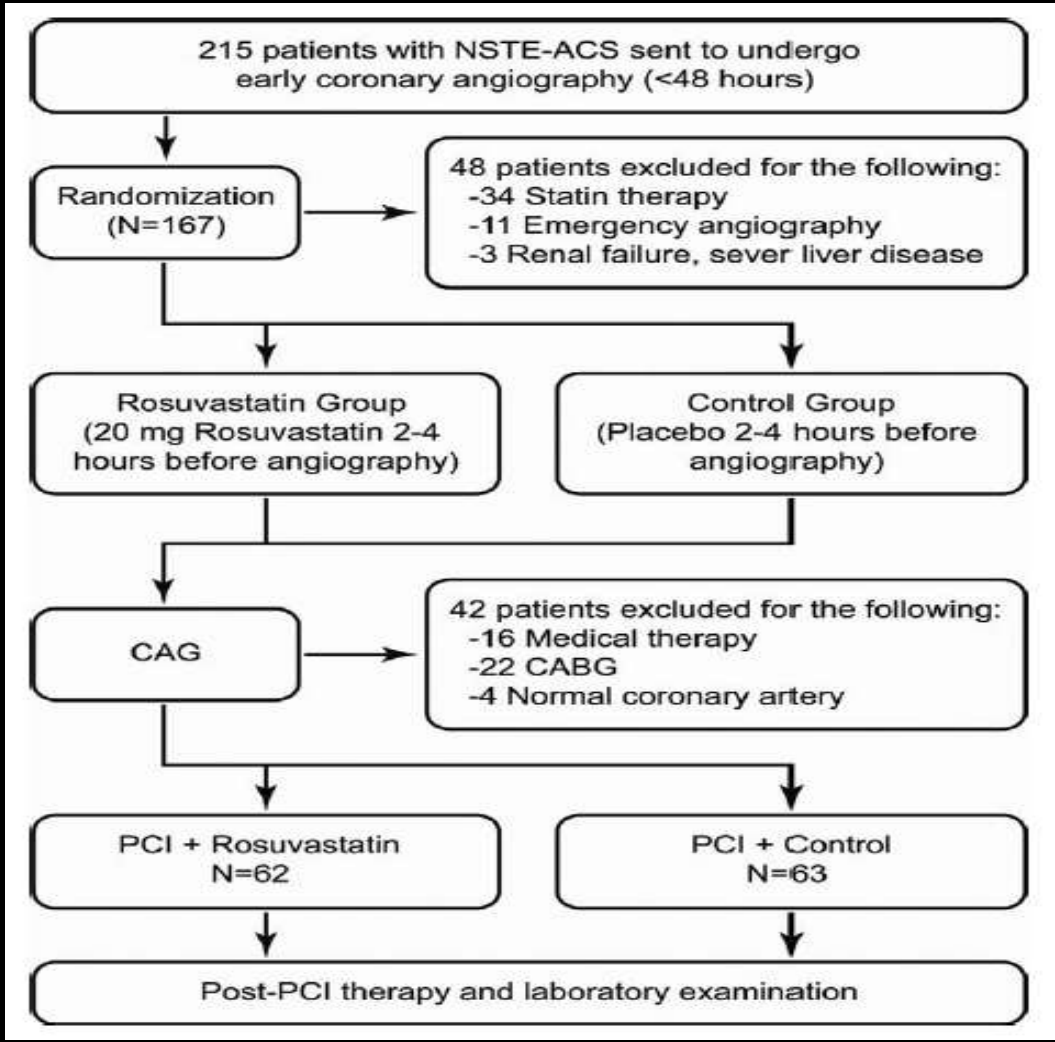
High-dose rosuvastatin loading therapy before PCI may reduce postprocedural myocardial infarction in patients with ACS, possibly via the inhibition of both IL-6 and CRP

Wang Z et al. **J Cardiovasc Pharmacol Ther.2013 Jan 29.**

Study Design

JCPT **Chinese ACS pts**
Wang et al

<Flow chart of the study>



Wang Z et al. **J Cardiovasc Pharmacol Ther.2013 Jan 29.**

20mg loading dose of rosuvastatin prior to PCI decrease the incidence of MI and MACE

Chinese ACS pts
Wang et al

<The Incidence of Primary End Points at 1 Month in the 2 Groups>

Variable	Rosuvastatin (n=62)	Control (n=63)
Cardiac death(%)	0 (0)	0 (0)
Myocardial infarction (%)	5 (8.1)	14 (22.2)
Target vessel revascularization (%)	0 (0)	0 (0)
Total MACEs(%)	5 (8.1)	14 (22.2)

The rate compared with the rosuvastatin group was significantly different (p<.01)

<The Proportion of Patients With Cardiac Markers Elevated Above the ULN>

Variable	Pre-PCI	6h	24h	3d
Elevated CK-MB in rosuvastatin group(%)	3(4.8)	10(16.1)**	12(19.4) **	8(12.9)*
Elevated CK-MB in control group(%)	4(6.3)	20(31.7)*	22(34.9)*	19(30.1)*
Elevated cTnL in rosuvastatin group(%)	9(14.5)	19(30.6) **	21(33.9) **	17(27.4)
Elevated cTnL in control group(%)	11(17.5	31(49.2)*	33(52.3)*	25(39.7)*

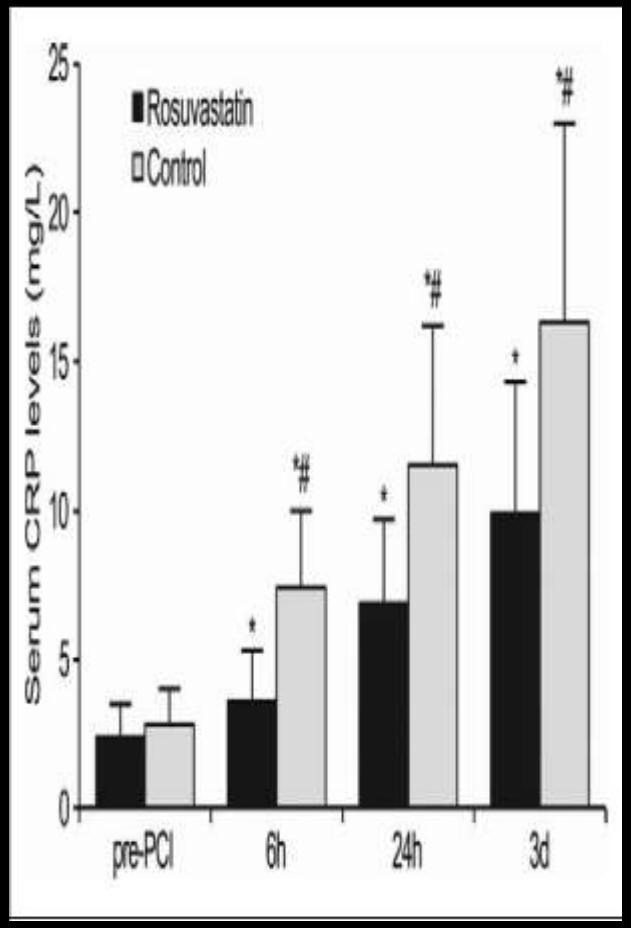
*The rate compared with the rprePCI rate was significantly different (p<.05)
** The rate compared with the rate in the control group was significantly different(P<.05)

Wang Z et al. **J Cardiovasc Pharmacol Ther.2013 Jan 29.**

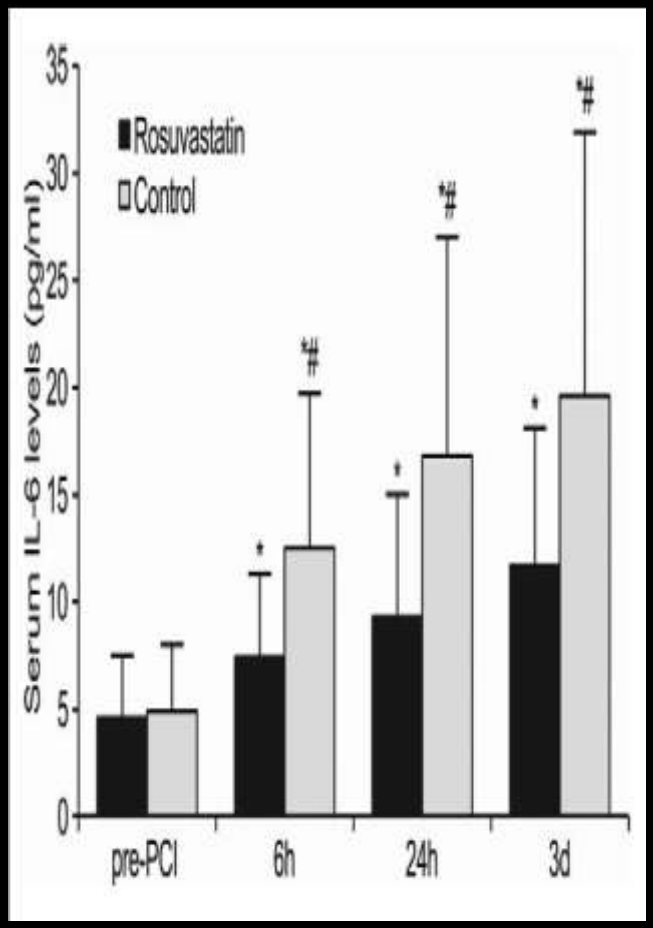
Loading with rosuvastatin substantially inhibited the elevation in hsCRP and IL-6 in ACS after PCI

JCPT Chinese ACS pts
Wang et al

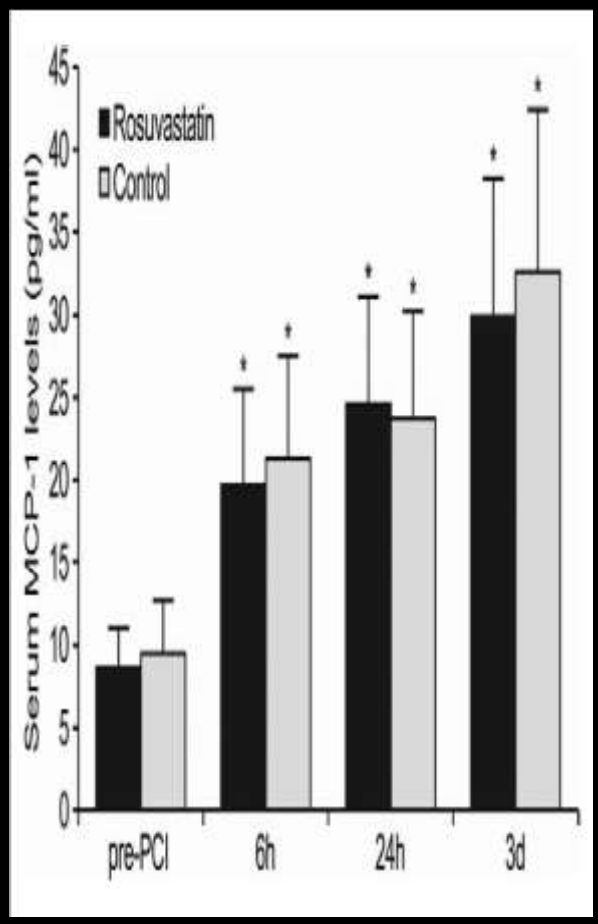
<hs-CRP level>



<IL-6 level>



<MCP-I level>



*P <0.01 versus pre-PCI
#P <0.01 versus the rosuvastatin group

Wang Z et al. **J Cardiovasc Pharmacol Ther.2013 Jan 29.**

The role of statin in the treatment of acute coronary syndrome

c. protective effect against contrast- induced acute kidney injury

Contrast-induced acute kidney injury is an important complication in the use of iodinated contrast media

- A significant number of cases of hospital-acquired AKI
- A concern to cardiologists in recent years because of its adverse effect on prognosis
- Addition to health care costs
- Many hospitalized patients have compromised renal function which is the most important risk factor for contrast-induced AKI.

McCullough PA J Am Coll Cardiol. 2008 Apr 15;51(15):1419-28.

But the result of previous studies have proved disappointing [PROMISS trial with simvastatin 80mg]

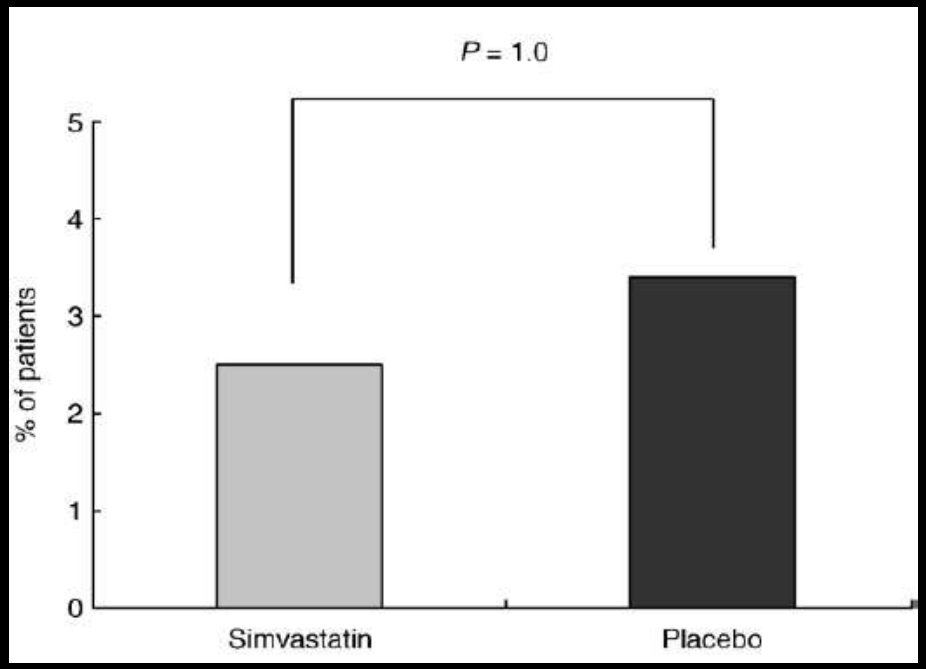
Primary end point—peak increase in SCr

SCr (mg/dL)*	Simvastatin (n = 118)	Placebo (n = 118)	P
Baseline	1.286 ± 0.418	1.248 ± 0.364	.455
Follow-up	1.288 ± 0.445	1.265 ± 0.512	.714
Absolute change	0.002 ± 0.164	0.017 ± 0.230	.559

*To convert values for creatinine to micromoles per liter, multiply by 88.4.

Changes in baseline SCr after administration of contrast agent

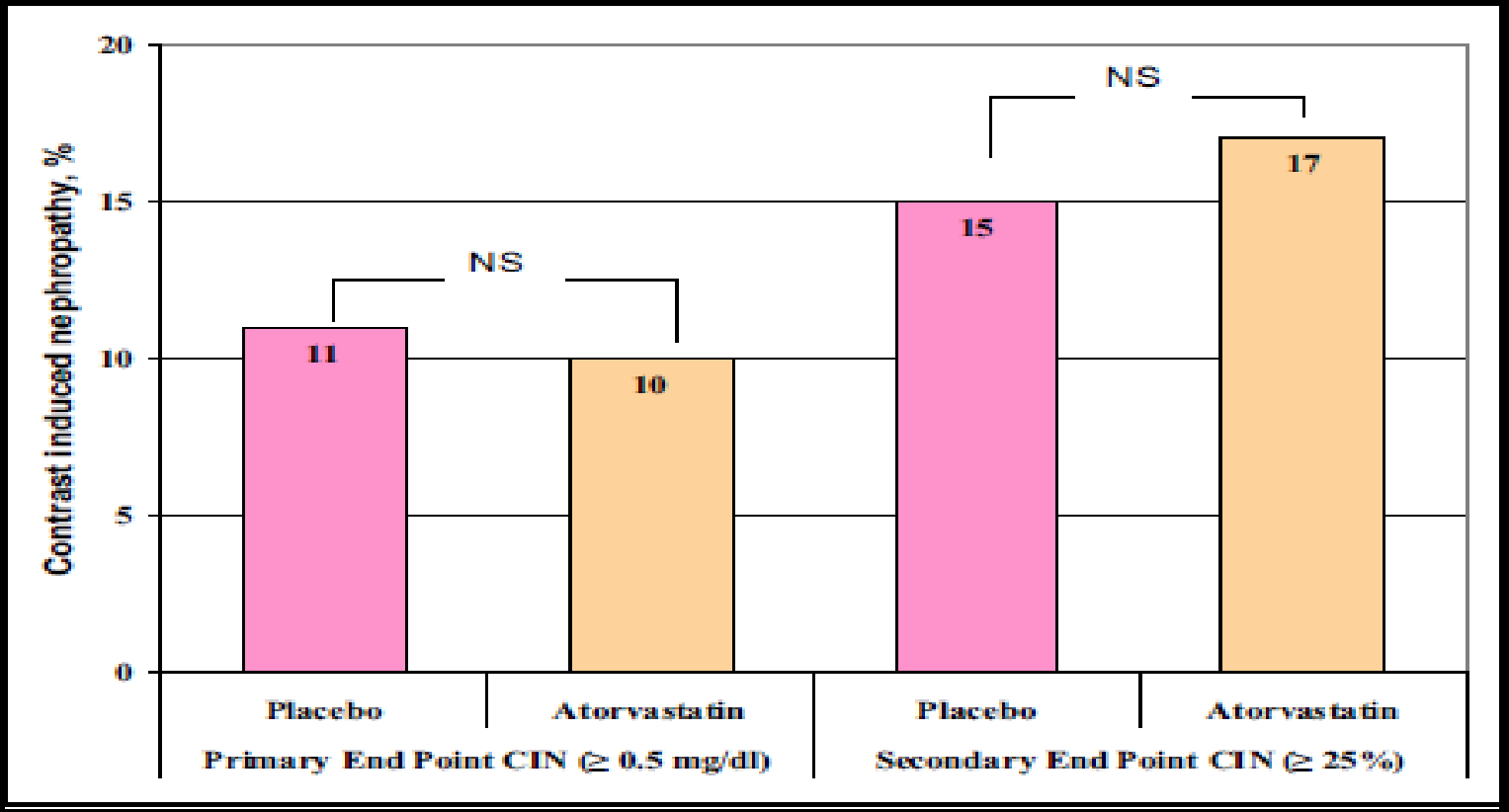
Secondary end point—incidence of CIN



Incidence of CIN. The secondary end point, the incidence of CIN defined as a ≥25% or ≥0.5 mg/dL increase in baseline SCr within 48 hours of contrast administration

Jo SH et al. Am Heart J. 2008 Mar;155(3):499.e1-8. .

But the result of previous studies have proved disappointing
[Trial with Atorvastatin 80mg]



(Left) Incidence of primary end point, i.e., absolute increase of **creatinine 0.5 mg/dl over baseline value within 5 days after administration of radiographic contrast medium.** ***(Right) Incidence of secondary end*** **point, i.e., relative increase of creatinine 25% over baseline value within 5 days after contrast agent administration.**

Toso A et al. Am J Cardiol. 2010 Feb 1;105(3):288-92.

PRATO-ACS

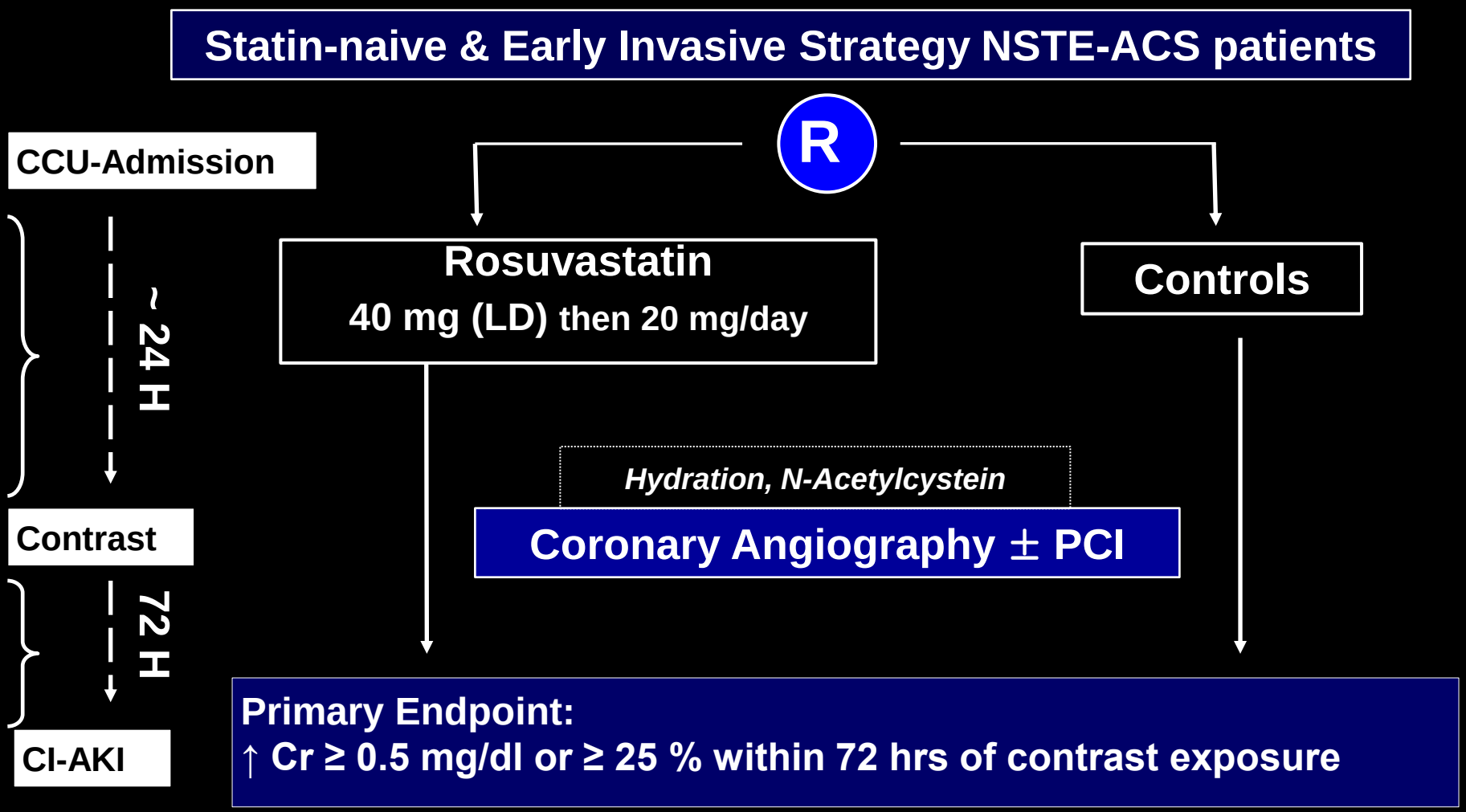
Early high-dose Rosuvastatin for Contrast-Induced Nephropathy Prevention in Acute Coronary Syndrome

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

Method – Study design

PRATO-ACS



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

Method
Additional protocol details

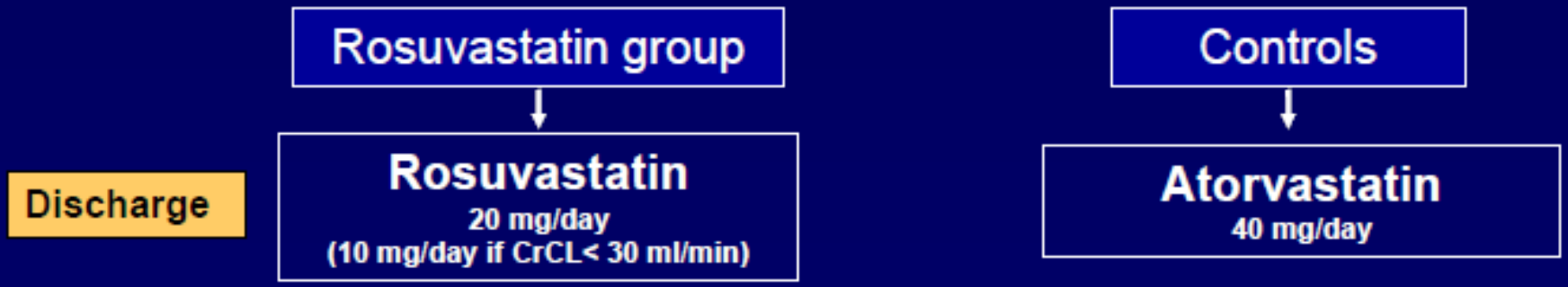
Antiplatelet treatment:

ASA (300 mg LD, 100 mg/day MD)

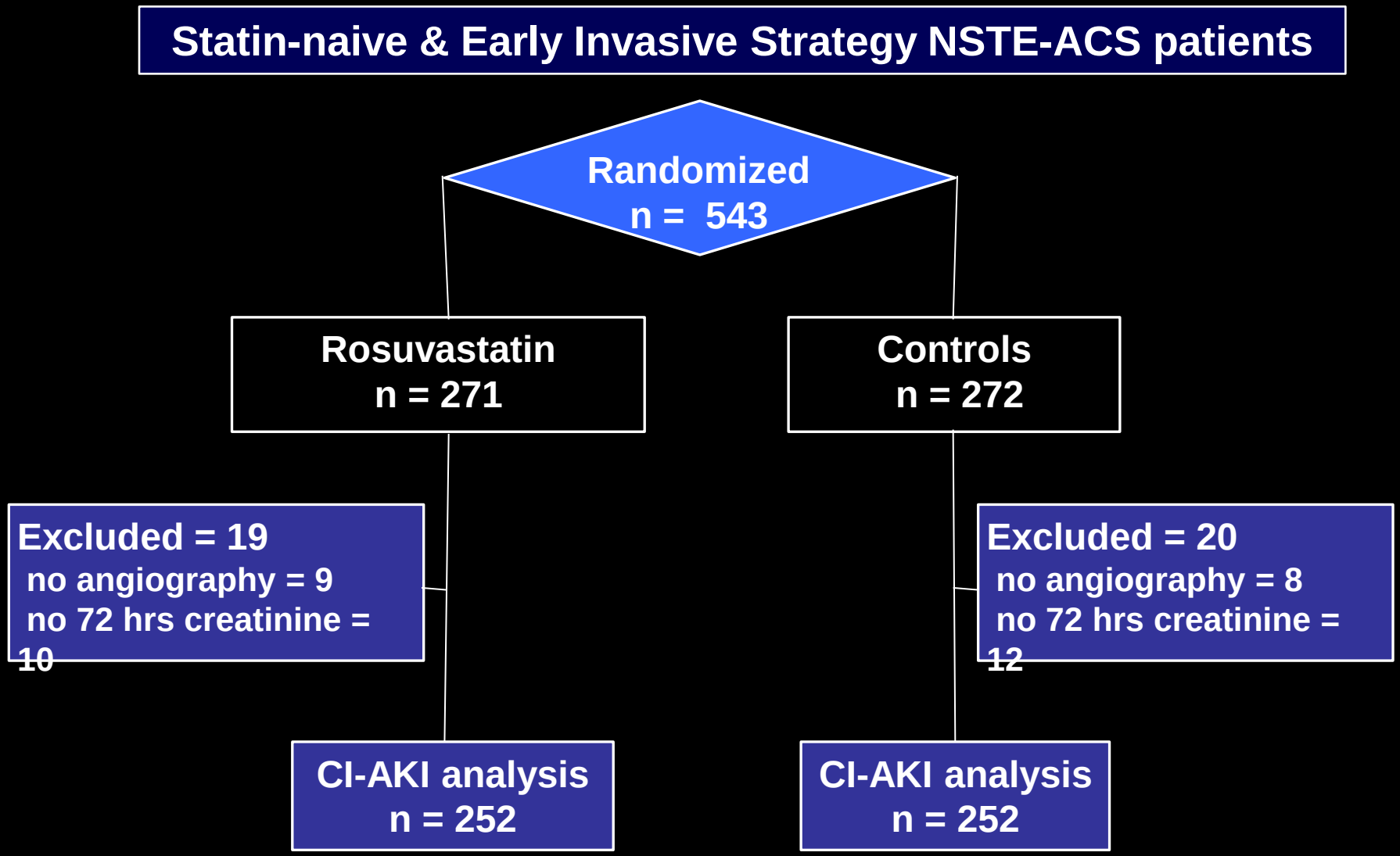
Clopidogrel (600 mg LD, 150 mg/day→ discharge)

- Hydration i.v.12 hrs pre and post contrast medium (isotonic saline 1 ml/kg/h or 0.5 ml/kg/h if LV-EF ≤ 40%)
- Oral N-Acetylcystein 24 hrs pre and post contrast medium (2400 mg/day)
- Nonionic, dimeric iso-osmolar contrast medium (Iodixanol) & Power injector (*ACIST*)

At discharge: Clopidogrel 75 mg/day, ASA 100 mg/day &



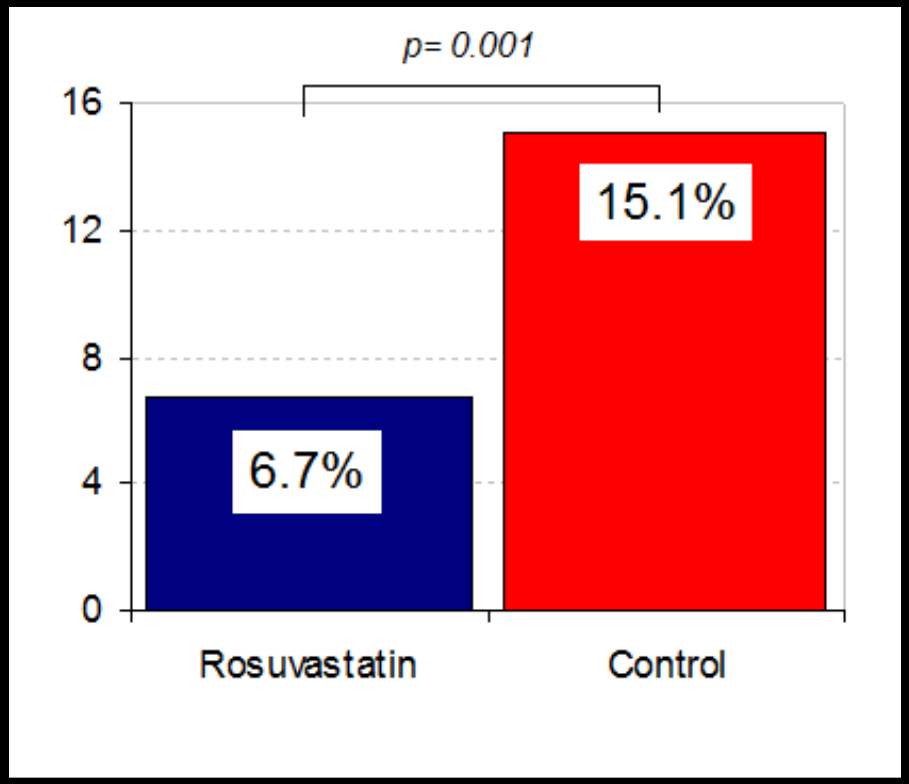
Study flow



J Am Coll Cardiol. 2013 Sep 25. pii: S0735-1097(13)05355-2. doi: 10.1016/j.jacc.2013.04.105.

CI-AKI Primary Endpoint

(ε 0.5 or ε 25% within 72 hrs)



ORcrude (95% CI):

0.41 (0.22 - 0.74)

ORadjusted (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

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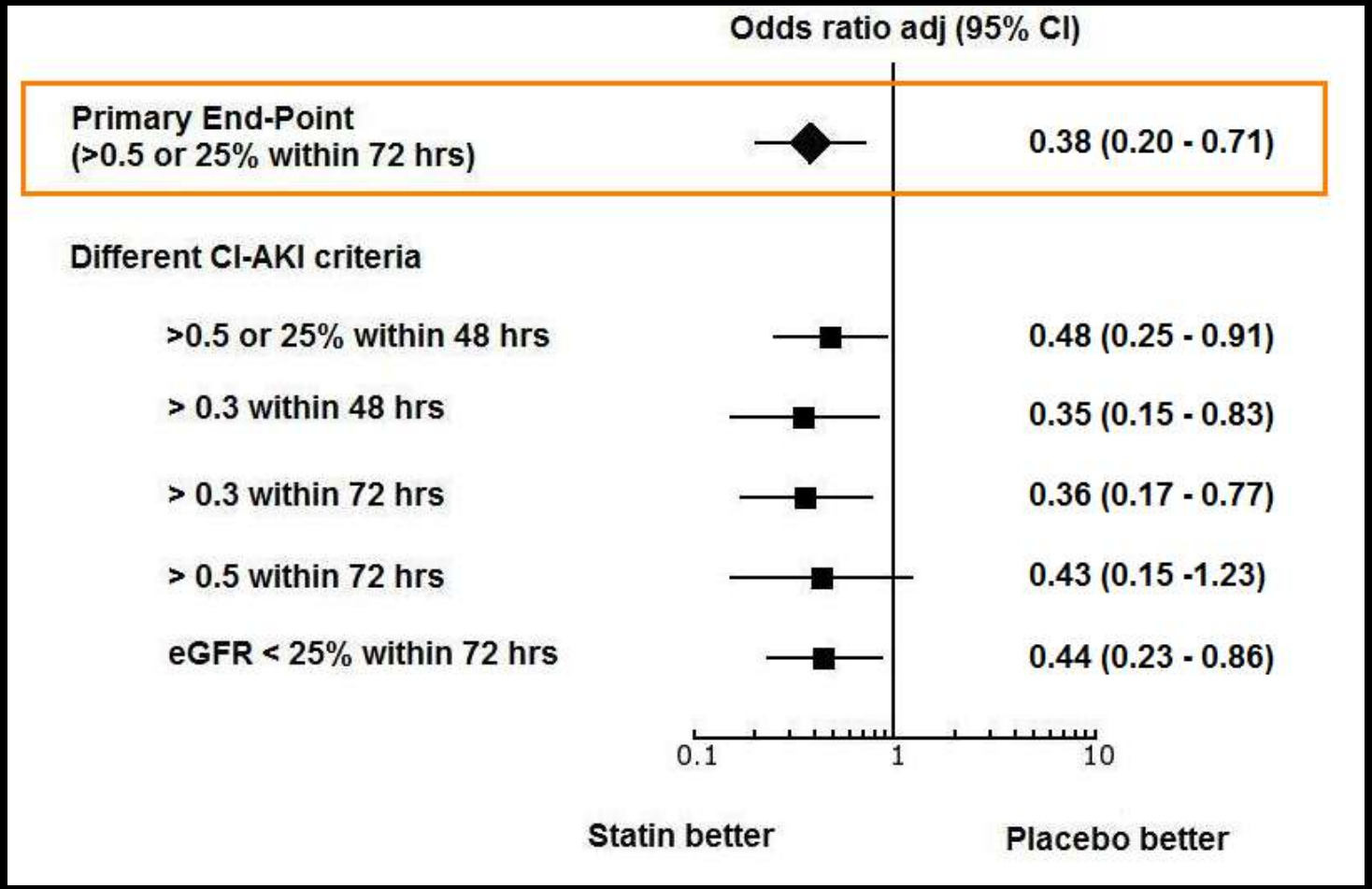
Additional Endpoints:

1.Different CI-AKI criteria



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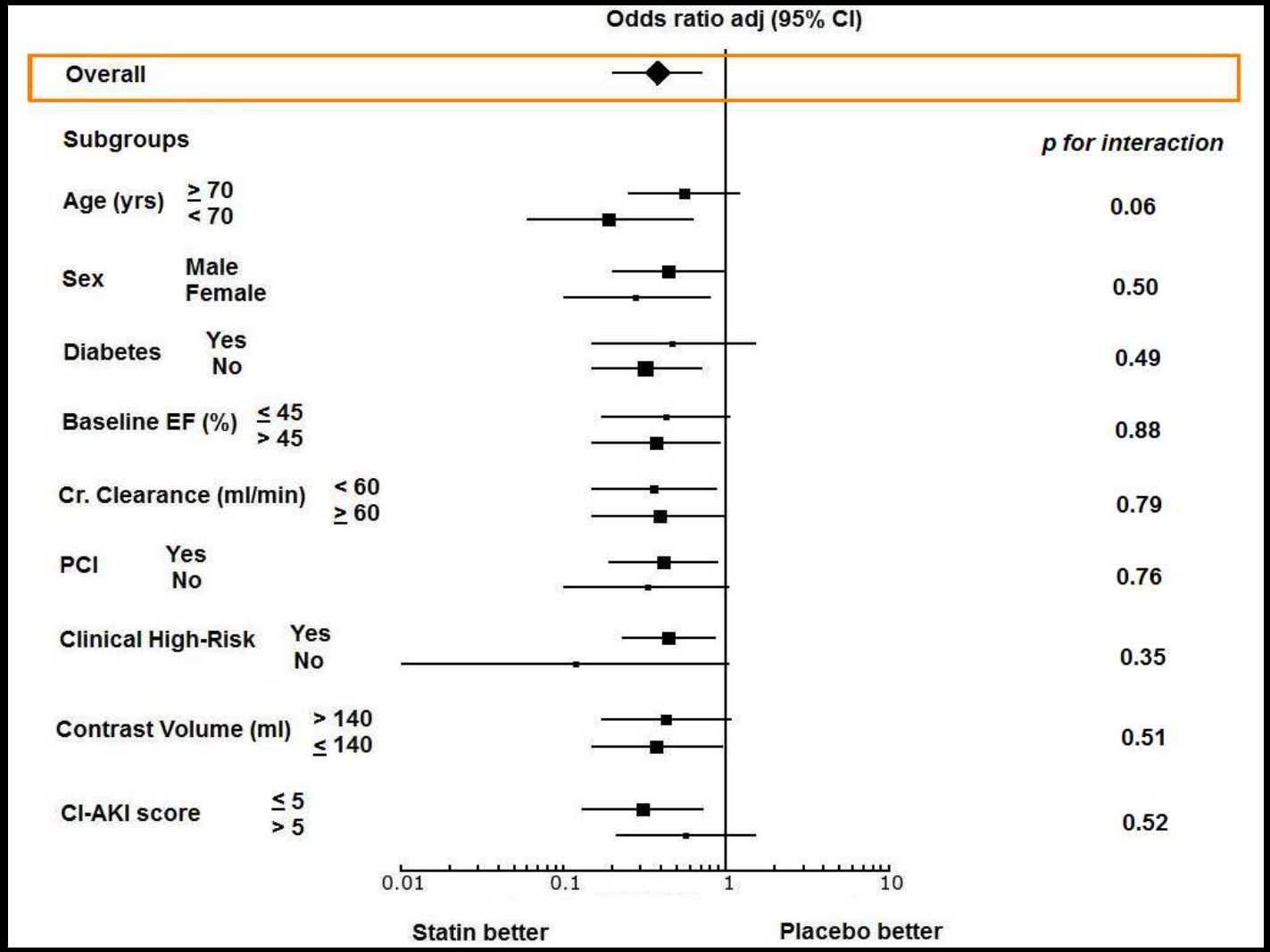
Additional Endpoints:

2.Pre-specified Subgroups

PRATO-ACS



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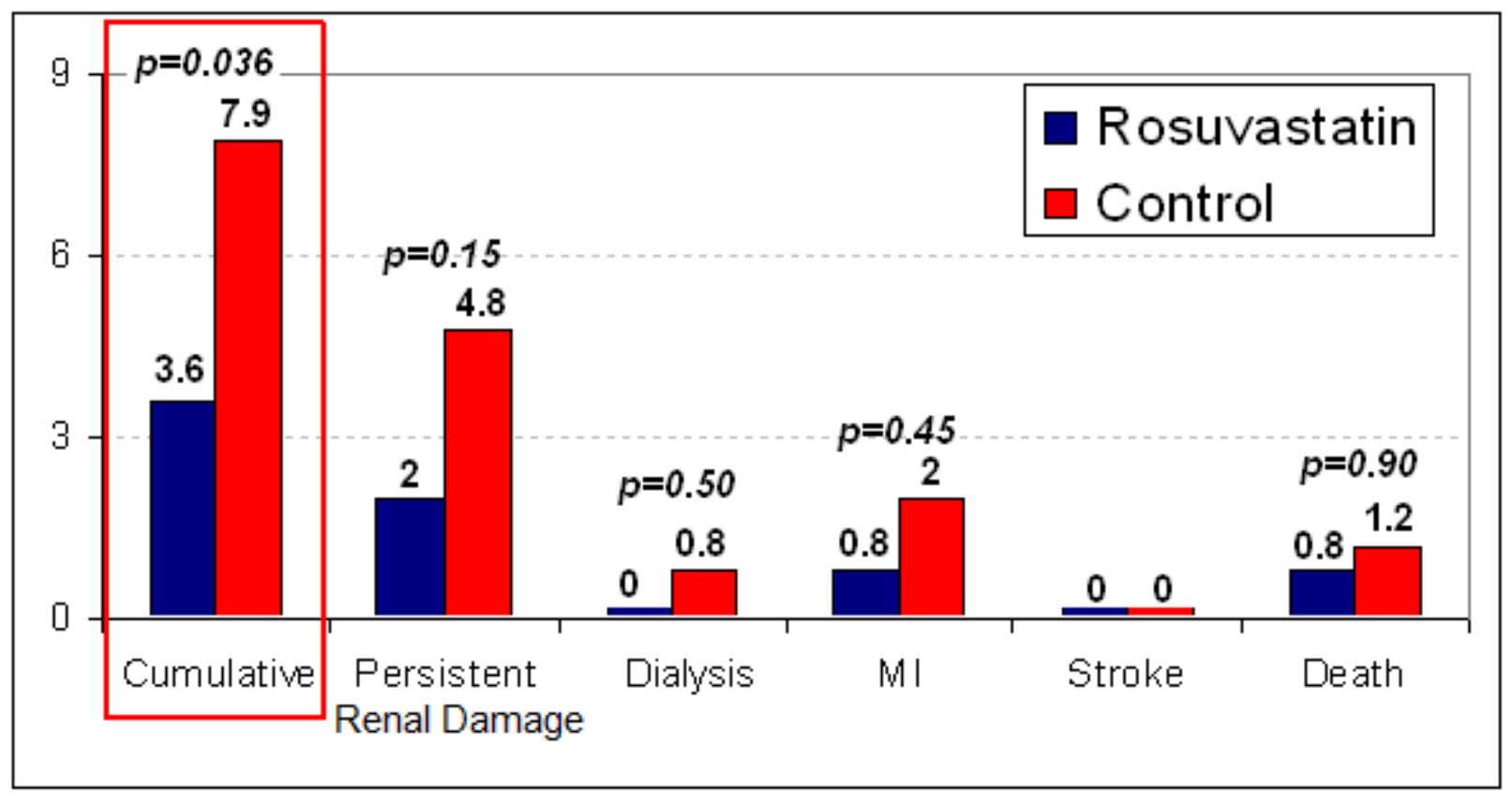
Additional Endpoints:

3. Adverse Clinical Events (30 days)

PRATO-ACS



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Short-Term Rosuvastatin(10mg) Therapy for Prevention of Contrast-Induced Acute Kidney Injury in Patients with Diabetes and Chronic Kidney Disease

J Am Coll Cardiol.2013 Sep 25. pii: S0735-1097(13)05353-9. doi:10.1016/j.jacc.2013.09.017.

Study Hypothesis

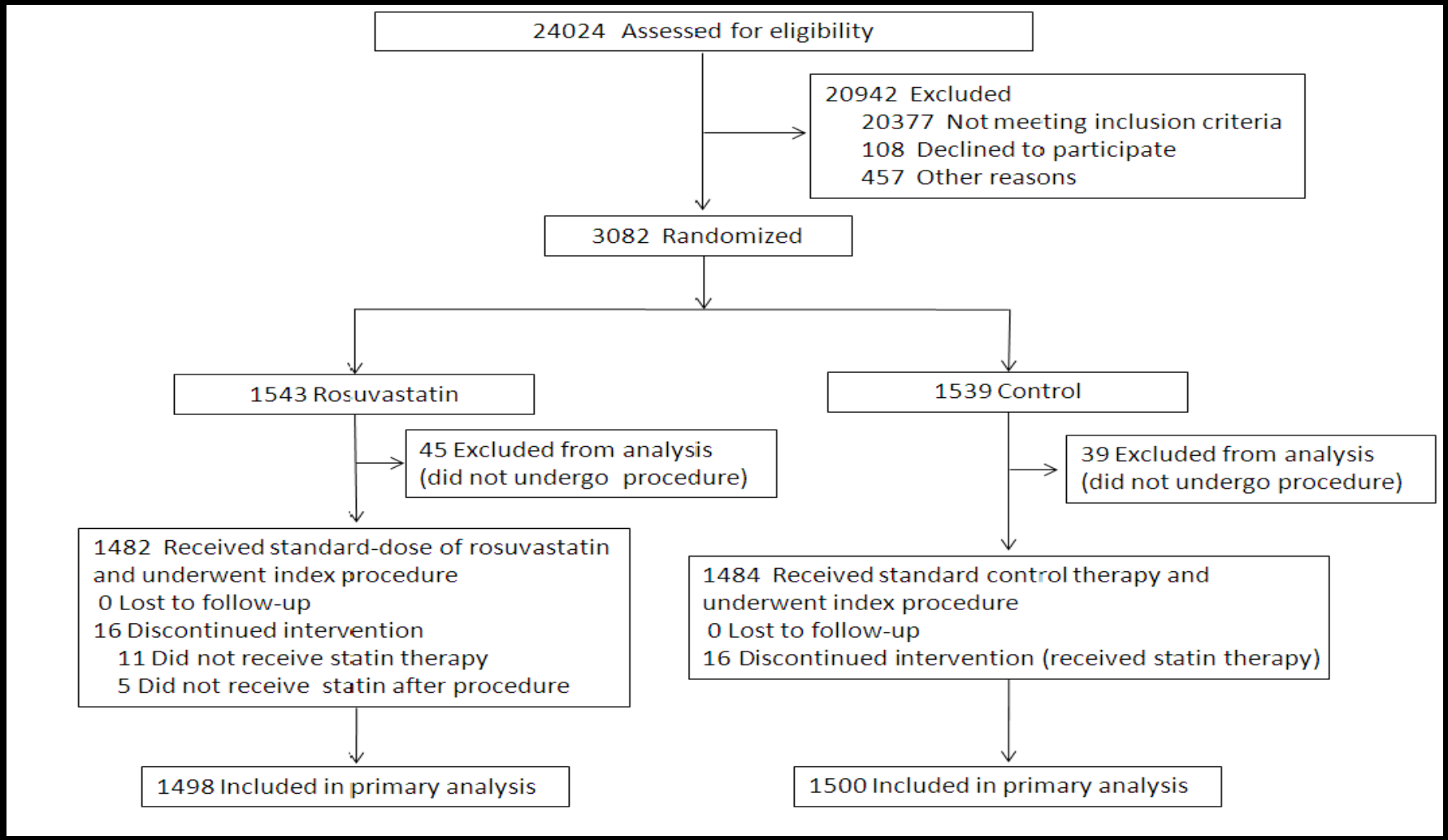
Contrast-induced acute kidney injury (CIAKI) is a major complication with adverse outcomes after contrast media injection.

Although the risk of developing CIAKI is low in patients with normal renal function, it is dramatically higher in patients with conditions such as diabetes mellitus (DM) or chronic kidney disease. Therefore, strategies to prevent CIAKI in DM patients with CKD are urgently needed.

Inflammation may contribute to the pathogenesis of CIAKI and renal protection by statin during contrast media exposure could be due to attenuation of inflammatory responses

J Am Coll Cardiol.2013 Sep 25. pii: S0735-1097(13)05353-9. doi:10.1016/j.jacc.2013.09.017.

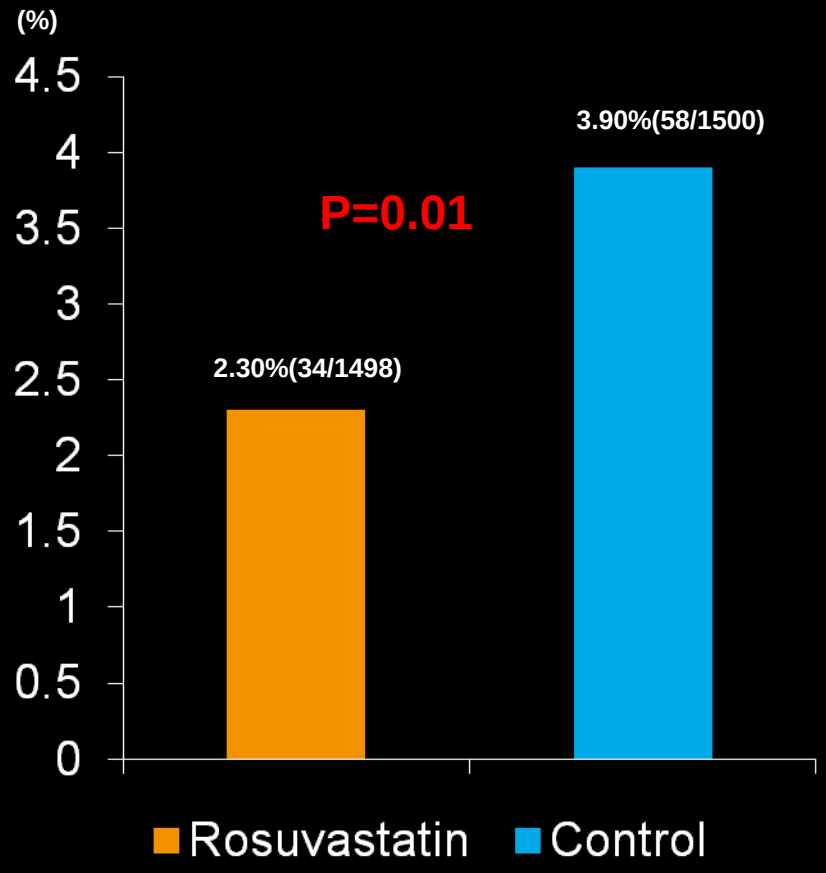
Study flow



J Am Coll Cardiol.2013 Sep 25. pii: S0735-1097(13)05353-9. doi:10.1016/j.jacc.2013.09.017.

Study result

< Primary endpoint: Occurrence of CIAKI>



< Clinical 30-day follow-up >

Variables	Rosuvastin group (n=1498)	Control group (n=1500)	P-Value
All-cause deaths, n(%)	3 (0.2)	5 (0.3)	0.73
Dialysis/ Hemofiltration n(%)	0 (0.0)	2 (0.1)	0.50
Worsening Heart failure* n(%)	39 (2.6)	64 (4.3)	0.02

*** Defined by change of NYHA classification (class change ≥1)**

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Multivariable analysis for CIAKI predictors of CIAKI

Variables	OR	95%CI	*P*-value
Rosuvastatin	0.60	(0.39, 0.94)	0.03
Male	1.09	(0.67, 1.78)	0.73
Age	0.999	(0.973, 1.026)	0.94
BMI	0.98	(0.91, 1.05)	0.57
ACS	1.86	(1.17, 2.95)	0.01
Prior myocardial infarction	0.89	(0.50, 1.58)	0.69
Diabetes history	0.92	(0.71, 1.20)	0.55
NYHA functional classification	1.61	(1.14, 2.29)	0.01
Hemoglobin	0.986	(0.972, 0.999)	0.01
eGFR (<60mL/min/1.73m^2)	1.77	(1.31, 2.40)	<0.01
Contrast agent dose	1.002	(0.999, 1.005)	0.12
Hydration	0.83	(0.53, 1.31)	0.43
ACEI/ARB	1.15	(0.63, 2.10)	0.65
Beta-blocker	0.94	(0.54, 1.61)	0.82

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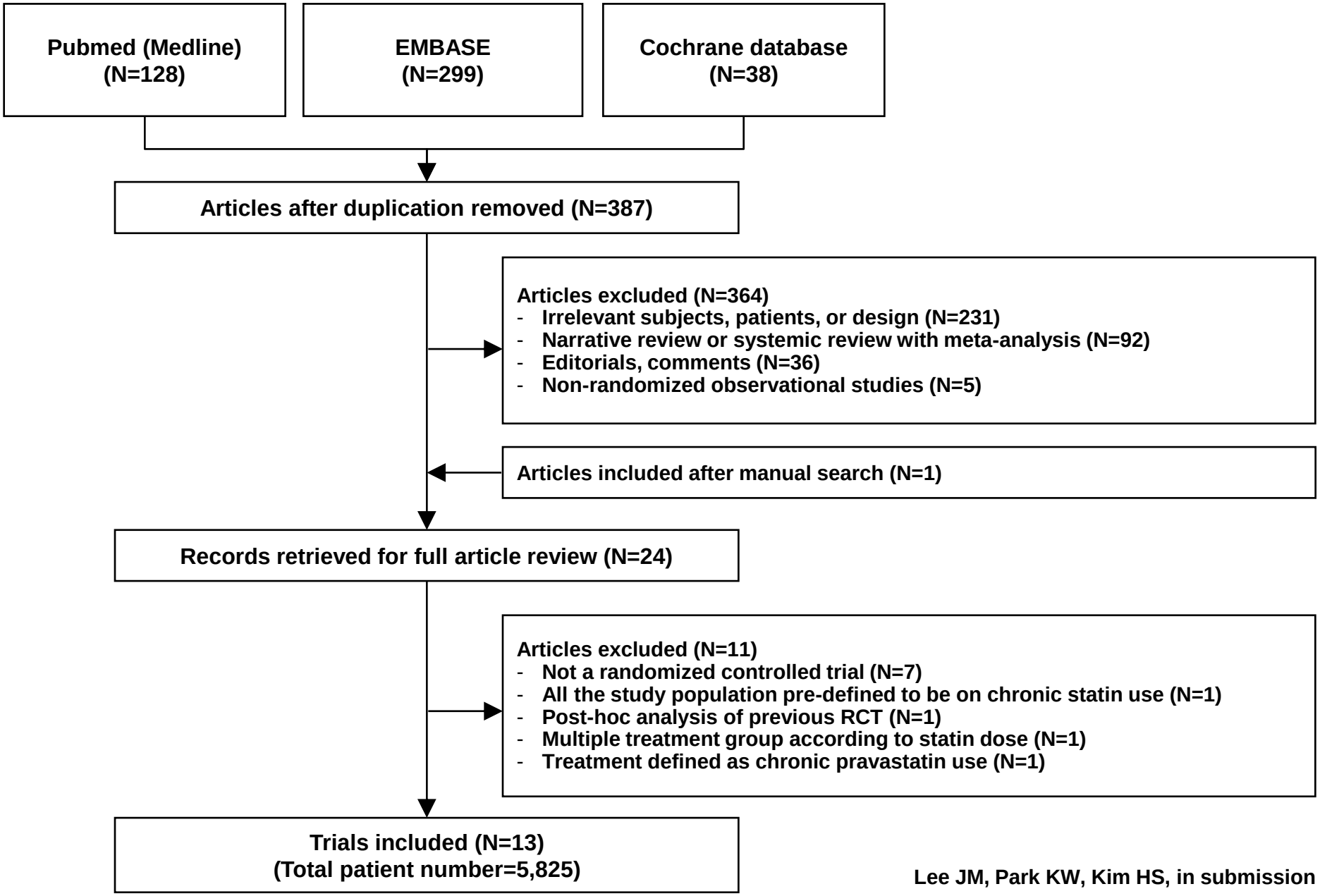
Meta-Analysis: Effect of Statin in Preventing CIAKI



Lee JM, Park KW, Kim HS, in submission

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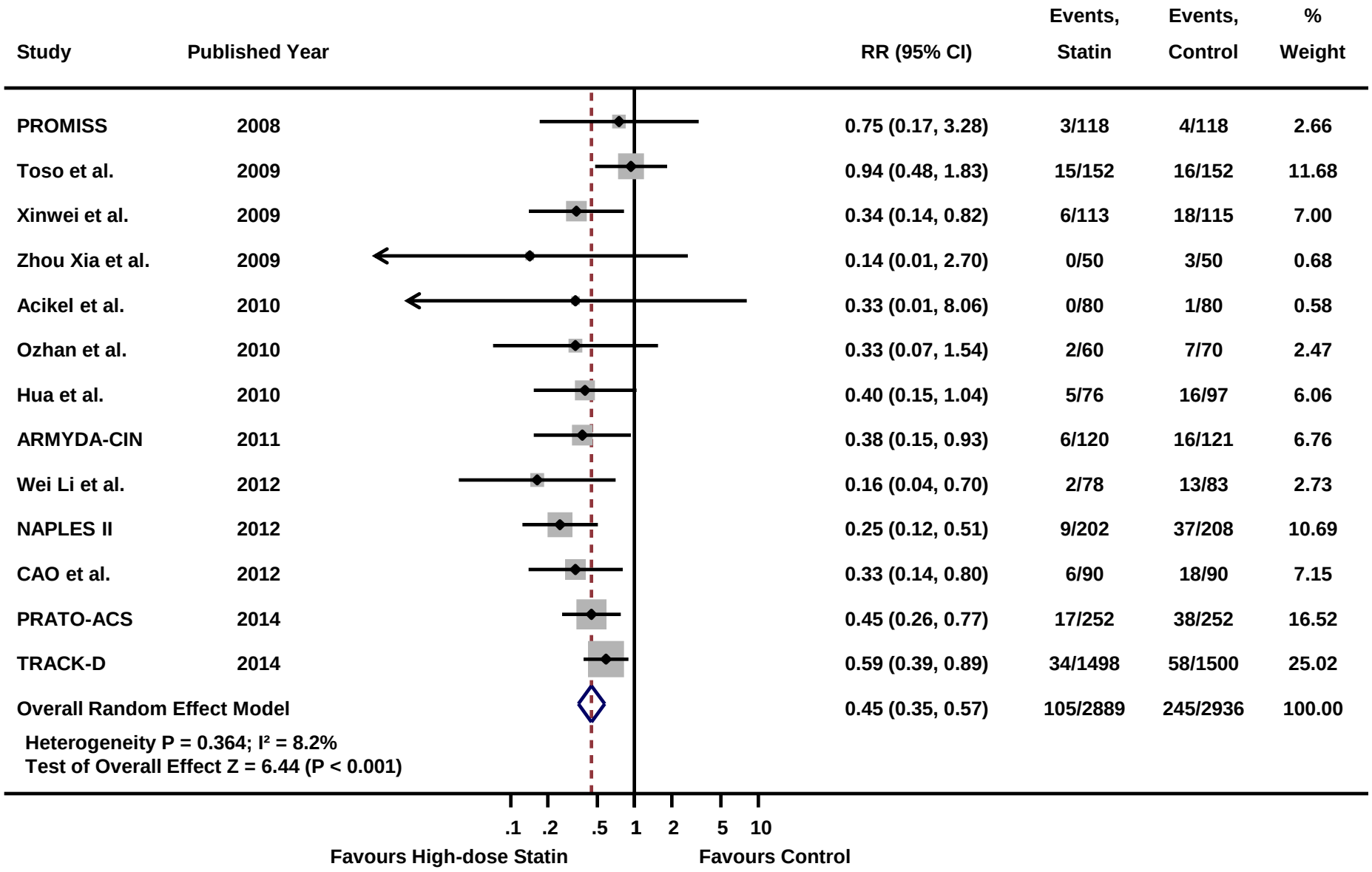

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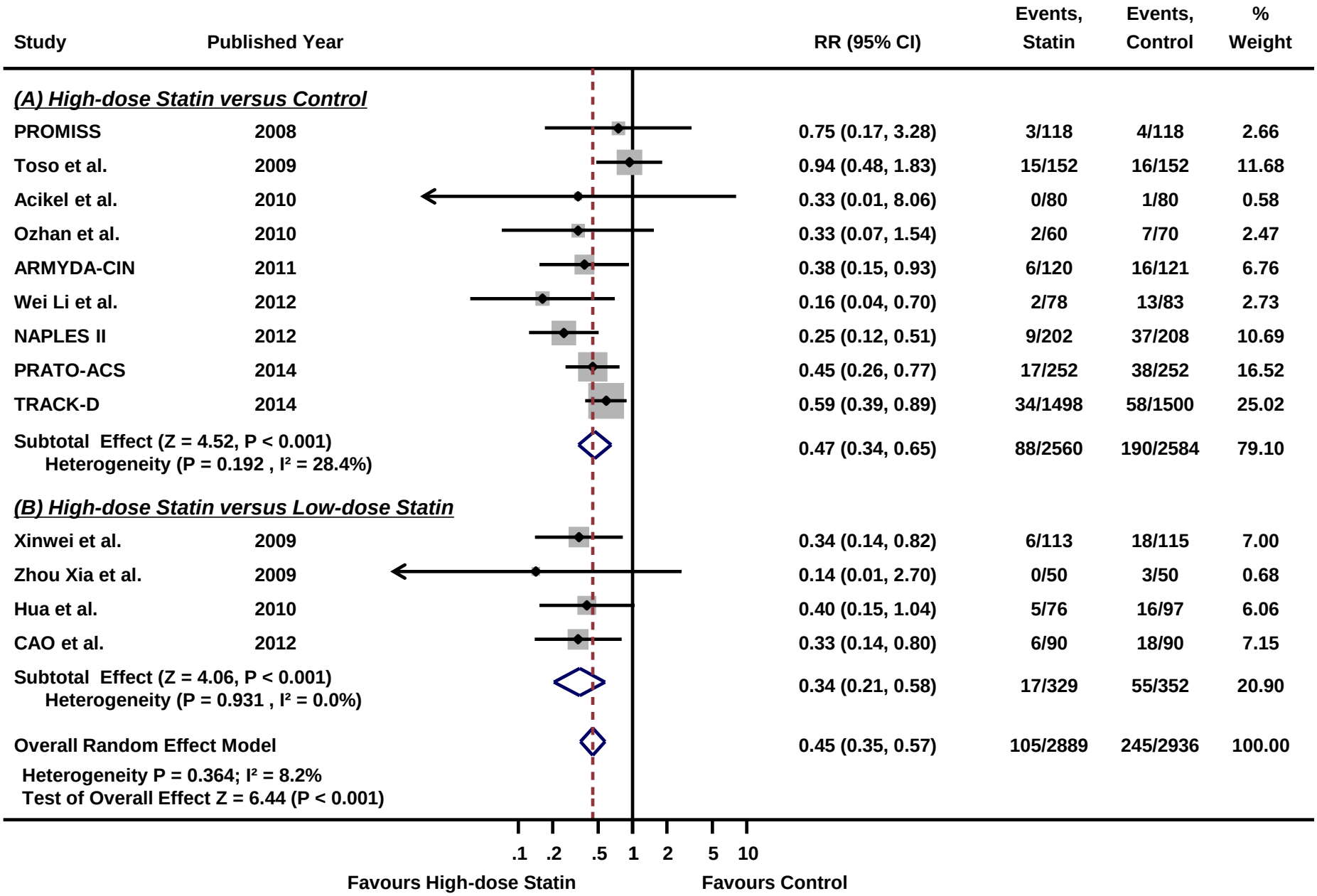

Lee JM, Park KW, Kim HS, in submission

Summary

- Early and intensive statin treatment in patients with ACS improved clinical outomes.
- High dose of Rosuvastain was the most effective among current therapies in reducing LDL-C and increasing HDL-C in ACS patients .
- Pre-treatment with a statin was associated with reduced in-hospital MACE.
- Based on the anti-inflammatory, anti-oxidant and anti-thrombotic effect, high dose of rosuvastatin loading before PCI significantly improved 12-month clinical outcomes and reduced adverse event in patients with ACS including CKI.