Early and Intensive Statin Treatment in Patients with Acute Coronary Syndromes

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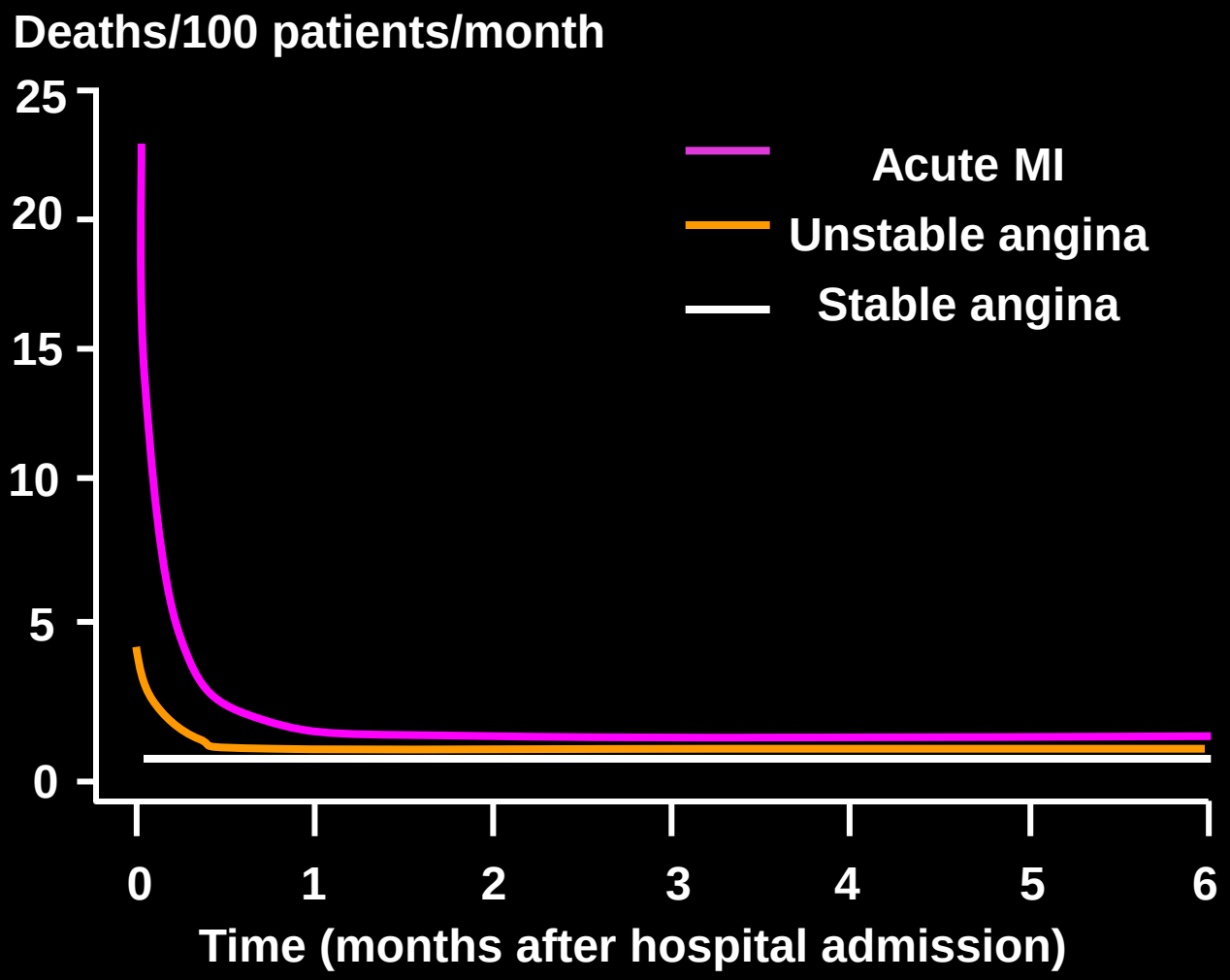
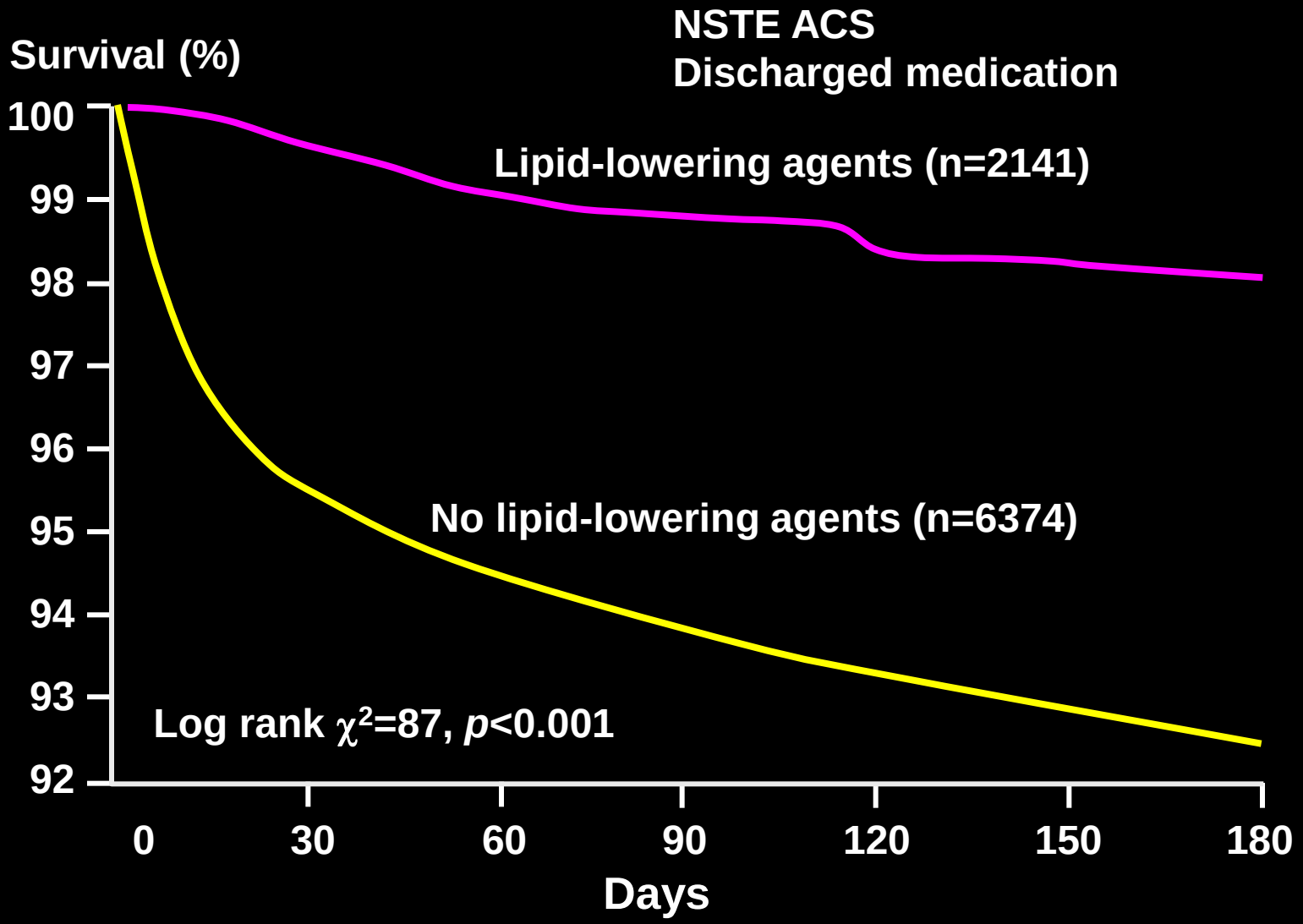
Most fatalities occur within the first 30 days after ACS



Braunwald (1996)

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



Aronow et al (2000)

Rationale of Statin therapy for ACS

Gives constant reduction in risk	most effective when absolute risk is highest
Other non-lipid-lowering effects	eg anti-inflammatory, effects on endothelial dysfunction
May stabilize plaque	maximum benefit when given early
Patient already in hospital	patient more likely to adhere to therapy
Discharged on statin therapy	underscores need for continued statins

Intensive versus moderate lipid lowering with statins

Statin started within 12 days of hospital presentation

Table III. Details of lipid reduction therapy

Trial name	Statin arm	Less intensive lipid reduction arm
L-CAD[9]	Pravastatin 40mg + cholestyramine +/− nicotinic acid (if needed to achieve LDL-C <130 mg/dL). Those already at goal at enrollment, were started on pravastatin 20mg	Usual care. Lipid reduction therapy was determined by the family physician. Only 13 patients were treated with antilipid therapy (8 patients received a statin)
PTT[10]	Pravastatin 40mg	Placebo
FLORIDA[11]	Fluvastatin 80mg (given in a divided dose)	Placebo
Colivicchi et al.[12]	Atorvastatin 80mg	The goal was for all patients to have levels of LDL-C <100 mg/dL. For those already at goal, no lipid-lowering therapy was given. For all others, atorvastatin or current therapy was used to achieve goal. At follow-up, 12 patients received atorvastatin (mean dose 18mg), 14 patients received simvastatin (mean dose 19mg), and 8 patients received pravastatin (mean dose 37mg)
PROVE-IT[13]	Atorvastatin 80mg	Pravastatin 40mg
ESTABLISH[14]	Atorvastatin 20mg	Usual care. A cholesterol absorption inhibitor was initiated for LDL-C >150 mg/dL
A-to-Z[15]	Simvastatin 80mg for the duration of trial, after 1 month of simvastatin 40mg	Simvastatin 20mg for the duration of the trial, after 4 months of placebo

LDL-C = low-density lipoprotein-cholesterol.

Am J Cardiovasc Drugs. 2007;7(2):135-41.

Intensive versus moderate lipid lowering with statins

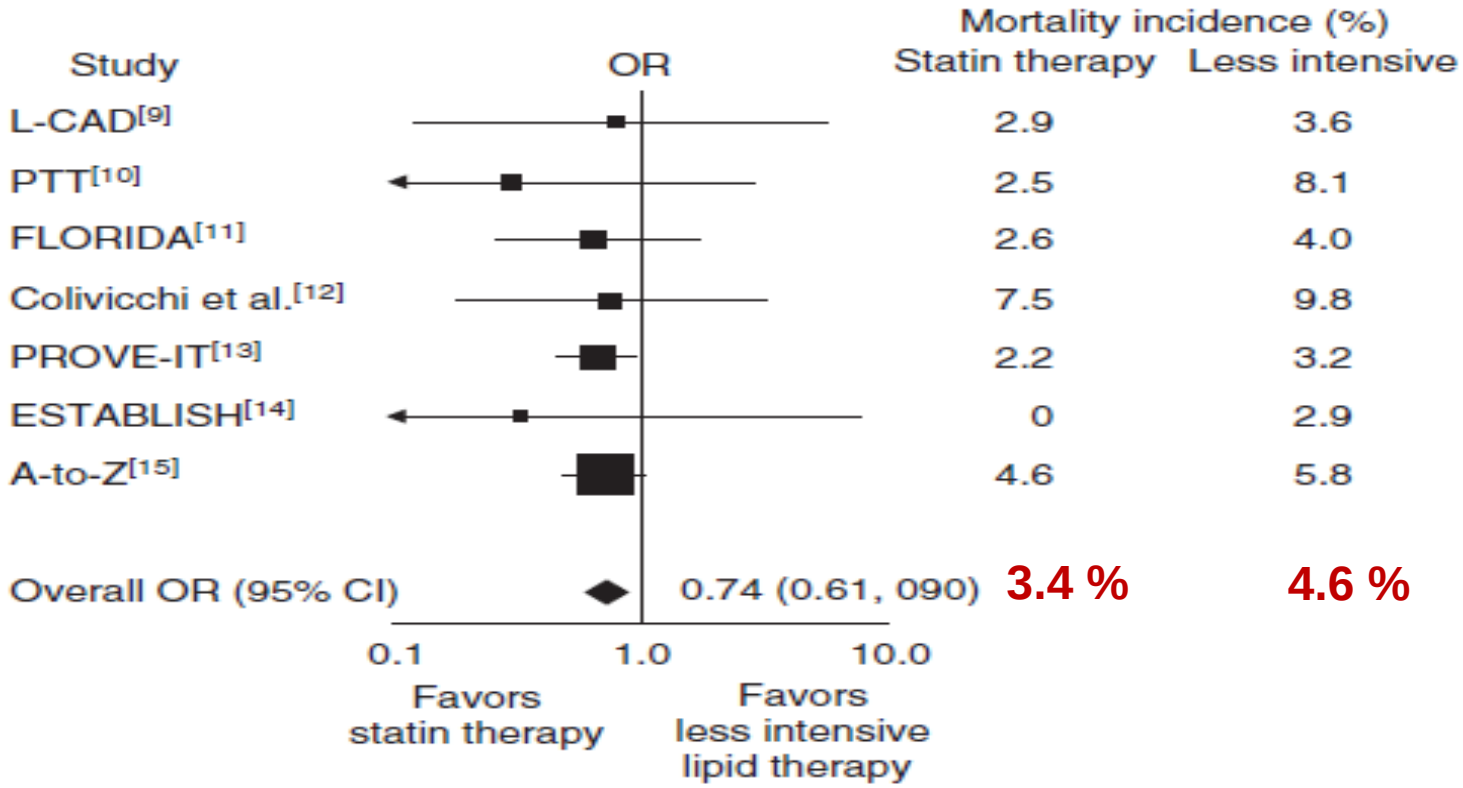
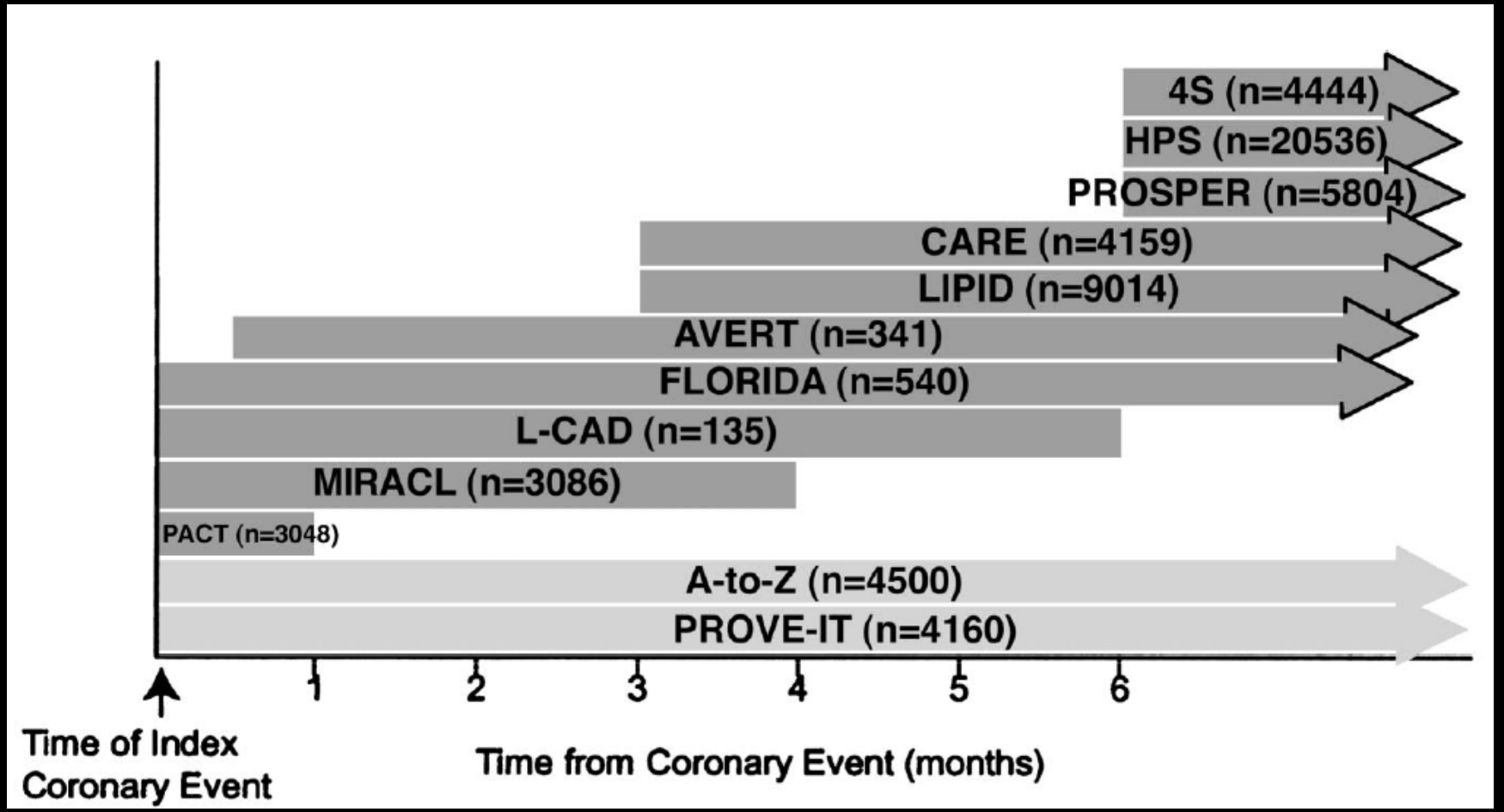


Fig. 3. Odds ratio (OR) of all-cause mortality for statin therapy compared with less intensive therapy at a mean follow-up of 23 months. The results demonstrate a long-term survival benefit from initiation of statin therapy.

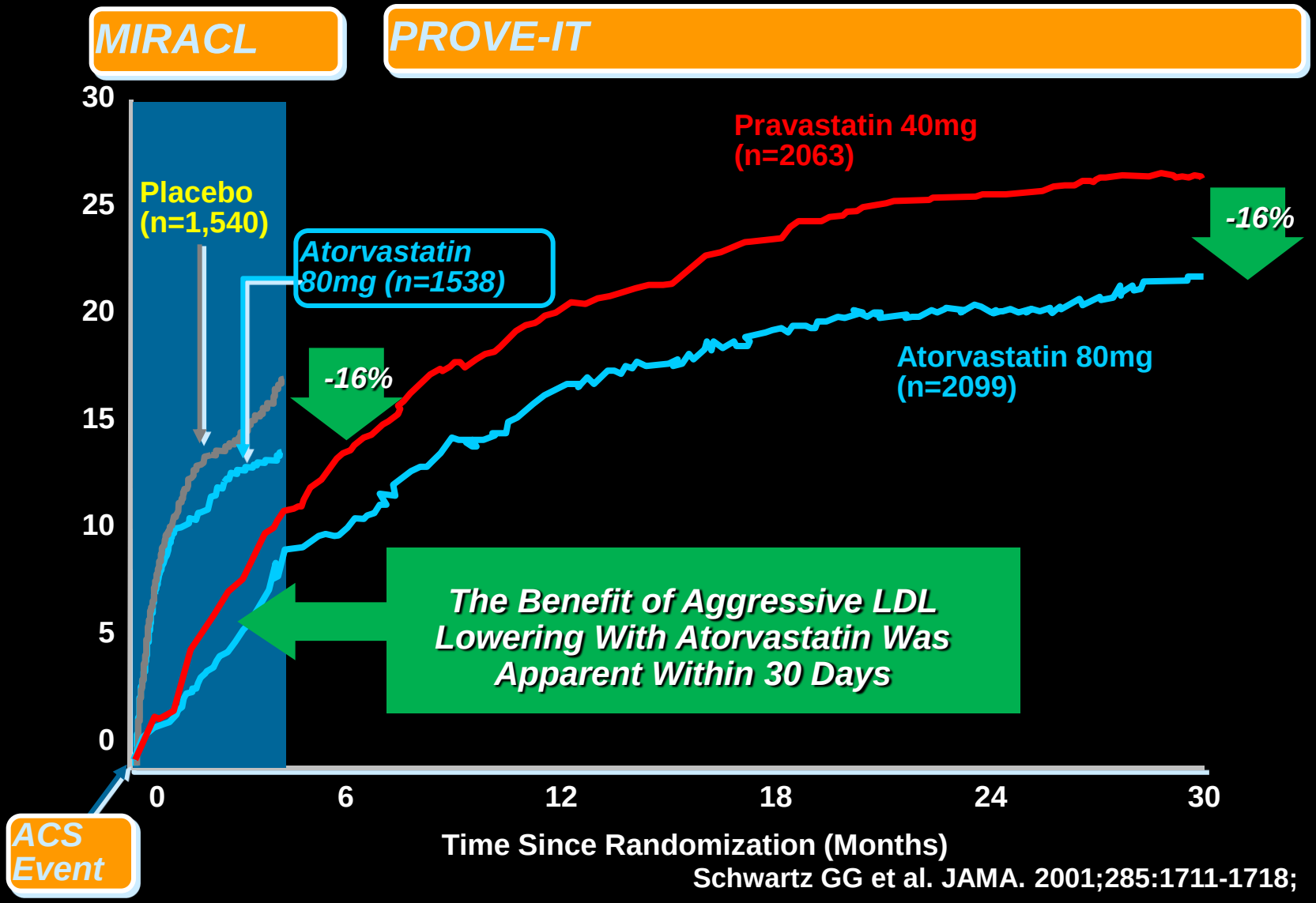
Am J Cardiovasc Drugs. 2007;7(2):135-41.

Time of initiation of statin therapy



Crit Pathways in Cardiol 2003;2:188–196

Early Benefits of High dose statin in ACS



Schwartz GG et al. JAMA. 2001;285:1711-1718;

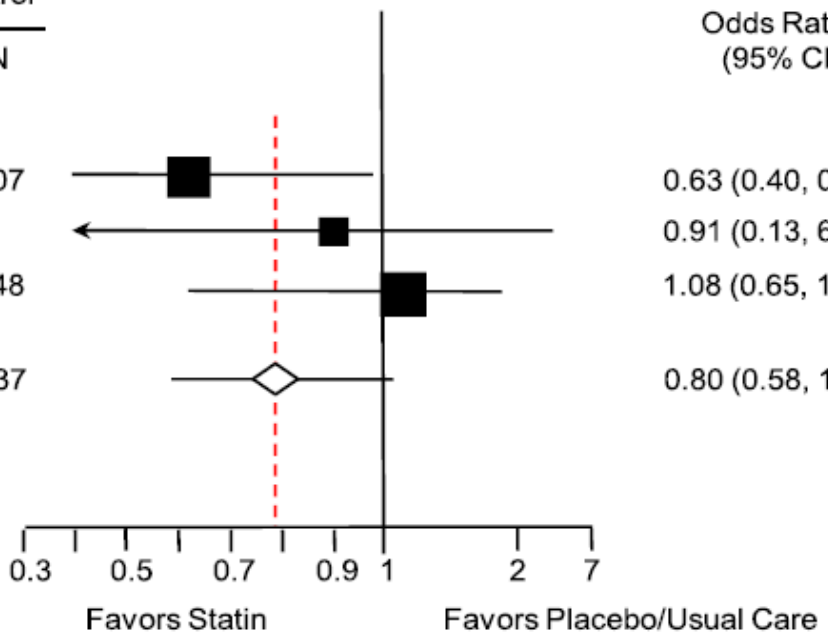
Cannon CP et al. N Engl J Med. 2004; 350:1495-1504.

Very early initiation of Statin therapy

The mortality reduction of ACS patients from 10 statin RCTs
statin therapy (n=4,030) vs control group (n=4,022)

Sub-group	Number of Trials	Statin n/N	Control n/N	Odds Ratio (95% CI)	P-value
Mean time for initiation of statin					
1 day	4	32/1911	51/1907	0.63 (0.40, 0.99)	0.045
2 days	2	2/86	2/82	0.91 (0.13, 6.37)	0.925
3 days	1	32/1538	30/1548	1.08 (0.65, 1.78)	0.778
Overall	7	66/3535	83/3537	0.80 (0.58, 1.12)	

Test of Overall Effect p=0.194
I^2 = 0%

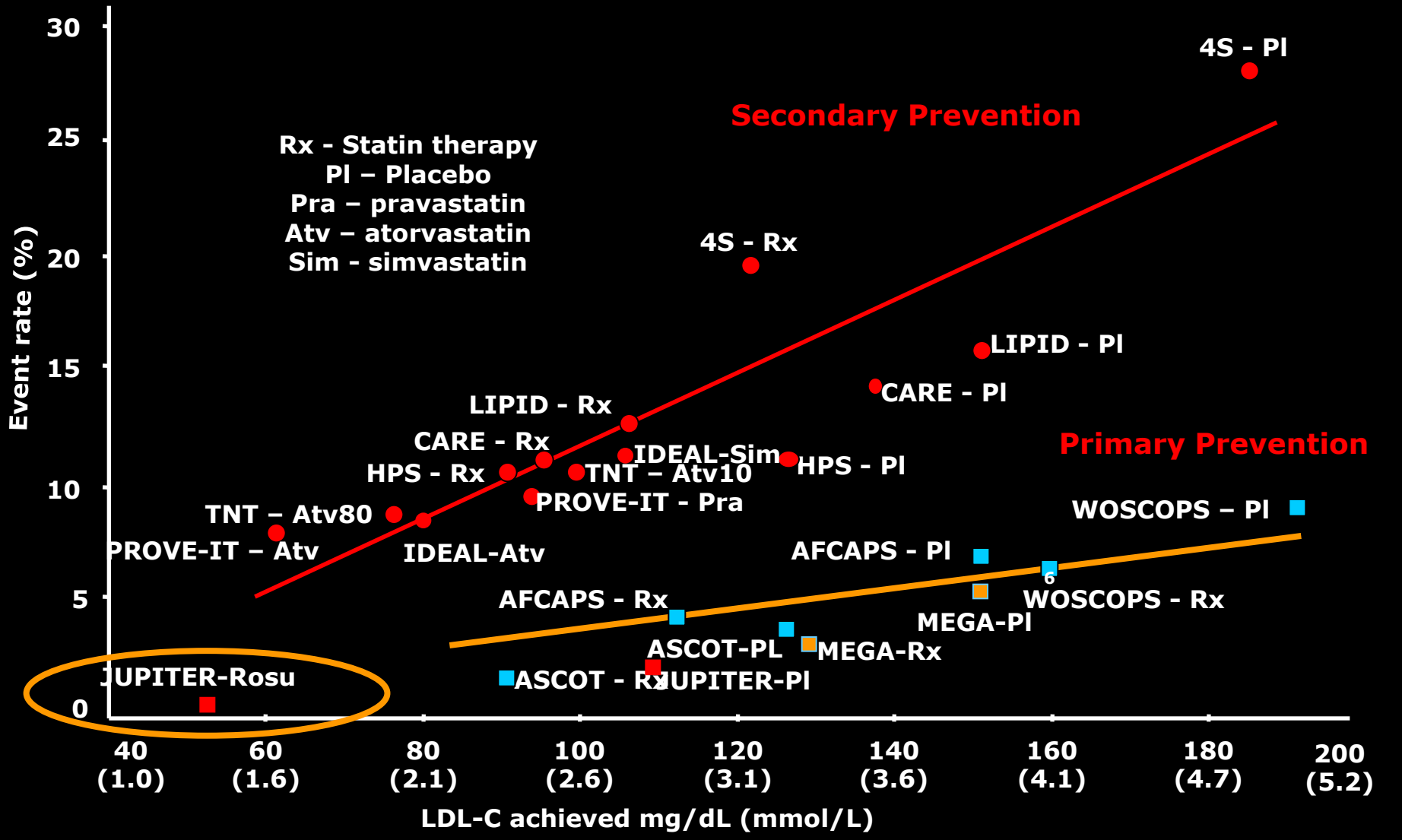


Acute Card Care. 2012 Mar;14(1):34-9.

Remaining issues

- **What about more intensive lipid lowering?**
- **How early should we start statin in patients with ACS?**

Relationship between LDL-C levels and CV event rate



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

Remaining issues

- **What about more intensive lipid lowering?**
  - **High does of rosuvastatin**
- **How early should we start statin in patients with ACS?**

Lipid-Modifying Efficacy and safety of Rosuvastatin versus Atorvastatin in ACS

LUNAR Study Design

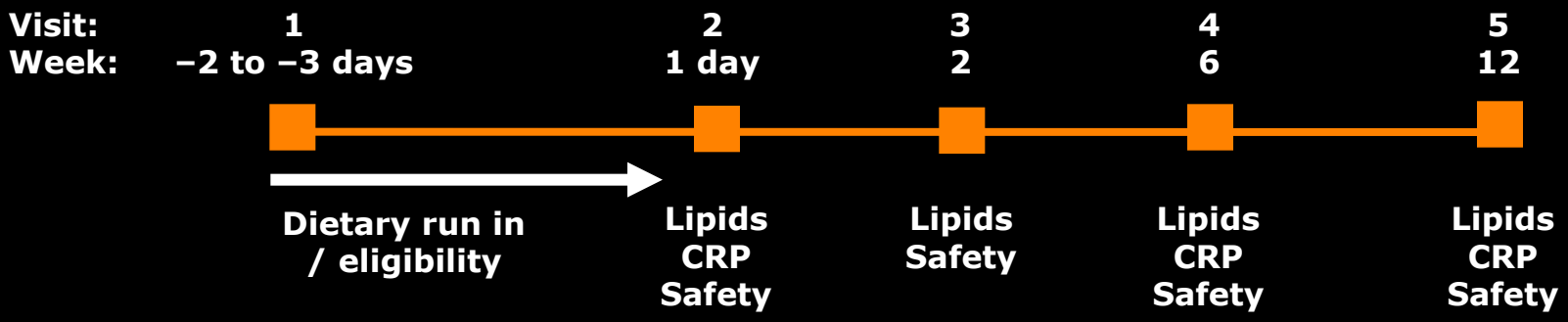
Patients (n=825), 18–75 years with:

- **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)

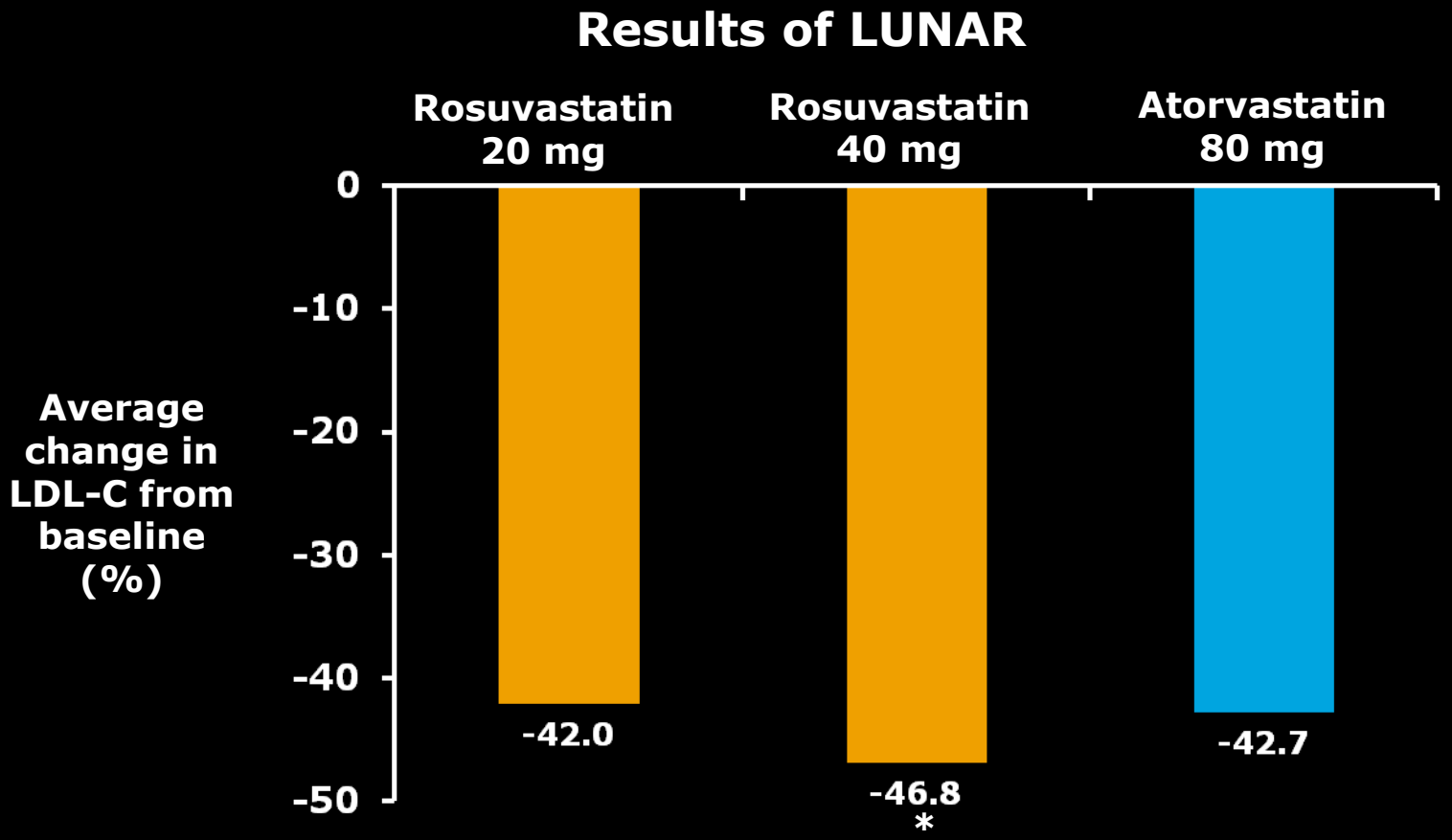
Rosuvastatin 40 mg (n=270)

Atorvastatin 80 mg (n=278)



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

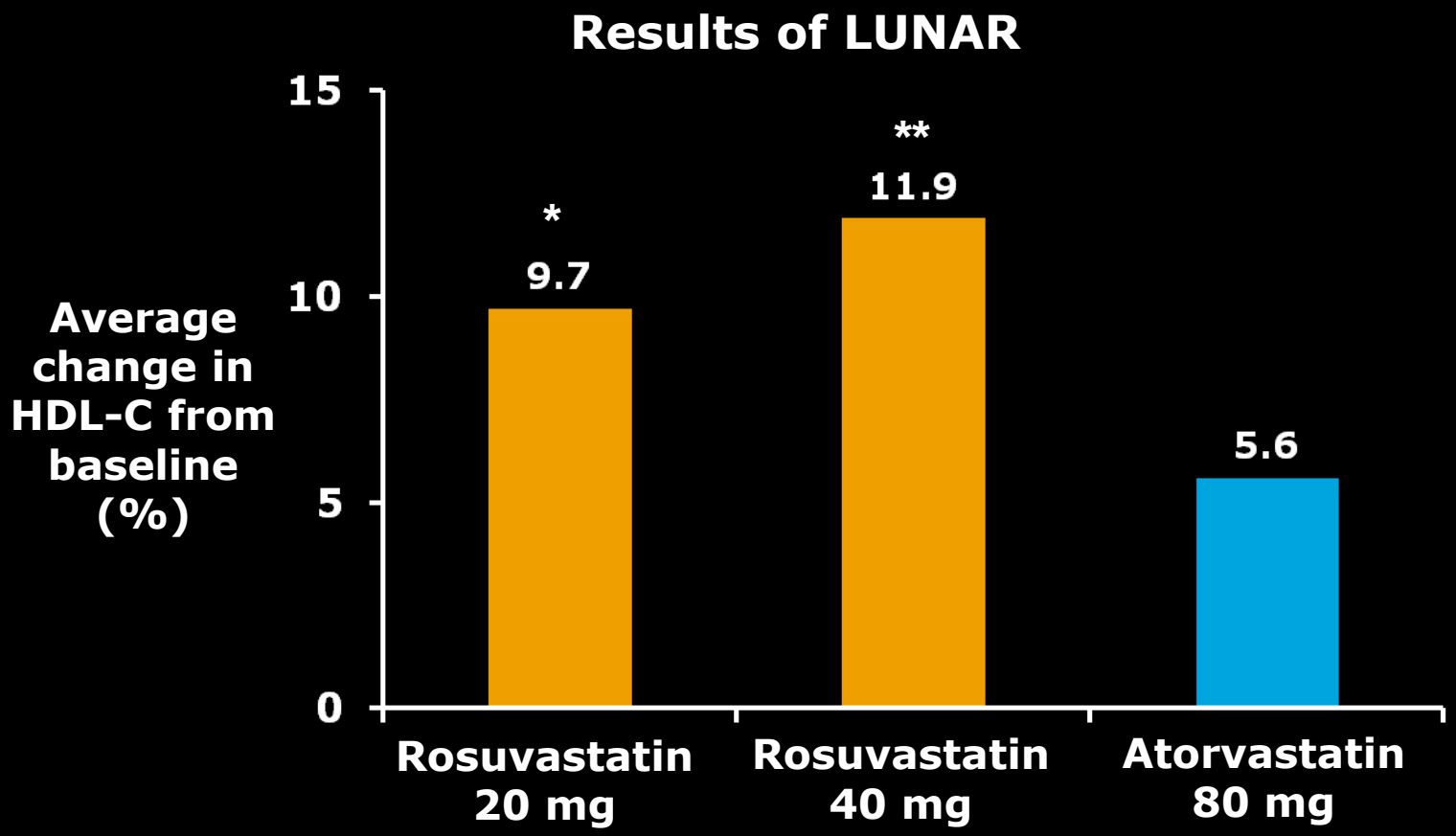
Rosuvastatin 40 mg Reduces LDL-C more than Atorvastatin 80 mg in ACS



*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

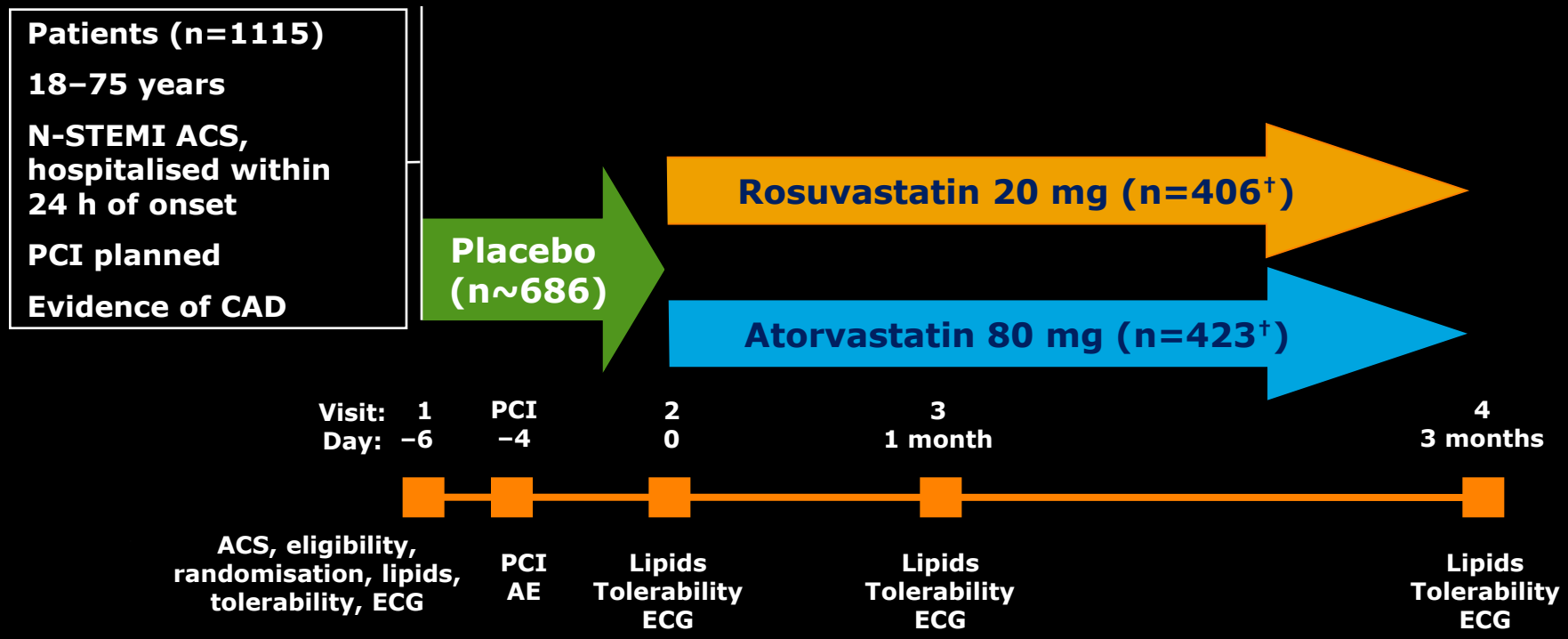
Pitt B et al. Am J Cardiol 2012; 109:1239-46

Comparison of serious adverse events between two statins

Variable	RSV20 (n = 267)	RSV40 (n = 263)	ATV80 (n = 269)
Any serious adverse event	28 (10.5%)	23 (8.7%)	38 (14.1%)
Serious cardiovascular adverse event	9 (3.4%)	5 (1.9%)	6 (2.2%)
Unstable angina	4 (1.5%)	3 (1.1%)	3 (1.1%)
Myocardial infarction	5 (1.9%)	2 (0.8%)	2 (0.7%)
Cerebrovascular accident	0	0	1 (0.4%)
Withdrawal owing to adverse event	10 (3.7%)	16 (6.1%)	25 (9.3%)
Musculoskeletal and connective tissue disorders	5 (1.9%)	6 (2.3%)	17 (6.3%)
Death	0	2 (0.8%)	1 (0.4%)

Lipid-Modifying Efficacy of Rosuvastatin versus Atorvastatin in ACS

The CENTAURUS Study



ACS=acute coronary syndrome; PCI=percutaneous coronary intervention; CAD=coronary artery disease; AE=adverse event; ECG=electrocardiogram
†n=number of patients randomized and received at least one dose of study medication

Lablanche JM. Arch Cardiovasc Dis 2010;103:160-169

Effect of Rosuvastatin and Atorvastatin on the ApoB/ApoA-I Ratio

Results From CENTAURUS

ApoB/ApoA-I Change (%)	Rosuvastatin 20 mg	Atorvastatin 80 mg	Estimated Difference Median [CI]	p
At 1 month:				
Median	−44.4	−42.9	−2.6 [−4.5, −0.0]	0.02
Mean ± SD	−43.1 ± 16.5	−40.5 ± 16.3		
At 3 months:				
Median	−44.4	−44.4	0.0 [−2.5, +1.7]	0.87
Mean ± SD	−41.2 ± 20.1	−41.7 ± 17.1		

ITT=intent-to-treat; Apo=apolipoprotein

Wilcoxon rank-sum test with Hodges-Lehman estimate of median difference between late rosuvastatin 20 mg and late atorvastatin 80 mg

Lablanche JM. Arch Cardiovasc Dis 2010;103:160-169

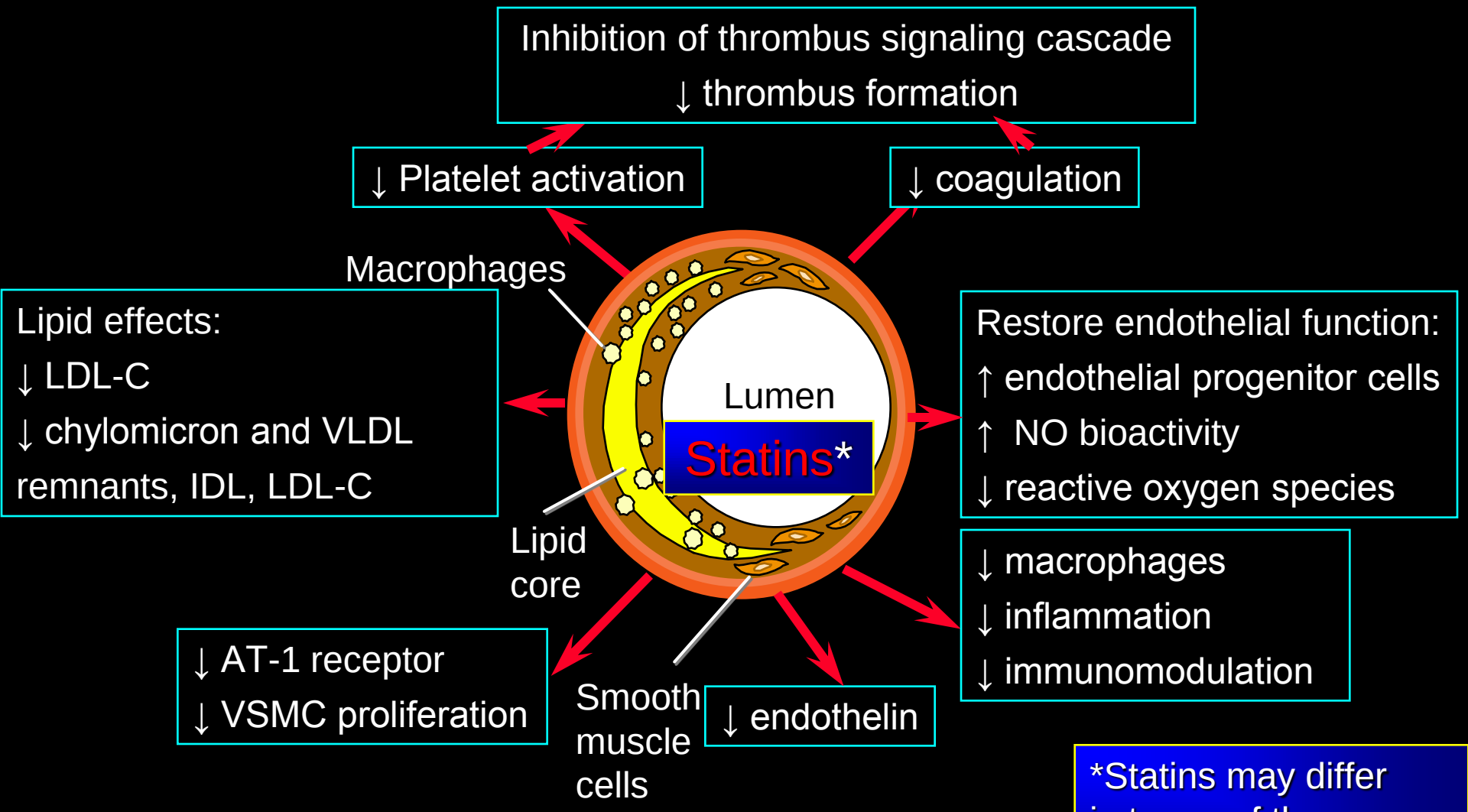
Remaining issues

- **What about more intensive lipid lowering?**
  - **High does of rosuvastatin**
- **How early should we start statin in patients with ACS?**
  - **Preloading of statin before percutaneous coronary intervention (PCI)**

Pre-medication reduces Myocardial Damages

- **PCI-related myocardial injury - The most frequent complication after PCI**
- **Can be significantly reduced and outcome improved with appropriate pharmacological treatment before PCI**
- **Medication for Anti-inflammation, Anti-thrombosis prior to PCI procedure**

Potential mechanisms of early & late benefit of statins in ACS & PCI



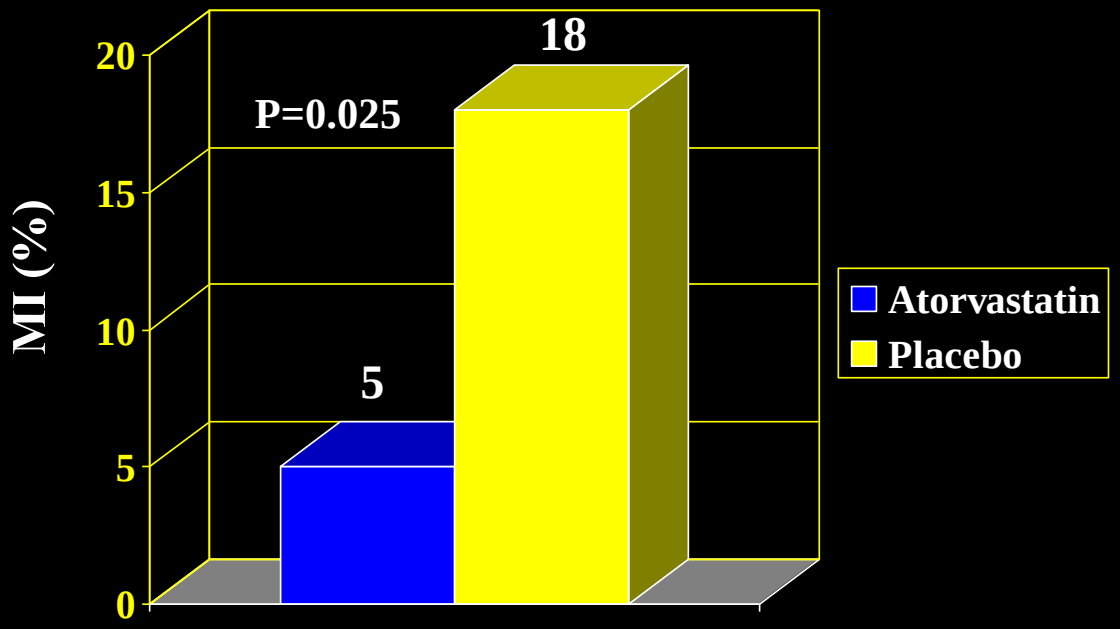
*Statins may differ in terms of these effects/mechanisms

Angeli F et al. Ther Advance Cardiovasc Therapeutics 2012 6(4) 163-174

ARMYDA

❖ The original ARMYDA trial demostrated that 7-day pretreatment with atorvastatin (40 mg/day) confers 81% risk reduction of peri-procedural MI in patients with Stable Angina undergoing elective PCI

Primary end point: Incidence of MI



Pasceri V, Patti G, Di Sciascio G, et al. Circulation 2004;110:674-678

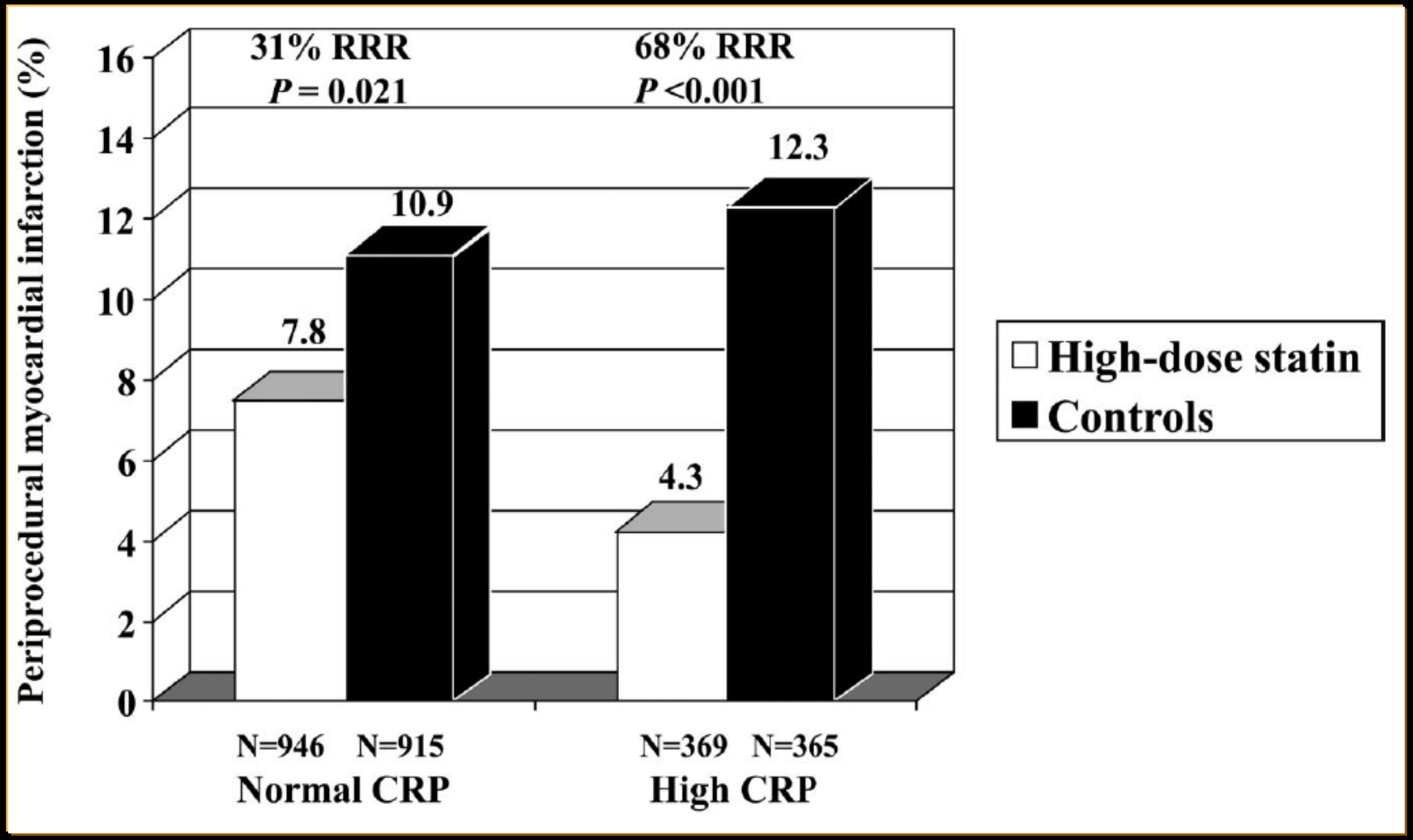
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Trials	Patients, n	Type of Population	Clinical Presentation	Type of Statin	Statin Regimen Before PCI	Statin Regimen After PCI*	Follow-Up
ARMYDA[16]	153	Statin naive	Stable angina	Atorvastatin	7-Day pretreatment with 40 mg/d vs placebo	Atorvastatin 40 mg/d	30 d
ARMYDA-ACS[18]	171	Statin naive	NSTE-ACS	Atorvastatin	80 mg 12 h before PCI+40 mg 2 h before PCI vs placebo	Atorvastatin 40 mg/d	30 d
ARMYDA-RECAPTURE[20]	383	Statin-treated	53% Stable angina; 47% NSTE-ACS	Atorvastatin	80 mg 12 h before PCI+40 mg 2 h before PCI vs placebo	Atorvastatin 40 mg/d	30 d
Briguori et al[17]	451	Statin naive	92% Stable angina/asymptomatic; 8% unstable angina	39% Simvastatin; 29% atorvastatin; 29% pravastatin; 3% fluvastatin	≥3-Day pretreatment (average 17 days) vs no statin pretreatment	The same statin as before PCI in the statin group and atorvastatin 20 mg/d in the control group	30 d
NAPLES II[21]	668	Statin naive	98% Stable angina/asymptomatic; 2% unstable angina	Atorvastatin	80 mg <24 h before PCI vs no-statin pretreatment	Atorvastatin 20 mg/d	30 d
STATIN STEMI[23]	171	Statin naive	STEMI	Atorvastatin	80 mg in the emergency room vs 10 mg	Atorvastatin 10 mg/d	30 d
Veselka et al[22]	200	Statin naive	Stable angina	Atorvastatin	2-Day pretreatment with 80 mg/d vs no statin pretreatment	NA	In-hospital
Yun et al[19]	445	Statin naive	NSTE-ACS	Rosuvastatin	40 mg 16 h before PCI vs no statin pretreatment	Rosuvastatin 10 to 40 mg/d	30 d
Bozbas et al[24]	93	Statin naive	Stable angina	Pravastatin	7-Day pretreatment with 10 mg/d vs 40 mg/d vs no statin pretreatment	Pravastatin 10 to 40 mg/d	In-hospital
Kinoshita et al[25]	42	Statin naive	Stable angina	Atorvastatin	5-20 mg/d ≥2 wk before PCI to reach LDL-C <70 vs <100 mg/dL	A to rvastatin 5 to 20 mg/d	6 mo
Jia et al[26]	228	Statin naive	29% STEMI; 71% NSTE-ACS	Simvastatin	7-Day pretreatment with 80 mg vs 20 mg	Simvastatin 20 mg/d	In-hospital
Hara et al[27]	37	Statin naive or statin treated	NSTE-ACS	Atorvastatin	20 mg 24 h before PCI vs no statin pretreatment	Atorvastatin 20 mg/d	30 d
Cay et al[28]	299	Statin naive	Stable angina	Rosuvastatin	40 mg 24 h before PCI vs no statin pretreatment	Rosuvastatin 10 to 40 mg/d	In-hospital

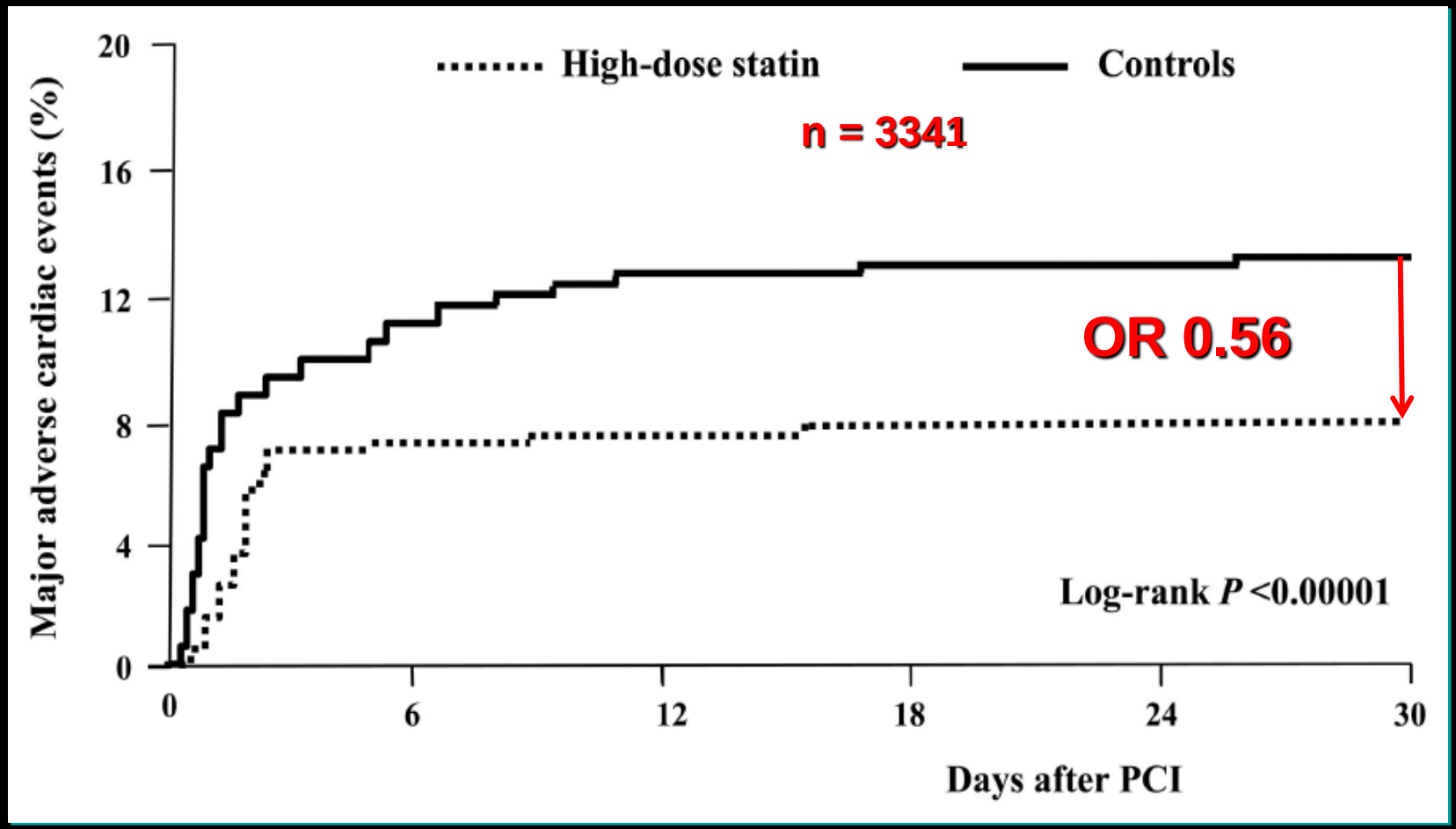
13 RCT's
3,341 patients

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



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

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



MACE : Death, MI, TVR

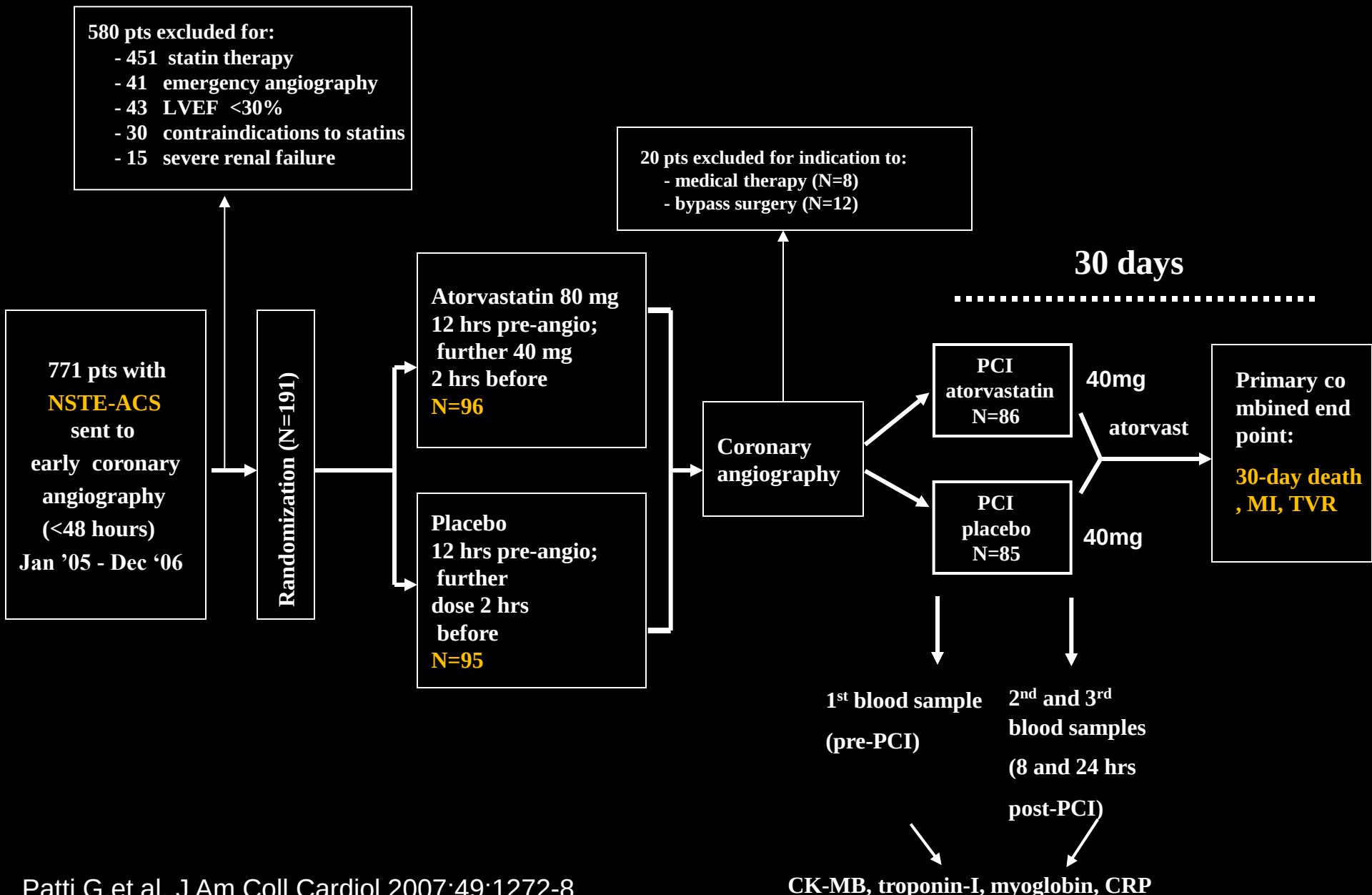
Patti et al. Circulation 2011;123:1622-32

Statin treatment and ACS patient outcome?

→ Statin loading before PCI

- High dose Statin and Caucasian patients
  - ARMYDA-ACS : Atorvastatin 80/40mg
- High dose Statin and Korean patients

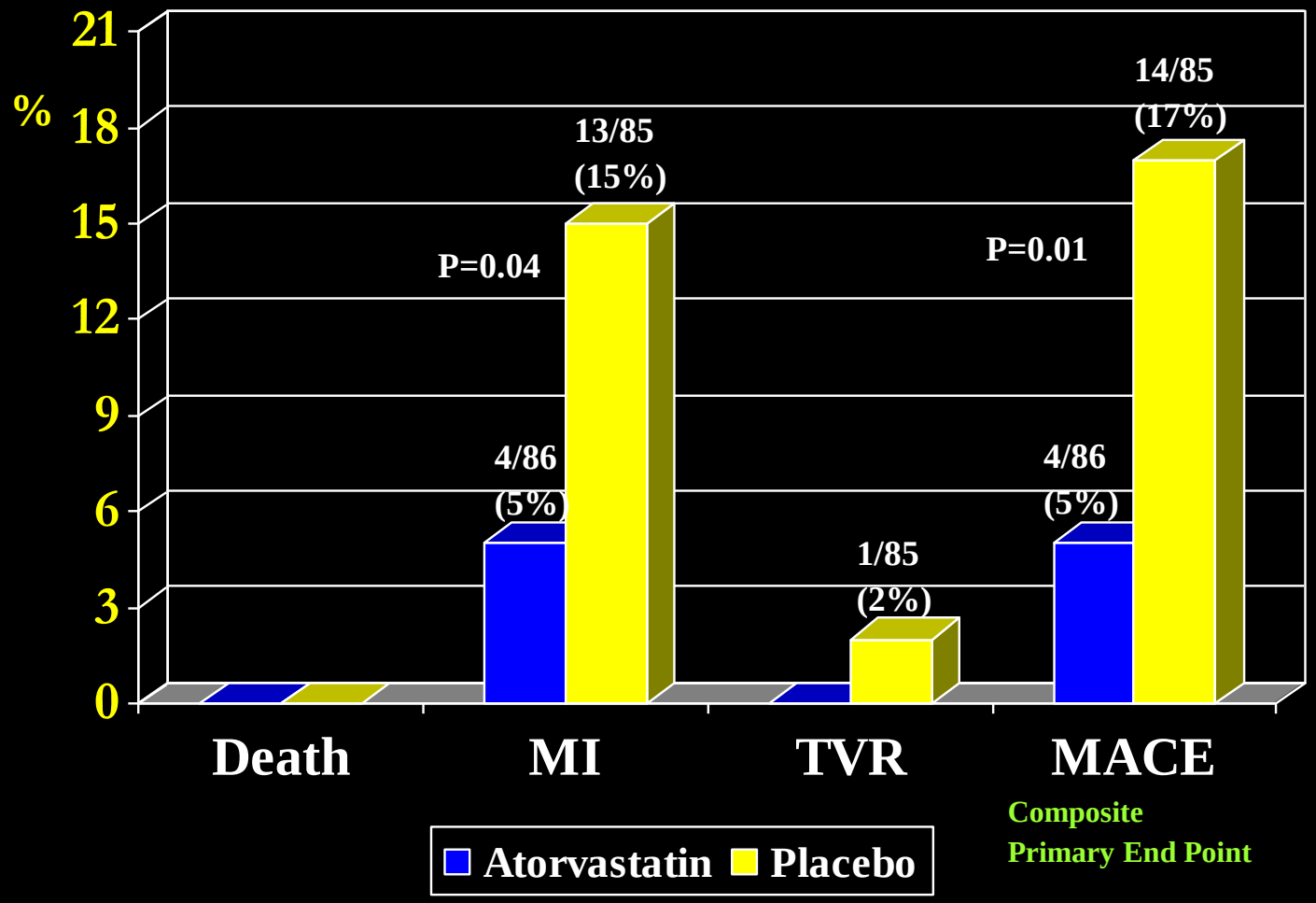
ARMYDA-ACS trial: Study design



Patti G,et al. J Am Coll Cardiol 2007;49:1272-8

ARMYDA-ACS

Individual and Combined Outcome Measures of the Primary End Point at 30 days



MI definition:

If normal baseline levels of CK-MB: post-procedural increase of CK-MB >2 times above UNL,

If elevated baseline levels of CK-MB: subsequent rise of >2 times in CK-MB from baseline value

Composite Primary End Point

Patti G,et al. J Am Coll Cardiol 2007;49:1272-8

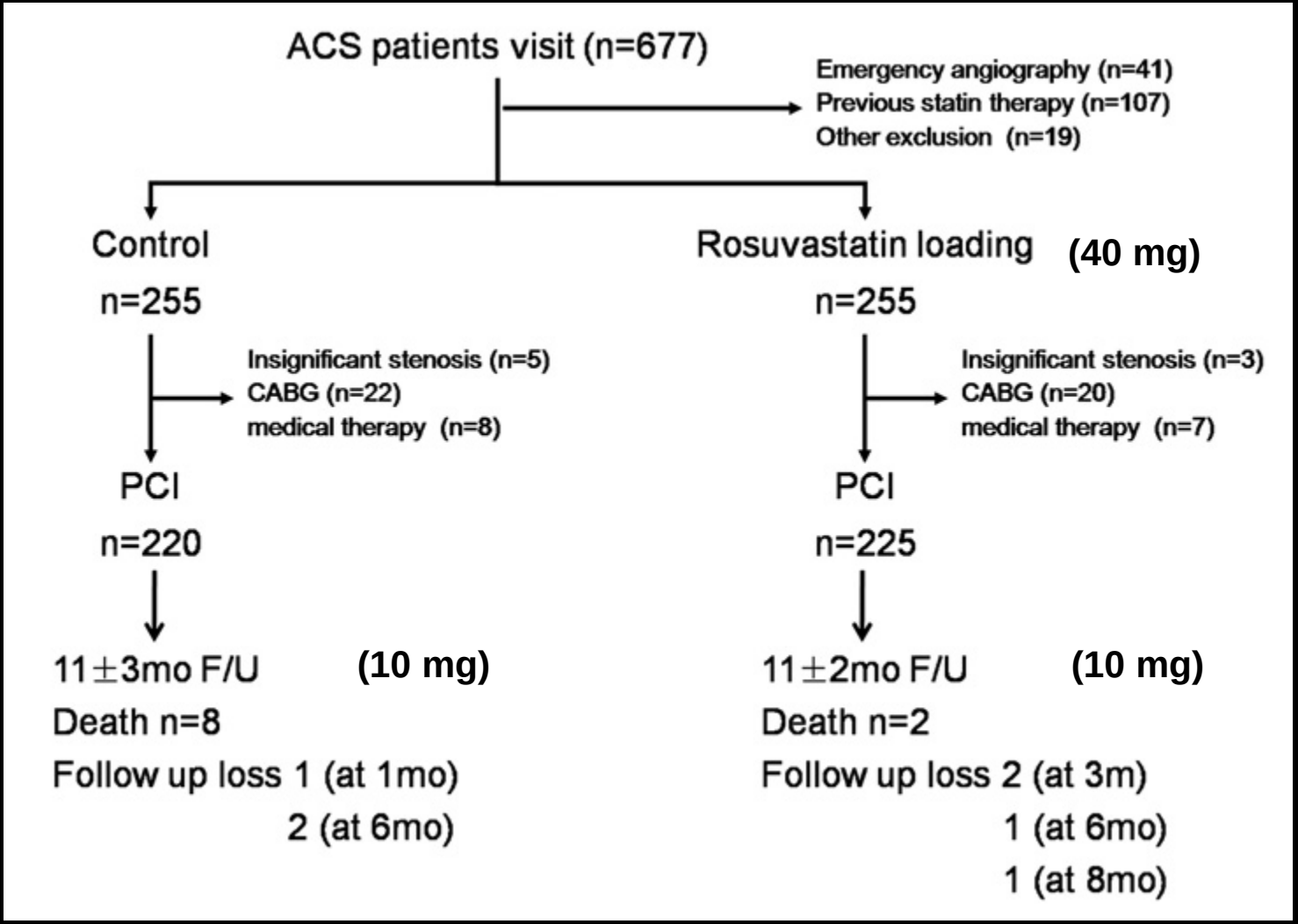
Statin treatment and ACS patient outcome?

→ Statin loading before PCI

- High dose Statin and Caucasian patients
  - ARMYDA-ACS : Atorvastatin 80/40mg
- High dose Statin and Korean patients
  - Yun KH, et al : rosuvastatin 40/10mg

Clinical effect of high loading dose of rosuvastatin before PCI for Korean ACS patients

<Flow chart of the study>



Yun KH et al. Int J Cardiol. 2011;146:68-72.

Baseline characteristics

Baseline clinical and procedural characteristics.

	Control group ($n=220$)	Rosuvastatin group ($n=225$)	p value
Age (years)	63 ± 11	64 ± 10	0.635
Male (%)	137 (62.3)	136 (60.4)	0.692
Hypertension (%)	121 (55.0)	123 (54.7)	0.944
Diabetes (%)	65 (29.5)	75 (33.3)	0.390
Current smoker (%)	80 (36.4)	83 (36.9)	0.908
Left ventricular EF (%)	60 ± 10	61 ± 11	0.328
Creatinine (mg/dl)	1.1 ± 0.5	1.0 ± 0.3	0.121
Total cholesterol (mg/dl)	202 ± 49	196 ± 44	0.165
Triglyceride (mg/dl)	174 ± 129	175 ± 119	0.943
HDL-cholesterol (mg/dl)	45 ± 12	44 ± 10	0.575
LDL-cholesterol (mg/dl)	124 ± 40	122 ± 38	0.497
Troponin T (ng/ml)	0.2 ± 0.6	0.2 ± 0.7	0.982
Multi-vessel disease (%)	118 (53.6)	126 (56.0)	0.616
ACC/AHA B2/C lesion (%)	165 (75.0)	169 (75.1)	0.978
Drug-eluting stent (%)	212 (96.4)	216 (96.0)	0.841
Stent diameter (mm)	3.2 ± 0.4	3.2 ± 0.4	0.060
Stent length (mm)	46 ± 29	45 ± 24	0.707
Stent number	1.7 ± 1.0	1.7 ± 0.8	0.858
Maximal pressure (atm)	17 ± 4	17 ± 3	0.331
Multi-vessel stenting (%)	70 (31.8)	80 (35.6)	0.404
Use of GPI (%)	18 (8.2)	14 (6.2)	0.424
Procedural complications (%)	28 (12.7)	24 (10.7)	0.499
Periprocedural MI (%)	25 (11.4)	13 (5.8)	0.035

Yun KH 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 KH et al. Int J Cardiol. 2011;146:68-72.

Incidence of periprocedural myocardial injury

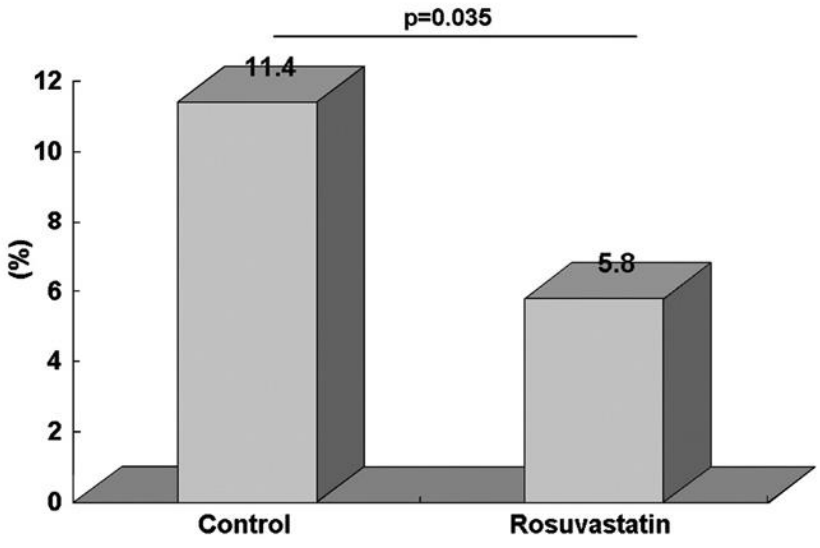


Fig. 2. Incidence of periprocedural myocardial injury, defined by post-procedural increase of creatine kinase-MB > 2 times above the upper limit of normal, in the control group and high dose rosuvastatin loading group.

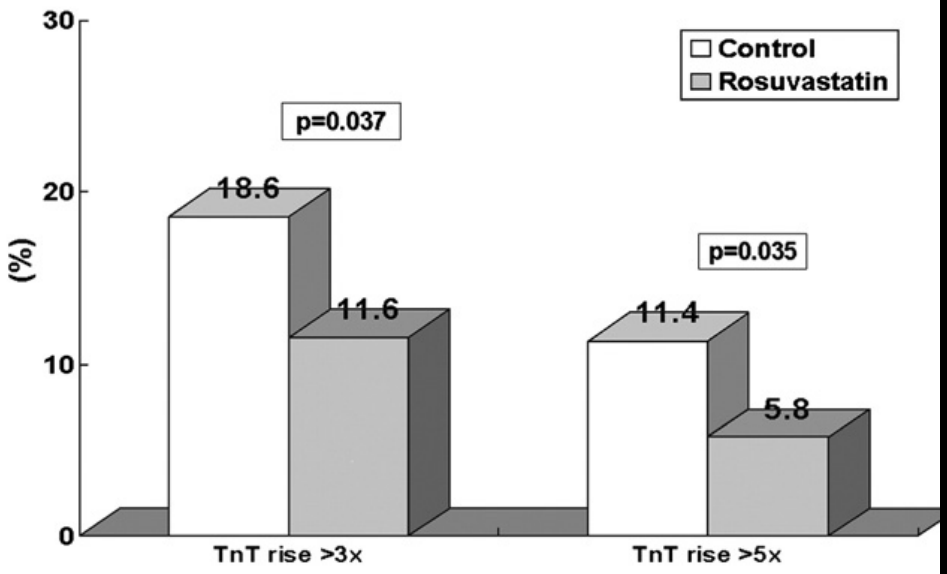
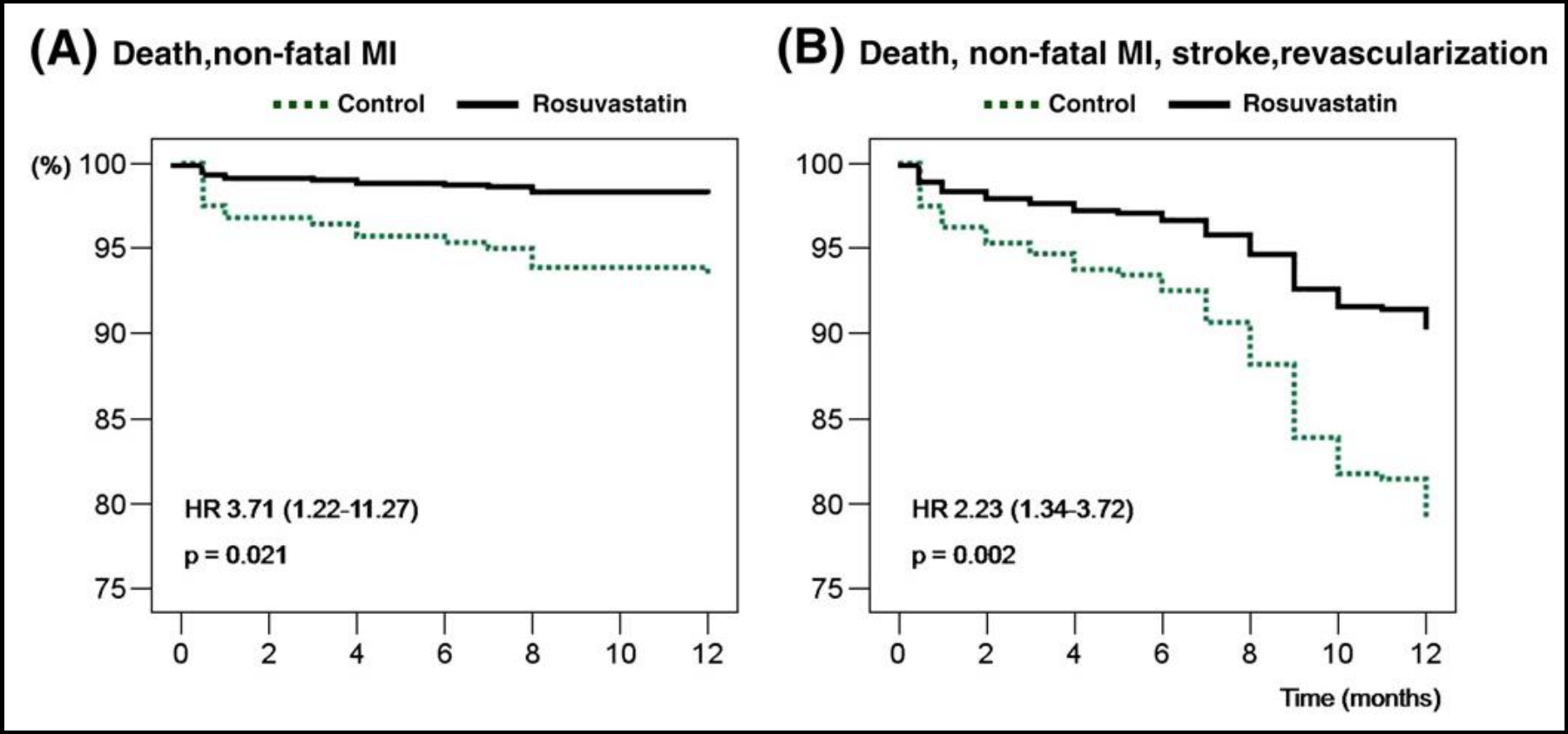


Fig. 3. Incidence of troponin T (TnT) elevation in control group a rosuvastatin loading group.

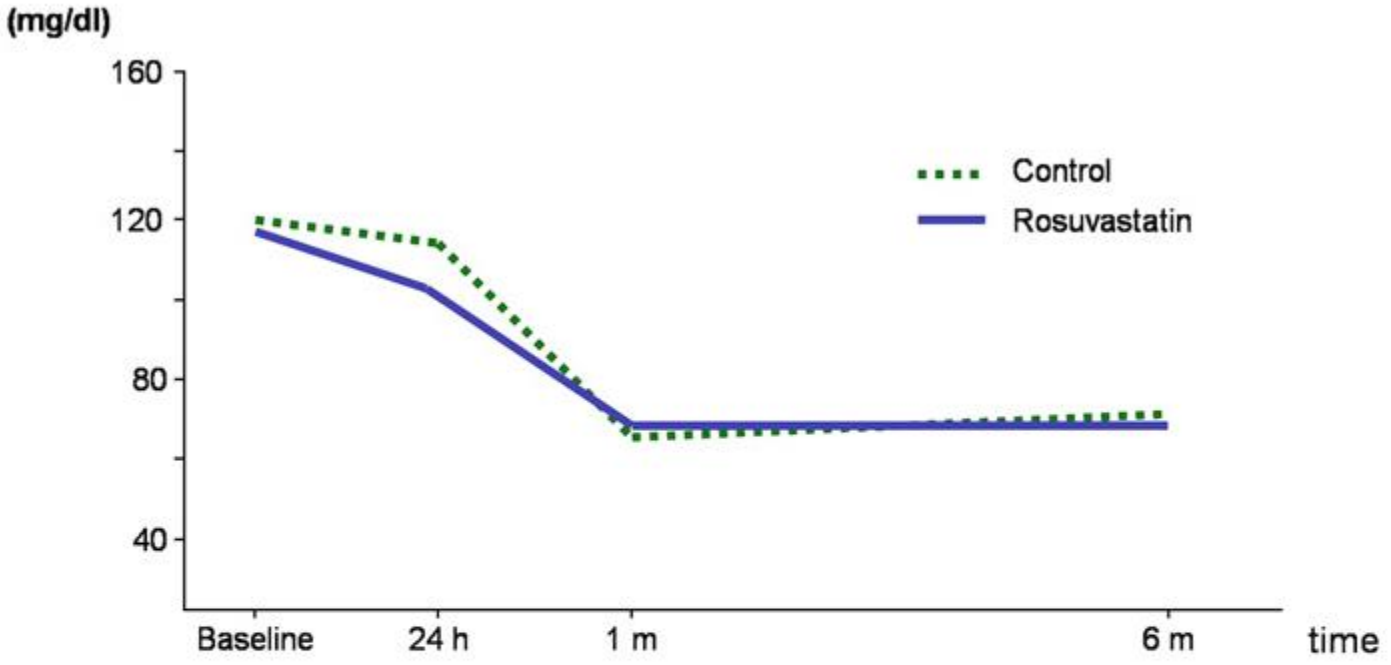
Yun KH et al. Int J Cardiol. 2009;137:246=51

Long term benefits of rosuvastatin loading before PCI for ACS



Yun KH et al. Int J Cardiol. 2011;146:68-72.

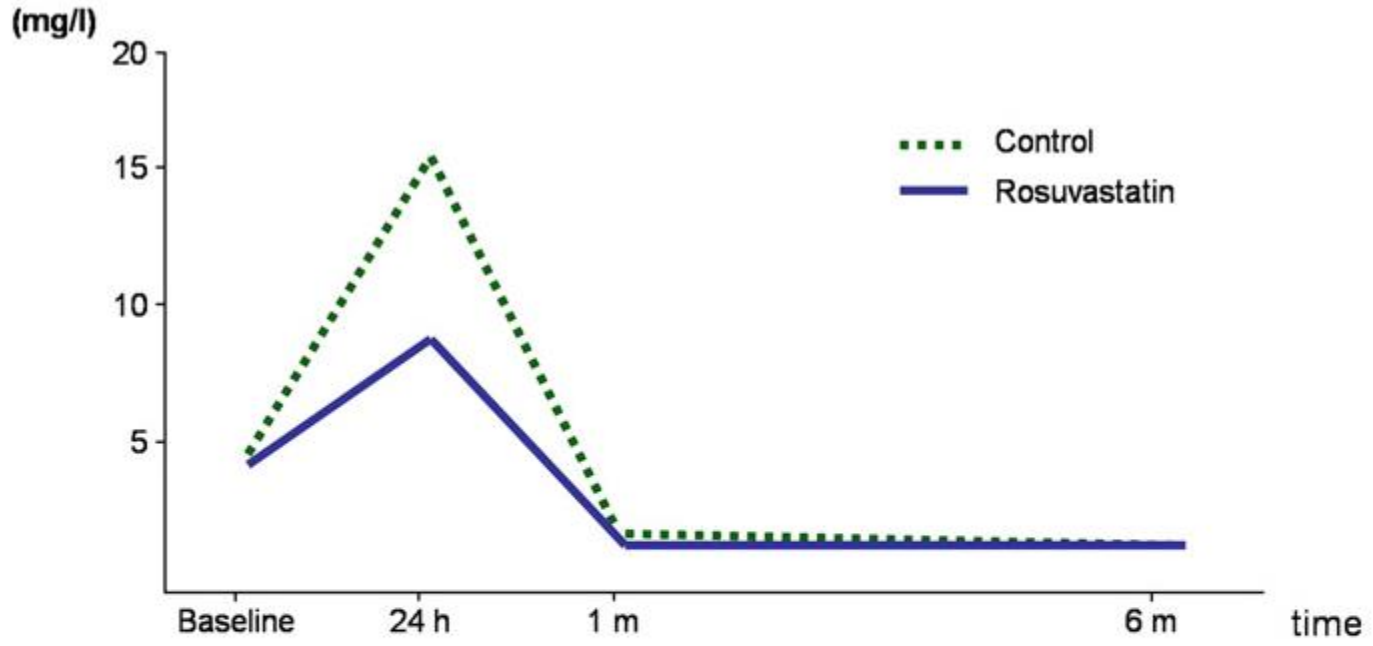
Change in LDL-cholesterol



	Baseline	24h after PCI	1 month	6 months
No. of patients	445	429	354	311
Control group (mg/dl)	123.8 ± 40.0	117.3 ± 32.9	69.6 ± 21.6	72.3 ± 22.5
Rosuvastatin group (mg/dl)	121.6 ± 38.1	104.8 ± 29.1	72.8 ± 24.3	73.2 ± 24.9
p value	0.497	<0.001	0.189	0.705

Yun KH et al. Int J Cardiol. 2011;146:68-72.

Change in high-sensitivity CRP



	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

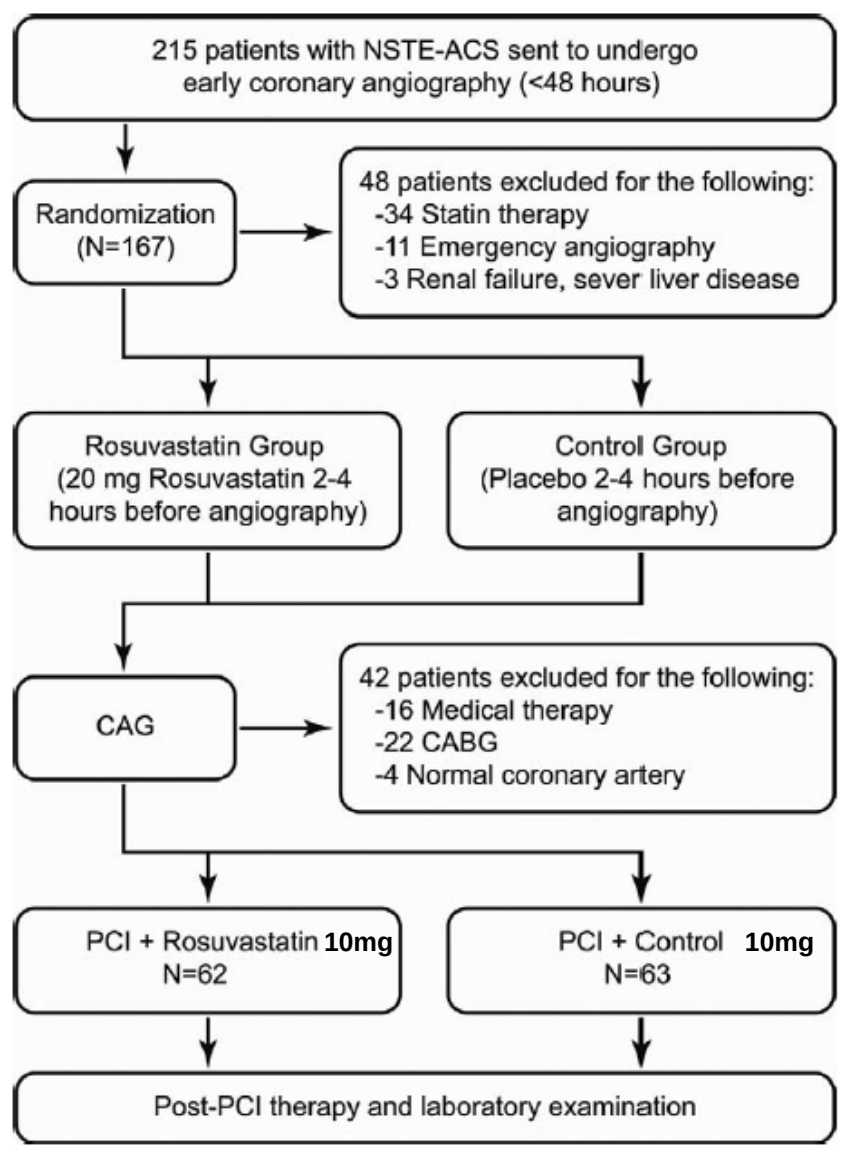
Yun KH et al. Int J Cardiol. 2011;146:68-72.

Statin treatment and ACS patient outcome?

→ Statin loading before PCI

- High dose Statin and Caucasian patients
- High dose Statin and Korean patients
  - Yun KH, et al : rosuvastatin 40/10mg
- High dose statin and Asian patients
  - Wang Z, et al : Rosuvastatin 20mg/10mg

Effect of Rosuvastatin loading before PCI for ACS patients



MI definition:

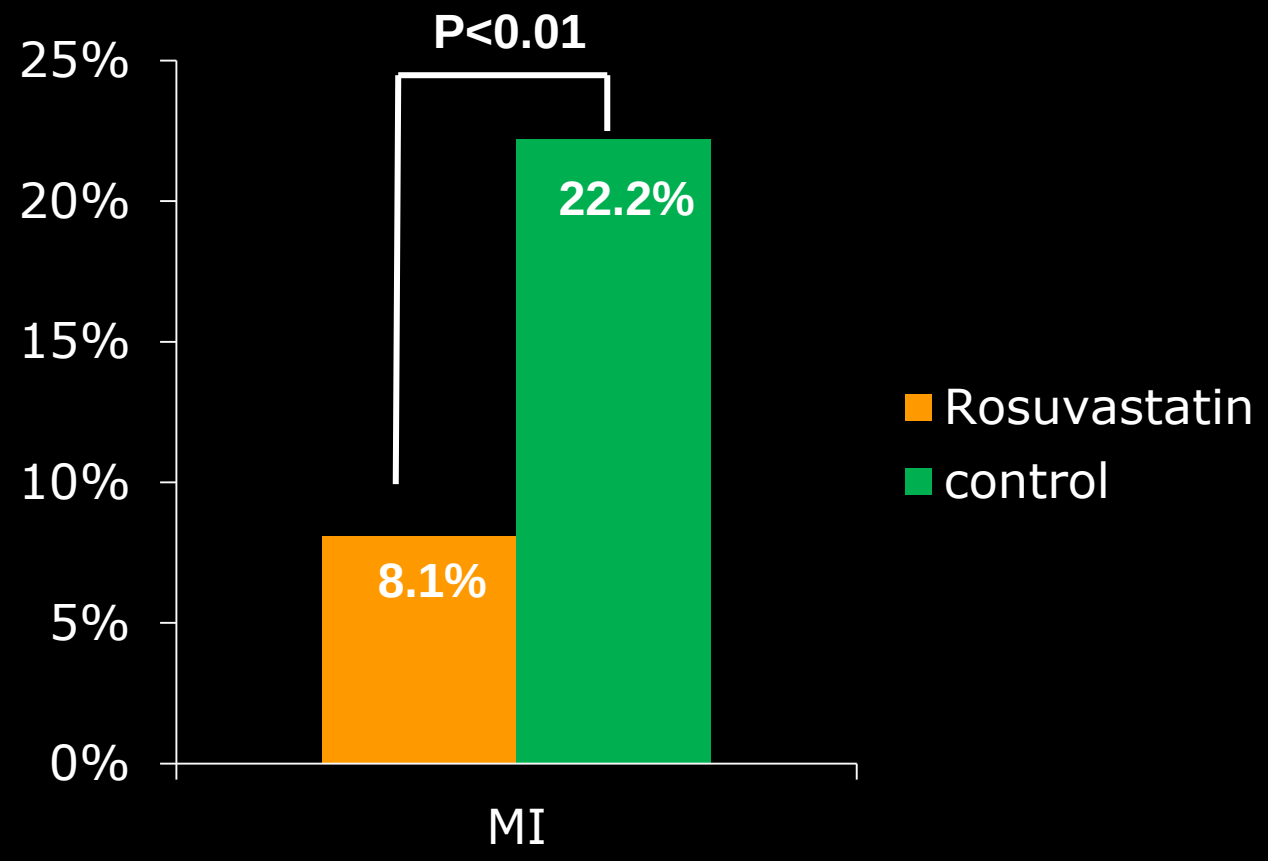
If normal baseline levels of CK-MB: post-procedural increase of CK-MB or cTnI >3 times above UNL,

If elevated baseline levels of CK-MB: subsequent rise of >3 times in CK-MB or cTnI from baseline value

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

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

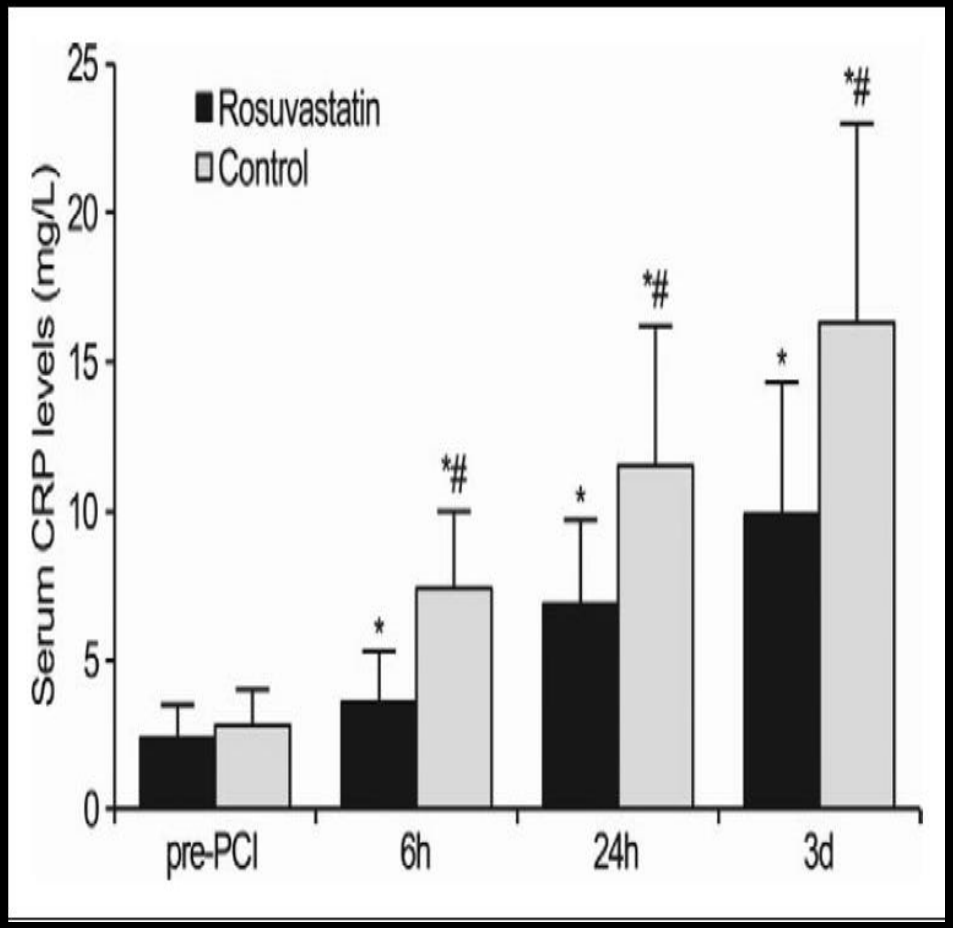
<The Incidence of Primary End Points at 1 Month in the 2 Groups>



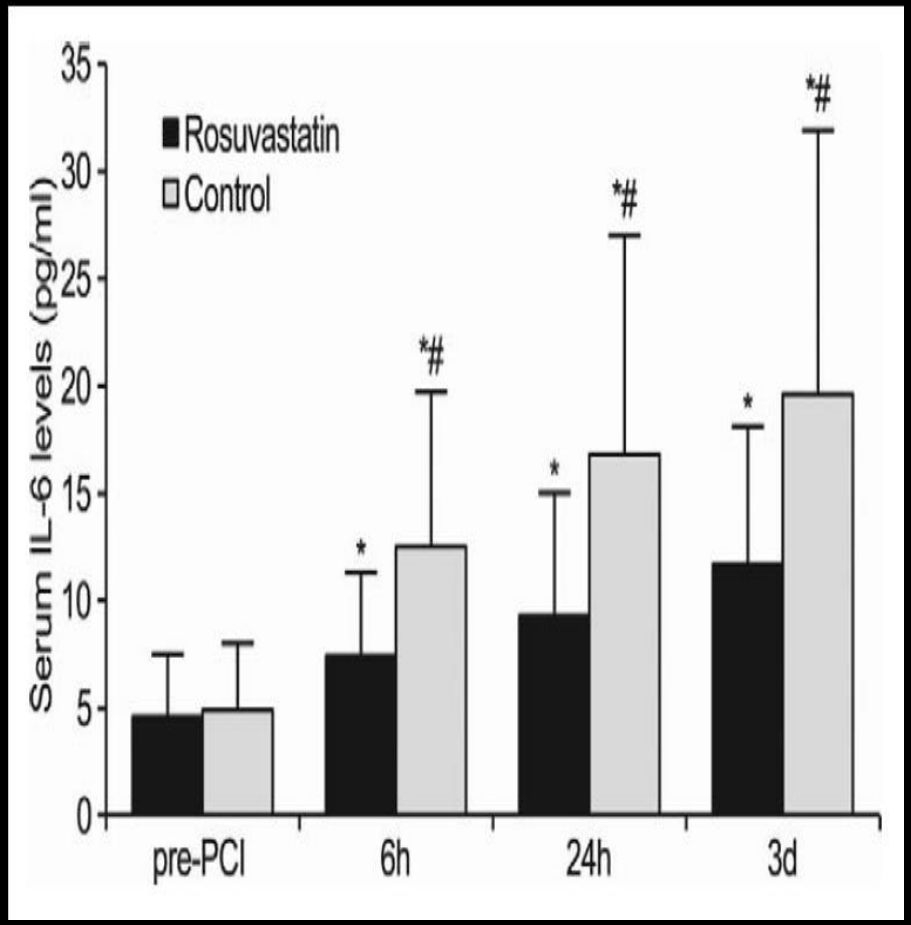
Wang Z et al. **J Cardiovasc Pharmacol Ther.2013 Jan 29.**

Effect of Rosuvastatin – hsCRP, IL-6 level

<hs-CRP level>



<IL-6 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.**

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

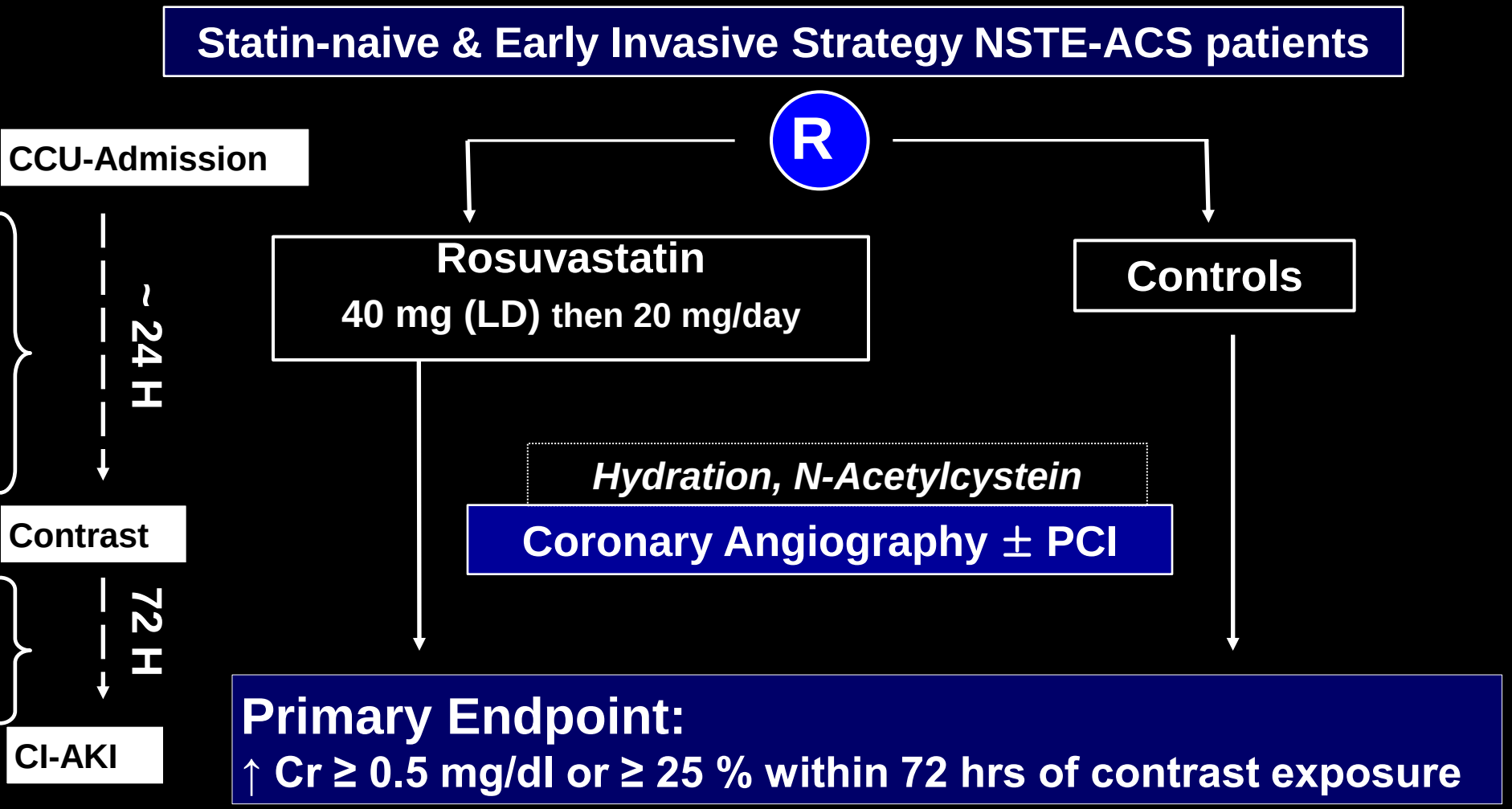
The PRATO-ACS (Protective effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome) Study

Anna Toso, MD

on behalf of the *PRATO-ACS* investigators

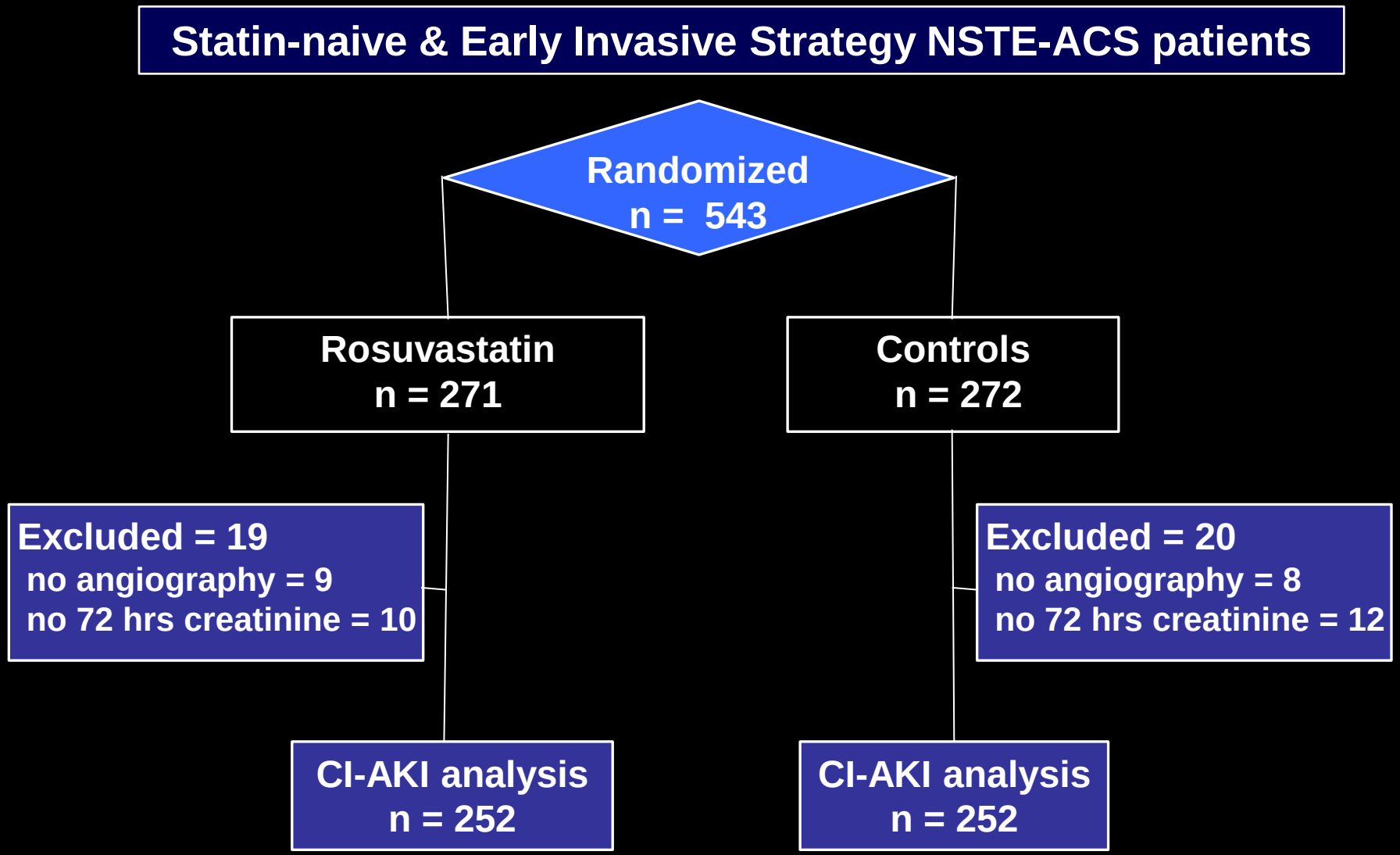
Methods

Study Design



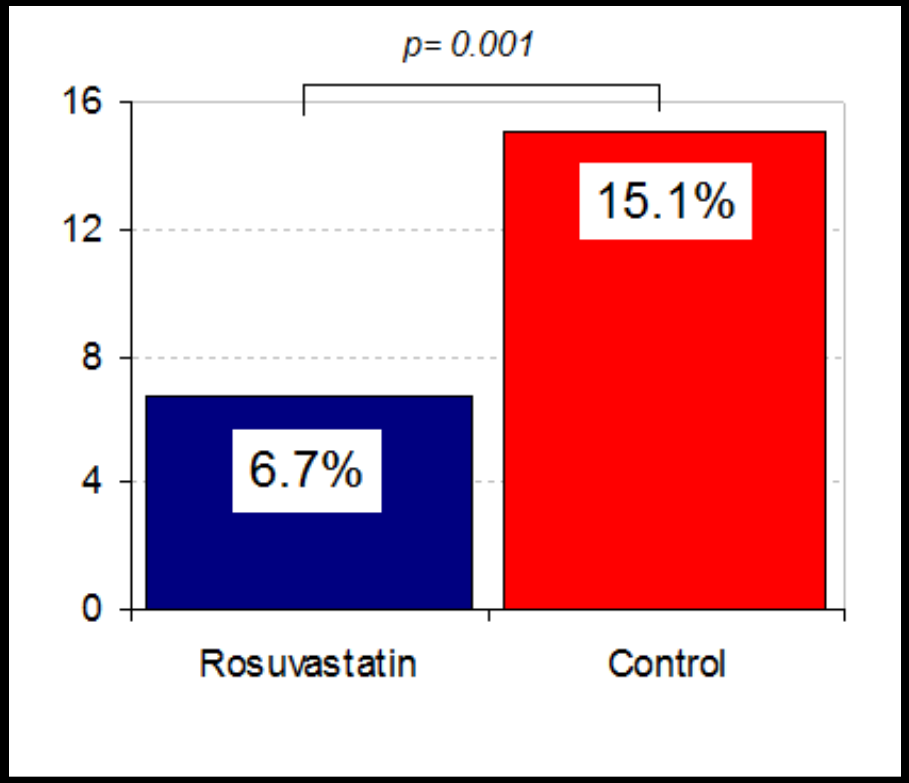
Sample size: assumed 18% CI-AKI in control and 50% reduction in treatment. With a 80% statistical power and 2-sided type 1 error of 5%; 15% drop out □ ~ 540 pts

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

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):

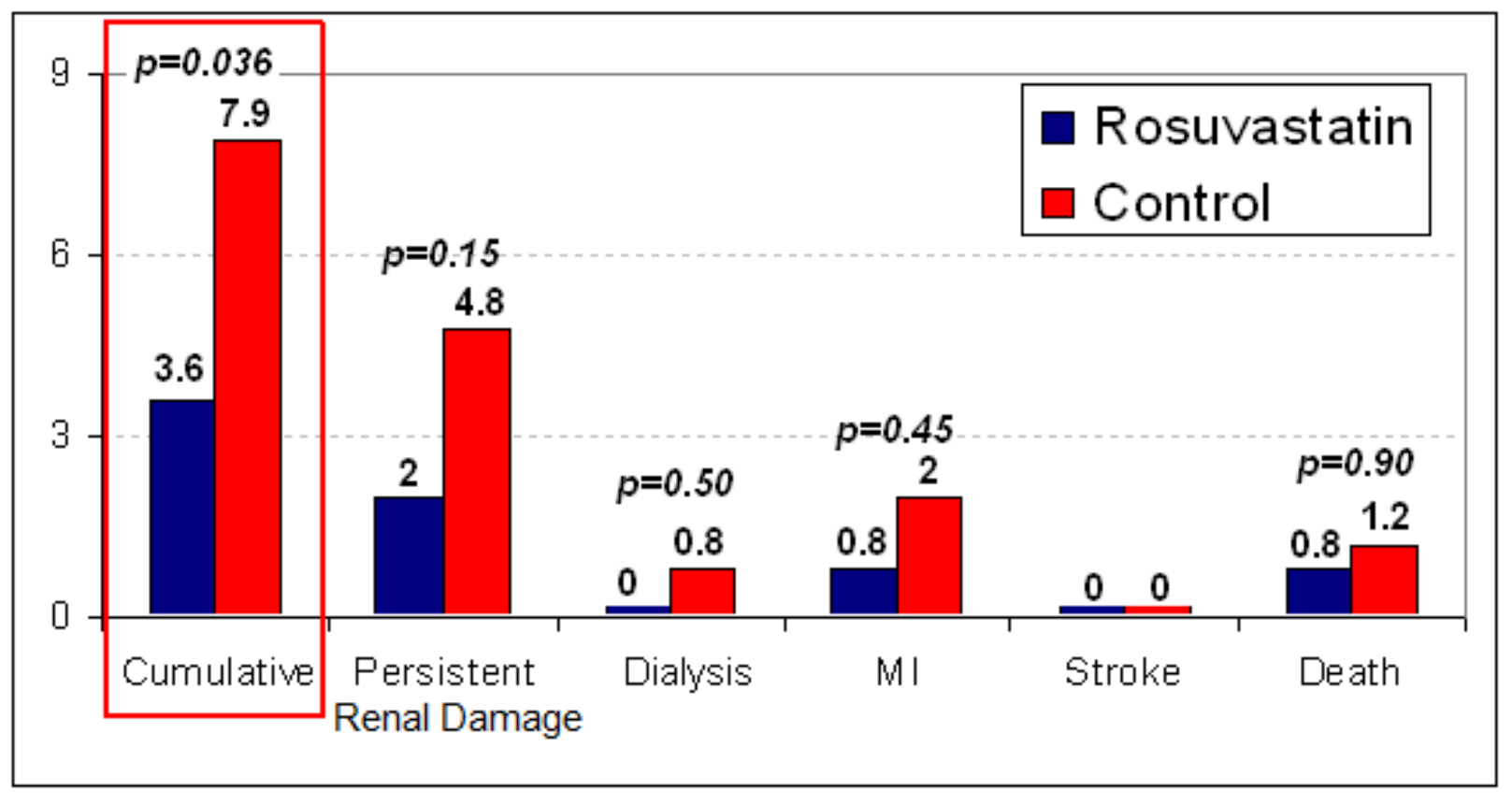
0.38 (0.20 – 0.71)

NNT = 12

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

Additional Endpoints:

3. Adverse Clinical Events (30 days)



Summary

- Early and intensive statin treatment in patients with ACS improved clinical outomes.
- High doses of Rosuvastain were more effective than high doses of Atorvastatin in reducing LDL-C and increasing HDL-C in ACS patients .
- High dose of rosuvastatin loading before PCI significantly improved 12-month clinical outcomes in patients with ACS who underwent an early invasive strategy.
- High dose rosuvastatin loading in statin-naïve patients with NSTE-ACS scheduled for early invasive strategy exerts additional preventive effects against CIN (w/ hydration & N-Acetylcystein).

경청해주셔서 감사합니다

Lipid Levels after ACS LUNAR study

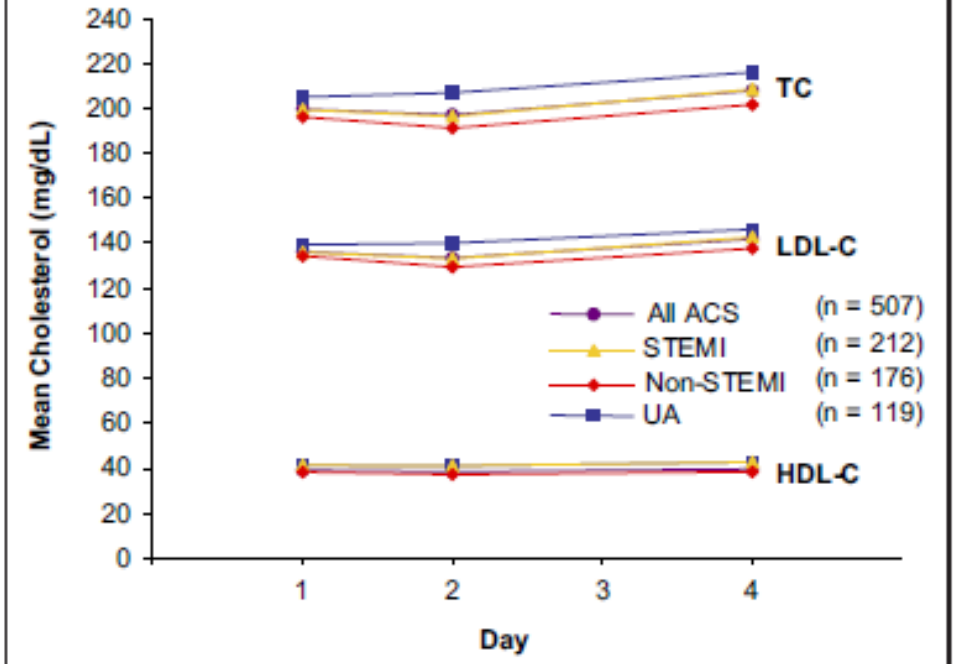


Figure 1 Mean Serum LDL-C, HDL-C, and TC Levels on Days 1, 2, and 4

ACS = acute coronary syndromes; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; STEMI = ST-segment elevation myocardial infarction; TC = total cholesterol; UA = unstable angina.

507 patients
STEMI 212
NSTEMI 176
UA 119

J Am Coll Cardiol 2008;51:1440-5