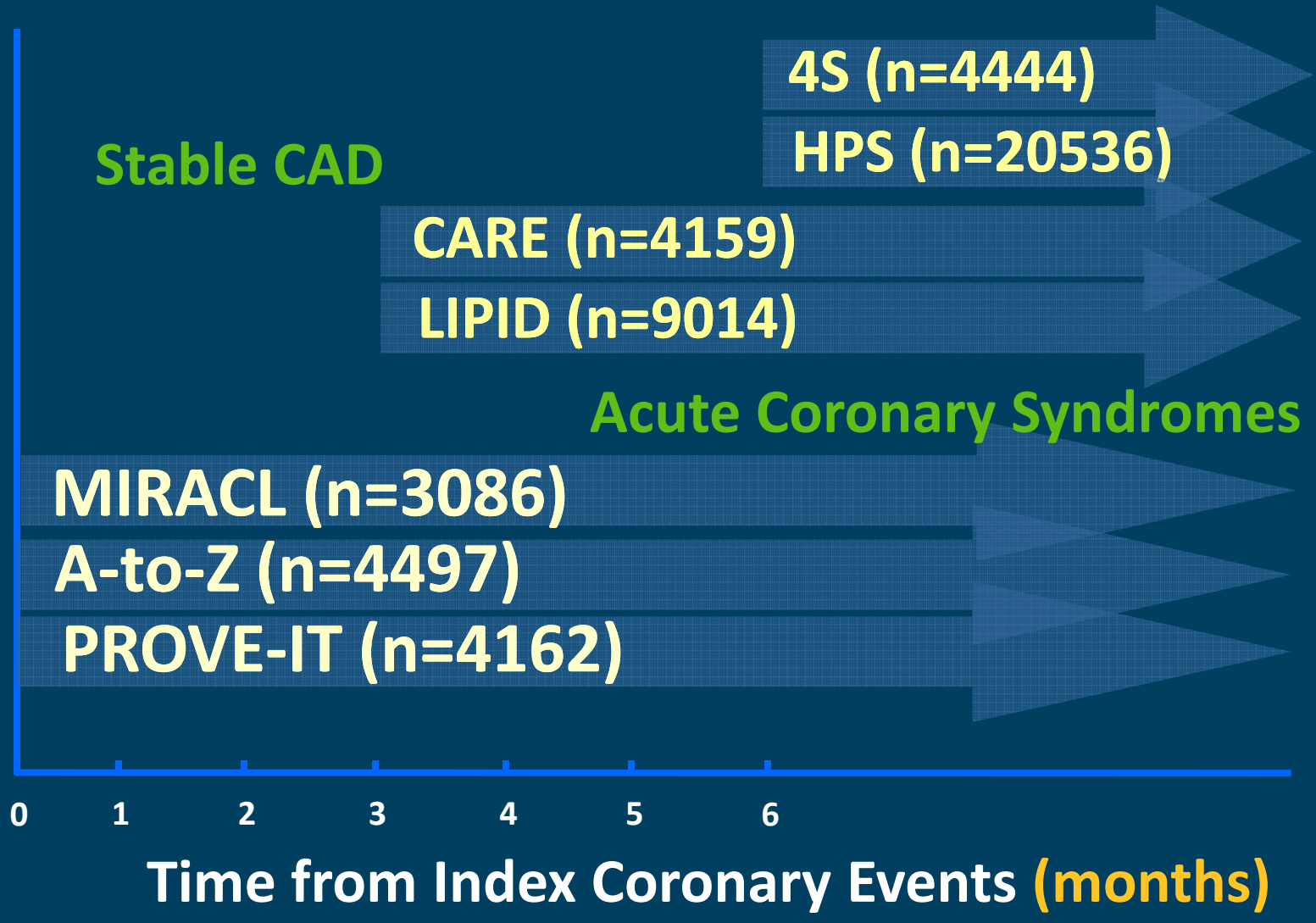
The Earlier, The Better: Quantum Progress in ACS

In-Ho Chae

Seoul National University College of Medicine

Quantum Leap in Statin Landmark Trials in ACS patients

Randomized Controlled Studies of Lipid-Lowering Therapy in Patients with ACS



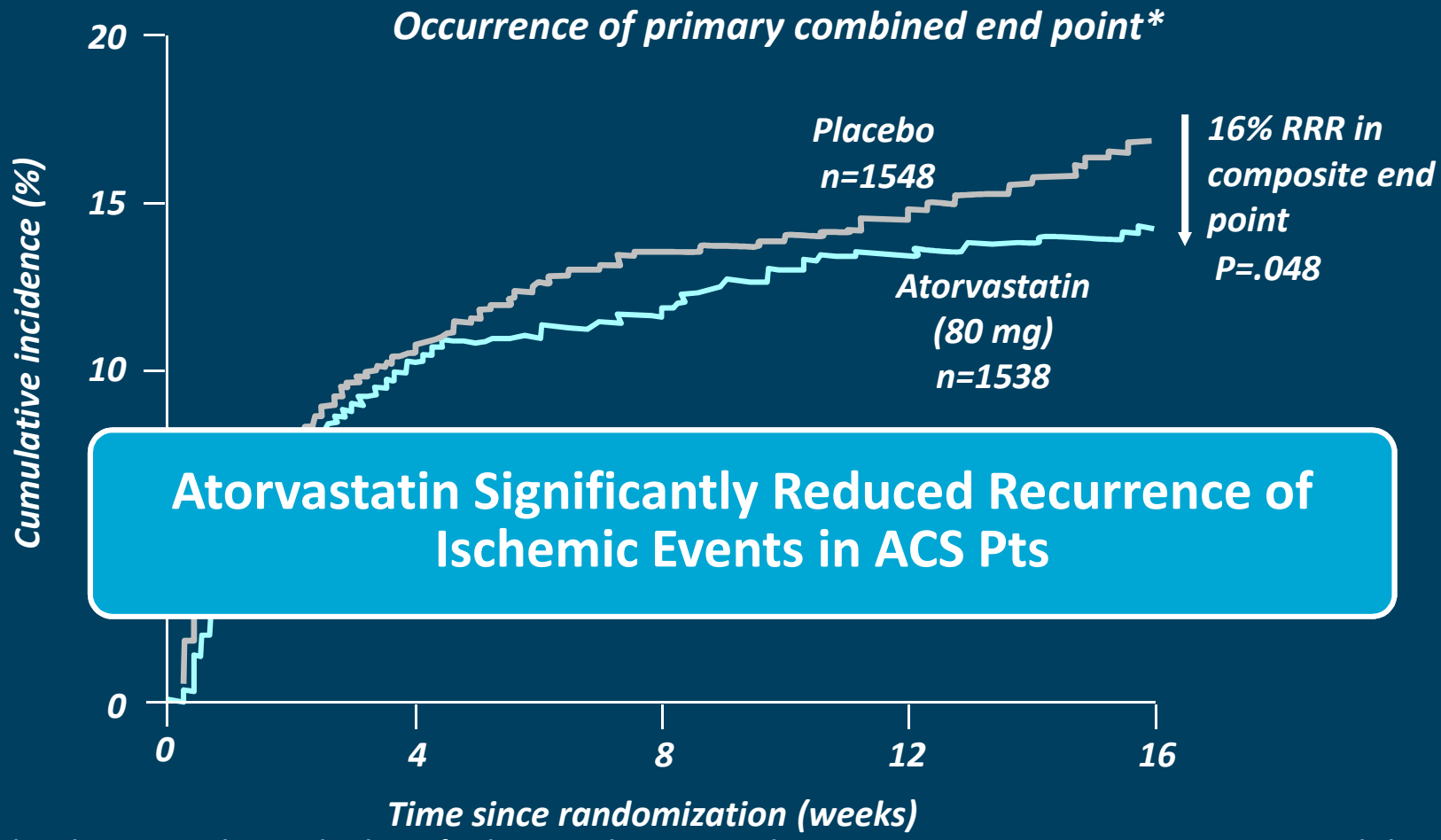
RCTs on Lipid-Lowering Therapy in ACS Patients

	Patients	Comparator	Study Period	N=
MIRACL Atorvastatin 80mg	UA or AMI	Placebo	16 weeks	3,086
PROVE-IT* Atorvastatin 80mg	Post ACS (within 10 days)	Pravastatin 40mg	24 months	4,162
Phase Z of A to Z Simvastatin 40-80mg	ACS, MI	Placebo+ Simvastatin 20mg	24 months	4,497

* PROVE-IT was sponsored by Bristol Myers Squibb and Sankyo

1. Schwartz GG et al. *JAMA*. 2001;285:1711-1718. 2. Cannon CP, et al. *N Engl J Med*. 2004;350:1495-1504. 3. de Lemos JA et al. *JAMA*. 2004;292:1307-1316.

MIRACL, A First RCT to Examine Benefit of Statin in ACS Patients

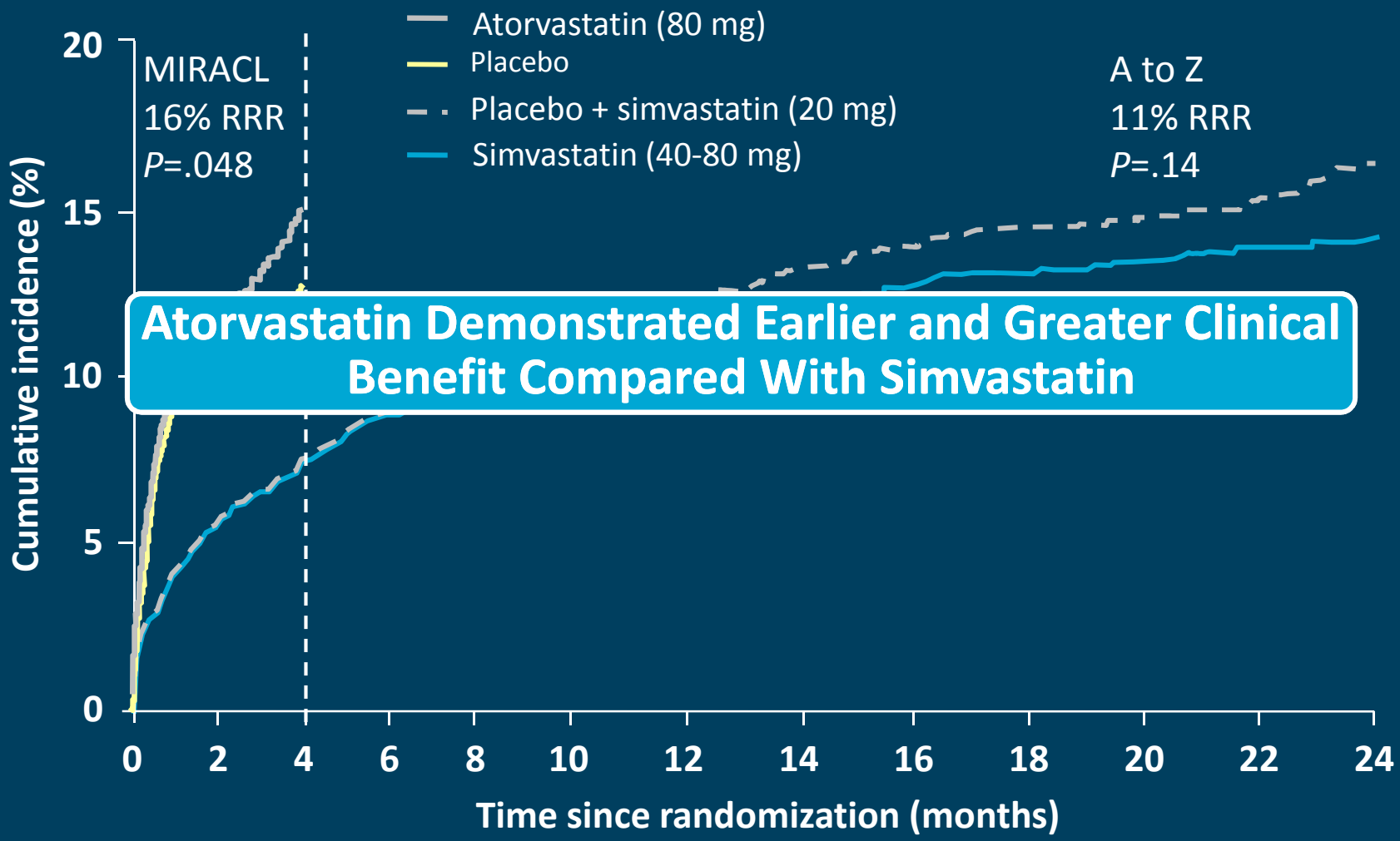


Atorvastatin Significantly Reduced Recurrence of Ischemic Events in ACS Pts

**Combined primary end point=death, nonfatal AMI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia requiring emergency rehospitalization.*
RRR=relative risk reduction.

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

MIRACL vs. A to Z: Earlier and Greater Clinical Benefit

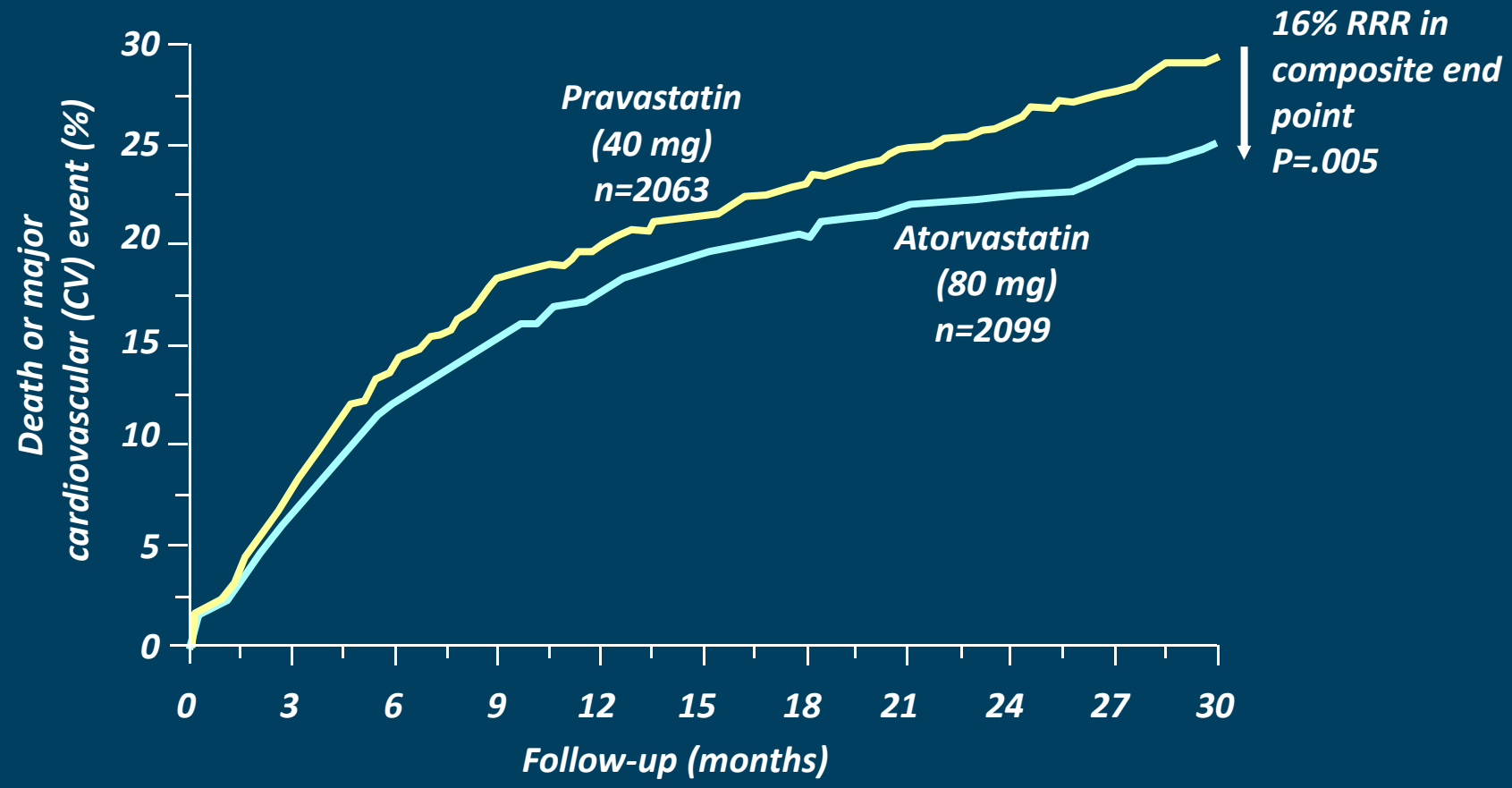


Adapted from Schwartz GG et al. *JAMA*. 2001;285:1711-1718; de Lemos JA et al. *JAMA*. 2004;292:1307-1316.

PROVE IT: Early and Sustained Benefit With Atorvastatin Compared With Pravastatin

Occurrence of primary composite end point

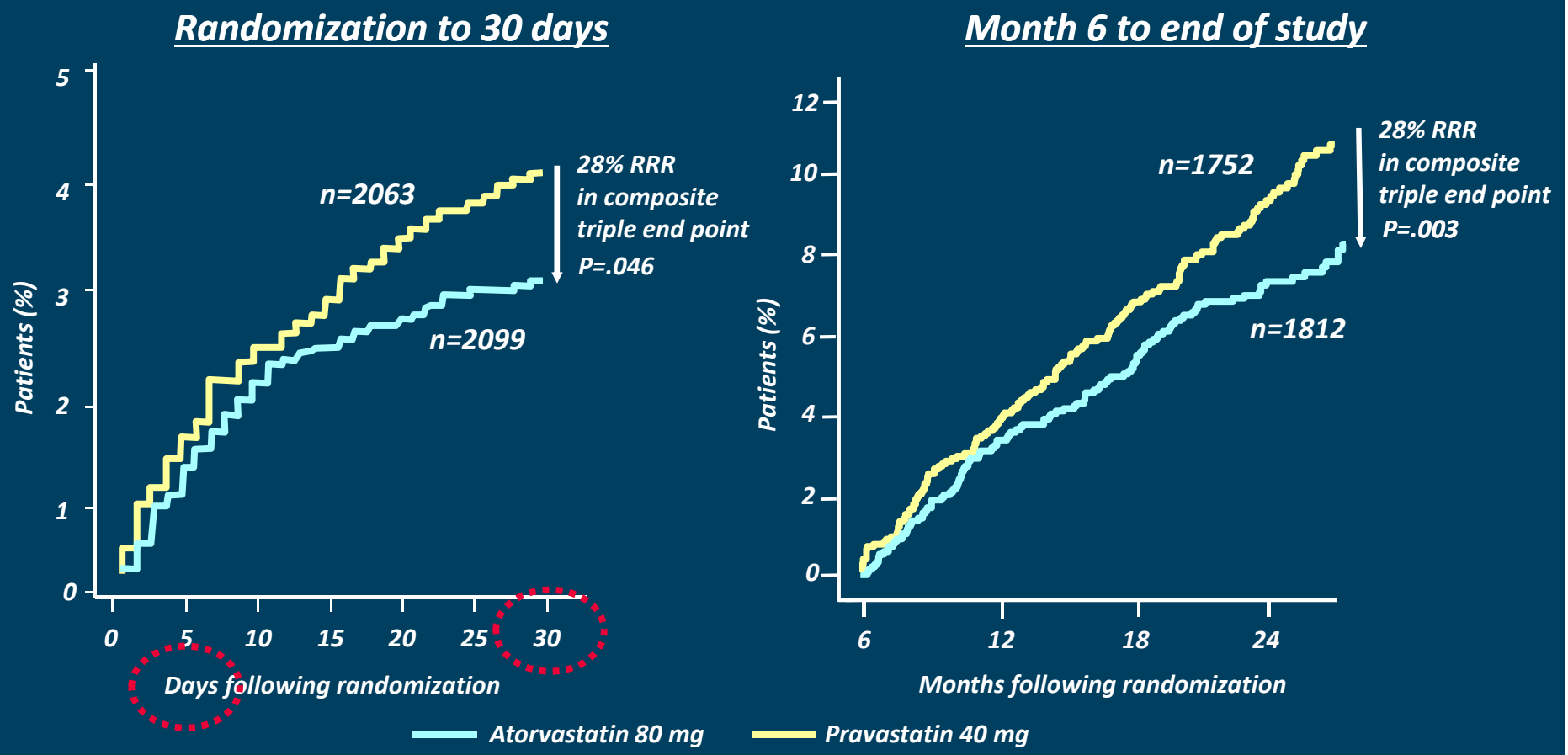
(death, MI, UA requiring rehospitalization, revascularization, stroke)



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

PROVE IT Sub-analysis: Intensive Therapy With Atorvastatin Provides Early and Long-Term Benefits in ACS Patients

Occurrence of composite triple end point
(death, MI, or rehospitalization with recurrent ACS)



Adapted from Ray KK et al. J Am Coll Cardiol. 2005;46:1405-1410.

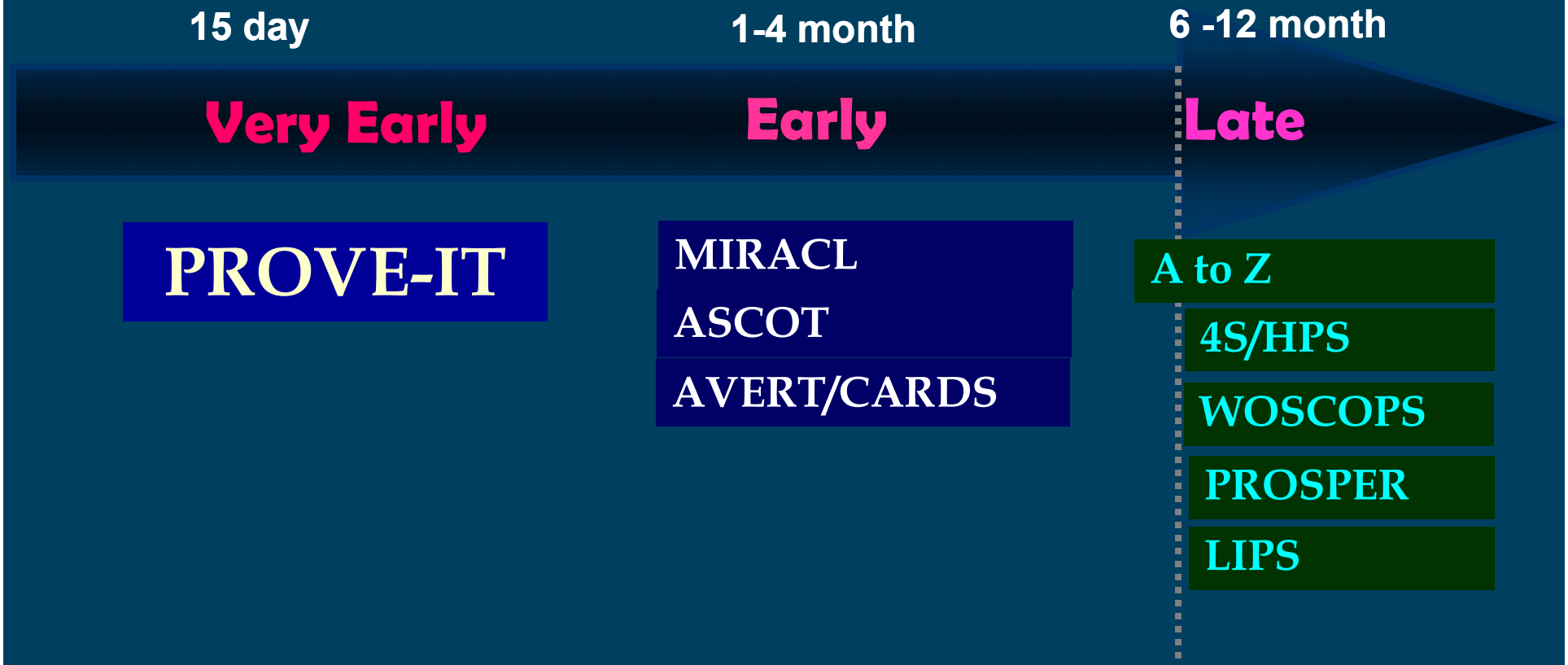
Atorvastatin Provided Higher Reductions in ACS Patients Despite Similar LDL-C Reduction

	A to Z	MIRACL	PROVE IT
Treatment	Simva (40 mg, 80 mg) vs placebo + simva 20 mg	Atorva 80 mg vs placebo	Atorva 80 mg vs prava 40 mg
No. of patients randomized	4497	3086	4162
LDL-C difference mmol/L (mg/dL)			
Early*	1.61 (62)	1.63 (63)	0.85 (33)
Late	0.41 (15)	NA	0.73 (28)
Event reduction (%)			
Early*	**0***	**16***	**18†**
Late‡	11 (NS)	NA	16

**Measured 120 days after randomization.*
†Measured 90 days after randomization.
‡Measured at trial completion—24 months for A to Z and PROVE IT.
mmol/L = mg/dL x .0259

Adapted from Nissen SE. JAMA. 2004;292:1365-1367.

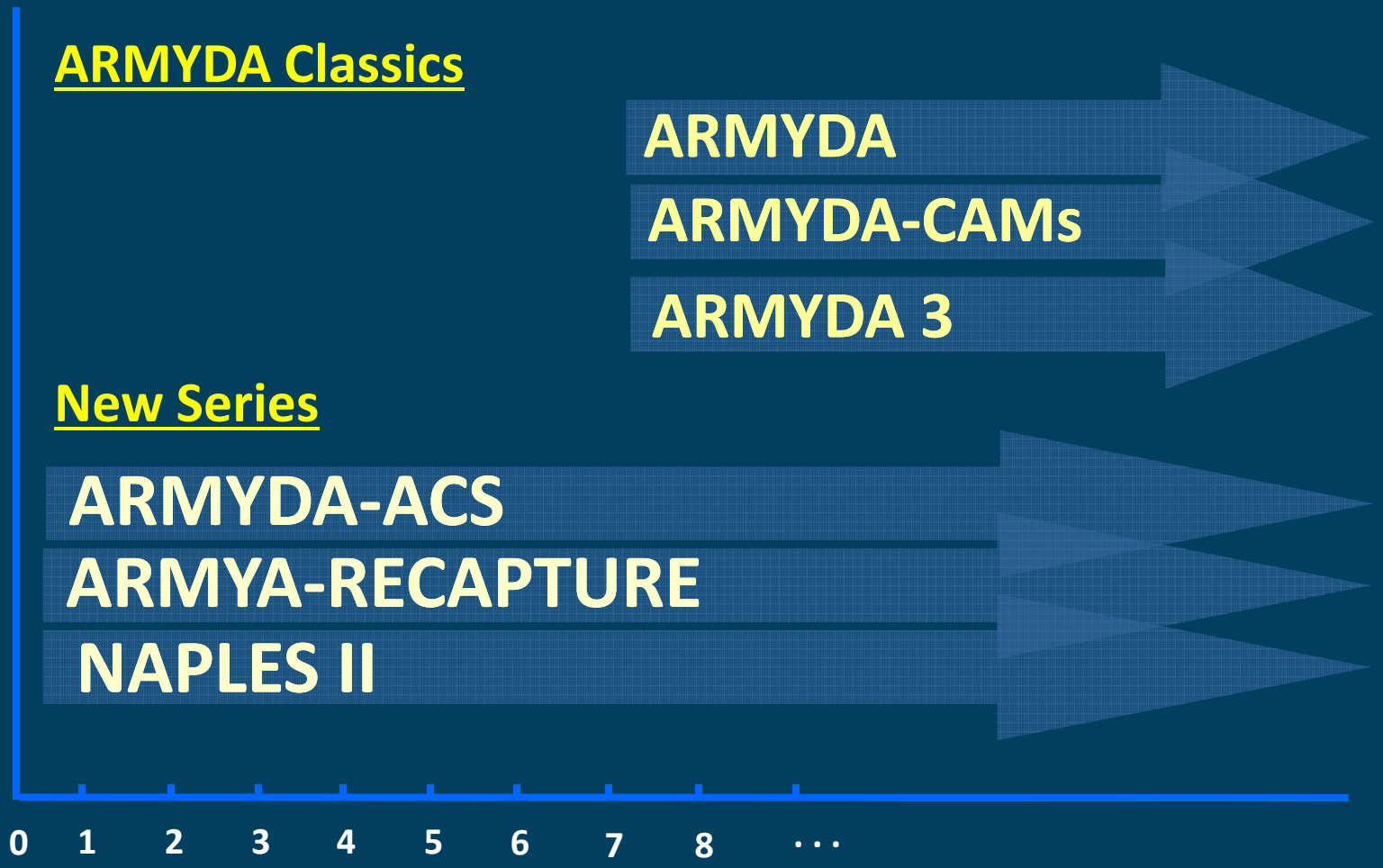
Early Benefits of Statin Therapy



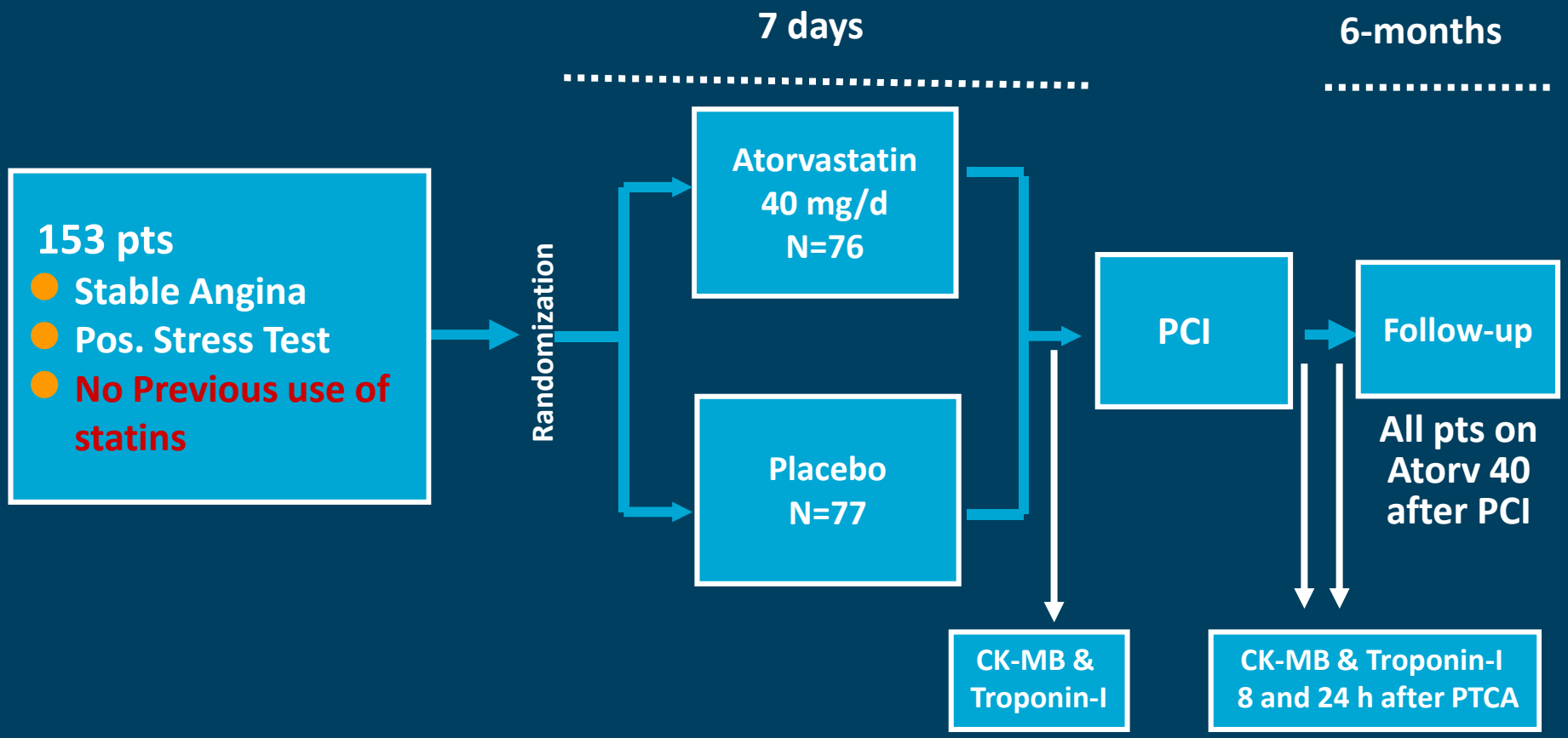
Faster than 15 days?

Upstream Atorvastatin Therapy Before PCI

Latest Trials on ACS….

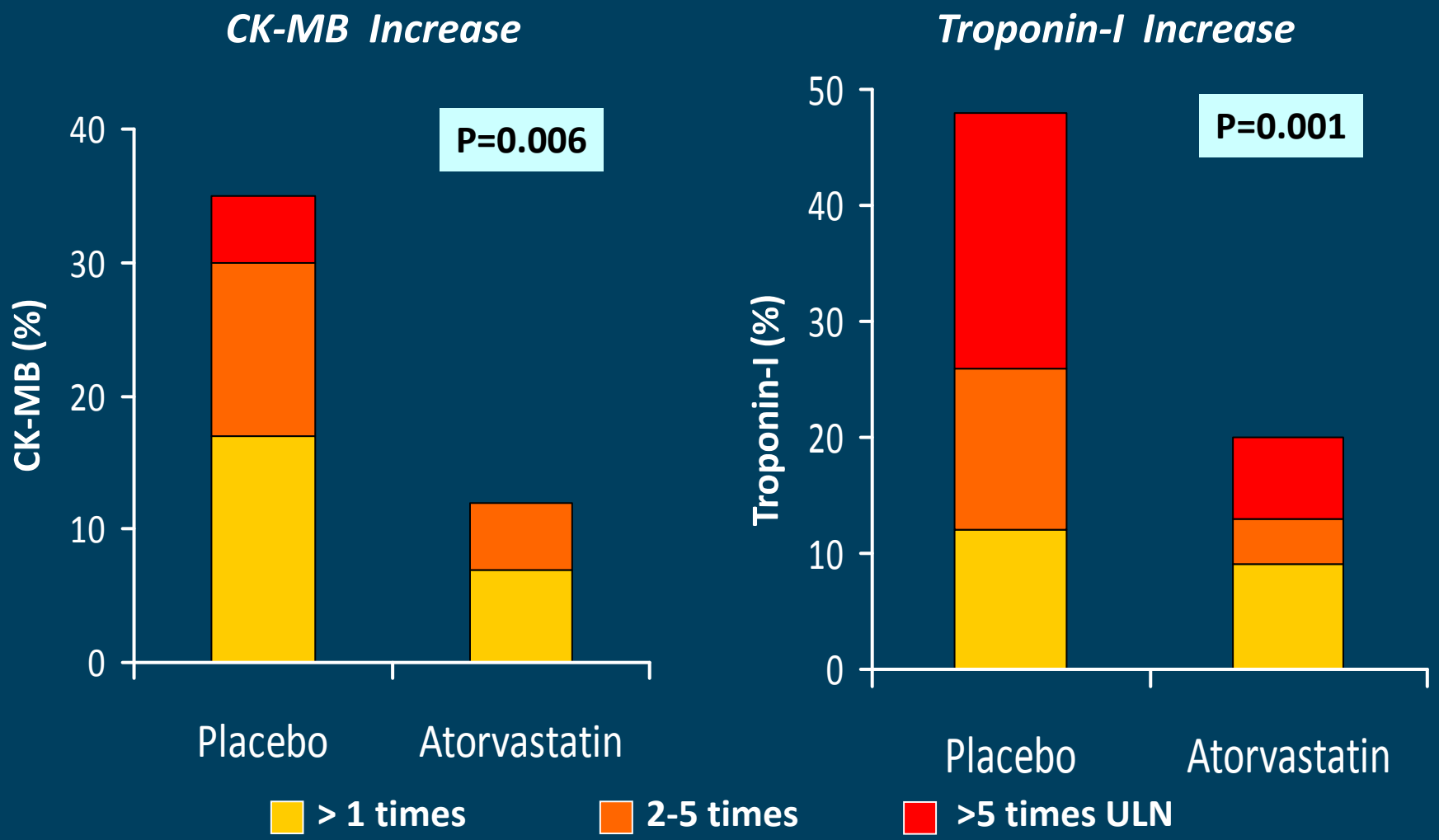


The Atorvastatin for Reduction of MYocardial Damage during Angioplasty (ARMYDA)



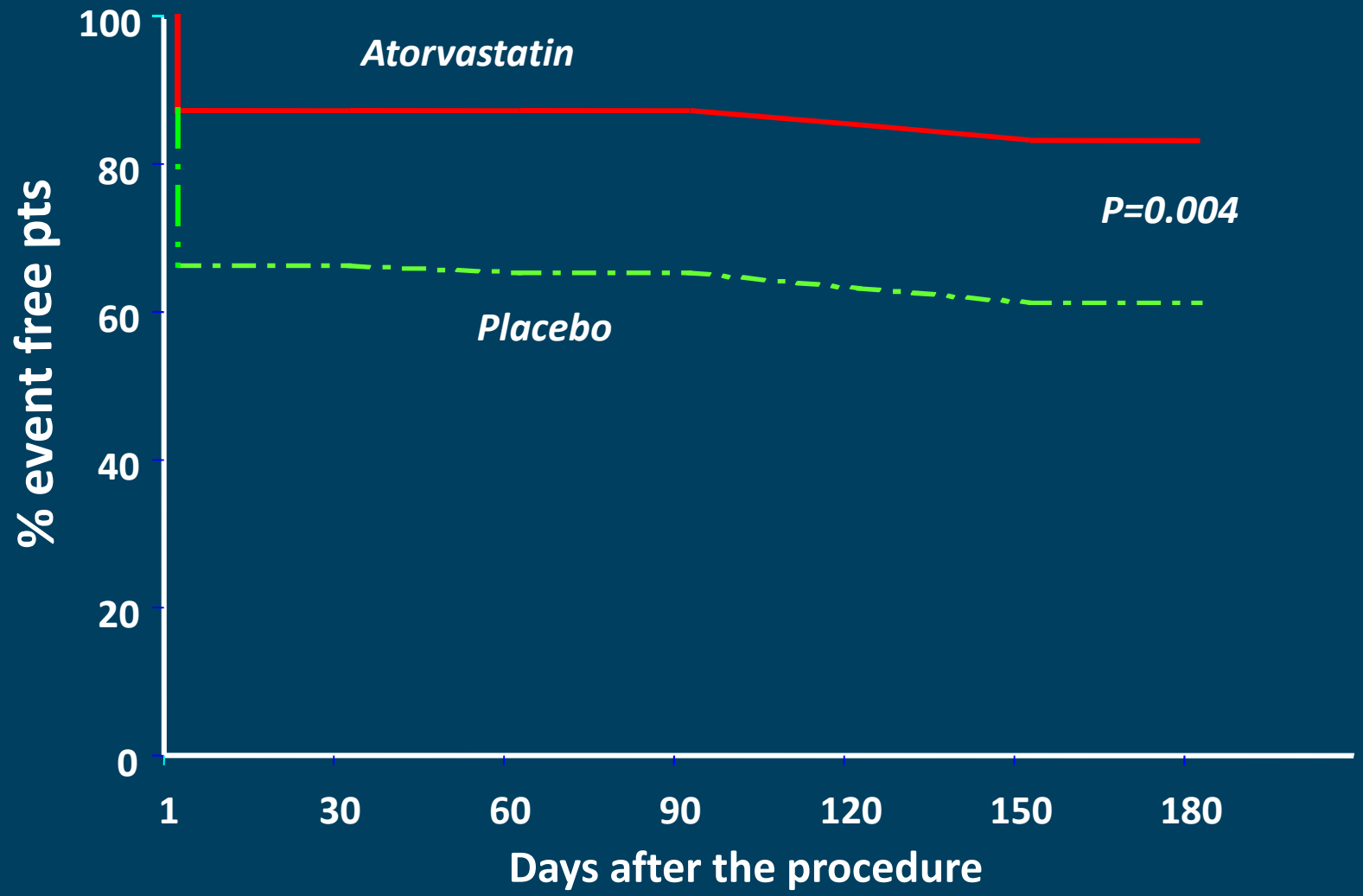
Circulation . 2004;110: 674-678

ARMYDA Study Results



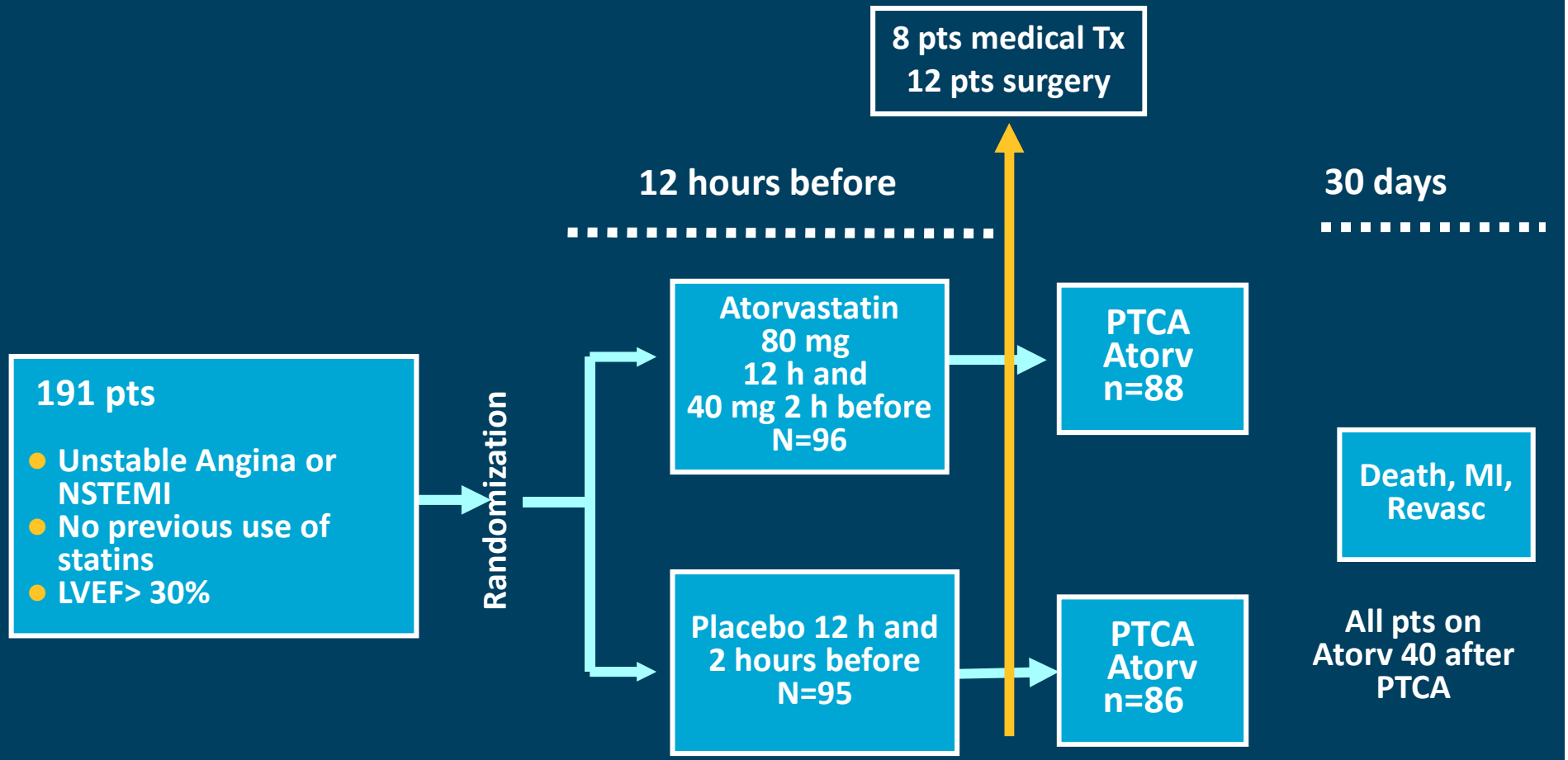
Circulation . 2004;110: 674-678

ARMYDA Result: MACE at 6 months



Circulation . 2004;110: 674-678

ARMYDA-ACS Study Design



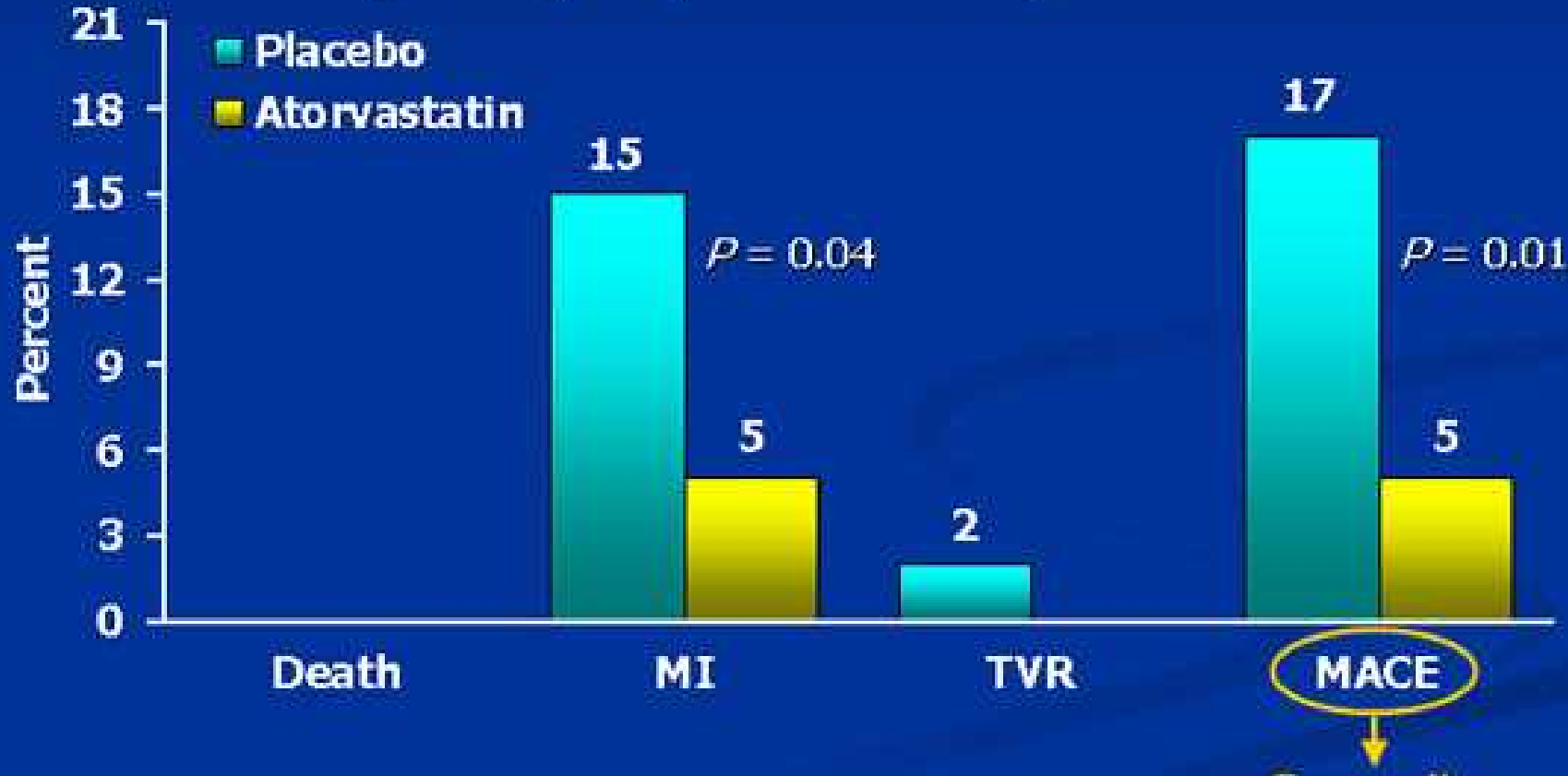
Inclusion Criteria: Patients with NSTEMI or Unstable Angina treated with early invasive strategy (angio at 12-24 hours)

Exlusion Criteria: Previous or current statin therapy; Need for emergency angio (<12 hours from admission); LVEF <30%; Controindications to statins, liver or renal failure

Patti G, et al. J Am Coll Cardiol. 2007;49:1272-1278

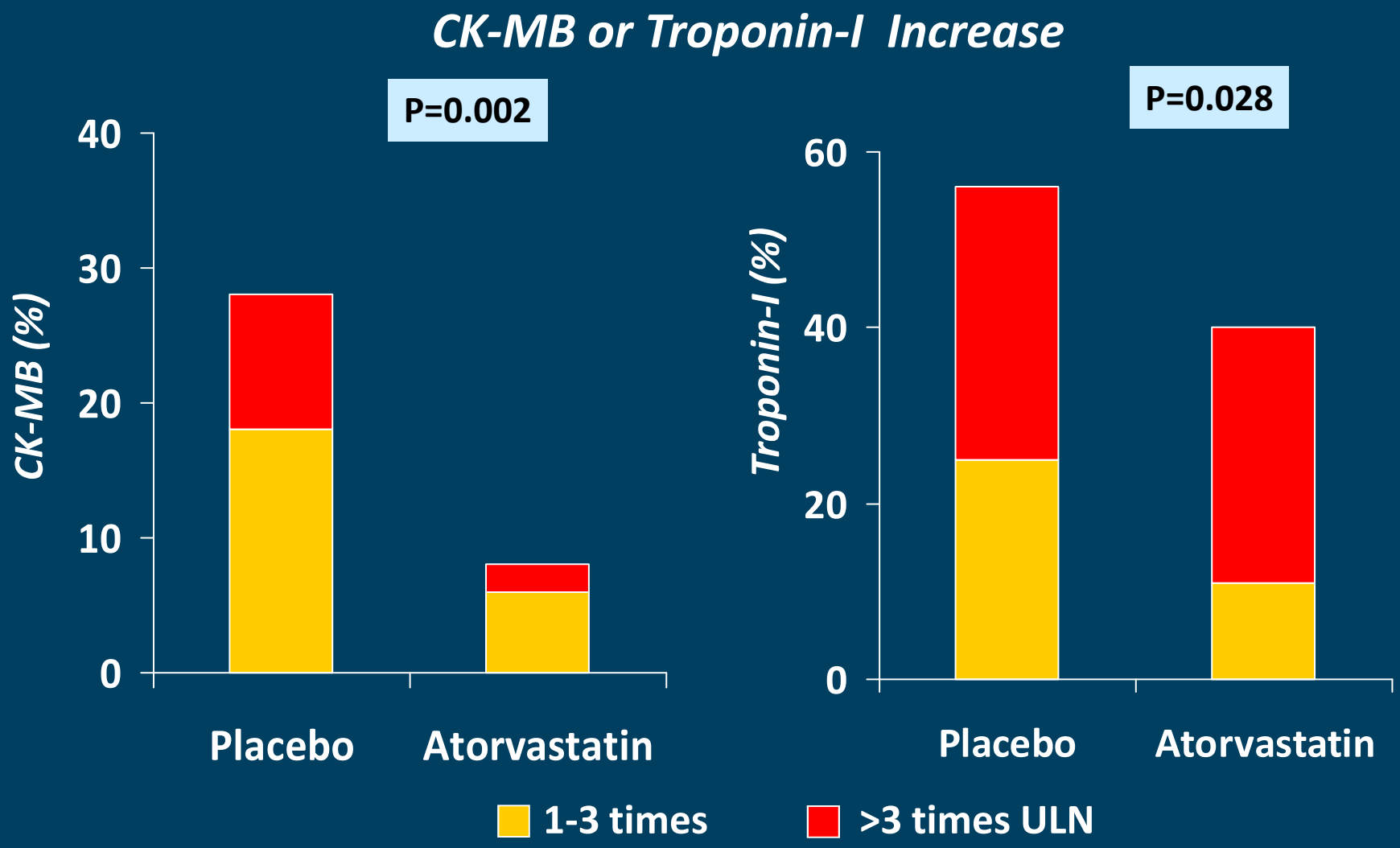
ARMYDA–ACS
Results

Individual and combined outcome measures of the primary endpoint at 30 days



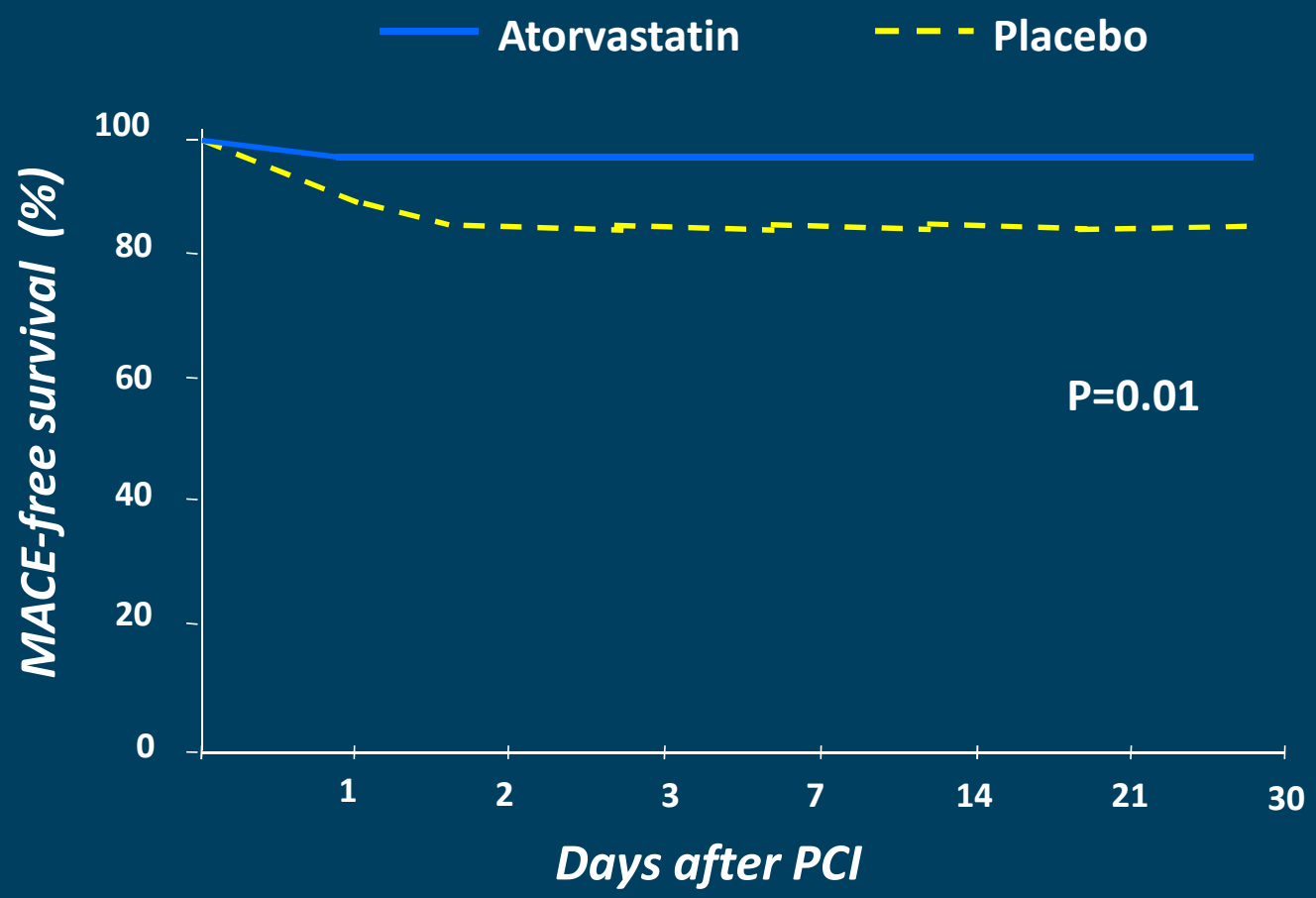
Patti G, et al. *J Am Coll Cardiol.* 2007;49:1272-1278.

AMRYDA-ACS Result: Secondary End Points



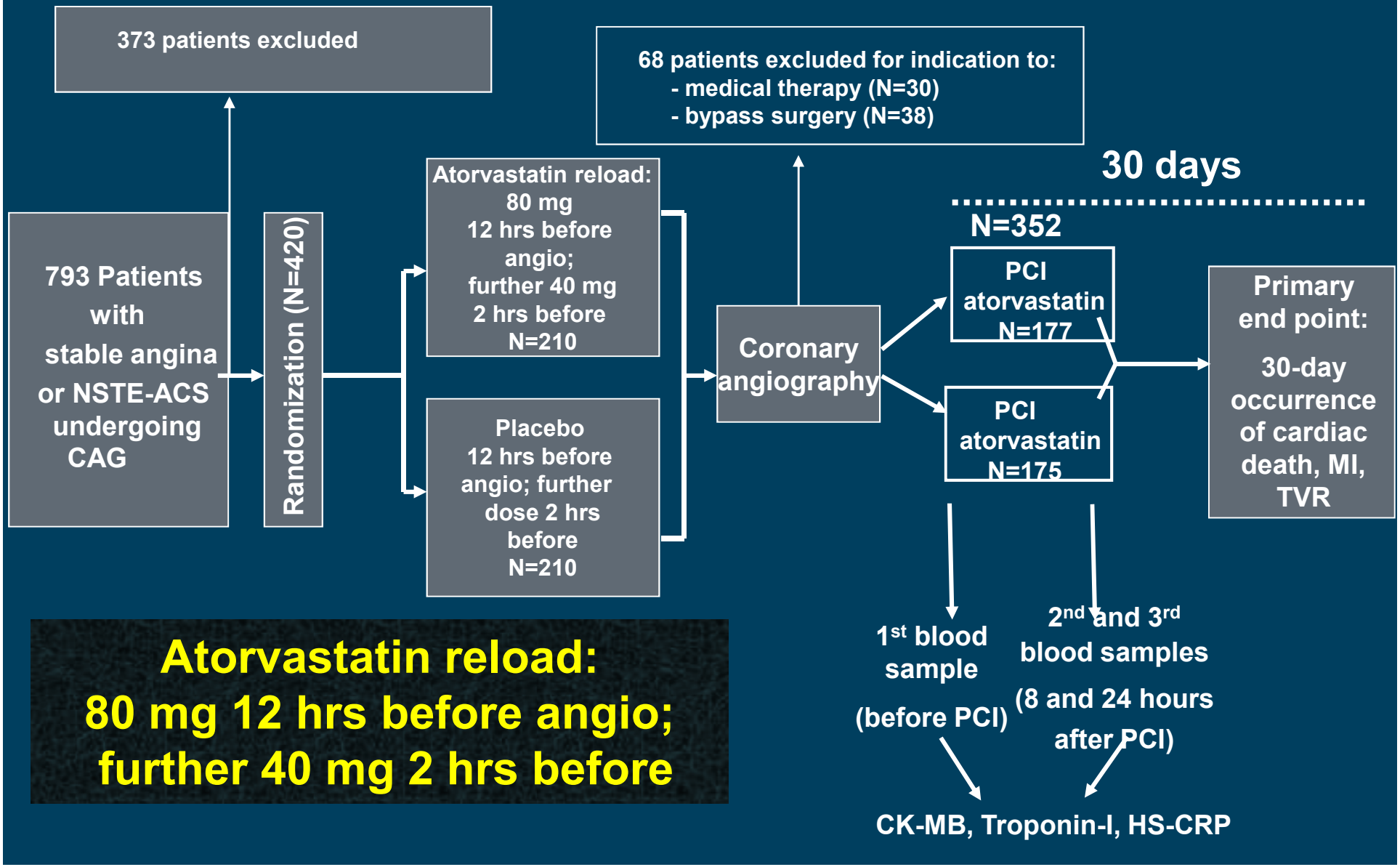
Patti G, et al. *J Am Coll Cardiol. 2007;49:1272-1278*

ARMYDA-ACS: Survival Curves



Patti G, et al. *J Am Coll Cardiol. 2007;49:1272-1278*

ARMYDA-RECAPTURE trial: Study design



ARMYDA-RECAPTURE trial

Inclusion criteria:

Patients on chronic (>30 days) statin therapy and stable angina or NSTE-ACS undergoing coronary angiography

Exclusion criteria:

- **ST- segment elevation acute myocardial infarction**
- **Non ST-segment elevation acute coronary syndrome with high risk features warranting emergency coronary angiography (<2 hours)**
- **Any increase in liver enzymes (AST/ALT)**
- **Left ventricular ejection fraction <30%**
- **Severe renal failure with creatinine >3 mg/dl**
- **History of liver or muscle disease**

ARMYDA-RECATURE: Clinical Features

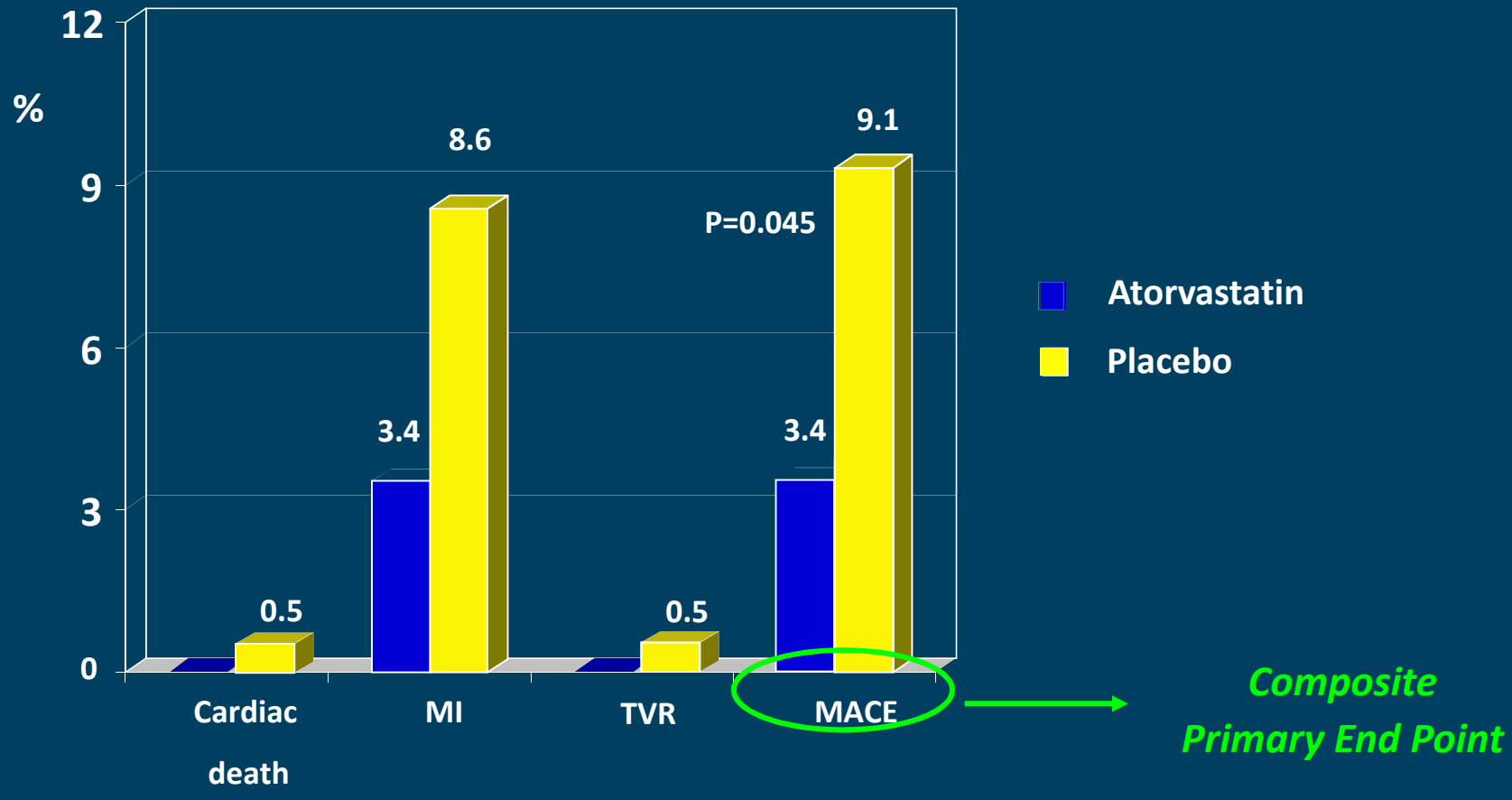
Variable	Atorvastatin (N=177)	Placebo (N=175)	P
Male sex	133 (75)	147 (84)	0.054
Age (years)	66±10	66±10	0.93
Diabetes mellitus	62 (35)	60 (34)	0.97
Systemic hypertension	138 (78)	148 (85)	0.15
Hypercholesterolemia	147 (83)	147 (84)	0.92
Previous MI	56 (32)	65 (37)	0.33
LDL-cholesterol (mg/dL)	92±15	93±16	0.55
Duration of statin therapy (months)	9.1±8.8	9.2±9.1	0.87
Serum creatinine (mg/dL)	1.01±0.34	1.06±0.29	0.26
Clinical pattern:			
Chronic stable angina	95 (54)	94 (54)	0.92
NSTEMI-ACS	82 (46)	81(46)	0.92
Multivessel coronary artery disease	83 (47)	93 (53)	0.29
Type of chronic statin therapy			
Atorvastatin	98 (55)	95 (54)	0.92
Simvastatin (+/- ezetimibe)	62 (35)	58 (33)	0.79
Rosuvastatin	10 (6)	13 (7)	0.65
Pravastatin	7 (4)	9 (5)	0.78

ARMYDA-RECATURE: Procedural Features

Variable	Atorvastatin (N=177)	Placebo (N=175)	P
Restenotic lesions	17 (10)	18 (10)	0.97
Lesion type B2/C	97 (55)	93 (53)	0.84
Multivessel intervention	32 (18)	32 (18)	0.93
Type of intervention			
Balloon only	13 (7)	11 (6)	0.86
Stent	164 (93)	164 (94)	0.86
Bifurcations with kissing balloon	4 (2)	4 (2)	0.73
No. of stents per patient	1.4±0.8	1.3±0.7	0.23
Use of drug eluting stents	58 (33)	64 (37)	0.52
Use of GP IIb/IIIa inhibitors	21 (12)	21 (12)	0.90
Anti-thrombin Tx during PCI			
Unfractionated heparin	159 (90)	155 (89)	0.84
Bivalirudin	18 (10)	20 (11)	0.84

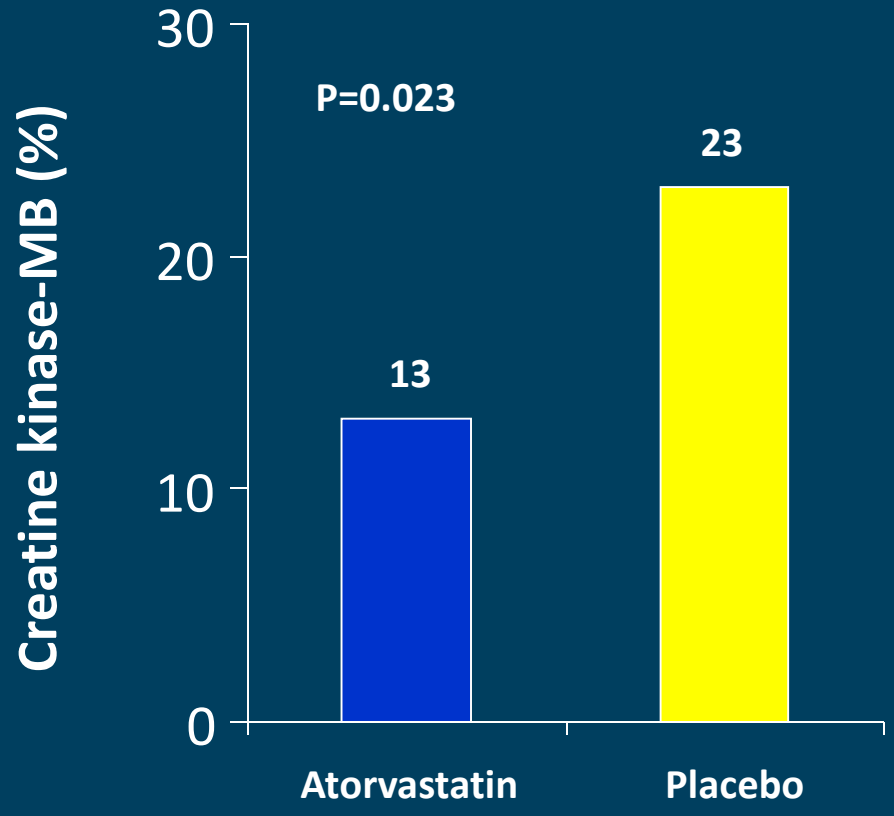
ARMYDA-RECAPTURE: RESULTS

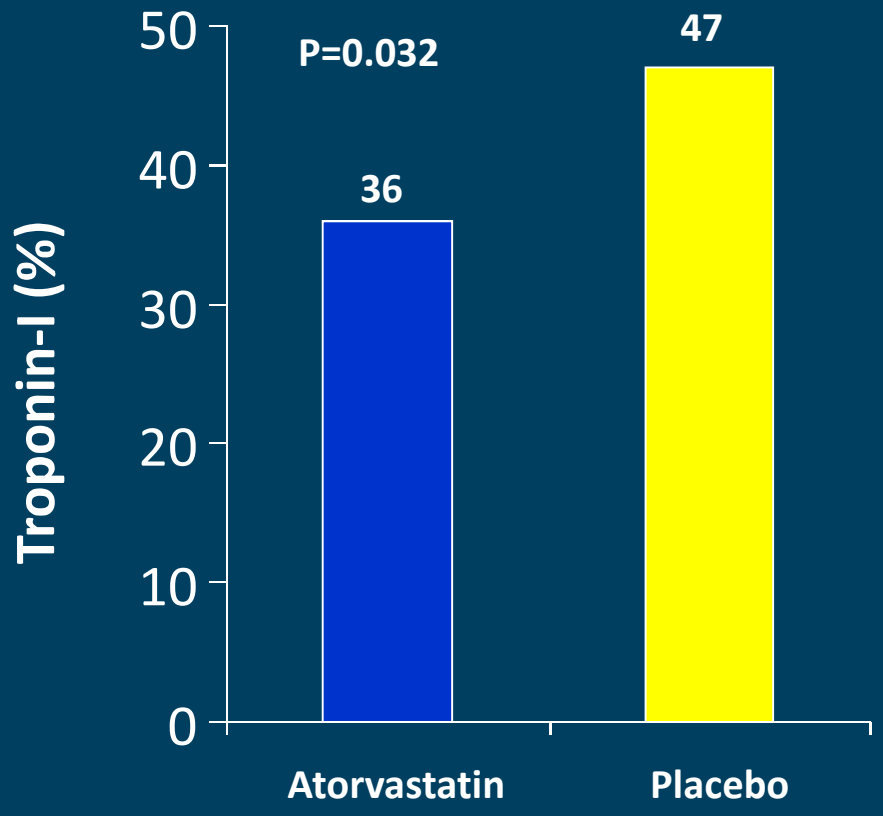
Individual and Combined Outcome Measures of the Primary Endpoint at 30 days



ARMYDA-RECAPTURE: Secondary endpoints

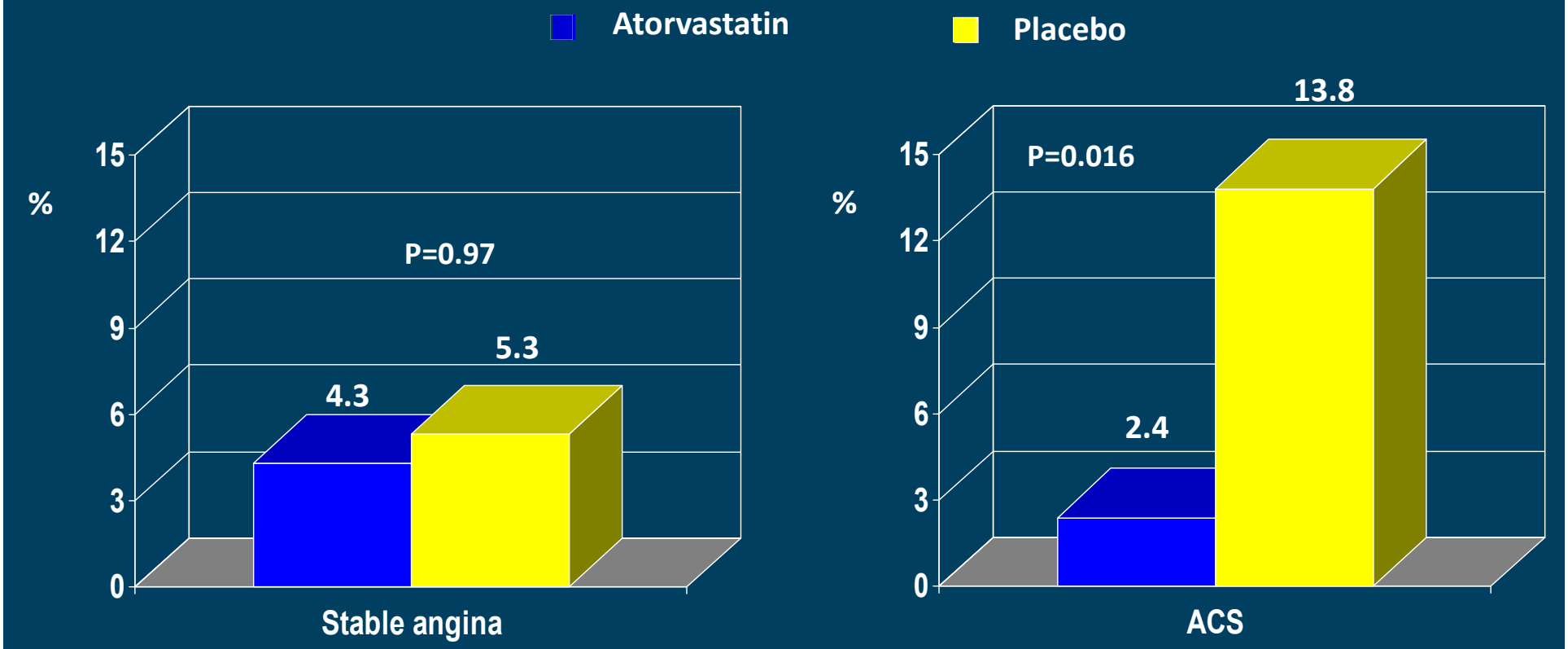
Proportion of patients with any post-PCI cardiac markers elevation





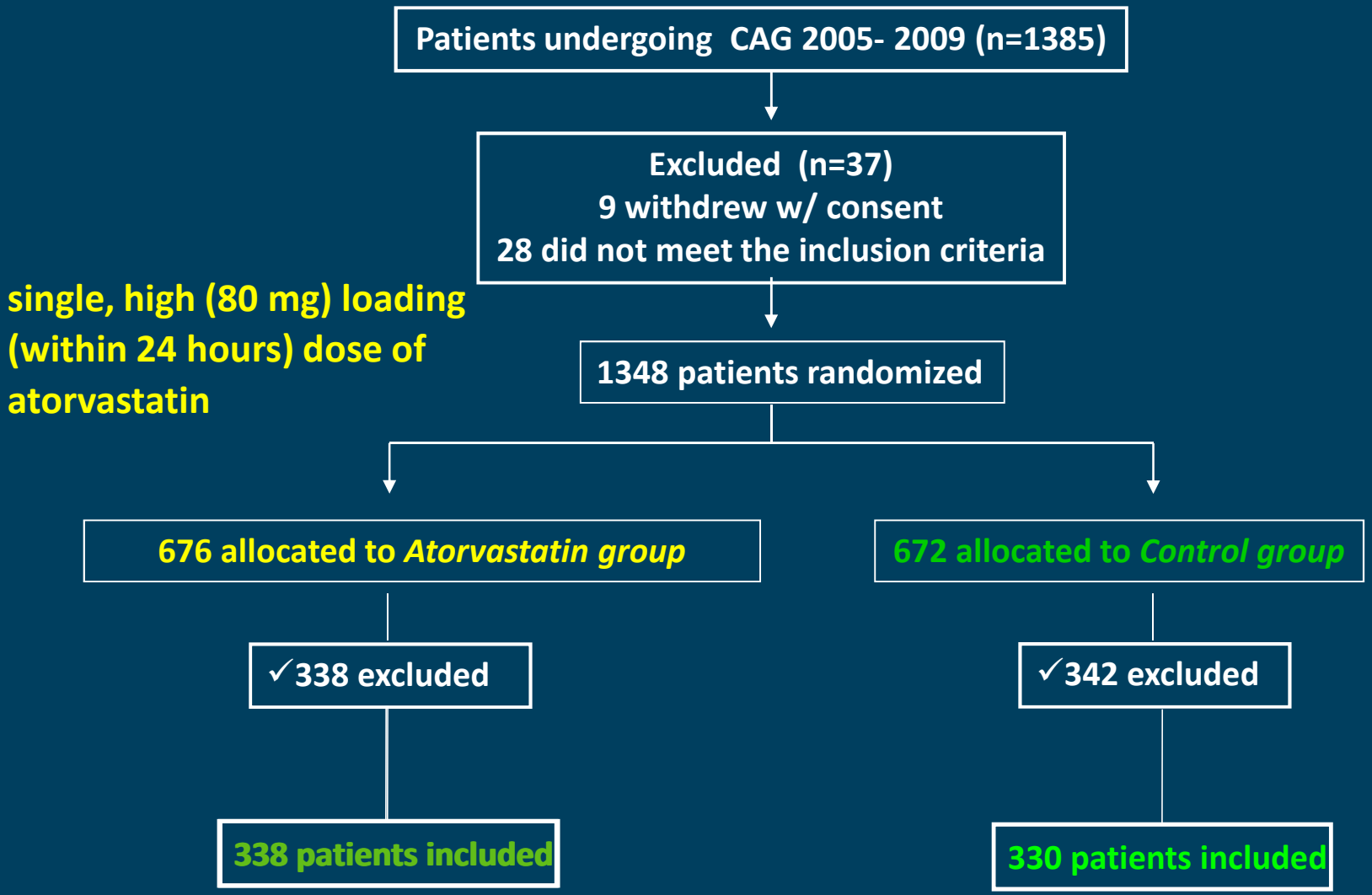
ARMYDA-RECAPTURE Secondary endpoints

MACE according to clinical presentation (stable angina or ACS)



Test for Interaction: z=2.0; P=0.022

NAPLES II : study design



Clinical Characteristics

	Atorvastatin Group (N=338)	Control Group (N=330)
Age, yrs (mean ± SD)	64 ± 9	65 ± 10
Male, %	266 (78.7%)	263 (79.7%)
BMI (kg/m^2)	27.8± 3.8	27.4 ± 3.5
Symptoms Asymptomatic Stable angina Unstable angina	 45 (13.3%) 285 (84.3% 8 (2.4%)	 34 (10.3%) 288 (87.3%) 8 (2.4%)
Family history for CAD	101 (30%)	112 (34%)
Diabetes mellitus	130 (38.6%)	121 (36.8%)
Hypertension, %	131 (78%)	125 (74.9%)
Current smoker, %	79 (24%)	66 (20%)
Prior MI, %	113 (33.4%)	97 (29.4%)
Prior PCI*, %	41 (12.1%)	31 (9.4%)
Prior CABG, %	24 (7.1%)	27 (8.1%)
LVEF, % (mean ± SD)	55.7 ± 9.5	55.5 ± 9.9
β-blockers	130 (38.5%)	129 (39.1%)

* Percutaneous intervention performed in a different vessel and/or lesion.

Angiographic & Procedural Characteristics

	Atorvastatin Group (N=338)	Control Group (N=330)
Multivessel stenting	37 (11%)	33 (10%)
Direct stenting	96 (28.5%)	100 (30.3%)
Atherectomy	5 (1.5%)	7 (2.1%)
No. treated vessel/patient	1.1 ± 0.5	1.1 ± 0.3
No. treated lesion/patient	1.3 ± 0.6	1.3 ± 0.6
CTO	64 (18.9%)	59 (17.9%)
Thrombus	6 (1.7%)	9 (2.7%)
Complex (B2/C) lesions	173 (51.3%)	177 (53.7%)
Bifurcation lesions	56 (16.7%)	55 (16.6%)
GP IIb/IIIa inhibitors	43 (12.7%)	46 (13.6%)
Calcified lesions	80 (23.7%)	88 (26.8%)

In-hospital Outcome

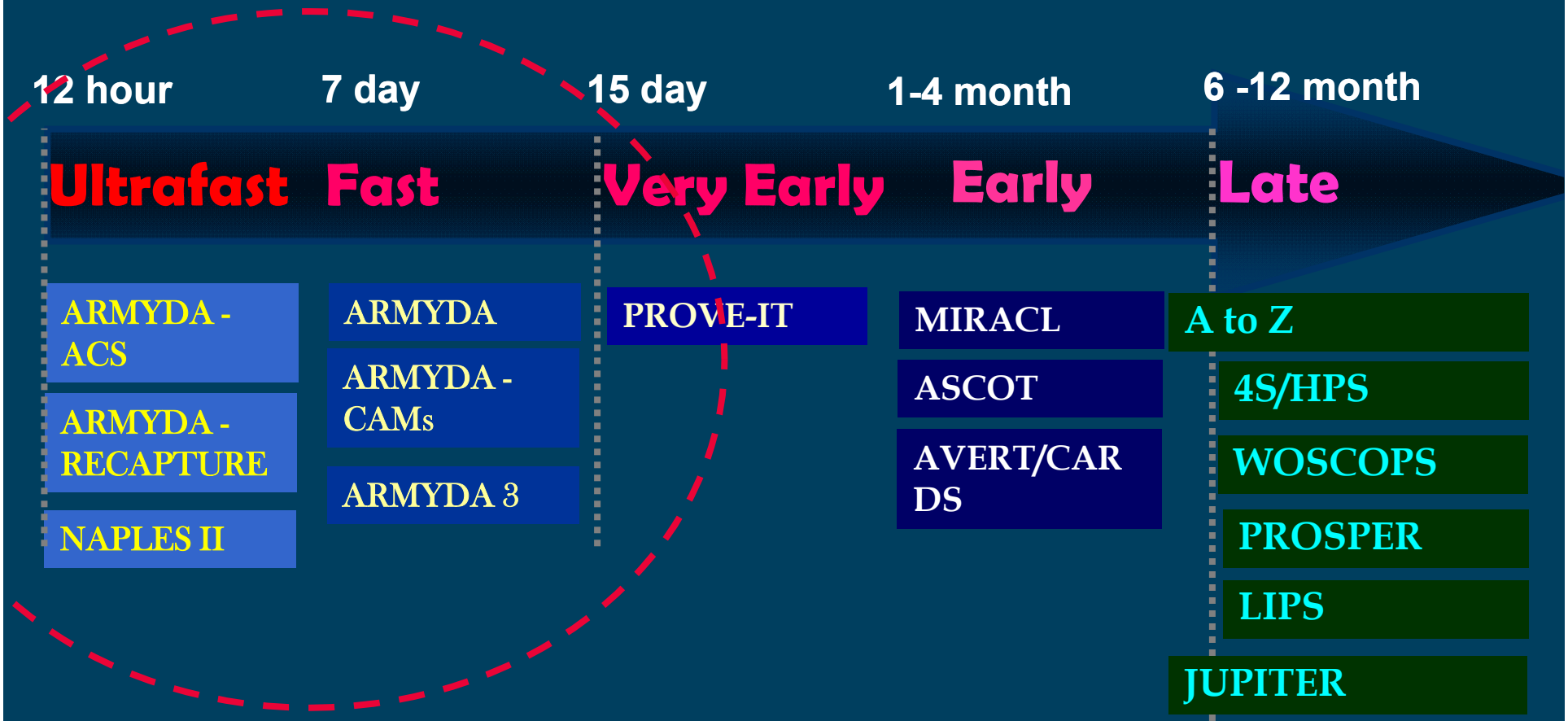
	Atorvastatin Group (N=338)	Control Group (N=330)	P value
Death	**1 (0.3%)**	**0**	**NS**
MI	**33 (9.8%)**	**52 (15.8%)**	**0.014**
Q-wave MI	**1 (0.3%)**	**0**	**NS**
Non Q-wave MI	**32 (9.5%)**	**52 (15.8%)**	**0.014**
Unplanned revasc	**0**	**0**	**-**
Stent thrombosis	**2 (0.58%)**	**1 (0.30%)**	**0.57**
Composite	**34 (10%)**	**52 (15.7%)**	**0.029**

- **A single, high (80 mg) loading (within 24 hours) dose of atorvastatin reduces the incidence of periprocedural non Q wave MI in elective PCI.**
- **This cardioprotective effect seems to be more pronounced in patients with high CRP level at baseline**

Upstream Atorvastatin Therapy Before PCI Summary

- Post-ACS period is associated with a high rate of serious recurrent events in 30 days after event. It shows an urgent need for more aggressive intervention and early statin benefits during the early post-ACS period.
- In ACS, early benefits become more important to choose statin with proven evidence (CV outcome) for recurrent events prevention post ACS.
- In ARMYDA-I, Recapture, NAPLES II findings may support a strategy of routine loading and reload with high dose atorvastatin early before intervention even in the background of chronic therapy
- In ARMYDA-ACS, even *a short-term atorvastatin pretreatment* prior to PCI may improve outcome in patients with Unstable Angina and NSTEMI.
- Early reduction in clinical events may be related more to pleiotropic effects (eg, greater reduction in inflammation).

Ultra-Fast Effects of Statin Therapy



Now, Beneficial Effects of Upstream Atorvastatin Therapy Before PCI proved.

Atorvastatin 80 and 40 mg

Then, what is the evidence for after PCI?

Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study

Atherosclerosis (2009),
doi:10.1016/j.atherosclerosis.2009.12.001

Study Purpose

To examine
whether the early initiation of statin
in patients with ACS
improves long-term prognosis

Study Design

Study population :

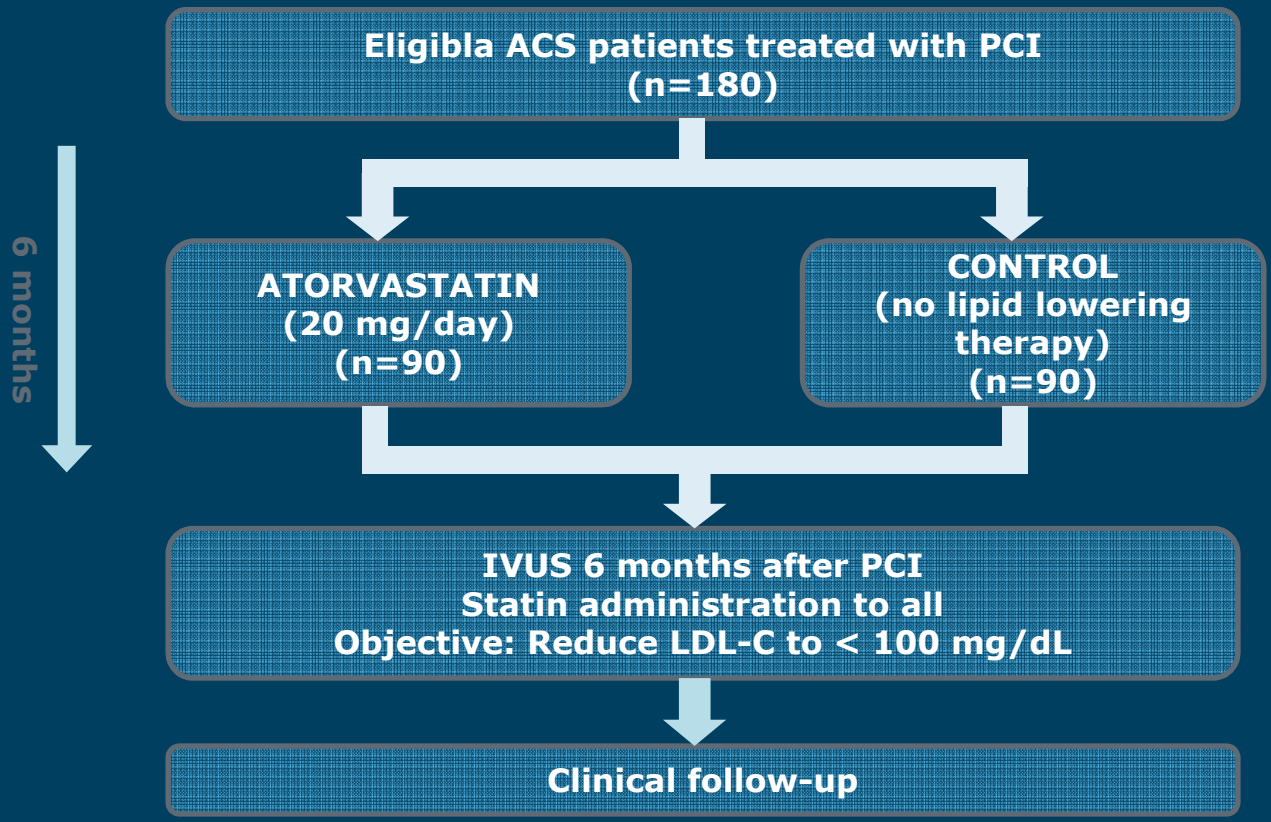
180 patients with ACS who underwent emergency percutaneous coronary intervention.

Study method :

- Prospective observational follow-up cohort study
- Patients were randomized to early intensive lipid-lowering therapy (n=90; atorvastatin 20 mg/day) or standard care (control, n=90) within 48 h of ACS onset. Six months after PCI, all patients were treated with statins(including atorvastatin, pitavastatin, pravastatin, simvastatin and fluvastatin)

- **Primary end points: The first occurrence of major adverse cardiac and cerebrovascular events(MACCE); that is, all-cause death, recurrent ACS and stroke.**

Study Design



Change of blood parameters

Blood parameters of patients at baseline and follow-up at 6 months.

	Baseline			Follow-up		
	Atorvastatin (n=89)	Control (n=89)	*p* value	Atorvastatin (n=85)	Control (n=84)	*p* value
Total cholesterol (mg/dL)	**183.1 ± 36.6**	**191.1 ± 38.7**	**0.174**	**148.1 ± 32.1***	**190.6 ± 30.1**	**<0.001**
Reduction in TC (%)				**28.1 ± 32.1***	**-2.6 ± 25.3**	**<0.0001**
HDL-C (mg/dL)	**45.8 ± 13.0**	**43.4 ± 12.2**	**0.107**	**48.1 ± 13.2**	**47.9 ± 17.6**	**0.567**
Triglyceride (mg/dL)	**110.2 ± 67.7**	**127.3 ± 59.7**	**0.247**	**130.5 ± 96.8***	**139.2 ± 97.1**	**0.261**
LDL-C (mg/dL)	**115.3 ± 33.6**	**122.3 ± 36.3**	**0.114**	**72.2 ± 36.7****	**111.2 ± 38.2**	**<0.0001**
Reduction in LDL-C (%)				**33.8 ± 38.2****	**5.8 ± 37.1**	**<0.0001**
LDL/HDL ratio	**2.8 ± 1.1**	**2.9 ± 1.2**	**0.476**	**1.7 ± 0.8**	**2.6 ± 1.0**	**<0.001**
Lipoprotein(a) (mg/dL)	**21.9 ± 16.2**	**23.3 ± 15.8**	**0.316**	**23.2 ± 20.6**	**26.0 ± 19.3**	**0.228**
Apolipoprotein A1 (mg/dL)	**113.0 ± 21.3**	**108.0 ± 21.1**	**0.355**	**126.3 ± 23.5**	**122.7 ± 21.6**	**0.438**
Apolipoprotein B (mg/dL)	**86.3 ± 19.6**	**93.7 ± 21.2**	**0.067**	**68.9 ± 20.1****	**96.1 ± 19.3**	**<0.001**
Apolipoprotein E (mg/dL)	**3.84 ± 0.84**	**3.88 ± 0.95**	**0.945**	**3.32 ± 0.93**	**4.37 ± 1.25**	**<0.001**
HbA1c (%)	**5.9 ± 1.4**	**6.0 ± 1.5**	**0.938**	**5.6 ± 0.8**	**5.6 ± 1.0**	**0.429**
Insulin (μU/mL)	**12.2 ± 10.2**	**11.0 ± 9.9**	**0.374**	**7.7 ± 4.3****	**6.7 ± 4.5***	**0.113**
hs-CRP (mg/L)	**9.5 ± 17.8**	**8.5 ± 18.3**	**0.244**	**1.3 ± 1.8****	**1.8 ± 3.0****	**0.889**

TC, Total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein. Values are means ± SD. $p<0.05$ was considered statistically significant.

* $p<0.05$ (baseline versus follow-up).

** $p<0.01$ (baseline versus follow-up).

Change of blood parameters

One year after ACS onset:

- **LDL-C values** :
  - atorvastatin group (early statin): 85.5±22.8 mg/dL
  - control group (late statin): 96.1±20.3 mg/dL (p=0.025)

MACCE development

(during the entire follow up period 4.2±1.9 years)

- Atorvastatin group : 16

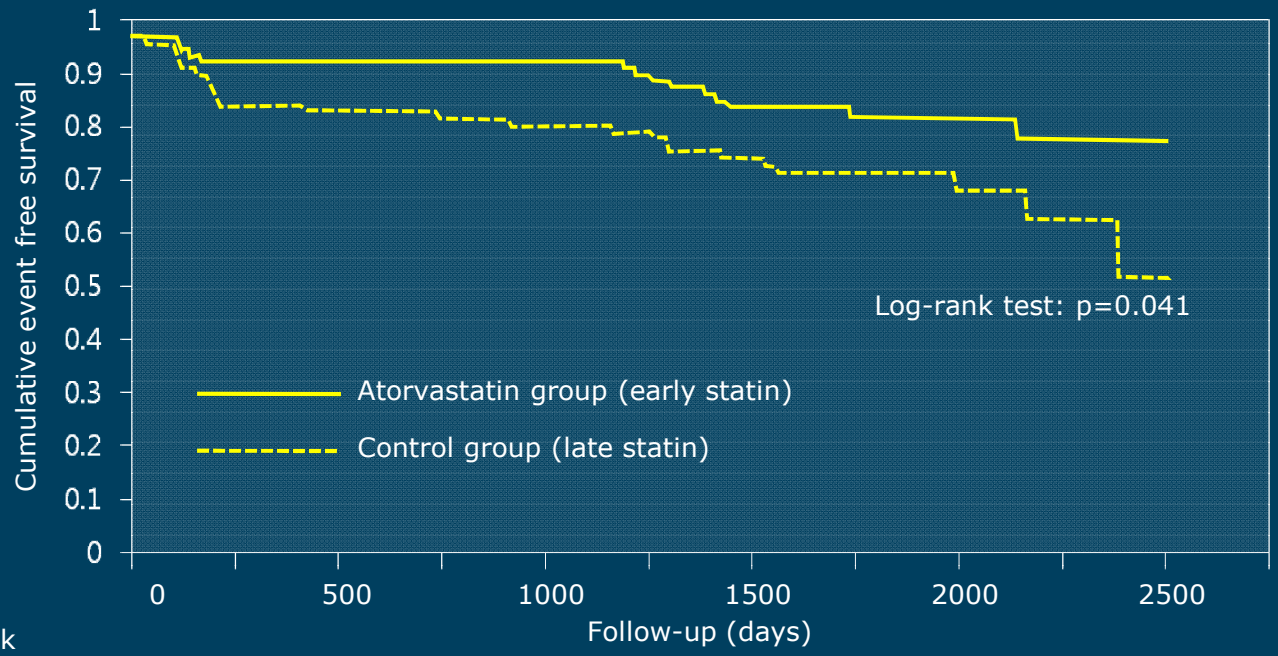
  (death, n=4; ACS, n=10; stroke, n=2)

- control group : 27

  (death, n=6; ACS, n=18; stroke, n=3)

Cumulative event-free survival

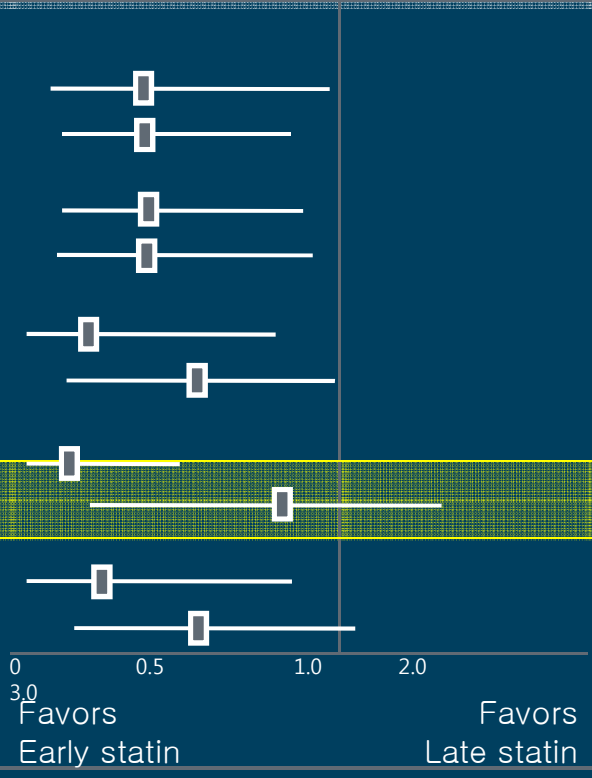
Significantly higher in the atorvastatin than in the control group. (p=0.041)



No. at Risk						
Atorvastatin	**89**	**81**	**80**	**62**	**27**	**3**
Control	**89**	**71**	**69**	**55**	**23**	**1**

A high baseline LDL-C value amplified the beneficial effect of early statin therapy on non-fatal cardiovascular events

Baseline Characteristics	ACS and Stroke / Number	Hazard ratio	Hazard ratio (95%CI)	*p* value
Hypertension				
Yes	24 / 109		0.49 (0.10–1.88)	0.306
No	9 / 69		0.51 (0.21–1.14)	0.103
Diabetes				
Yes	17 / 69		0.55 (0.19–1.44)	0.225
No	16 / 109		0.54 (0.18–1.46)	0.226
Class of ACS				
AMI	15 / 103		0.34 (0.09–1.01)	0.051
Unstable angina	18 / 75		0.70 (0.27–1.79)	0.459
LDL-C				
≥ 118 mg/dL	18 / 88		0.21 (0.05–0.64)	0.004
< 118 mg/dL	15 / 90		1.06 (0.38–3.17)	0.901
hs-CRP				
≥ 3.0 mg/L	17 / 86		0.43 (0.15–1.11)	0.082
< 3.0 mg/L	16 / 92		0.77 (0.27–2.07)	0.608



Estimates of hazards ratios for recurrent ACS and stroke in groups given statin early (atorvastatin group) and late (control group).

Conclusion

The first long-term follow-up study of ACS patients after revascularization

- Initiation of statin therapy immediately after ACS conferred long-term benefits and 6 months of intensive lipid-lowering therapy improved long-term clinical outcomes after PCI in patients with ACS

- The patients with ACS should be managed more strictly for other coronary risk factors (diabetes, hypertension and negative lifestyle habits).

- The anti-inflammatory properties of Atorvastatin may play an important role in the long-term benefits by administration soon after ACS.

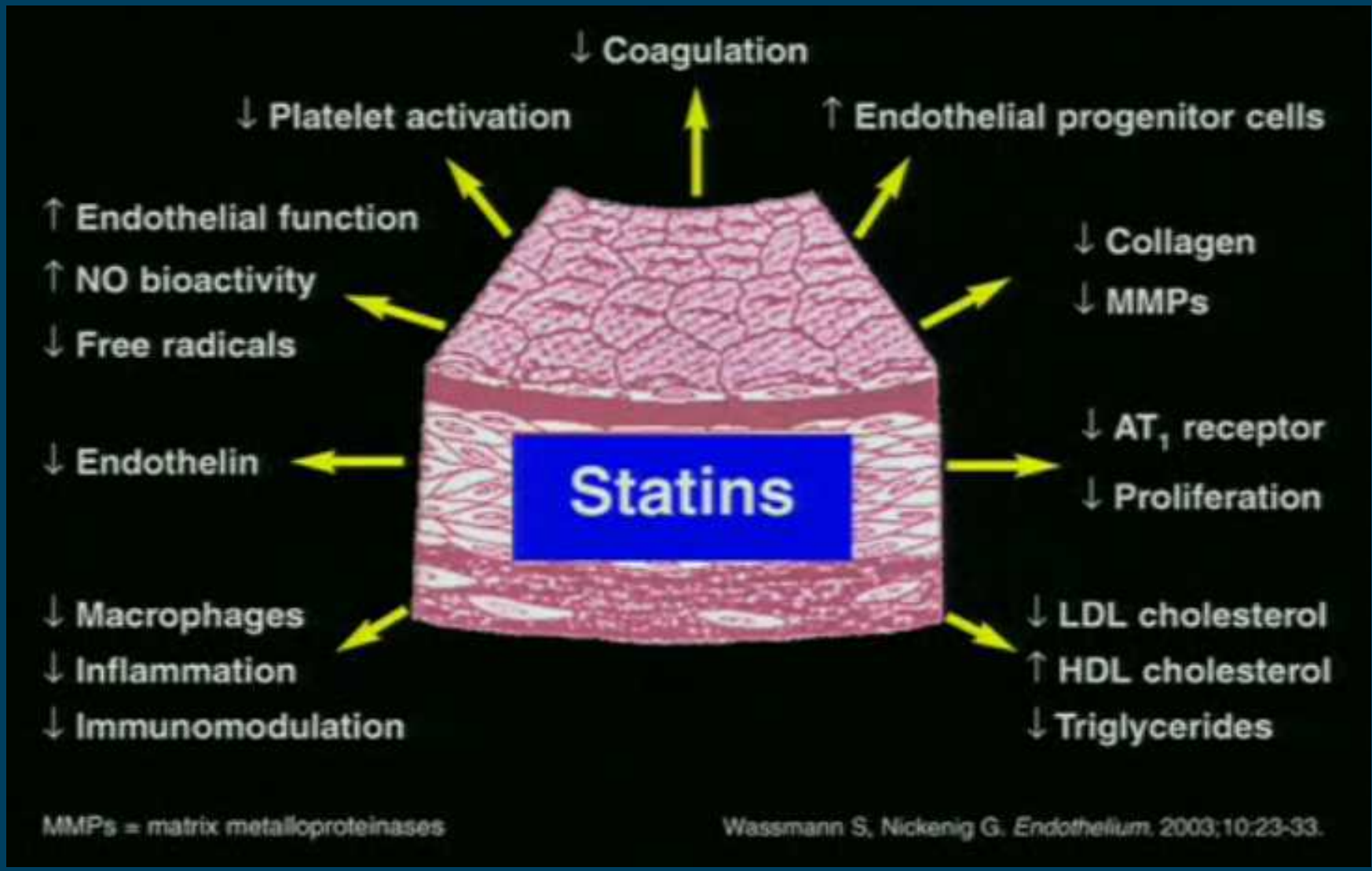
Atorvastatin 80 and 40 mg

Atorvastatin 20mg~40mg

Full Package for PCI Patients

Reloading high dose Atorvastatin prior to PCI and maintaining with Atorvastatin treatment after PCI are rising a new stream to treat PCI patients

Pleotropic Effects of Statins on the Vessel Walls



Conclusion (1)
The Earlier, The Better

- Quantum progress in ACS
  - Benefits observed as early as 30 days after initiation of statin therapy
  - MIRACL (atorvastatin 80 mg vs placebo) and PROVE IT(atorvastatin 80 mg vs pravastatin 40 mg), significant reductions in the primary end point observed at 4 months
- Atorvastatin provided higher reductions in ACS Patients despite similar LDL-C reduction suggesting statin difference.
- In ACS, early reduction in clinical events may be related more to pleiotropic effects (eg, greater reduction in inflammation)
- Early benefits may be related more to LDL-independent (pleiotropic) effects of statins, whereas both lipid-dependent and -independent effects may be responsible for longer-term benefits

Conclusion (2)
Statin Package for ACS patients before and after PCI

- Recent several data demonstrate that a short-term pre-treatment with high-dose atorvastatin is associated with improved clinical outcomes.

- This finding may support a routine treatment with high-dose atorvastatin early prior to PCI.

- Moreover, another recent data showed that atorvastatin 20 mg routine therapy for ACS patients after PCI improve the survival rate.