NAPLES II
Novel Approaches for Preventing or Limiting Event Study
Impact of a Single High Loading Dose of Atorvastatin on Periprocedural Myocardial Infarction

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Background

- **Periprocedural non-Q MI is a frequent and prognostically important complication of PCI [1] .**

- **The available data suggest that statin prevent periprocedural MI [2-3]**

- **Statin administration should be started at least 3 - 7 days before the procedure [2]**

- **It is unknown whether a single, high (80 mg) loading (within 24 hours) dose of atorvastatin may reduce the rate of periprocedural MI.**
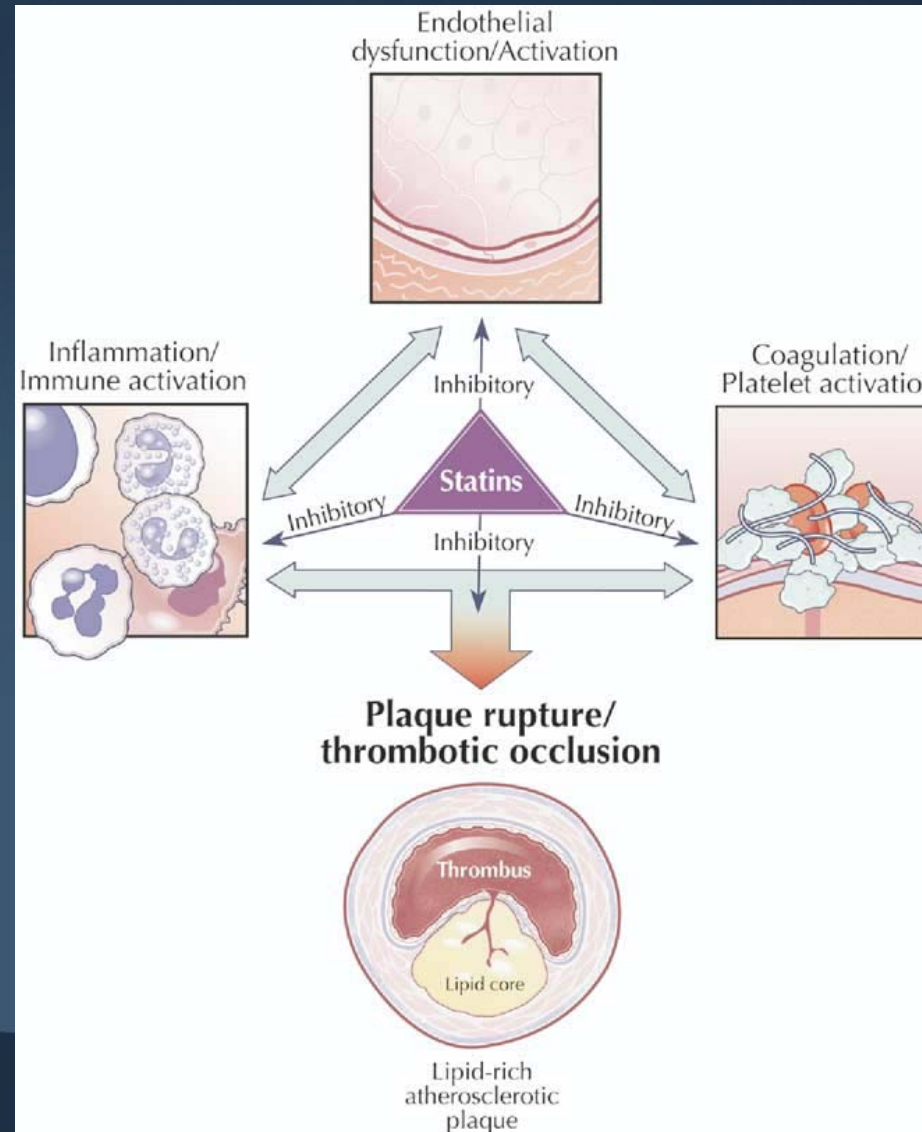
[1] Hermann J. *Eur Heart J* 2005; 25: 2493
[2] Pasceri V. et al. . *Circulation* 2004;110:674-8
[3] Briguori C et al. *Eur Heart J* 2004;25:1822-8

Pleiotropic effects

Background

- **An immediate significant effect of just a single dose of statin has been previously reported**

  - Ostadal et al. demonstrated that a single dose of cerivastatin at the time of admission of patients with unstable angina or non-ST elevation MI positively influences the inflammatory parameters CRP and interleukin-6 at 24 hours (*Mol Cell Biochem* 2003;246:45-50)

  - Romano et al. described that a 24-h treatment with lovastatin and simvastatin induces inhibition of monocyte chemotactic protein-1 (MCP-1) synthesis in mononuclear and endothelial cells in vitro (*Lab Invest* 2000;80:1095-1100)

  - Statins indeed have beneficial effects on endothelial function by a rapid increase in nitric oxide bioavailability; this effect has been observed as early as 3 hours following statin administration (Laufs et al. *Circulation* 1998;97:1129-1135)

Purpose

- **To assess whether a single, high (80 mg), loading (within 24 hours) dose of atorvastatin is effective in preventing elevation of biomarkers of MI following elective coronary stent implantation.**
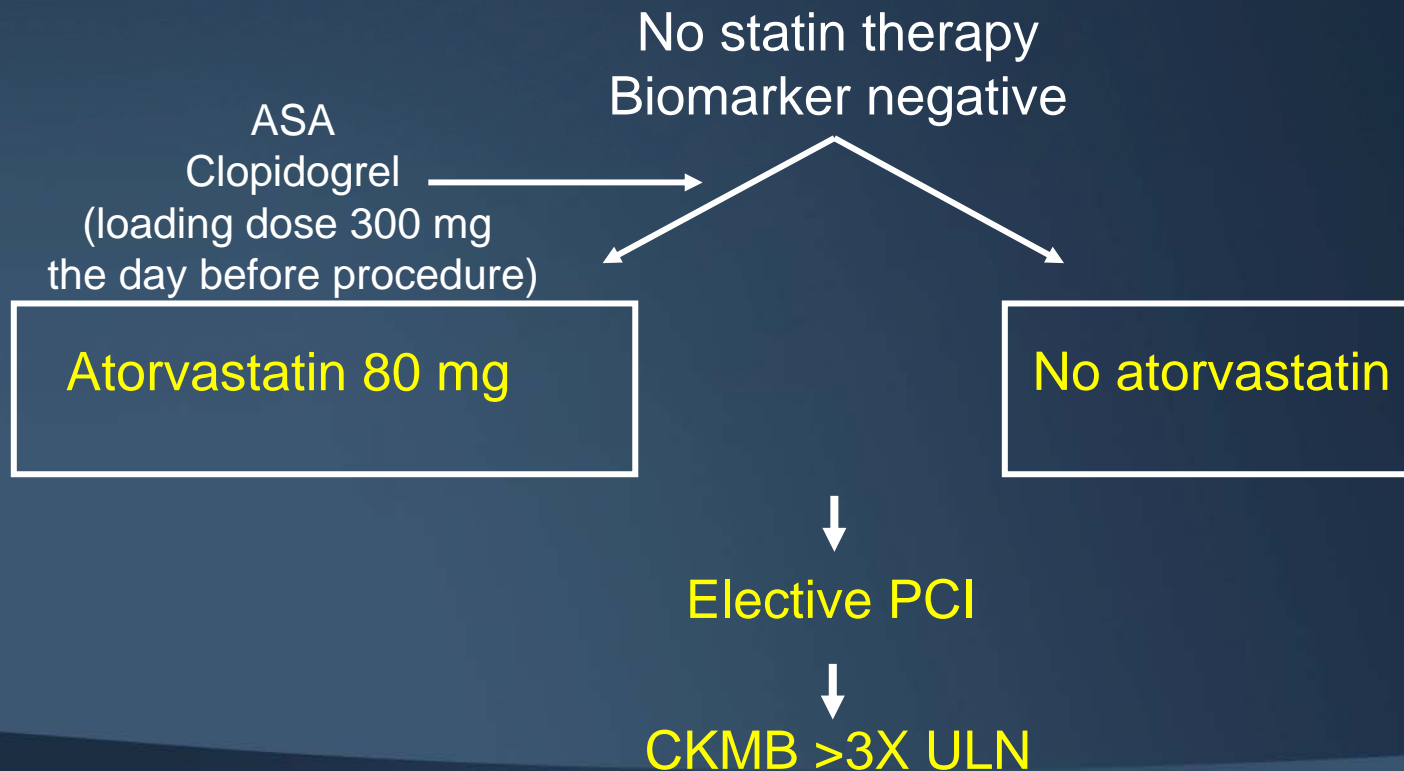
NAPLES II

- **DESIGN:** **Prospective, randomized, double-arm, 2-center clinical, spontaneous study**

Elective PCI in de novo lesions, in native coronary artery

No statin therapy
Biomarker negative

ASA
Clopidogrel
(loading dose 300 mg
the day before procedure)

Atorvastatin 80 mg

No atorvastatin

Elective PCI

CKMB >3X ULN

Sample size

- ## Hypothesis:
    - **Riduction in the primary endpoint from 15% in the *Control* group to 8% in the *Atorvastatin* group[1-2]**

- ## Sample size:
    - **A total of 650 patients (325 each group) will be necessary to gave the study 80% power and a significance level <0.05**

[1] Pasceri V. et al. . *Circulation* 2004;110:674-8
[2] Briguori C et al. *Eur Heart J* 2004;25:1822-8

Inclusion criteria

- **Age $\geq$18 y**
- ***De novo* lesion in a native coronary artery**
- **Elective PCI**
- **Normal cardiac biomarkers**
- **No statin therapy**

Exclusion criteria

- Primary or rescue PCI
- ACS with elevated cardiac markers
- Pregnancy
- Restenotic lesion
- SVG or LIMA treatment
- Active statin therapy
- History of intolerance to statin

Definitions

- **Non-Q wave MI:**
  - **CKMB $\geq$3X ULN**

- **Q wave MI:**
  - **CKMB $\geq$2X ULN with new significant Q waves in $\geq$2 contiguous leads**

Thygesen K et al. *Eur Heart J* 2007;28:2525-38.8

Clinical Characteristics

	Atorvastatin Group (N=338)	Control Group (N=330)
Age, yrs (mean $\pm$ SD)	64 $\pm$ 9	65 $\pm$ 10
Male, %	266 (78.7%)	263 (79.7%)
BMI (kg/m^2)	27.8$\pm$ 3.8	27.4 $\pm$ 3.5
Symptoms		
Asymptomatic	45 (13.3%)	34 (10.3%)
Stable angina	285 (84.3%	288 (87.3%)
Unstable angina	8 (2.4%)	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 $\pm$ SD)	55.7 $\pm$ 9.5	55.5 $\pm$ 9.9
β-blockers	130 (38.5%)	129 (39.1%)

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

Biochemical Characteristics

	Atorvastatin Group (N=338)	Control Group (N=330)
Serum creatinine, median (IQR)	1.16 (1.00-1.32)	1.18 (1.00-1.35)
GFR (ml/min/1.73 m^2)	65 ± 17	64 ± 19
GFR < 60	124 (36.6%)	140 (42.4%)
Fibrinogen, mg/dL	379 ± 123	363 ± 100
Lipid, mg/dL		
Total Cholesterol	211 ± 46	210 ± 42
LDL-C	126 ± 35	129 ± 37
HDL-C	48 ± 11	48 ± 12
Tryglicerides	159 ± 88	151 ± 88

Rate of high CRP
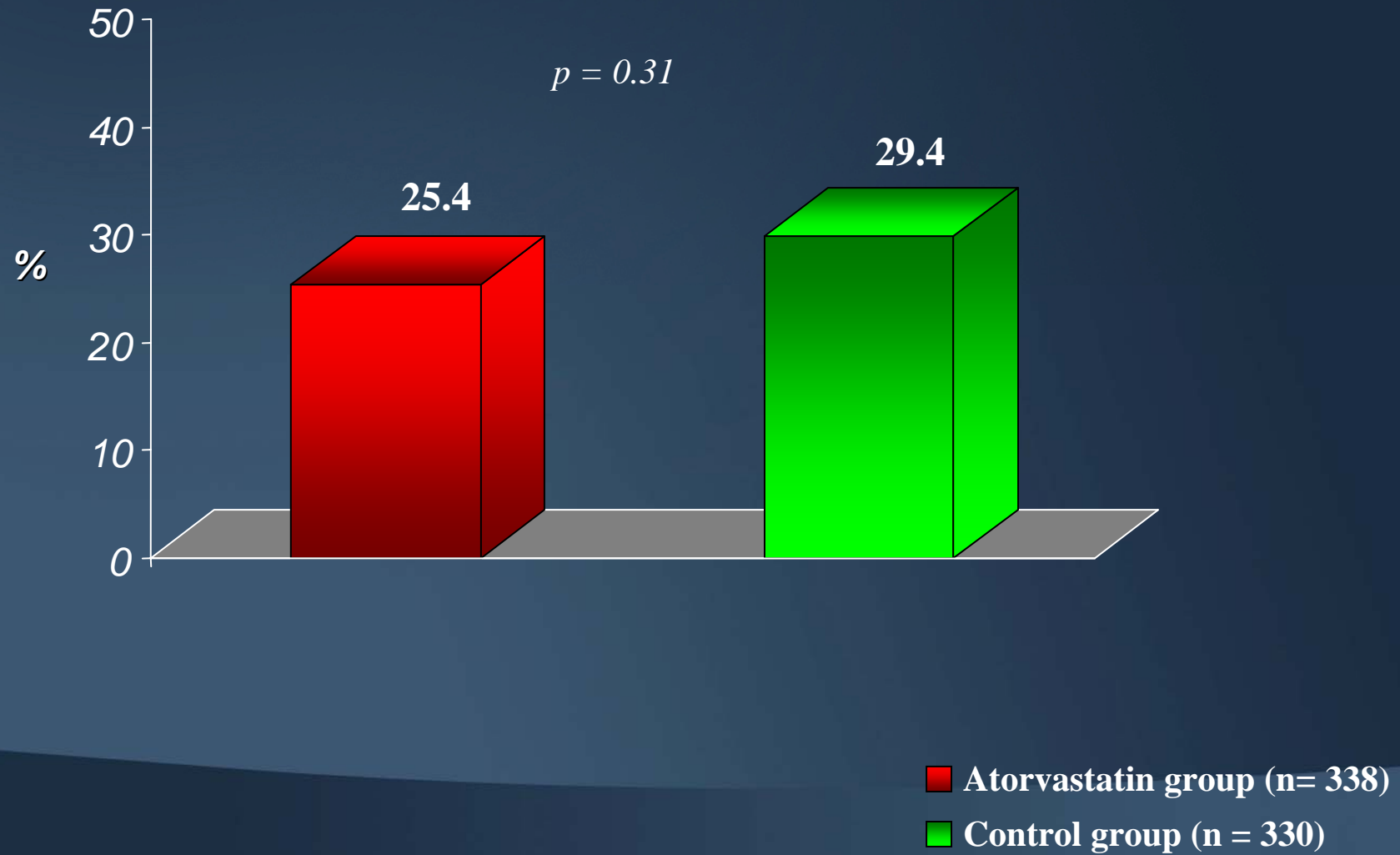
Angiographic & Procedural Characteristics

	Atorvastatin Group (N=338)	Control Group (N=330)
Distribution of CAD		
1-vessel	128 (37.9%)	125 (37.9%)
2-vessel	121 (35.8%)	117 (35.5%)
3-vessel	89 (26.3%)	88 (26.6%)
Target vessel	371	366
LAD	186 (50.1%)	185 (50.5%)
Cx	72 (19.5%)	71 (19.4%)
RCA	107 (28.8%)	105 (28.5%)
LM	6 (1.6%)	6 (1.6%)
Lesion site	436	426
Ostial	46 (10.7%)	47 (11%)
Proximal	193 (44.2%)	189 (44.4%)
Mid	161 (36.9%)	172 (40.4%)
Distal	35 (8.2%)	18 (4.2%)

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%)

Angiographic & Procedural Characteristics

	Atorvastatin Group (N=338)	Control Group (N=330)
Preprocedural QCA		
RVD, mm	3.16 ± 0.62	3.23 ± 0.59
MLD, mm	0.51 ± 0.44	0.51 ± 0.40
DS, %	85 ± 12	84 ± 13
Lesion length, mm	18 ± 10	19 ± 8
Postprocedural QCA		
RVD, mm	3.36 ± 0.61	3.41 ± 0.58
MLD, mm	3.34 ± 0.61	3.37 ± 0.60
DS, %	2 ± 6	2 ± 3
Stent length, mm	30 ± 16	30 ± 16
Max inflation pressure, atm	15 ± 4	15 ± 4
TIMI flow grade pre		
0/1	54 (16%)	54 (16.5%)
2/3	284 (84%)	276 (83.5%)
TIMI flow grade post		
0/1	1 (0.3%)	0
2/3	337 (99.7%)	330 (100%)
BA ratio	1.05 ± 0.12	1.03 ± 0.09

Angiographic Complications

	Atorvastatin Group (N=338)	Control Group (N=330)	P
Major dissection	1 (0.59%)	3 (0.90%)	0.68
Abrupt closure	1 (0.29%)	0	0.48
Slow/No reflow	2 (0.59%)	8 (2.40%)	0.06
Thrombus formation	2 (0.59%)	0	0.50
Side branch closure/compromise	5 (1.48%)	7 (2.12%)	0.57
Distal embolization	2 (0.59%)	2 (0.60%)	1.00
Perforation	2 (0.59%)	2 (0.60%)	1.00
Any of the above	16 (4.7%)	22 (6.6%)	0.31

CKMB >3X ULN
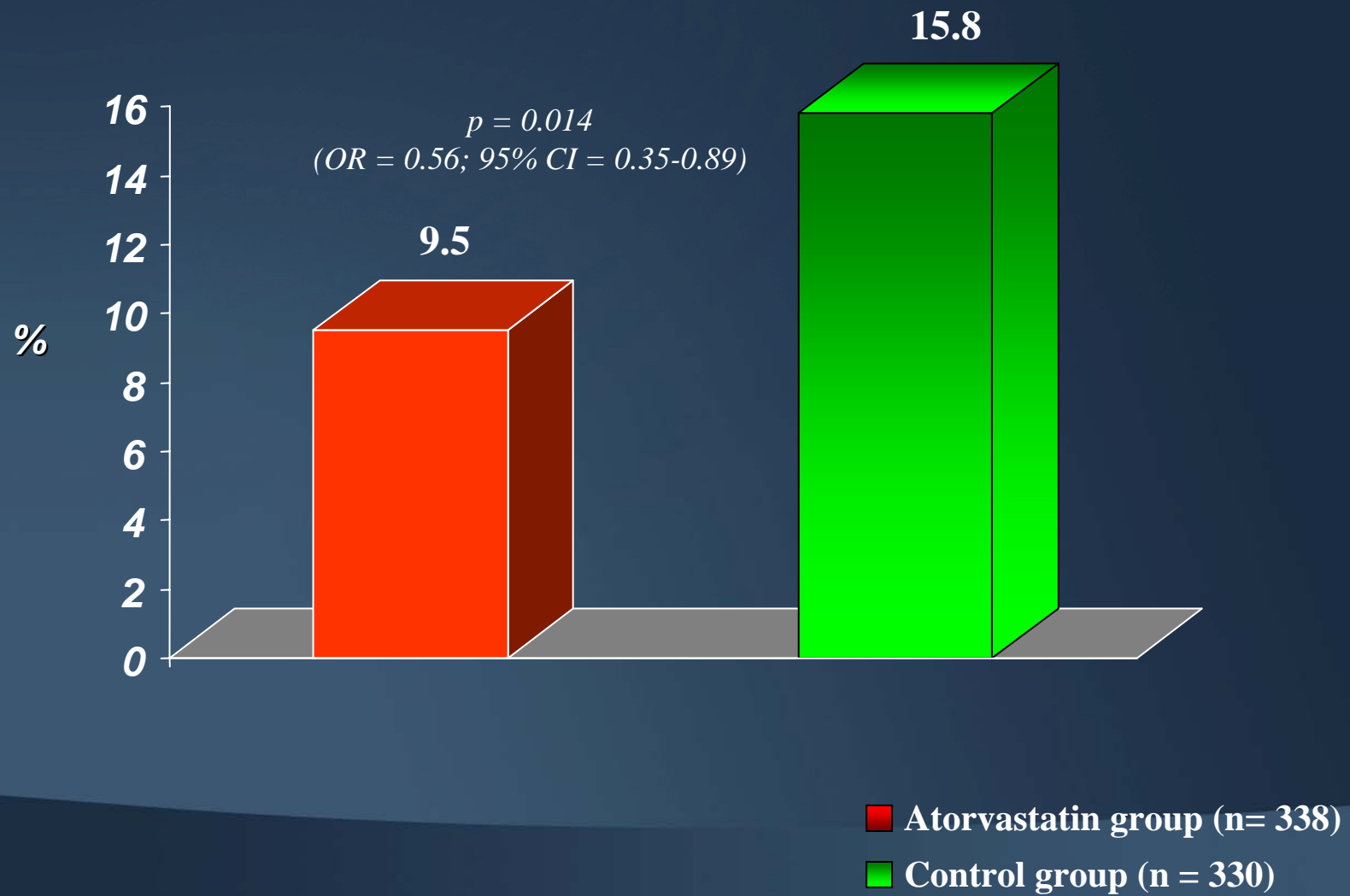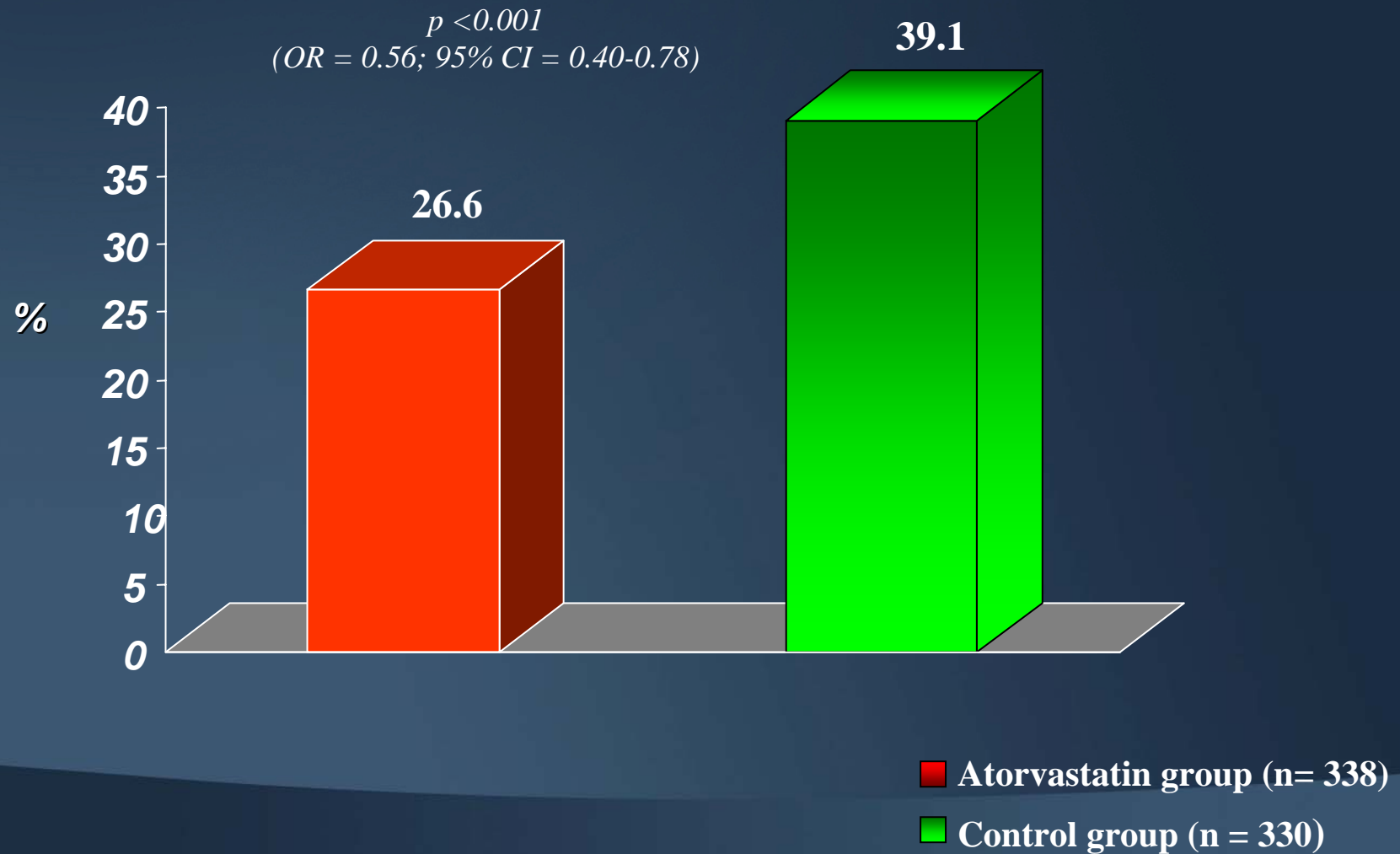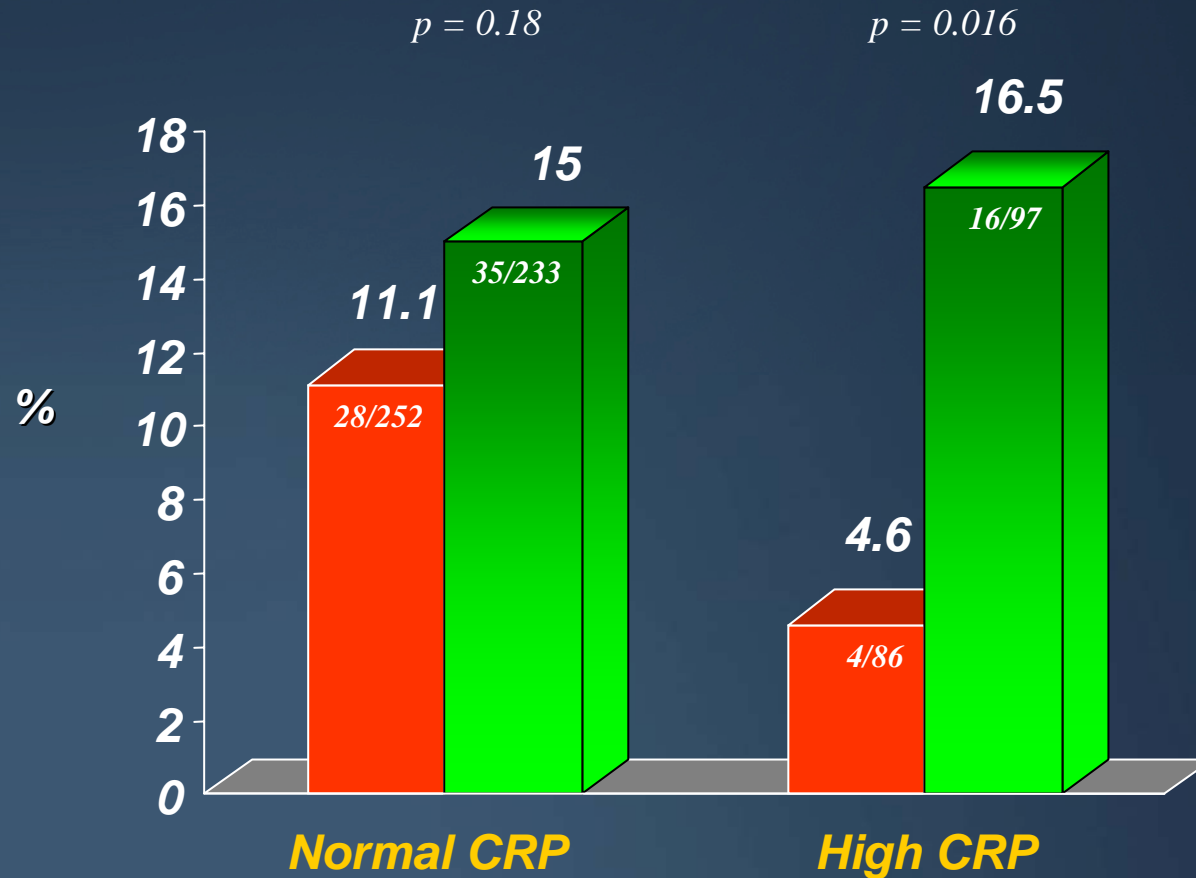
p = 0.014
(OR = 0.56; 95% CI = 0.35-0.89)

9.5

15.8

%

Atorvastatin group (n= 338)

Control group (n = 330)

cTnI >3X ULN

TnI ≥ 3X ULN & CRP
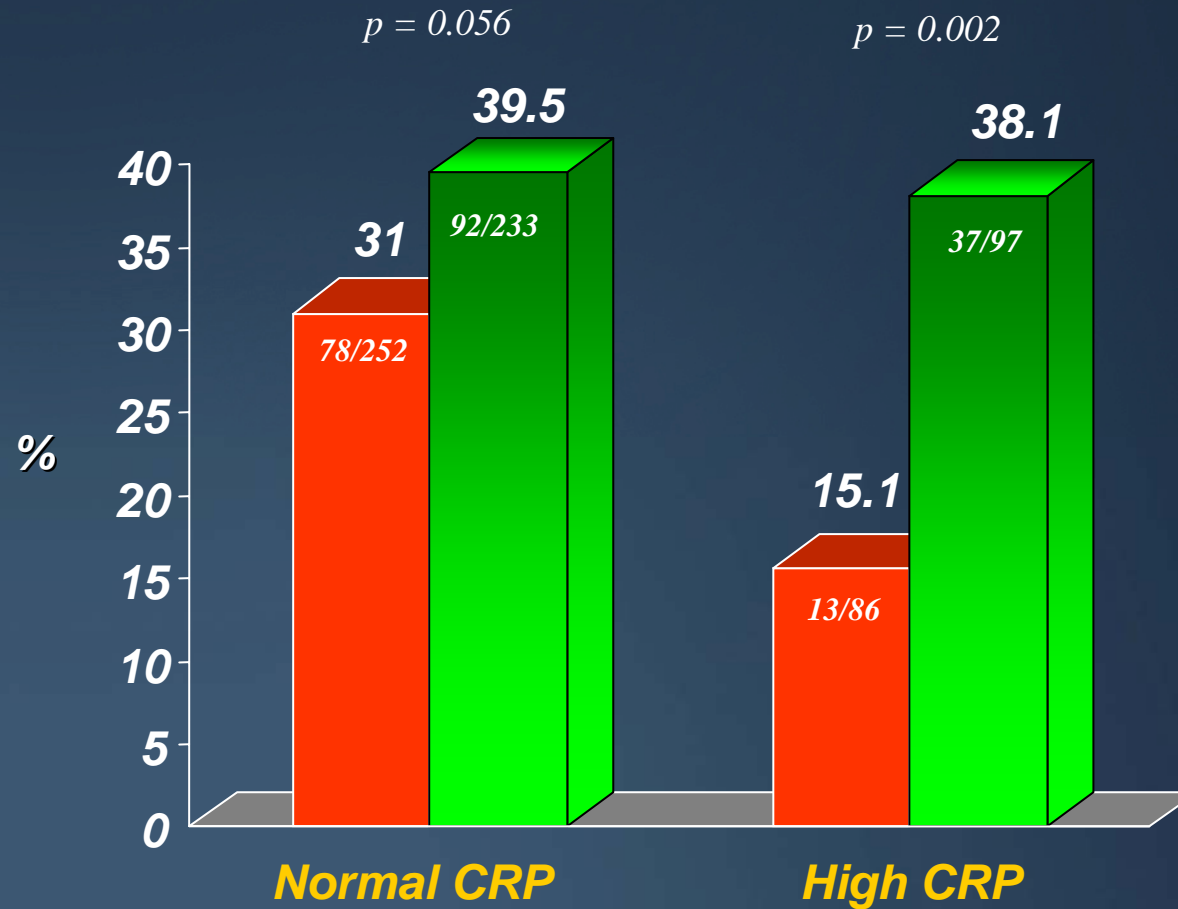
In-hospital outcome

	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

Conclusions

✪ **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**