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

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on behalf of the *PRATO-ACS* investigators

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Contrast Nephropathy

Role of Statins

Anti-lipidemic and pleiotropic properties (anti-oxidant, anti-inflammatory, anti-thrombotic) may have a nephro-protective effect improving endothelial function and reducing oxidative stress.

Uncertainties include:

-type and dose
-timing
-target population

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

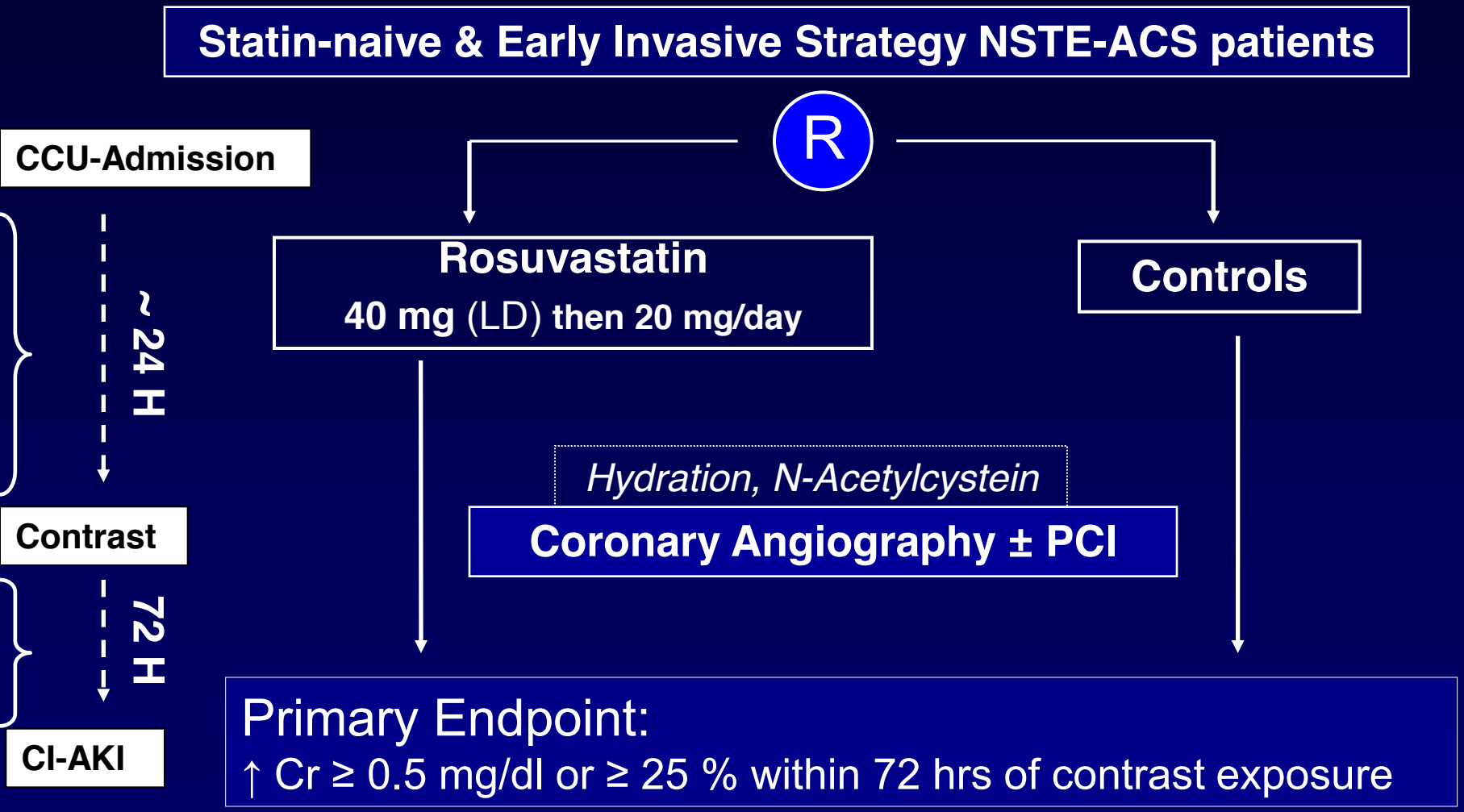
Methods

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

1. CI-AKI defined by other criteria:

↑ Cr ≥ 25 % or ≥ 0.5 mg/dl within 48 hrs

↑ Cr ≥ 0.3 mg/dl within 48 hrs

↑ Cr ≥ 0.5 mg/dl within 72 hrs

↑ Cr ≥ 0.3 mg/dl within 72 hrs

↓ eGFR ≥ 25% within 72 hrs

Methods
Additional End-points

2. CI-AKI in pre-specified subgroups

- Age < or ≥ 70 yrs
- Gender
- Diabetes mellitus
- Creatinine Clearance < / ≥ 60 ml/min
- LV-EF ≤ / > 45%
- CI-AKI Mehran risk score ≤ / > 5
- Contrast volume administered ≤ / > 140 ml
- PCI procedure
- Clinical Risk Level (at least one of the following):
  - Age ≥ 70
  - Diabetes mellitus
  - Creatinine Clearance < 60 ml/min
  - LV-EF ≤ 45%

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*

Methods

Additional Protocol Details

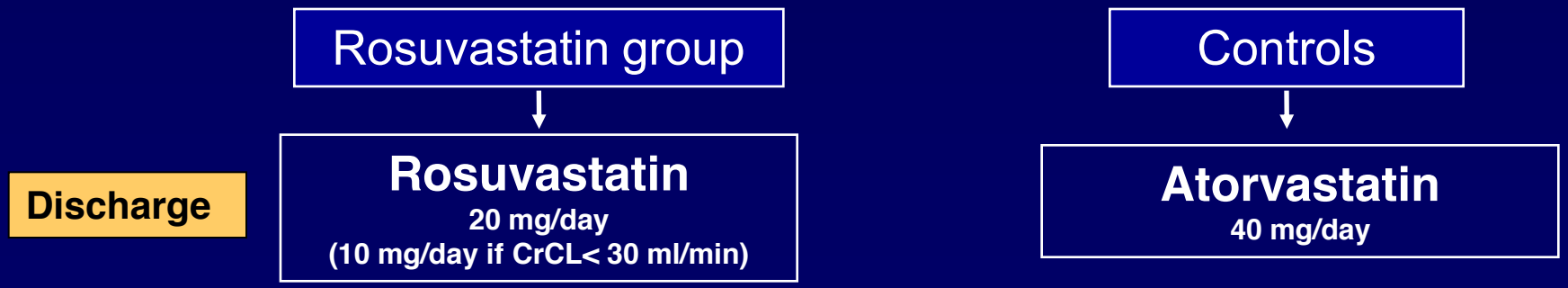
Antiplatelet treatment:

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

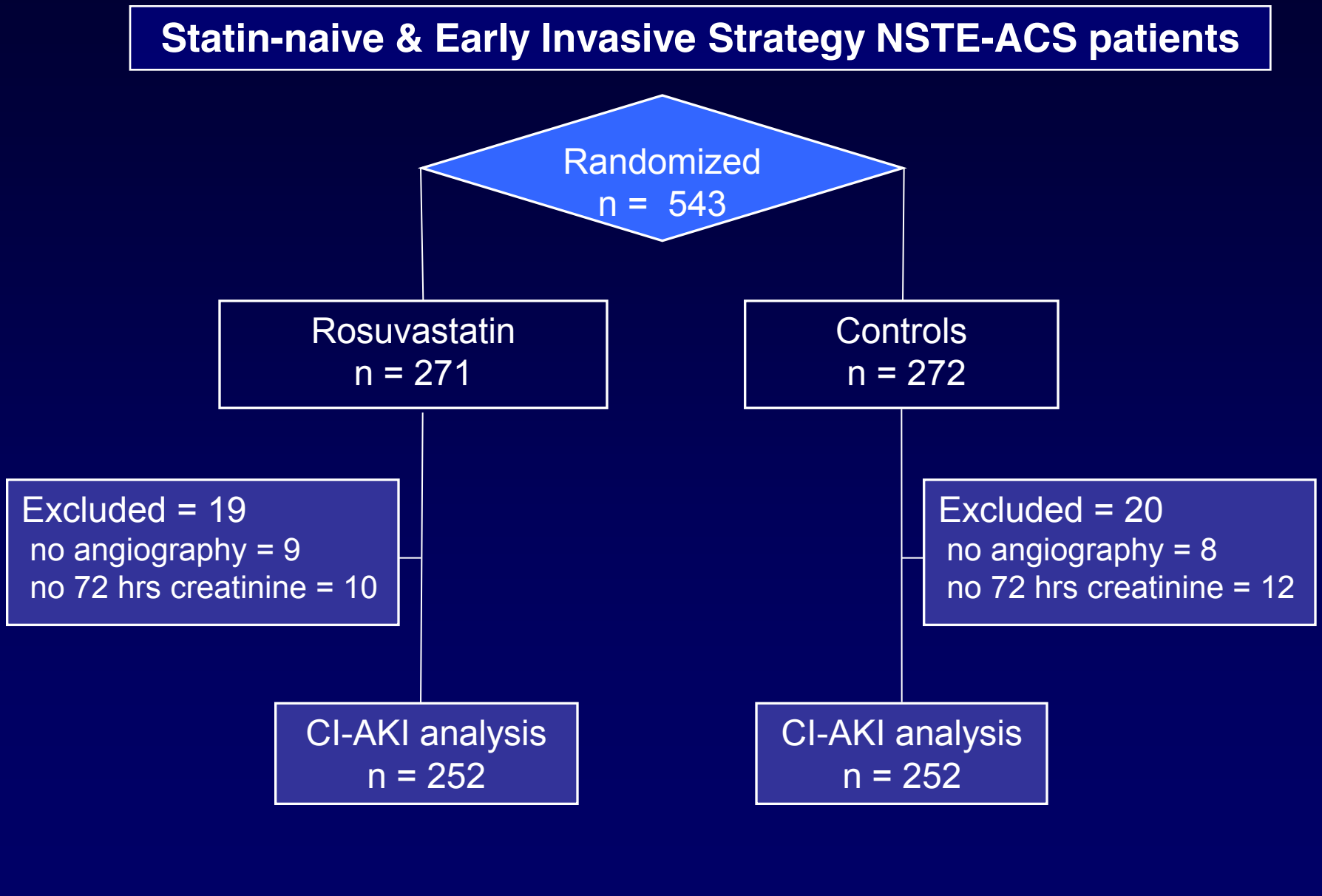
Clopidogrel (600 mg LD, 150 mg/day→ discharge)

- 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


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

Baseline Characteristics

Biochemical

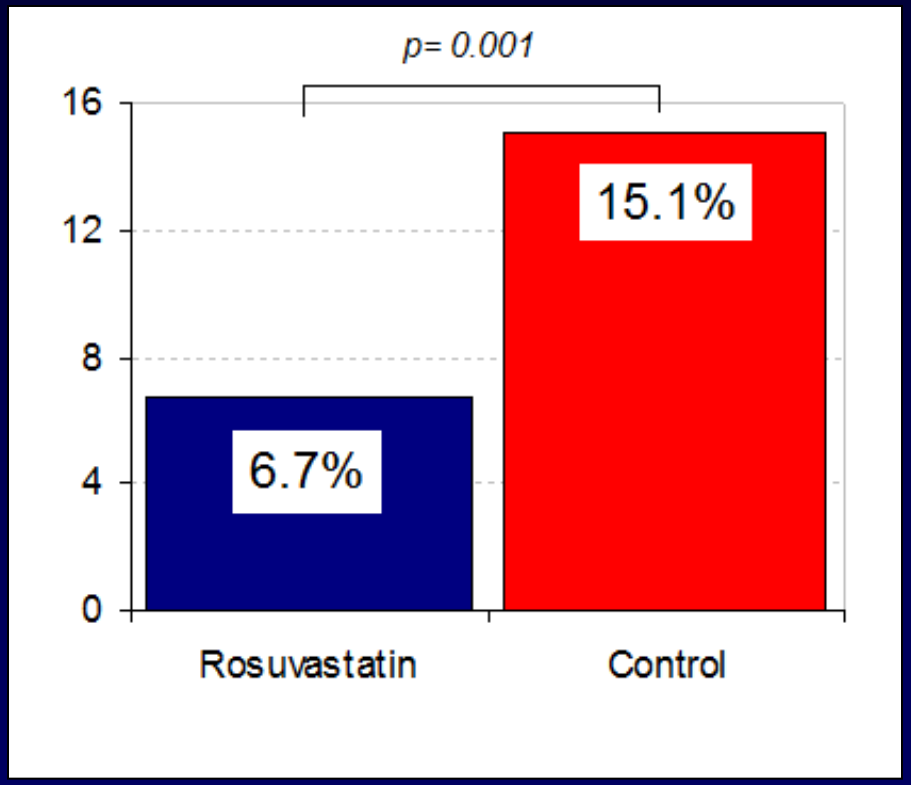
	Rosuvastatin	Control	*p value*
Serum creatinine (mg/dl)	0.95 ± 0.27	0.96 ± 0.28	0.89
Creatinine Clearance (ml/min)	69.9 ± 24.4	69.3 ± 24.9	0.81
Haemoglobin (mg/dl)	14.1 ± 1.6	14.1 ± 1.6	0.77
hs-CRP (mg/dl)	0.43 (0.21-1.18)	0.52 (0.20-1.28)	0.57
cTn-I (ng/ml)	2.3 ± 5.1	2.5 ± 7.0	0.41
CK-MB (ng/ml)	19.2 ± 3 5.2	23.1 ± 48.8	0.34
LDL - Cholesterol (mg/dl)	135.2 ± 38.6	135.8 ± 42.7	0.85
HDL - Cholesterol (mg/dl)	40.2 ±13.7	42.3 ± 13.3	0.08
Triglycerides (mg/dl)	119.7 ± 62.8	118 ± 73	0.78
Glycaemia (mg/dl)	131.7 ± 50.1	137.3 ± 53.4	0.23

Procedural data

	Rosuvastatin	Control	*p value*
Randomization-to-Contrast time (hrs)	22.5 (14 – 43)	23 (15 – 45.5)	0.79
Multivessel disease, %	48.8	47.6	0.78
Contrast volume (ml)	149.7 ± 86.8	138.2 ± 77.8	0.14
Contrast volume >140 ml	46.4	40.1	0.15
Therapeutic strategy, %			0.70
Medical treatment	21.4	23.8	
CABG	10.7	11.9	
PCI	67.9	64.3	
PCI data			
Multivessel PCI	33.9	28.3	0.21
Contrast volume (ml)	183 ± 80	172 ± 72	0.18
Contrast volume >140 ml, %	64.9	59.8	0.20
CI-AKI Mehran risk score, median (IQR)	3 (1 – 6)	2 (1 – 5)	0.36
≤ 5, %	74.2	76.6	
>5, %	25.8	23.4	

CI-AKI Primary Endpoint

(≥ 0.5 or ≥ 25% within 72 hrs)



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

0.41 (0.22 - 0.74)

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

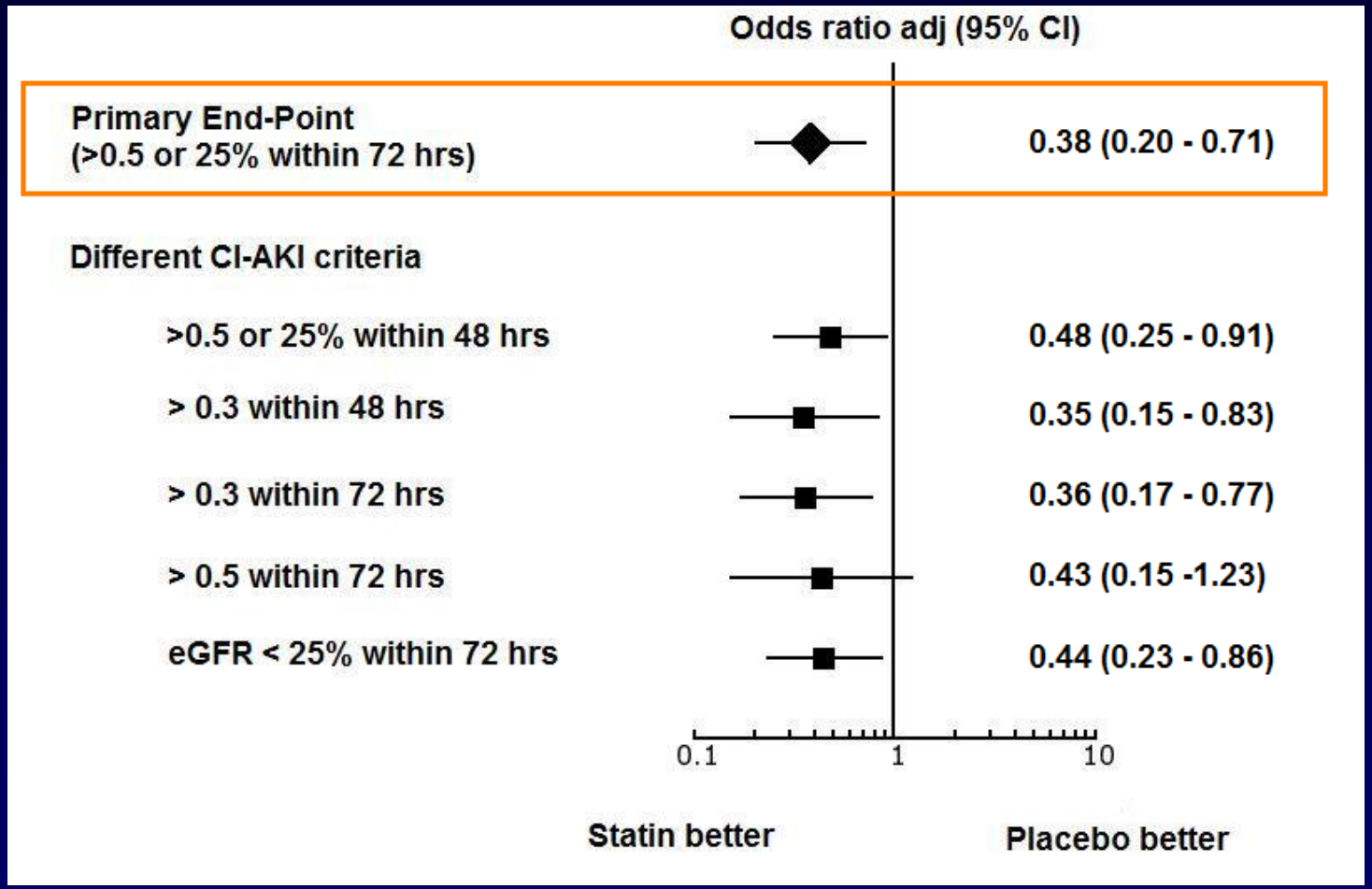
0.38 (0.20 – 0.71)

NNT = 12

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

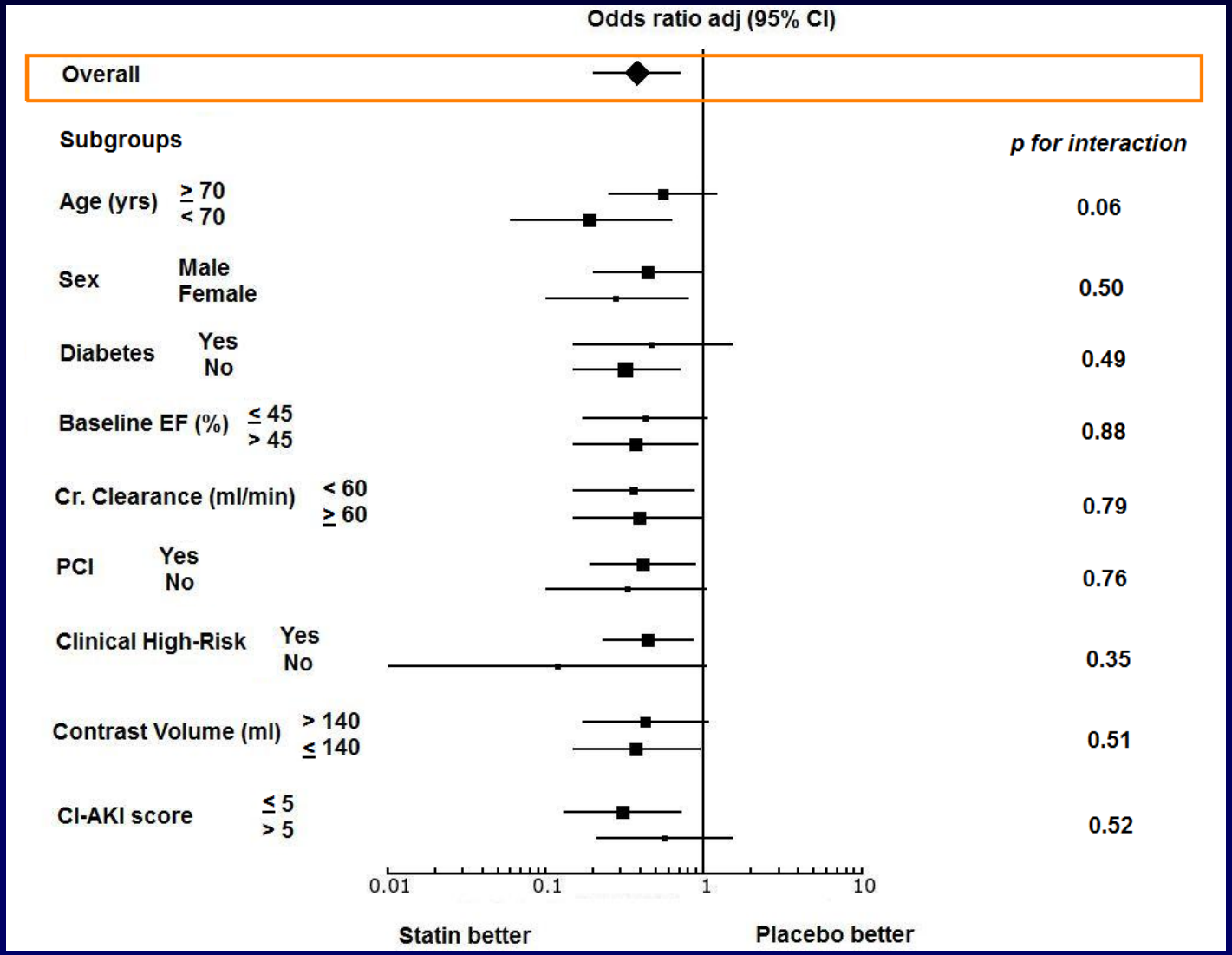
Additional Endpoints:

1.Different CI-AKI criteria



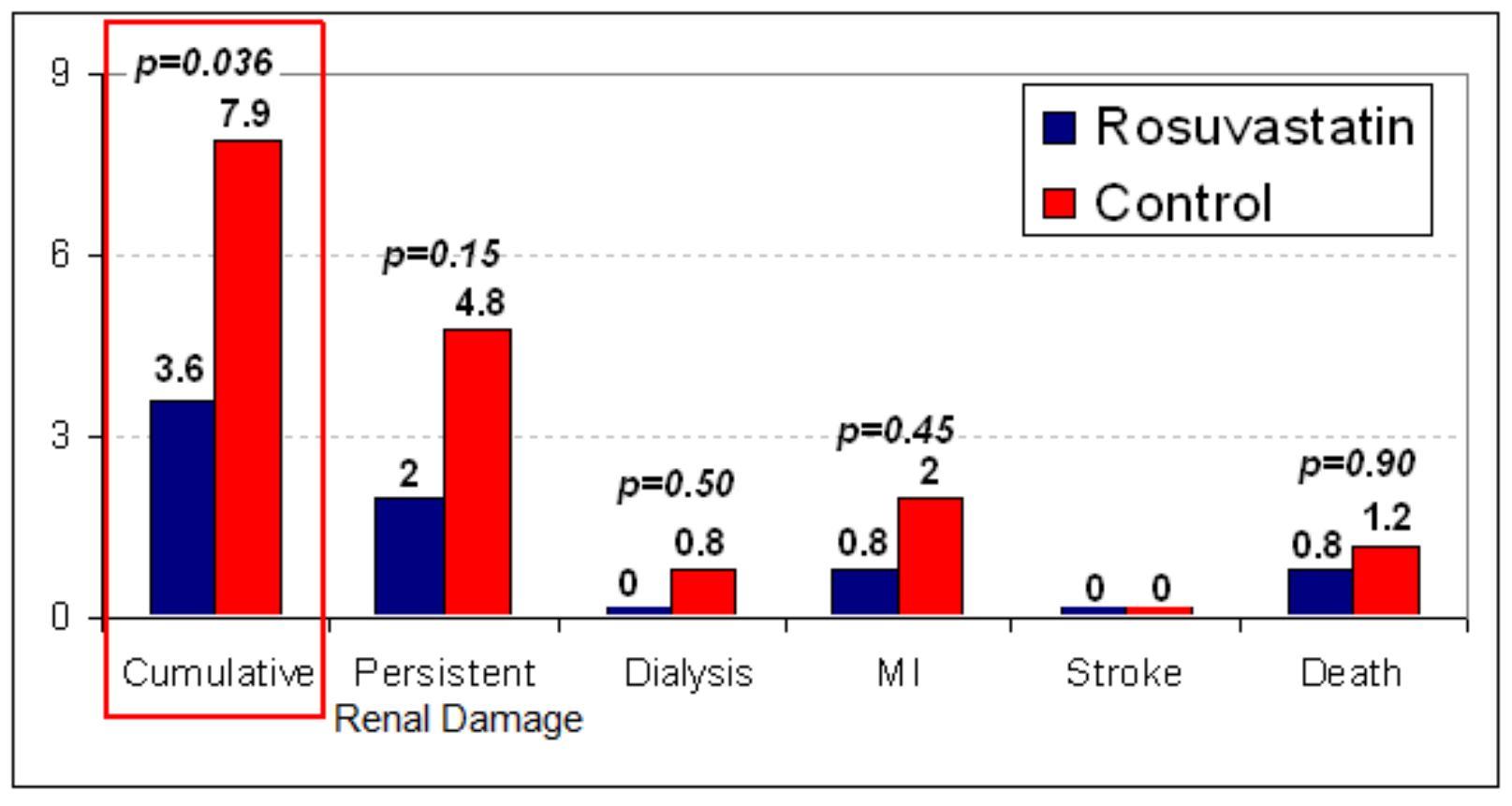
Additional Endpoints:

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.

Conclusions-2

This study suggests that in NSTE-ACS patients scheduled for early invasive strategy high-dose statins should be given *on admission* and in any case must precede the angiographic procedure in order to reduce renal complications after contrast medium administration.


Thank you for your attention!