

ORIGINAL ARTICLE

Rosuvastatin in Older Patients with Systolic Heart Failure

John Kjekshus, M.D., Ph.D., Eduard Apetrei, M.D., Ph.D.,
Vivencio Barrios, M.D., Ph.D., Michael Böhm, M.D., Ph.D., John G.F. Cleland, M.D.,
Jan H. Cornel, M.D., Ph.D., Peter Dunselman, M.D., Ph.D., Cândida Fonseca, M.D.,
Assen Goudev, M.D., Ph.D., Peer Grande, M.D., Ph.D., Lars Gullestad, M.D., Ph.D.,
Åke Hjalmarson, M.D., Ph.D., Jaromir Hradec, M.D., Ph.D.,
András Jánosi, M.D., D.Sc., Gabriel Kamenský, M.D., Ph.D., Michel Komajda, M.D.,
Jerzy Korewicki, M.D., Ph.D., Timo Kuusi, M.D., Ph.D., François Mach, M.D.,
Vyacheslav Mareev, M.D., Ph.D., John McMurray, M.D., Naresh Ranjith, M.D.,
Maria Schaufelberger, M.D., Ph.D., Johan Vanhaecke, M.D., Ph.D.,
Dirk J. van Veldhuisen, M.D., Ph.D., Finn Waagstein, M.D., Ph.D., Hans Wedel, Ph.D.,
and John Wikstrand, M.D., Ph.D., for the CORONA Group*

ABSTRACT

BACKGROUND

Patients with systolic heart failure have generally been excluded from statin trials. Acute coronary events are uncommon in this population, and statins have theoretical risks in these patients.

METHODS

Affiliations for authors are listed in the Appendix. Address reprint requests to Dr. Kjekshus at the Department of Cardiology, University of Oslo, Rikshospitalet University Hospital, Oslo, Norway, or at jkjeksh@medisin.uio.no.

Background

- **Benefits of statins largely due to plaque stabilization and reduction in acute coronary occlusion - BUT such events rarely reported in prior, non-statin, heart failure trials**
 - **However, coronary occlusion may underlie many sudden (and some pump failure) deaths in heart failure. If so, statins could reduce the risk for these deaths in heart failure**
 - **Pleiotropic effects of statins (e.g. on inflammation/endothelial function) may also be beneficial in heart failure**
- **Conversely, reducing lipoproteins may be harmful – they may be beneficial in removing endotoxins entering circulation through the intestinal wall, which may be leaky in heart failure?**
 - **Low cholesterol levels are associated with a worse outcome – levels are already low in many patients with heart failure**
 - **Reducing coenzyme Q10 and selenoproteins may be harmful - leading to skeletal and cardiac myopathy**
- **Against this background, and the fact that patients with heart failure had largely been excluded from prior statin trials, we undertook the CORONA trial**

Patients and Power Calculation

Inclusion criteria

- Systolic HF of ischemic etiology
- Age ≥ 60 years
- Ejection fraction ≤ 0.40 (NYHA III/IV) or ≤ 0.35 (NYHA II)
- Receiving optimal HF therapy

Main exclusion criteria

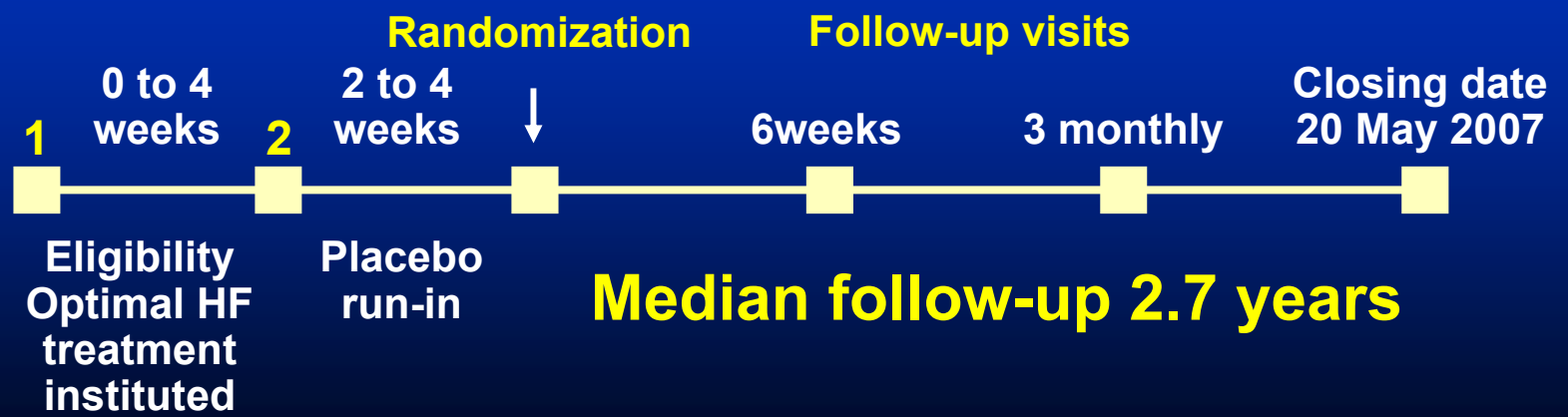
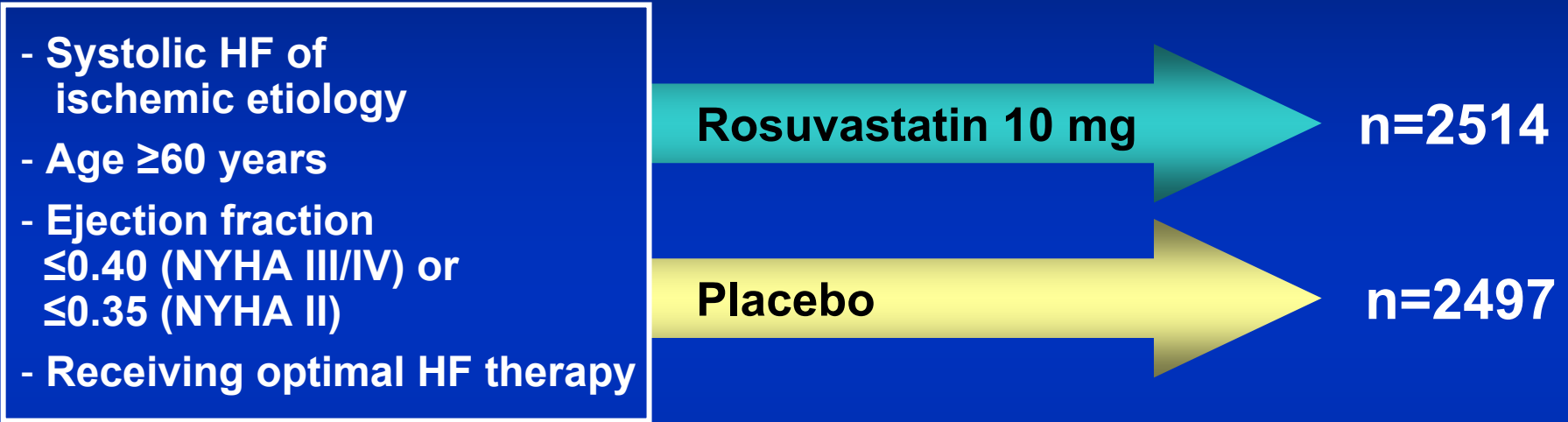
- Requiring treatment with a lipid lowering drug according to investigator
- Liver disease or ALT > 2 x upper limit of normal (ULN)
- Severe renal disease or s/creatinine > 2.5 mg/dL (220 $\mu\text{mol/L}$)
- Muscle disease or CK > 2.5 x ULN

Power calculation

- Yearly placebo hazard rate of 10.4% for the primary out-come (cardiovascular death, non-fatal MI or non-fatal stroke)
- Assumed no effect of treatment for the first 10 months, and thereafter a 22% risk reduction (mean overall risk reduction estimated to 16.1% taking into account also withdrawals)
- 1422 patients with a primary event were needed to provide a 90% power to detect such a reduction in risk with a two-sided alpha of 0.05

Study Design

371 centres in 21 countries (Europe and S. Africa)



Pre-specified Primary and Secondary Endpoints

Primary endpoint

- Cardiovascular death or nonfatal MI or non-fatal stroke^{1,2}

Secondary endpoints

- Total mortality²
- Any coronary event: sudden death; fatal or non-fatal MI; PCI; CABG; defibrillation of VF by an ICD; resuscitation from cardiac arrest; hospitalization for unstable angina^{1,2}
- All CV deaths; and cause-specific mortality for: sudden death; death from worsening heart failure; and death from myocardial infarction²
- Total number of CV hospitalizations; all heart failure hospitalizations; and all hospitalizations for unstable angina³

¹ Time to first event. ² Analyzed giving log rank p-value, and un-adjusted Cox for hazard ratio and 95% confidence interval. ³ Analyzed with permutation test

Baseline Characteristics

Variable	All randomized
Age (years)	73
Female sex	24 %
NYHA class	
II	37 %
III	62 %
IV	1.5 %
Ejection fraction	31 %
NT-pro BNP pmol/l median (interquartile range)	173 (73 to 368)
eGFR <60 ml/min/1.73 m ²	57 %

Medical History at Baseline

Medical history	All randomized
Myocardial infarction	60 %
Hypertension	63 %
Diabetes mellitus	29 %
PCI or CABG	25 %
Stroke	12 %
Atrial fibrillation (current)	24 %
Pacemaker	11 %
ICD	3 %

Heart Failure, Anti-platelet or Anti-coagulant Treatment at Baseline

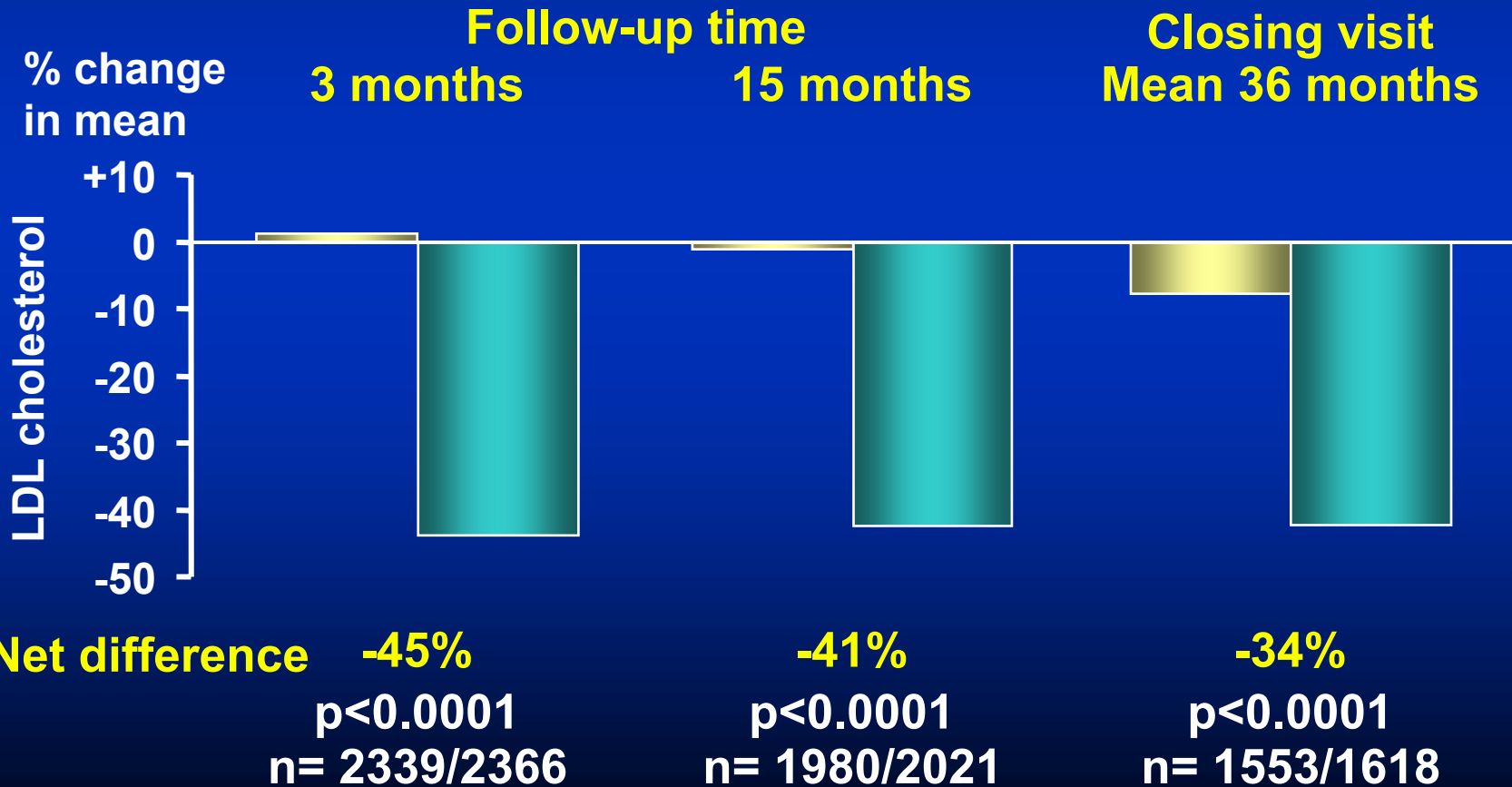
Medication	All randomized
Diuretic	88 %
ACE-I or ARB ¹	92 %
Beta-blocker	75 %
Aldosterone antagonist	39 %
Digitalis glycoside	33 %
Anti-platelet	59 %
Anti-coagulant	35 %
Anti-platelet or anti-coagulant	90 %

¹ AT₁-blocker

Mean LDL at Baseline and % Change During Follow-up

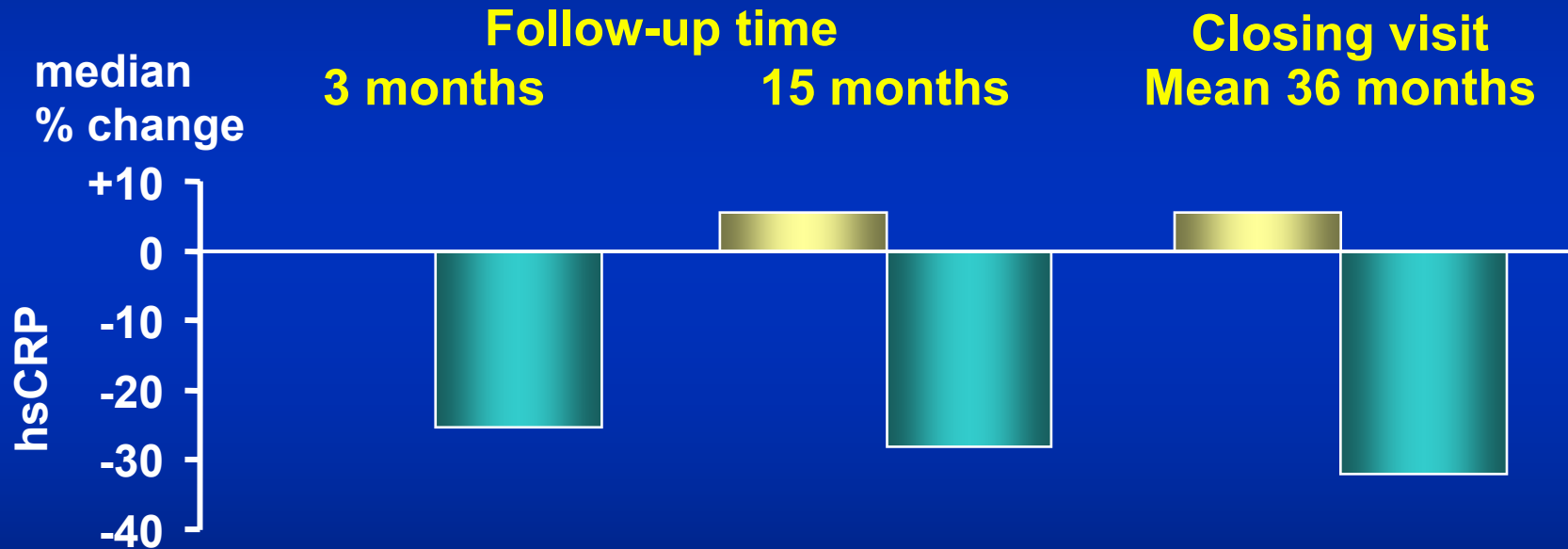
Baseline mean values

Placebo	3.56 mmol/L (137 mg/dL)	■
Rosuvastatin	3.54 mmol/L (137 mg/dL)	■



Median hsCRP at Baseline and % Change During Follow-up

Baseline median values		
Placebo	3.50 mg/L	
Rosuvastatin	3.50 mg/L	



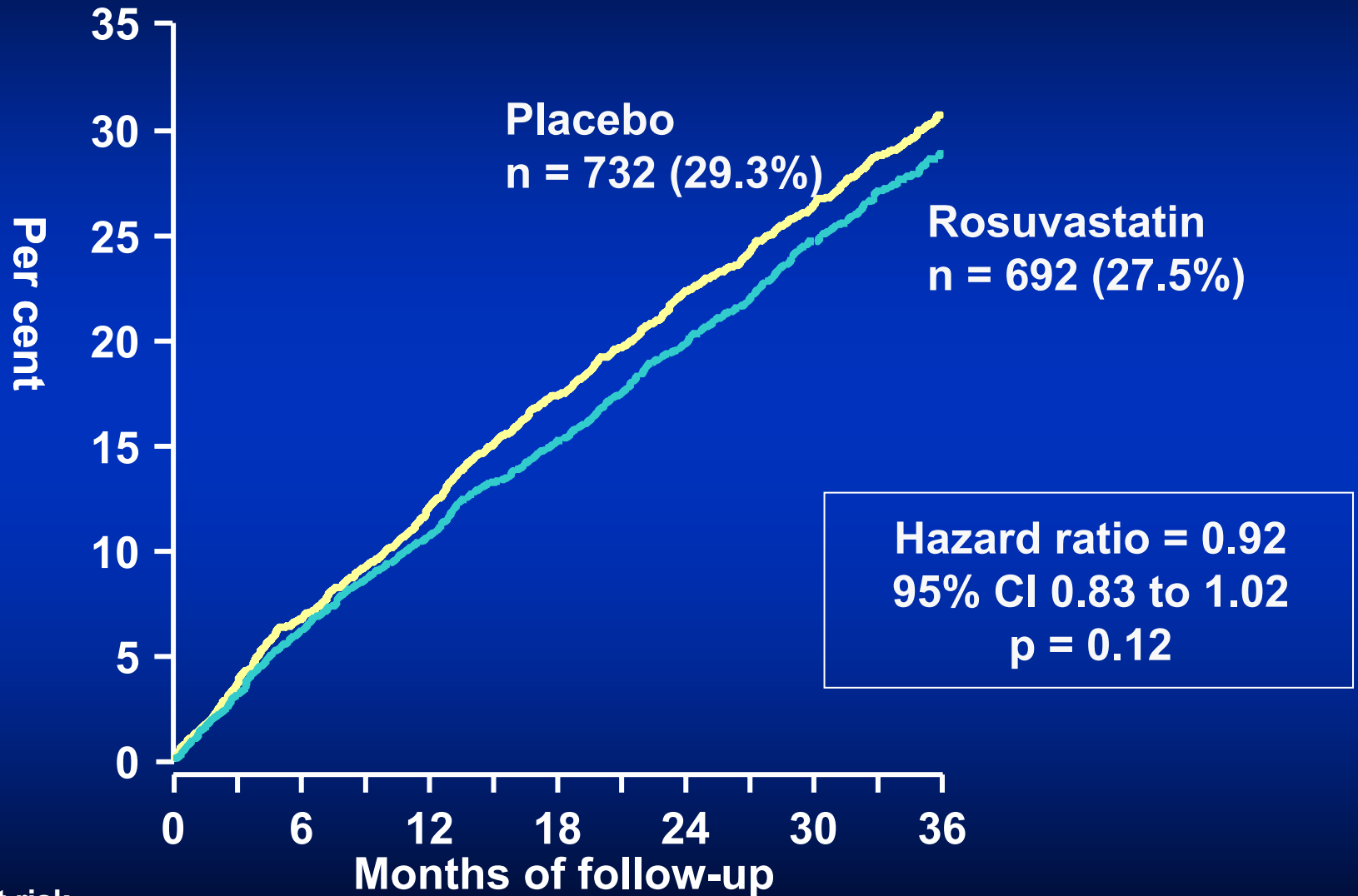
Net difference -25%
 p<0.0001
 n= 2310/2336

-34%
 p<0.0001
 n= 1957/1993

-37%
 p<0.0001
 n= 1534/1599

Primary Endpoint

CV Death or Non-fatal MI or Non-fatal Stroke



No. at risk

Placebo	2497	2315	2156	2003	1851	1431	811
Rosuvastatin	2514	2345	2207	2068	1932	1484	855

Primary Event Endpoint

Pre-specified Subgroups Analyzed for Safety Reasons

Highest risk tertile vs. other two tertiles or presence/absence of condition e.g. diabetes

Variable	Limit	Hazard ratio and 95% CI
Age	<77 ≥77	
Female		
Male		
NYHA II		
NYHA III and IV		
EF	≥0.30 <0.30	
BMI	≥26 <26	
SBP	≥122.5 <122.5	
DBP	≥73 <73	
HR	<75.5 ≥75.5	
Current smoking	No Yes	
Previous MI	No Yes	
Previous revascularization	Yes No	
Previous hypertension	Yes No	
Diabetes	No Yes	
Sinus rhythm		
Atrial fibrillation		
LDL	≥3.12 <3.12	
ApoB/ApoA1	<0.76 ≥0.76	
HDL	≥1.05 <1.05	
TG	≥2.12 <2.12	
eGFR _{MDRD}	≥51 <51	
NT-pro BNP	<277.6 ≥277.6	
hsCRP	<5.8 ≥5.8	
Antiplatelets	Yes No	
Anticoagulants	Yes No	
All randomized		



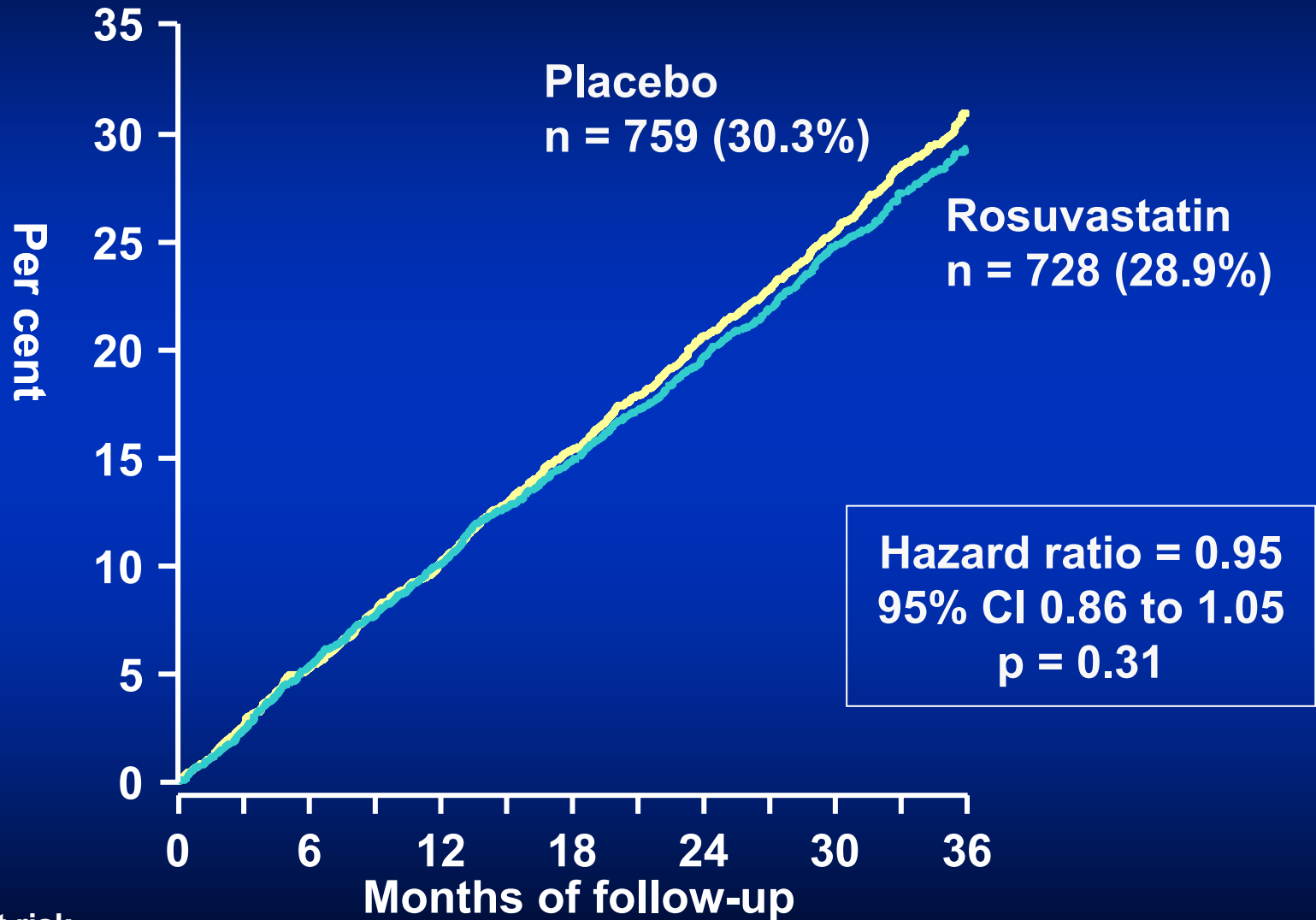
Primary Endpoint Component Events

Clinical event	Placebo	Rosuvastatin
All primary endpoints¹	732	692
- Cardiovascular death	487 (593) ²	488 (581)
- Non-fatal MI	141 (145)	115 (116)
- Non-fatal stroke	104 (106)	89 (91)

¹ Hazard ratio 0.92; 95 % CI 0.83 to 1.02; p=0.12

² Total number of patients with events given within brackets

Total Mortality

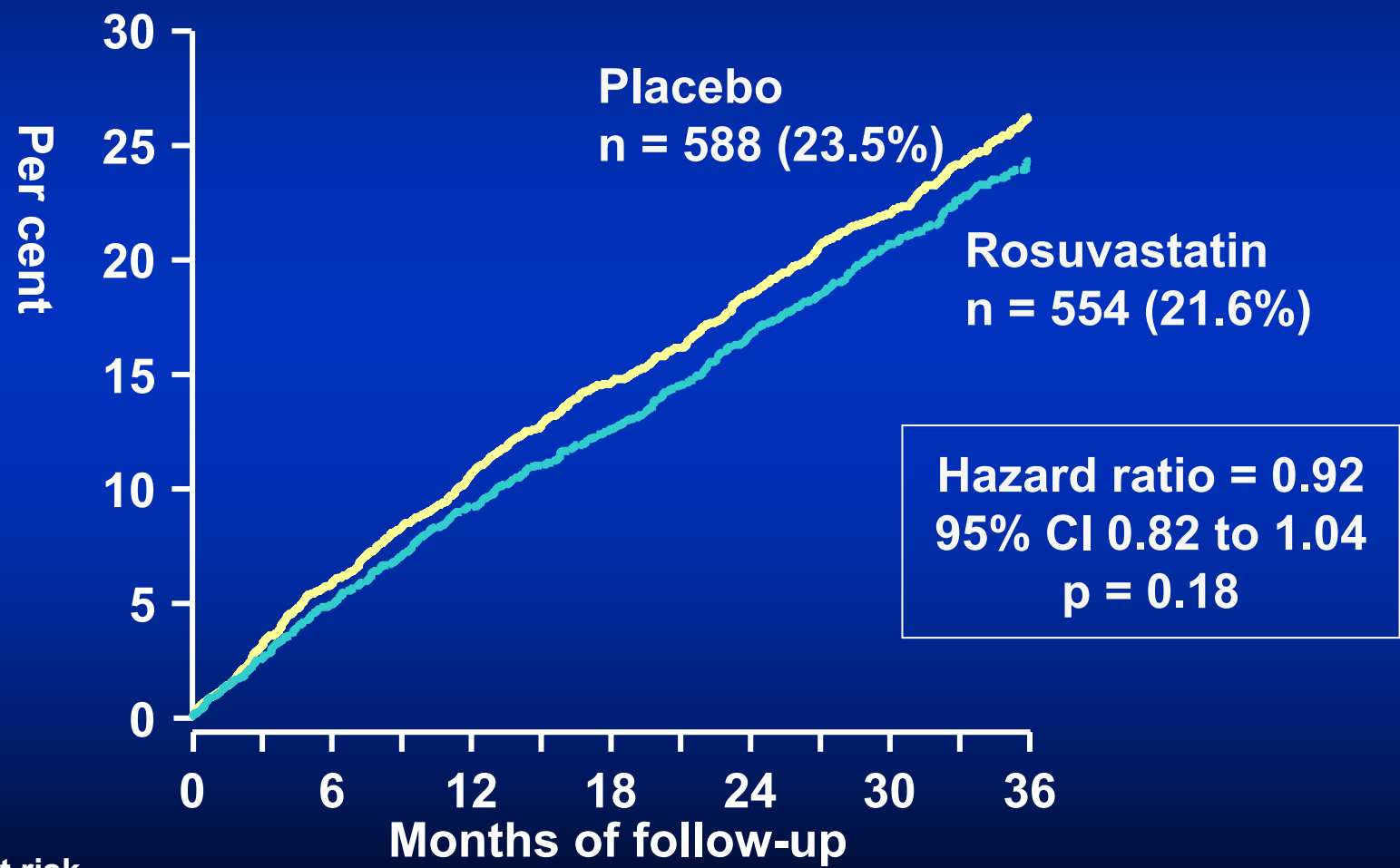


No. at risk

Placebo	2497	2365	2240	2112	1980	1545	881
Rosuvastatin	2514	2379	2260	2139	2018	1566	907

Any Coronary Event Endpoint

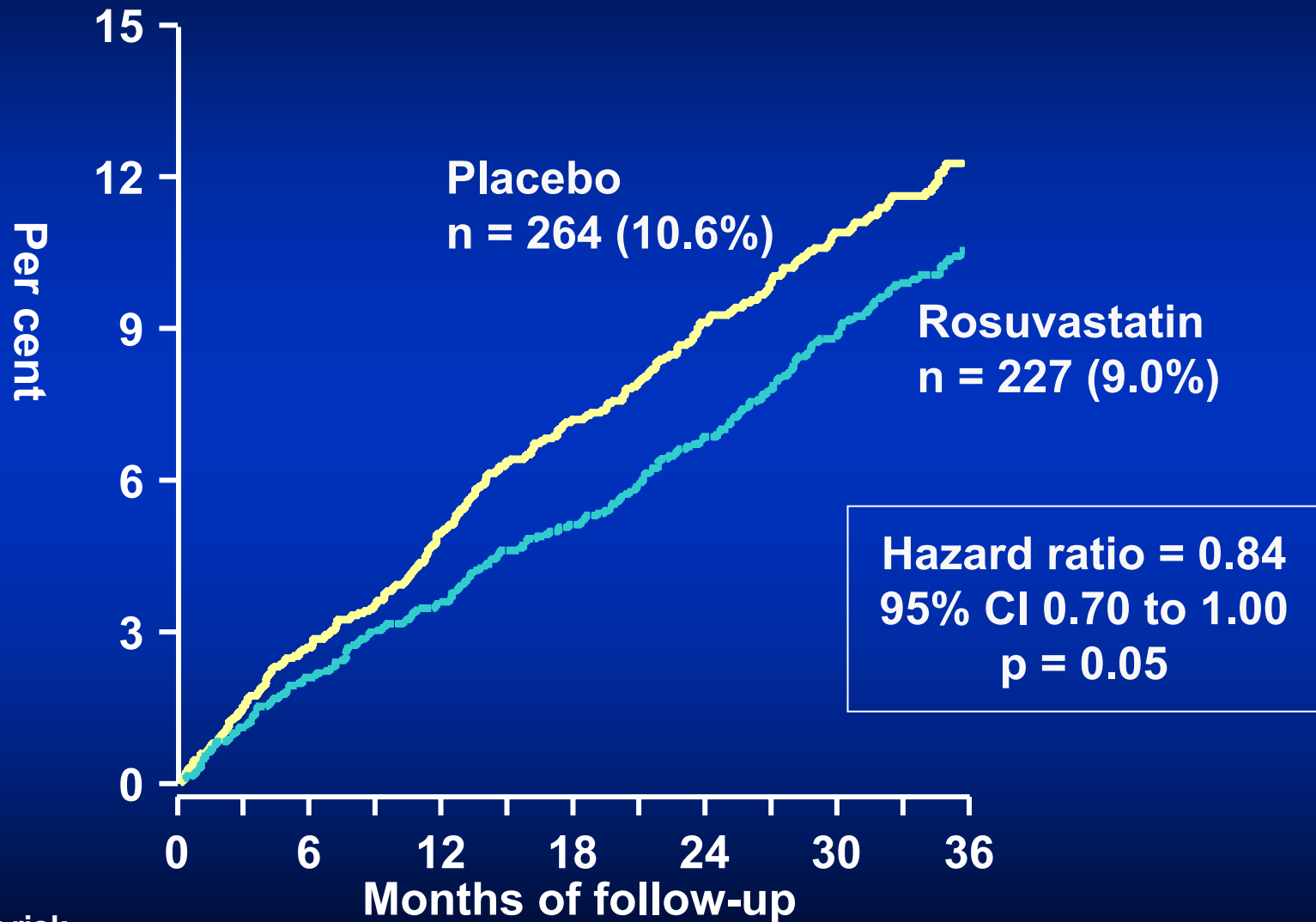
Sudden Death, Fatal or Non-fatal MI, PCI, CABG, Defibrillation by an ICD, Resuscitation after Cardiac Arrest or Hospitalization for Unstable Angina



No. at risk	0	6	12	18	24	30	36
Placebo	2497	2299	2127	1974	1819	1405	789
Rosuvastatin	2514	2332	2174	2029	1871	1427	817

Nonfatal or Fatal MI or Stroke

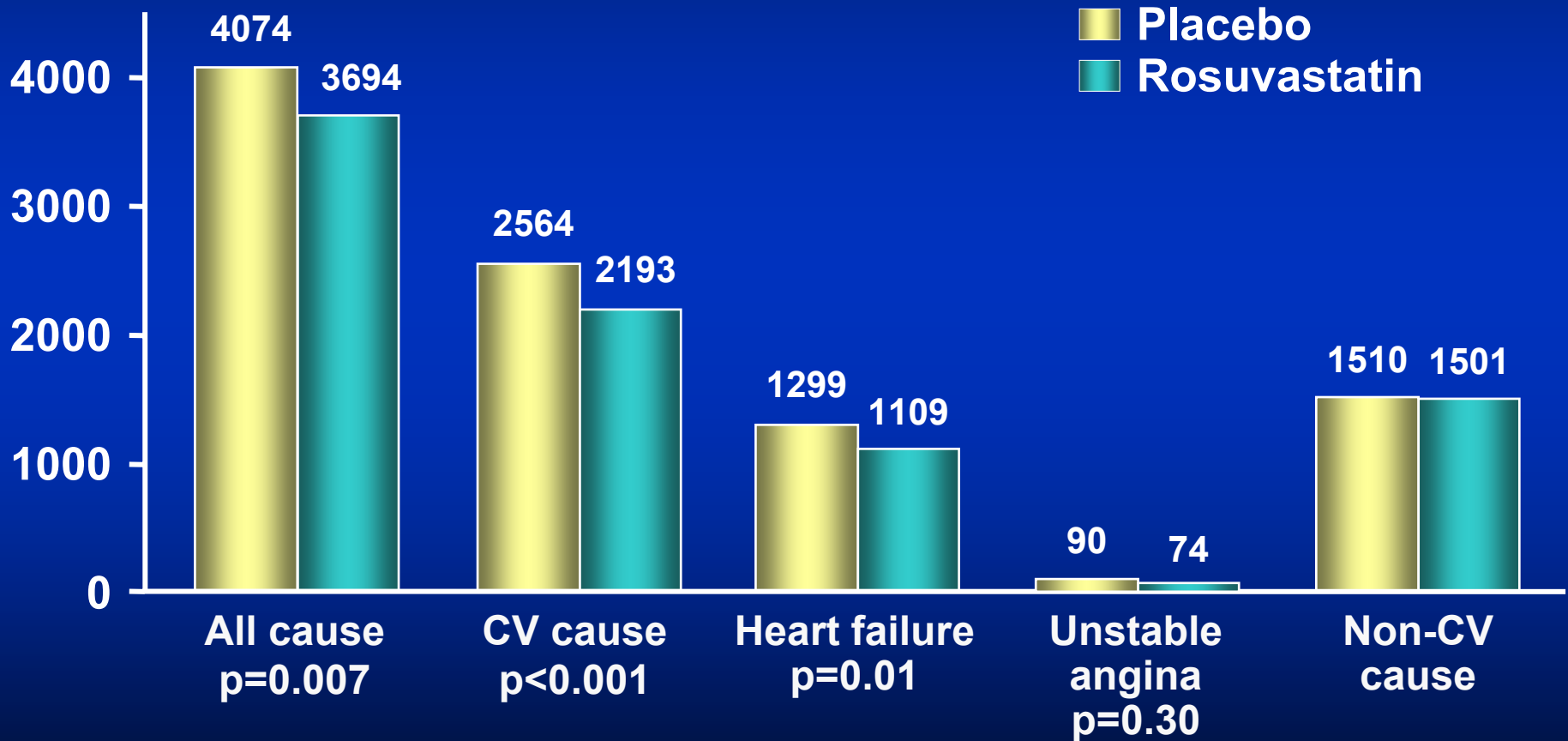
(Post hoc analysis)



No. at risk

Placebo	2497	2315	2156	2003	1851	1431	811
Rosuvastatin	2514	2345	2207	2068	1932	1484	855

Total Number of Hospitalizations



Permanent Premature Discontinuation of Study Medicine (excluding deaths)

Reason	Placebo	Rosuvastatin	p-value
All discontinuations¹	546	490	0.03
- Adverse event ²	302	241	0.004
- Unwillingness	162	187	
- Other reason	82	62	

¹ Hazard ratio 0.88; 95% confidence interval 0.78 to 0.99

² Hazard ratio 0.78; 95% confidence interval 0.66 to 0.92

Adverse Events

Item	Placebo n=2497 (n)	Rosuvastatin n=2514 (n)
All adverse events	13635	13258
All serious adverse events	5536	5146
ALT > 3 times ULN after random.		
At least once	24	25
More than once	5	3
Doubling of s/creatinine ¹	32	23
Any muscle symptoms ²	207	225
CK > 10 times ULN	3	1
CK > 10 times ULN + muscle symptoms ³	1	0
Rhabdomyolysis	0	0

¹ With follow-up value above ULN ²Active questioning or adverse event

³ Started after initiating physiotherapy

Conclusions

- In this previously unstudied population of older patients with moderate to severe systolic HF there was no significant reduction in the primary endpoint, total mortality, coronary event endpoint, sudden death or death from worsening heart failure. There were very few deaths from myocardial infarction (ns between groups)
- Total number of CV hospitalization ($p < 0.001$), and heart failure hospitalizations ($p = 0.01$) were reduced. There were very few hospitalizations for unstable angina (ns between groups)
- Rosuvastatin was well tolerated in this vulnerable and older population that was otherwise well treated

Interpretation

- The primary endpoint was not reduced to the extent anticipated (16% assumed vs 8% observed as estimated from the Hazard ratio, ns). This estimated treatment effect was consistent across patient subgroups
- Favorable trends were seen with rosuvastatin both for non-fatal myocardial infarction and non-fatal stroke, however statin treatment had no effect on cardiovascular death, which accounted for the majority of the primary events (68%)
- Assuming rosuvastatin did reduce the risk of acute athero-thrombotic events, our results suggest that the major etiology of CV deaths in this older, vulnerable population of otherwise well treated patients with advanced systolic HF may be a primary electrical event, related to ventricular dilatation and scarring, and not to an athero-thrombotic event