TURIN, 20TH—21ST NOVEMBER 2008

GREAT INNOVATIONS IN CARDIOLOGY

4TH JOINT MEETING WITH MAYO CLINIC

4TH TURIN CARDIOVASCULAR NURSING CONVENTION

SESSION IV:

THE NEW CARDIAC INTENSIVE CARE UNIT— NO LONGER THE CCU?

A. Maggioni (Firenze)

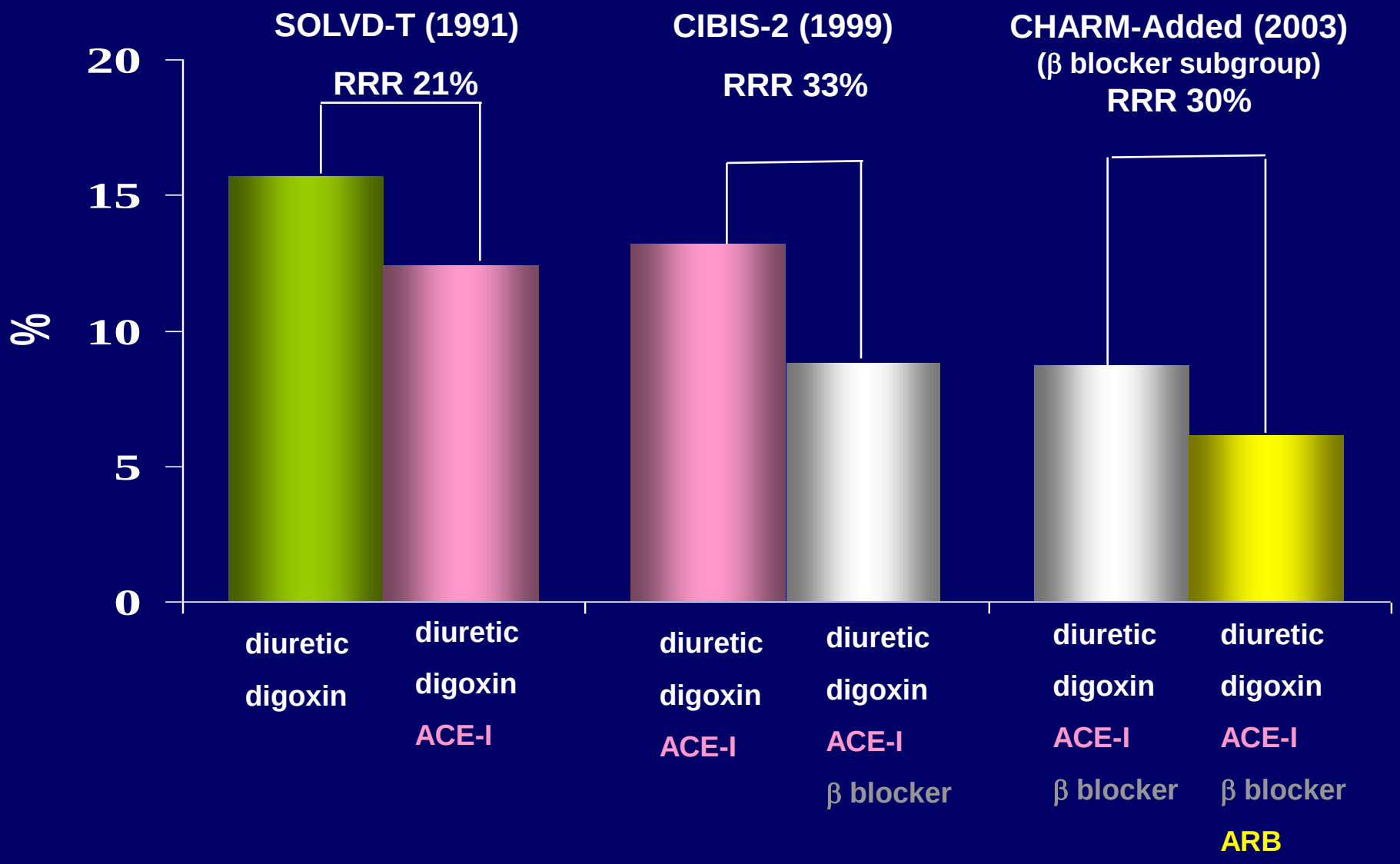
Lecture

New evidences in heart failure: GISSI HF

New evidences in heart failure: the GISSI-HF trial

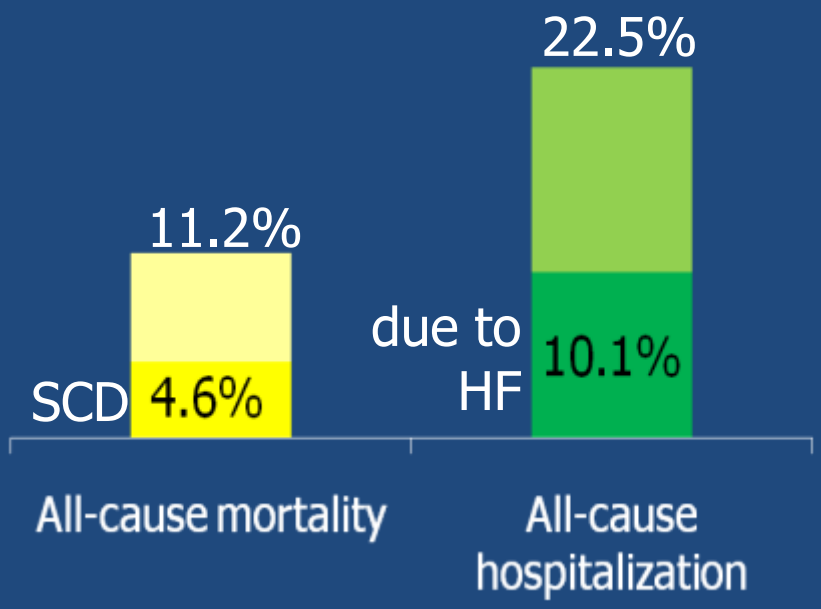
Aldo P Maggioni, MD
ANMCO Research Center
Firenze, Italy

Improving survival in chronic HF and LV systolic dysfunction: 1 year all-cause mortality



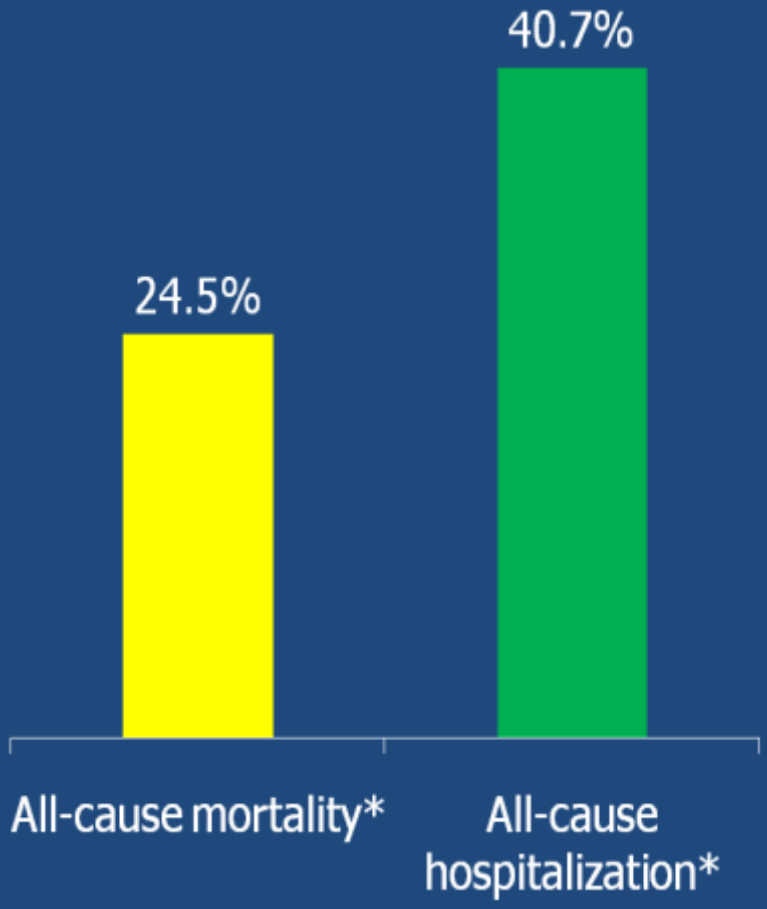
Outcomes of patients in clinical practice

IN-CHF Registry
1-year follow-up
(n. 8,627 patients)



Survey on Acute HF
6-month follow-up
(n. 2,806 patients)

* patients with worsening HF



GISSI Studies
1983-1998

IN-CHF Registry
1995-up to now

GISSI-HF
August 2002-March 2008

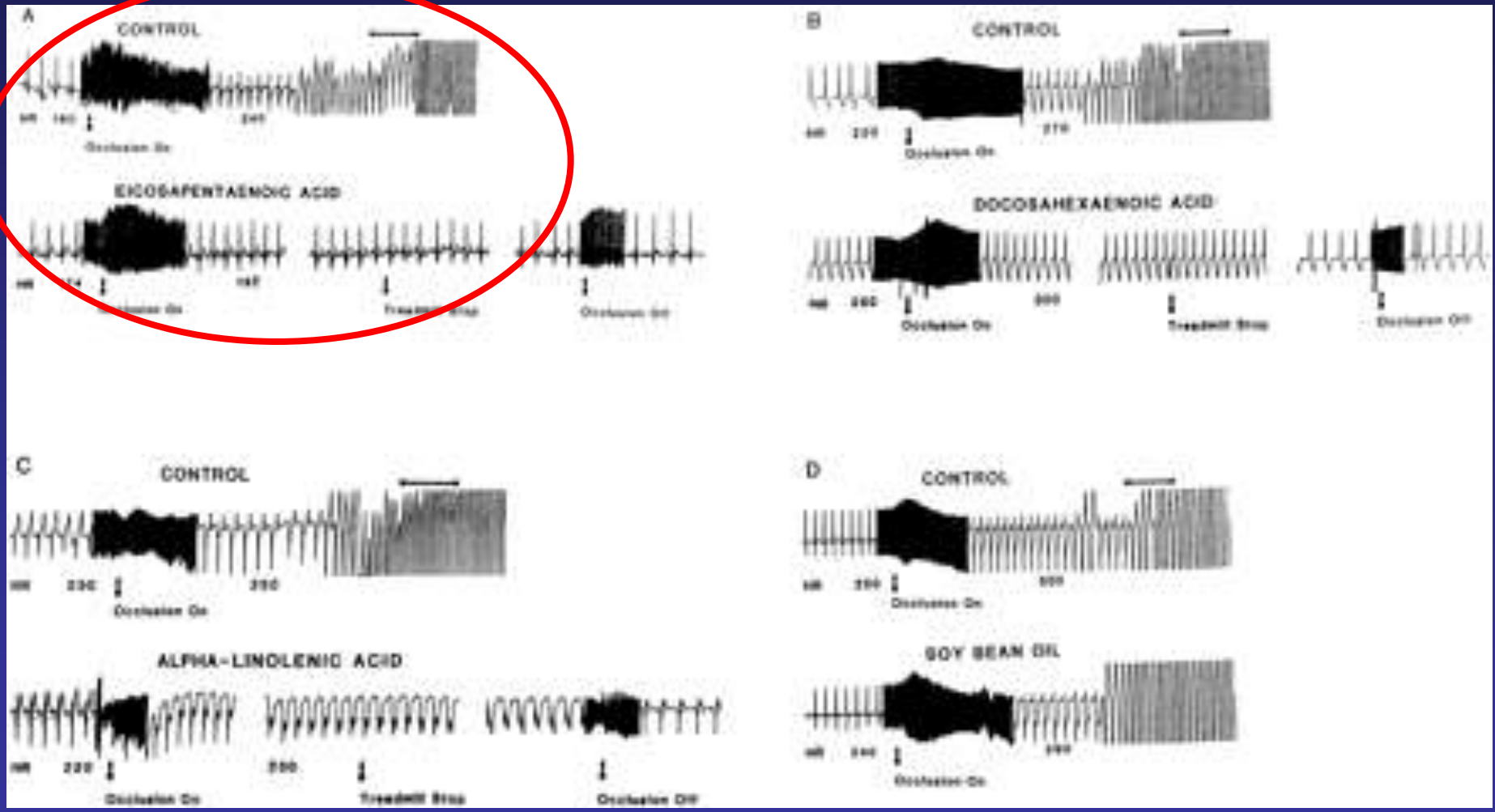
A new trial testing n-3 PUFA and rosuvastatin in 7000 patients with heart failure

GISSI-HF Rationale

- Why n-3 PUFA ?

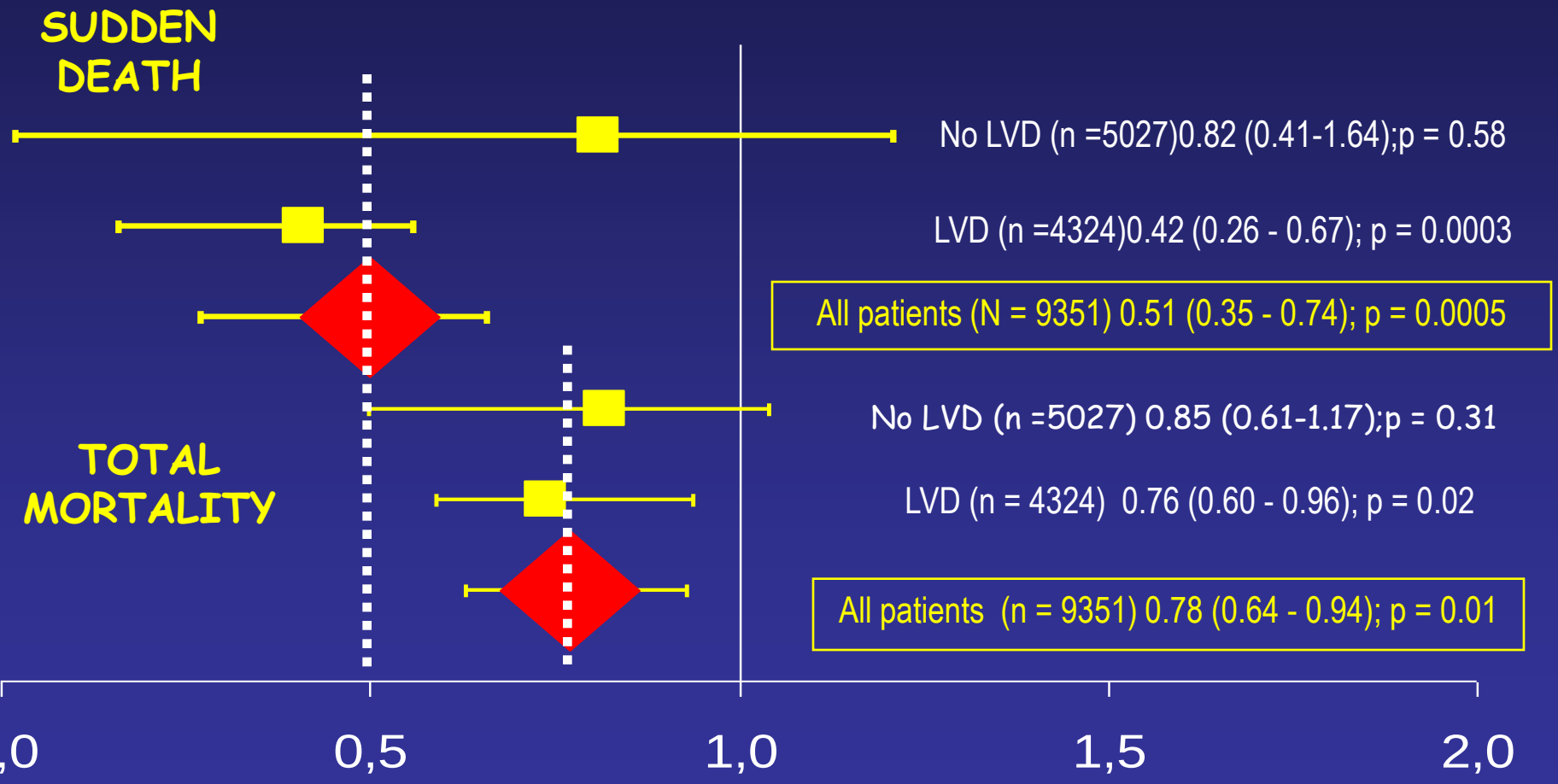
Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs

Circulation 1999; 99:2452-7



GISSI-Prevenzione:
Left Ventricular Systolic Dysfunction Sub-analysis

Hazard Ratio (CI 95 %) of PUFA on Total and Sudden death Mortality



ORIGINAL CONTRIBUTION

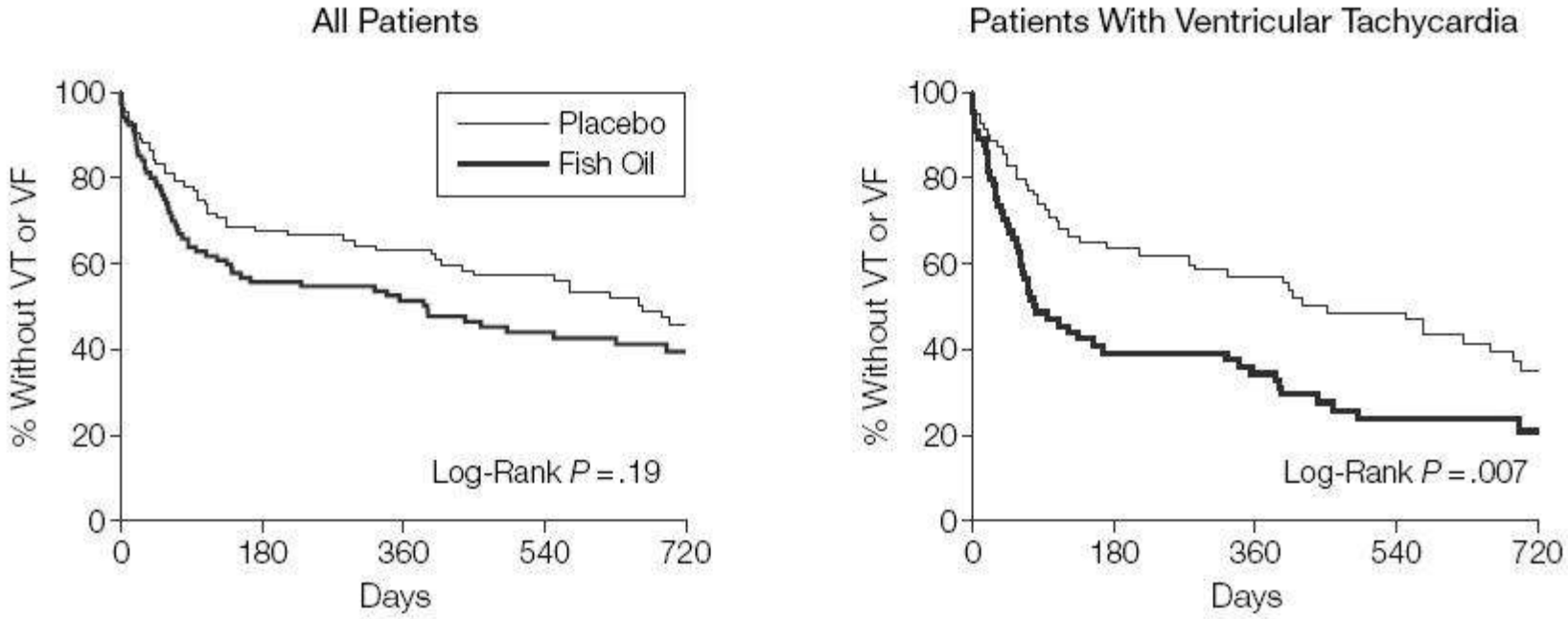
Fish Oil Supplementation and Risk of Ventricular Tachycardia and Ventricular Fibrillation in Patients With Implantable Defibrillators

A Randomized Controlled Trial

Merritt H. Raitt, MD

JAMA. 2005;293:2884-2891

Survival Curves for Time to First Episode of ICD Therapy for VT or VF in All Patients and in VT Patients by Fish Oil vs Placebo Group



No. at Risk					
Placebo	100	65	57	48	31
Fish Oil	100	56	47	35	19

69	43	37	30	18
64	26	22	14	8

GISSI-HF Rationale

- Why n-3 PUFA ?
- Why statins ?

Statins and Heart Failure

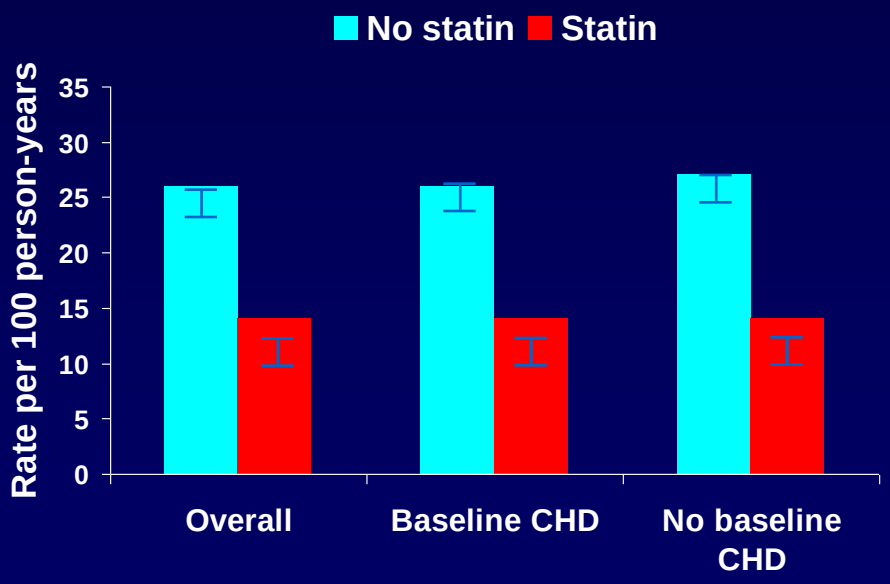
- **Pro**
  - Prevention of the progression of coronary atherosclerosis
  - Inhibition of pro-inflammatory cytokine activity
  - Improvement of endothelial NO production
  - Regulation of AT1 receptors
- **Cons**
  - Low concentrations of LDL are associated with a worse prognosis in patients with HF
  - Statins depress the production of ubiquinone, an essential component of the mitochondrial respiratory chain
  - Safety profile of statins in fragile patients with HF is undefined

Statin Use and Outcome in HF: Death and HF Hospitalization

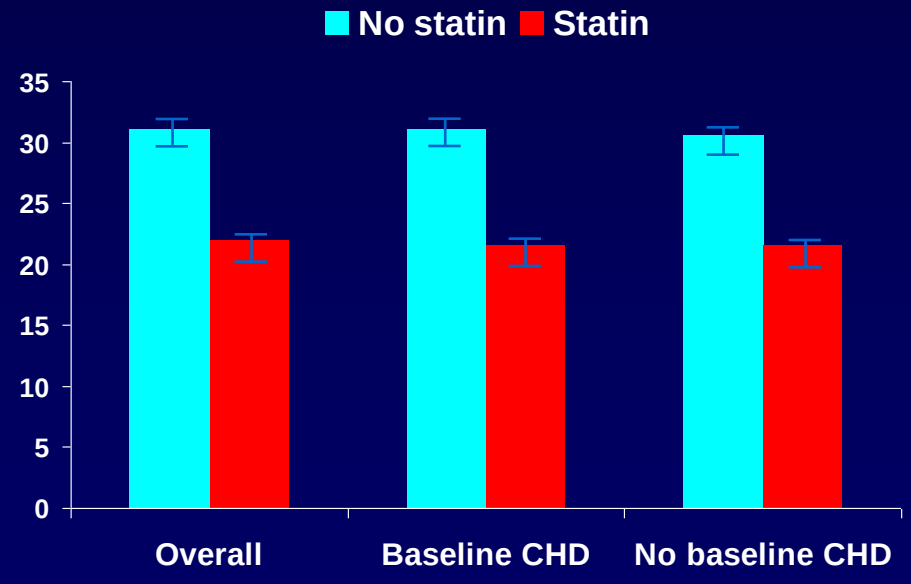
Ischemic vs Non-ischemic Etiology

Kaiser Permanente 24,598 patients with HF – propensity adjusted cohort study

Rate of death



Rate of hospitalization



Go et al JAMA 2006

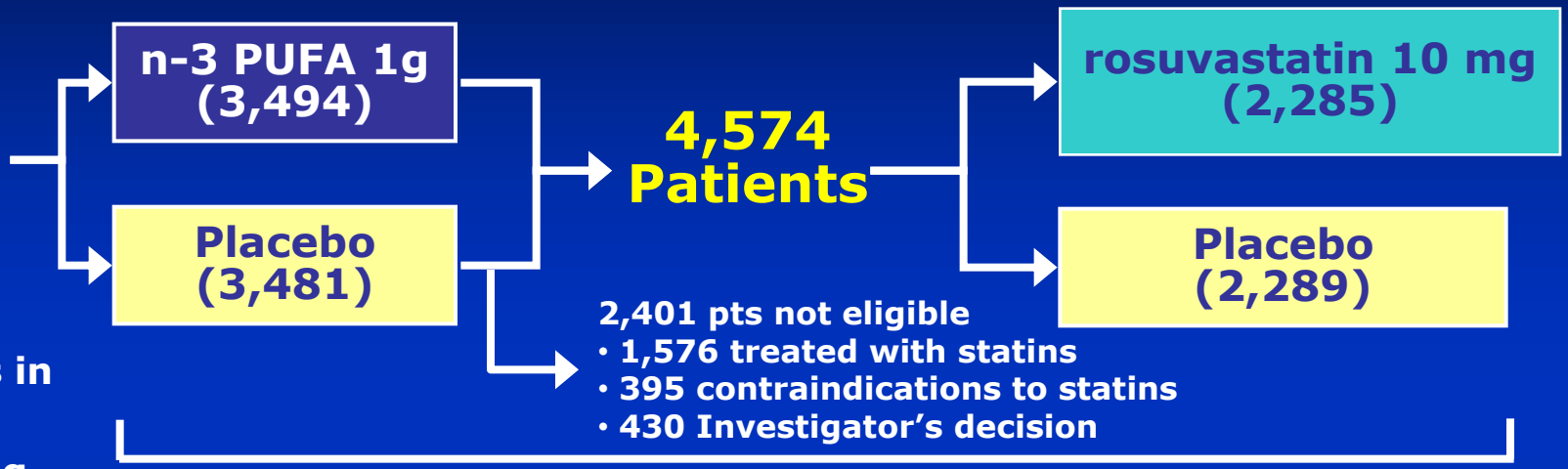
Statins and Heart Failure

- **Pro**
  - Prevention of the progression of coronary atherosclerosis
  - Inhibition of pro-inflammatory cytokine activity
  - Improvement of endothelial NO production
  - Regulation of AT1 receptors
- **Cons**
  - Low concentrations of LDL are associated with a worse prognosis in patients with HF
  - Statins depress the production of ubiquinone, an essential component of the mitochondrial respiratory chain
  - Safety profile of statins in fragile patients with HF is undefined
- **No available evidences**
  - All trials testing statins excluded patients with HF, thus no information were available regarding their benefit/risk profile in this clinical condition

GISSI – Heart Failure

Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico

All treatments of proven efficacy for chronic HF (e.g., ACE-inhibitors, beta-blockers, diuretics, digitalis, spironolactone) were positively recommended.



- 356 centers in Italy
- HF, receiving optimized therapy

3.9 years of follow-up

1, 3, 6, 12 months and then every 6 months until the end of the trial

15% RRR of all-cause mortality, from 25% to 21%; power = 90%; 2-sided α=0.045

Primary end points

- 15% reduction of all-cause mortality ($p < 0.045$)
- 20% reduction of all-cause mortality or CV hospitalizations ($p<0.01$)

Patients' characteristics

	n-3 PUFA (n. 3494)	Placebo (n. 3481)
Age (years), mean±SD	67±11	67±11
Females, n. (%)	777 (22)	739 (21)
BMI (kg/m^2), mean±SD	27±5	27±5
SBP (mmHg), mean±SD	126±18	126±18
Heart rate (bpm), mean±SD	72±13	73±14

BMI=body mass index; SBP=systolic blood pressure

Heart failure characteristics

	n-3 PUFA (n. 3494)	Placebo (n. 3481)
Etiology, n. (%)		
Ischemic	*1717 (49)*	*1750 (50)*
Dilatative	*1053 (30)*	*972 (28)*
Hypertensive	*493 (14)*	*543 (16)*
Other	*107 (3)*	*89 (3)*
Non detectable/Unknown	*124 (4)*	*127 (4)*
NYHA class, n. (%)		
II	*2226 (64)*	*2199 (63)*
III-IV	*1268 (36)*	*1282 (37)*
LVEF (%), mean±SD	33.0±8.5	33.2±8.5
LVEF >40%, n. (%)	333 (9.5)	320 (9.2)

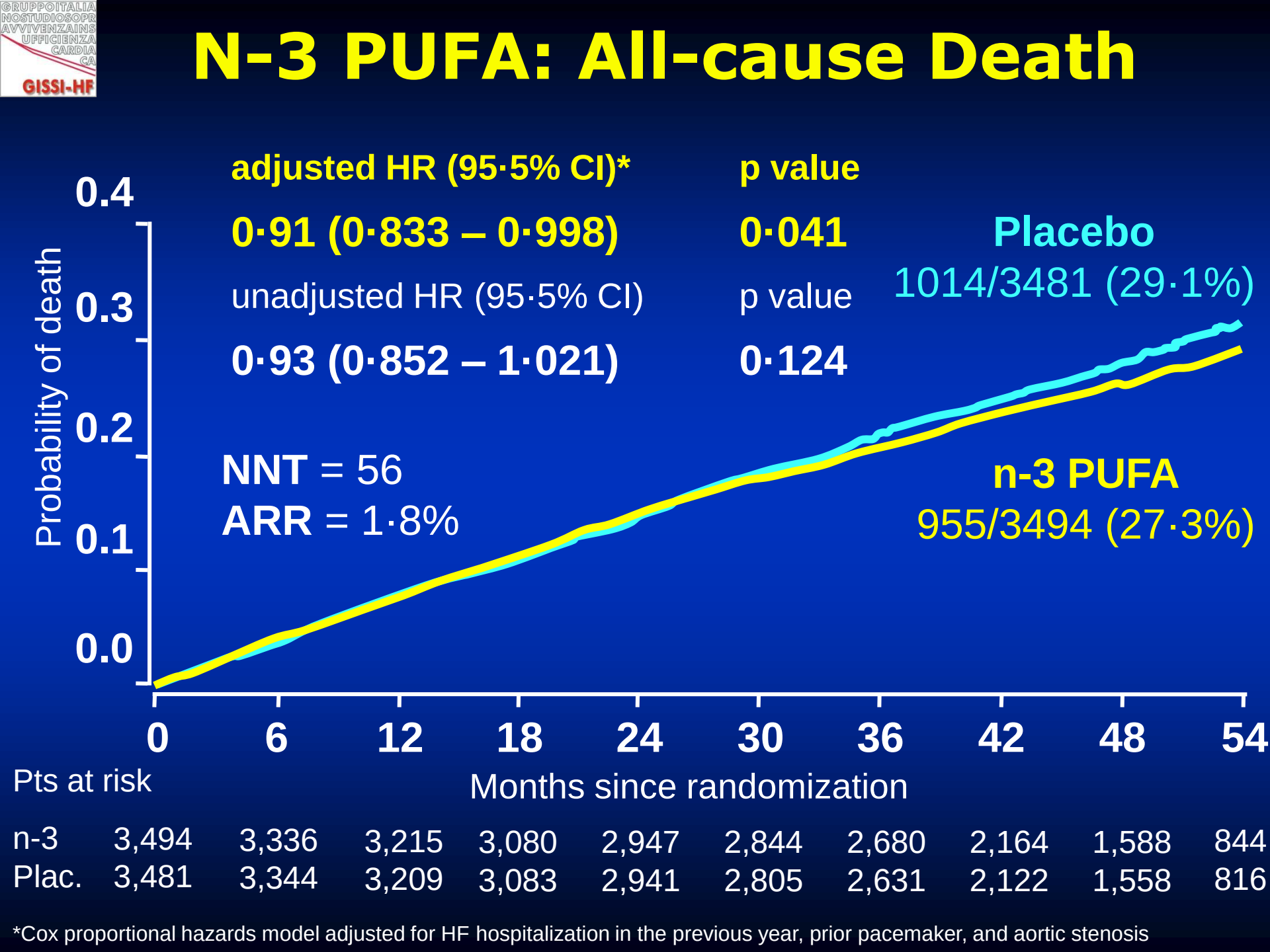
LVEF=left ventricular ejection fraction

Concomitant medical treatment

	n-3 PUFA (n. 3494)	Placebo (n. 3481)
ACE-inhibitors/ARBs (%)	93	93
Beta-blockers (%)	65	65
Spironolactone (%)	39	40
Diuretics (%)	89	90
Digitalis (%)	37	37
Oral anticoagulants (%)	29	28
Aspirin (%)	48	48
Nitrates (%)	35	35
Calcium-channel blockers (%)	10	10
Amiodarone (%)	19	20
Statin (open) (%)	22	23

ARBs=angiotensin receptor blockers;

N-3 PUFA: All-cause Death

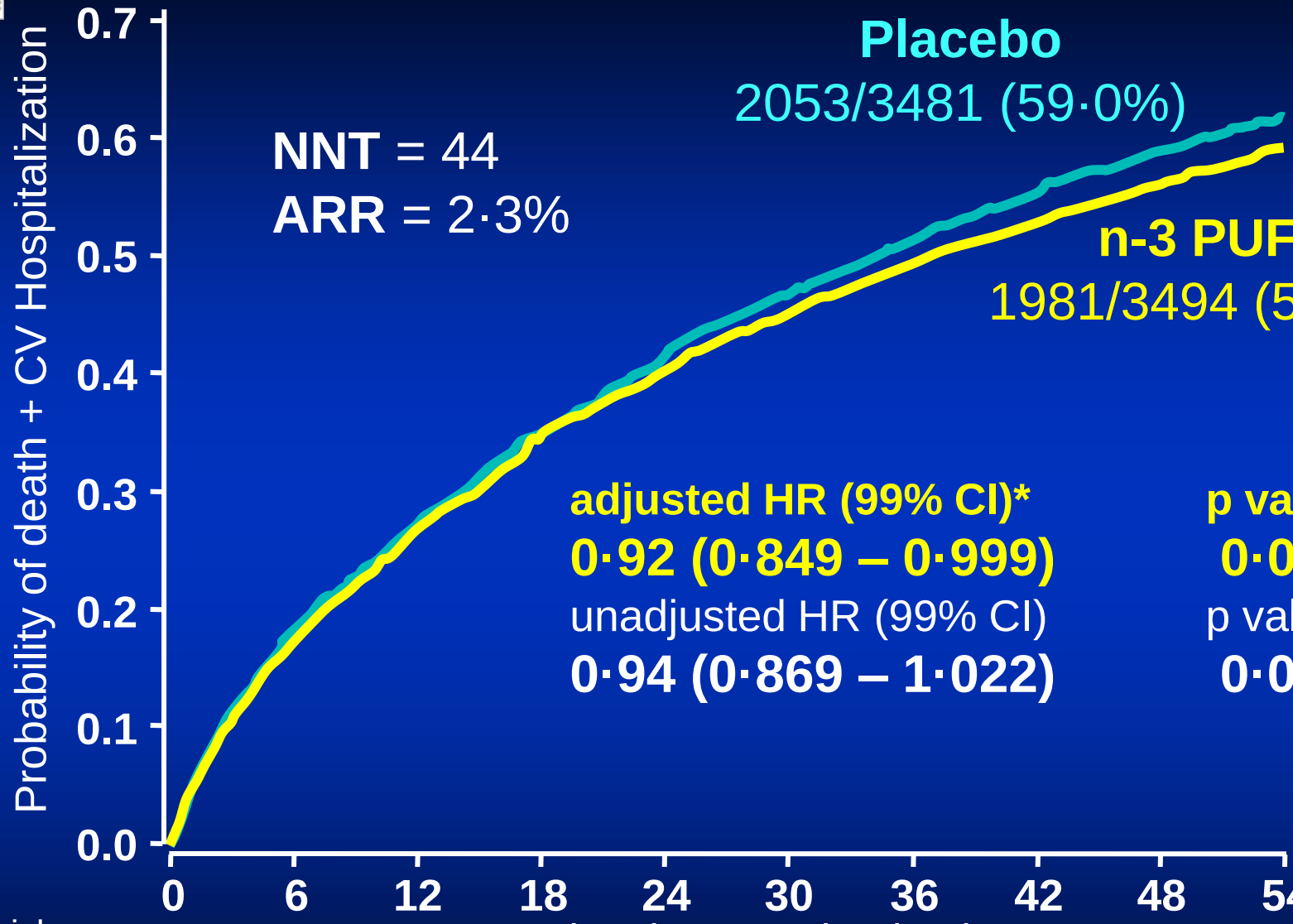


Pts at risk

n-3	3,494	3,336	3,215	3,080	2,947	2,844	2,680	2,164	1,588	844
Plac.	3,481	3,344	3,209	3,083	2,941	2,805	2,631	2,122	1,558	816

*Cox proportional hazards model adjusted for HF hospitalization in the previous year, prior pacemaker, and aortic stenosis

N-3 PUFA: Death + CV Hospitalization



adjusted HR (99% CI)*	p value
0·92 (0·849 – 0·999)	**0·009**
unadjusted HR (99% CI)	p value
0·94 (0·869 – 1·022)	**0·059**

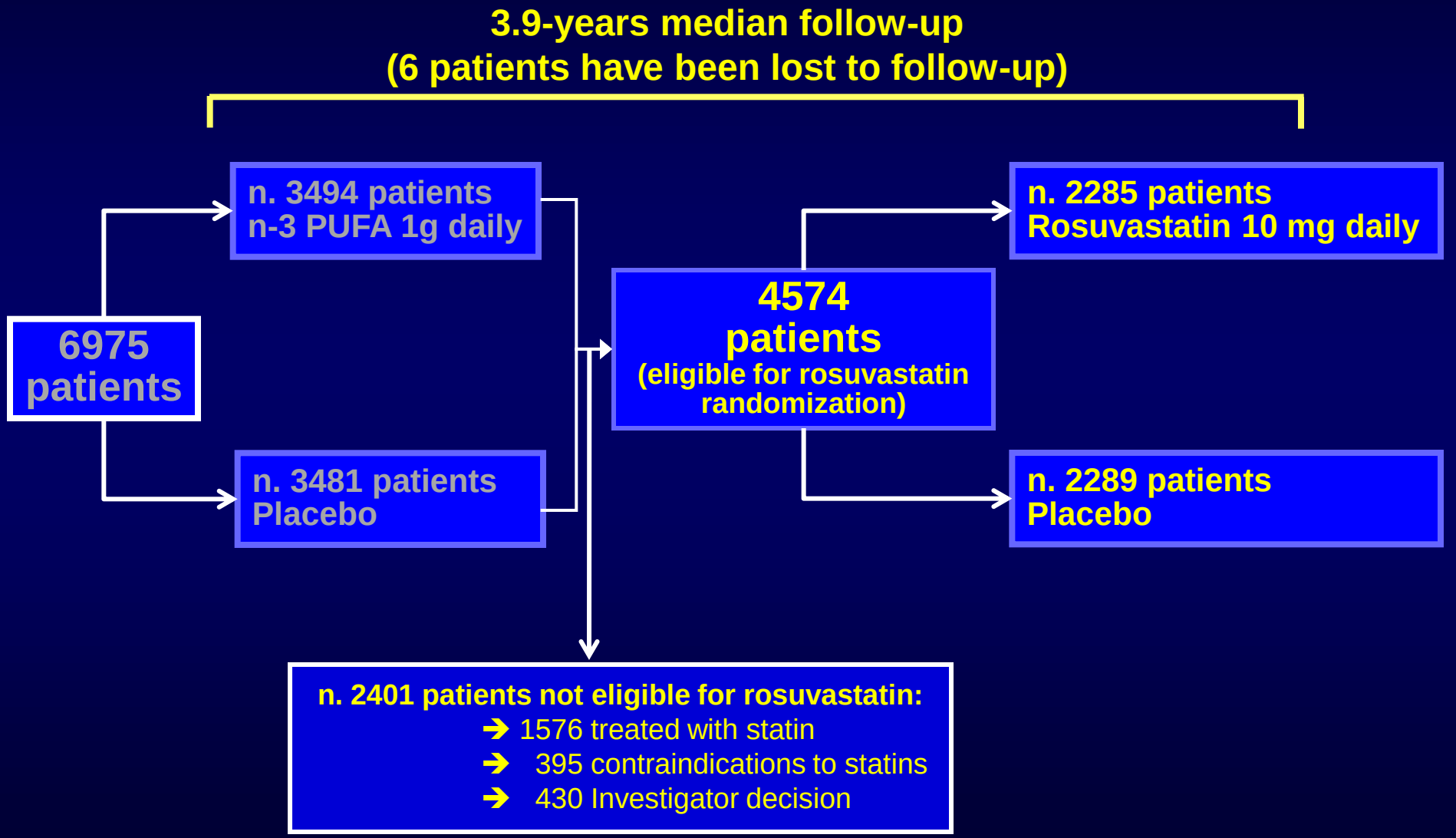
Pts at risk										
n-3 PUFA	3,494	2,876	2,543	2,261	2,066	1,896	1,718	1,342	949	502
Placebo	3,481	2,846	2,518	2,251	2,251	1,826	1,640	1,254	876	446

*Cox proportional hazards model adjusted for HF hospitalization in the previous year, prior pacemaker, and aortic stenosis

n-3 PUFA: Conclusions

- Long-term administration of 1g/day n-3 PUFA was effective in reducing both all-cause mortality and hospitalisations for CV reasons in the large population of patients with HF included in the GISSI-HF trial
- The benefit was moderate, smaller than expected (RRR 7%-9% vs assumed 15%) but it was:
  - obtained on top of recommended therapies
  - consistent across all the predefined subgroups
  - supported by per-protocol analysis (RRR 12%-14%)
- No adverse events were noted

GISSI-HF: Trial design



Heart failure characteristics

	Rosuvastatin (n. 2285)	Placebo (n. 2289)
Etiology, n. (%)		
Ischemic	*909 (39.8)*	*919 (40.2)*
Dilatative	*793 (34.7)*	*783 (34.2)*
Hypertensive	*409 (17.9)*	*414 (18.1)*
Other cause	*70 (3.1)*	*65 (2.8)*
Non detectable/Unknown	*104 (4.5)*	*108 (4.7)*
NYHA class, n. (%)		
II	*1398 (61.2)*	*1462 (63.9)*
III-IV	*887 (38.8)*	*827 (36.1)*
LVEF (%), mean±SD	33.4±8.8	33.1±8.7
LVEF >40%, n. (%)	236 (10.3)	225 (9.8)

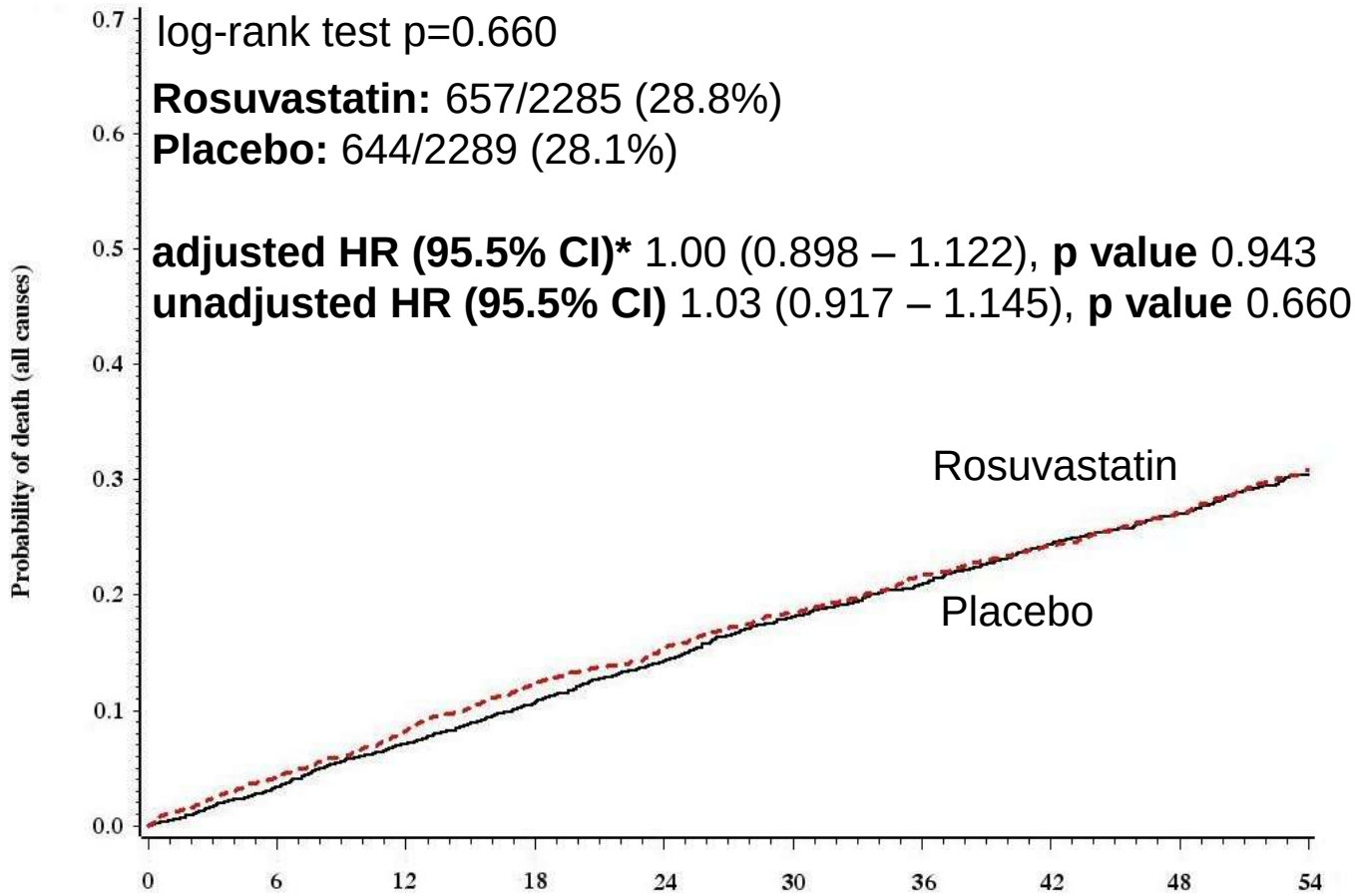
LVEF=left ventricular ejection fraction

Rosuvastatin: Time to all-cause death

log-rank test p=0.660

Rosuvastatin: 657/2285 (28.8%)
Placebo: 644/2289 (28.1%)

adjusted HR (95.5% CI)* 1.00 (0.898 – 1.122), **p value** 0.943
unadjusted HR (95.5% CI) 1.03 (0.917 – 1.145), **p value** 0.660

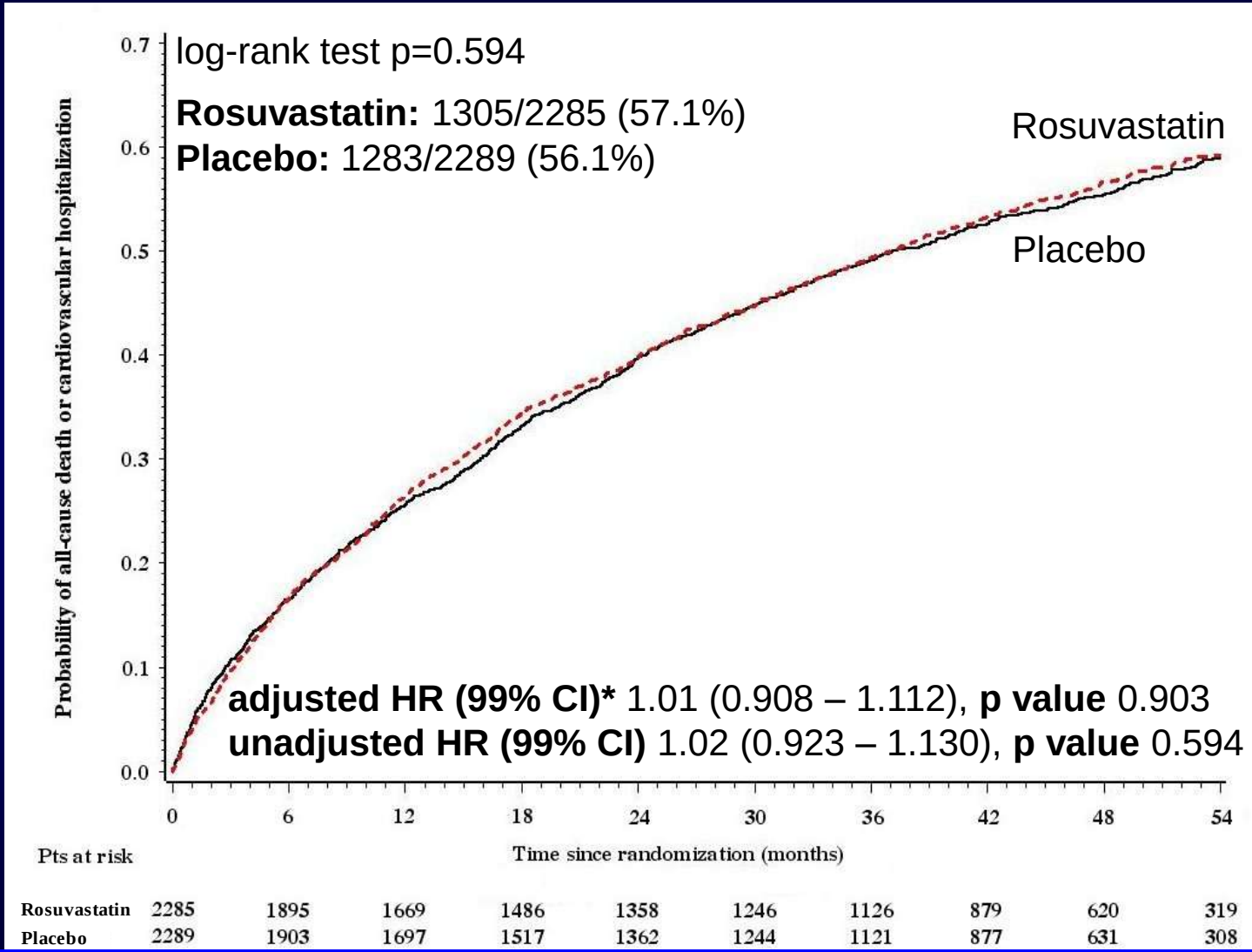


Pts at risk

Rosuvastatin	2285	2180	2085	1987	1913	1841	1744	1436	1055	523
Placebo	2289	2202	2115	2028	1935	1848	1750	1397	1045	518

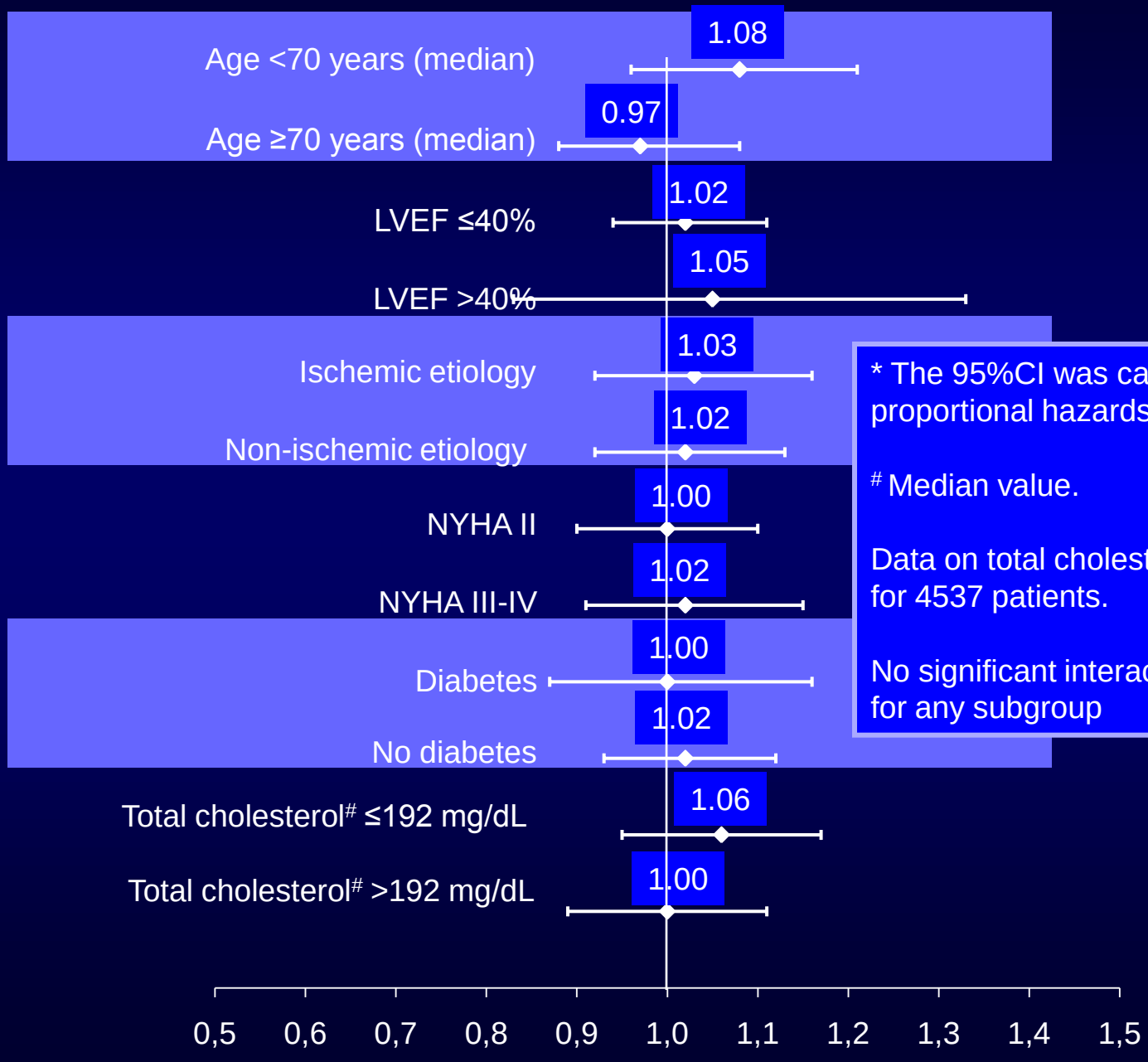
*Estimates were calculated using a Cox proportional hazards model, adjusting for:
hospitalisation for HF in the previous year, prior pace-maker, gender, diabetes, pathological Q waves, ARBs.

Rosuvastatin: Time to all-cause death or hospitalisation for CV reasons



*Estimates were calculated using a Cox proportional hazards model, adjusting for: hospitalisation for HF in the previous year, prior pace-maker, gender, diabetes, pathological Q waves, ARBs.

Rosuvastatin: Predefined subgroup analysis



* The 95%CI was calculated by Cox proportional hazards model.

Median value.

Data on total cholesterol were available for 4537 patients.

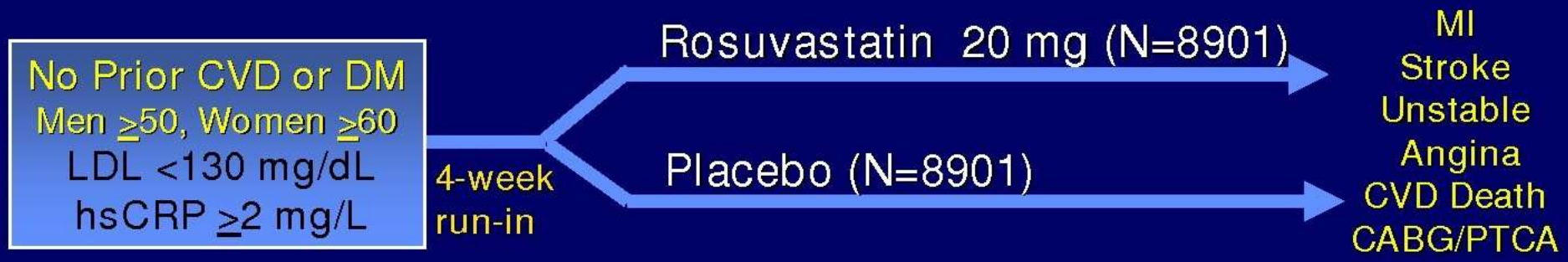
No significant interactions were shown for any subgroup

The role of statins after GISSI-HF

- The recommendations for primary and secondary prevention of CV events are not modified by the GISSI-HF results

JUPITER
Trial Design

JUPITER
Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP



Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Ridker et al, Circulation 2003;108:2292-2297.

JUPITER

Baseline Clinical Characteristics

	Rosuvastatin (N = 8901)	Placebo (n = 8901)
Age, years (IQR)	66.0 (60.0-71.0)	66.0 (60.0-71.0)
Female, N (%)	3,426 (38.5)	3,375 (37.9)
Ethnicity, N (%)		
Caucasian	6,358 (71.4)	6,325 (71.1)
Black	1,100 (12.4)	1,124 (12.6)
Hispanic	1,121 (12.6)	1,140 (12.8)
Blood pressure, mm (IQR)		
Systolic	134 (124-145)	134 (124-145)
Diastolic	80 (75-87)	80 (75-87)
Smoker, N (%)	1,400 (15.7)	1,420 (16.0)
Family History, N (%)	997 (11.2)	1,048 (11.8)
Metabolic Syndrome, N (%)	3,652 (41.0)	3,723 (41.8)
Aspirin Use, N (%)	1,481 (16.6)	1,477 (16.6)

All values are median (interquartile range) or N (%)

JUPITER

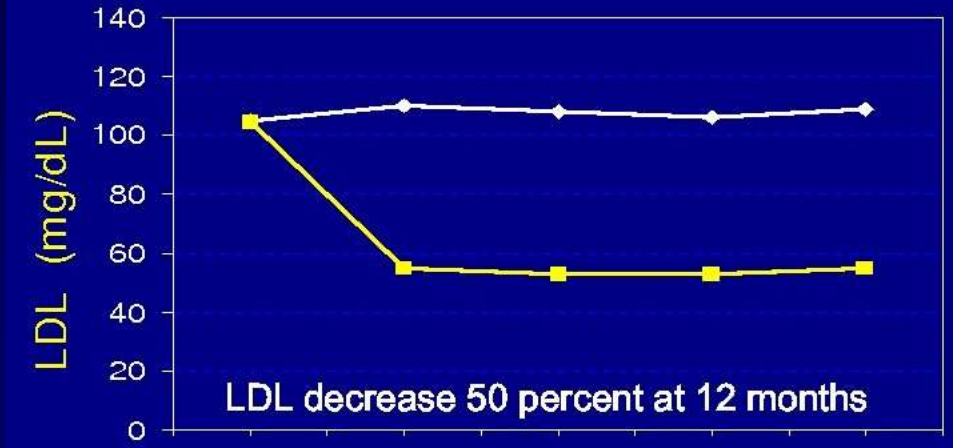
Baseline Blood Levels (median, interquartile range)

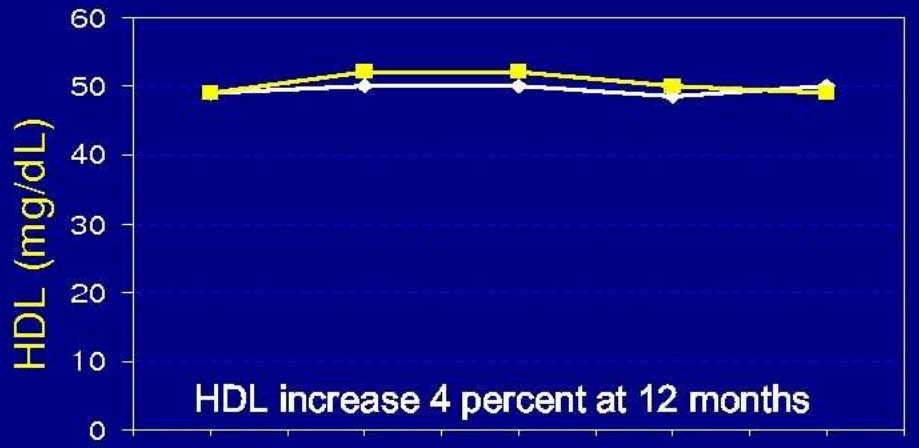
	Rosuvastatin (N = 8901)		Placebo (n = 8901)	
hsCRP, mg/L	4.2	(2.8 - 7.1)	4.3	(2.8 - 7.2)
LDL, mg/dL	108	(94 - 119)	108	(94 - 119)
HDL, mg/dL	49	(40 – 60)	49	(40 – 60)
Triglycerides, mg/L	118	(85 - 169)	118	(86 - 169)
Total Cholesterol, mg/dL	186	(168 - 200)	185	(169 - 199)
Glucose, mg/dL	94	(87 – 102)	94	(88 – 102)
HbA1c, %	5.7	(5.4 – 5.9)	5.7	(5.5 – 5.9)

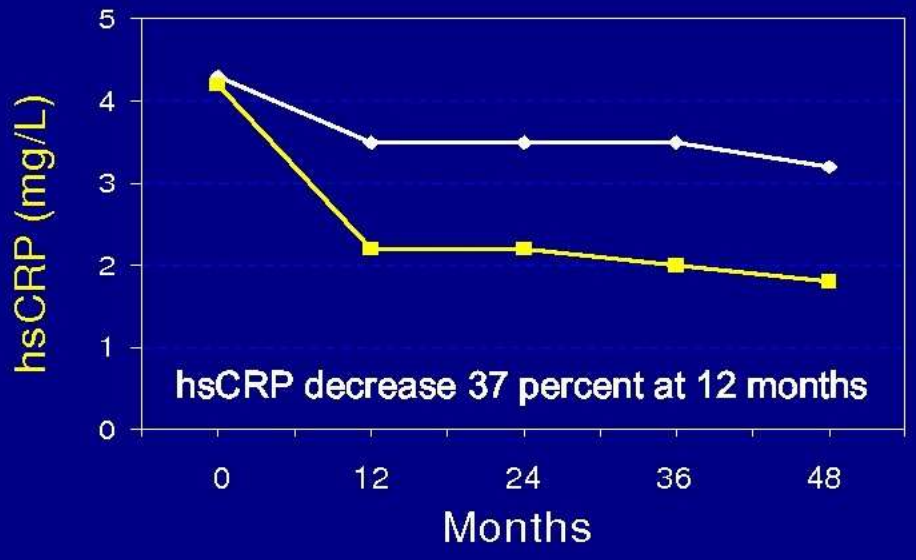
All values are median (interquartile range). [Mean LDL = 104 mg/dL]

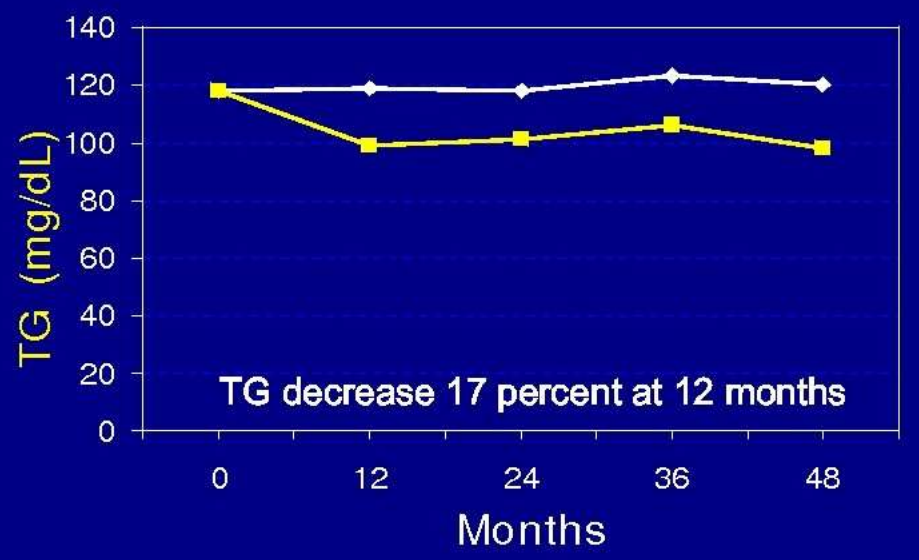
JUPITER

Effects of rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP









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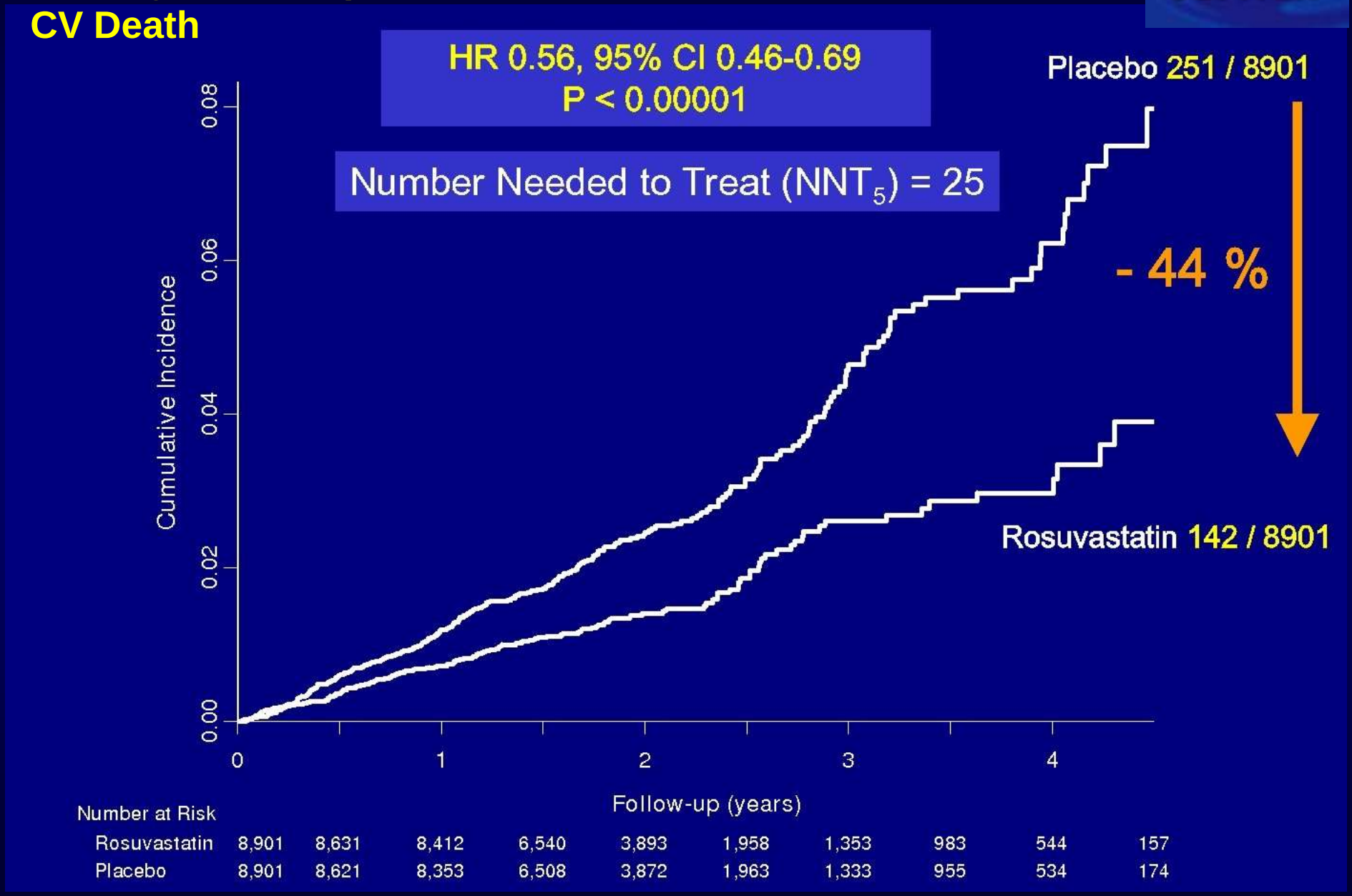
Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death



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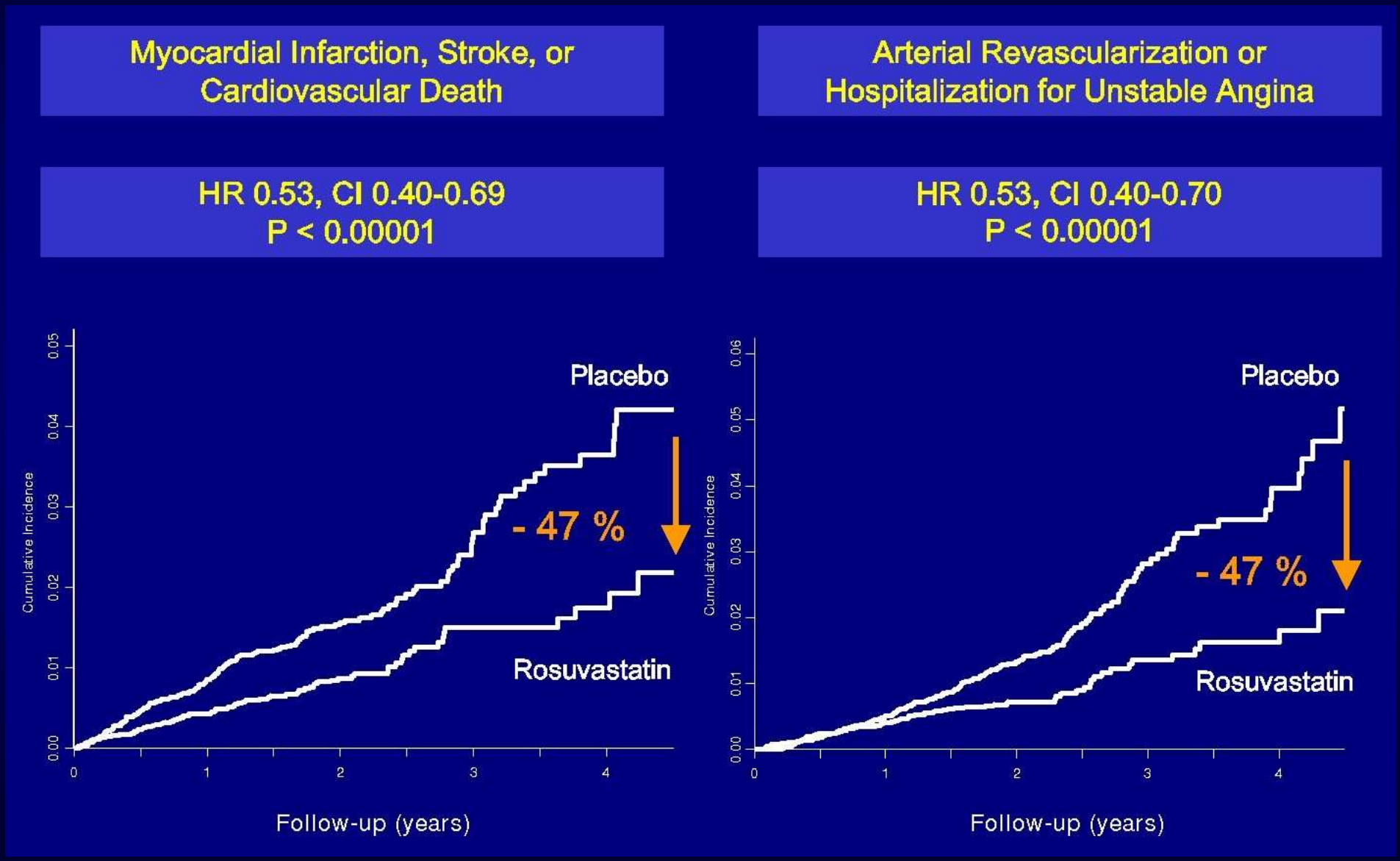
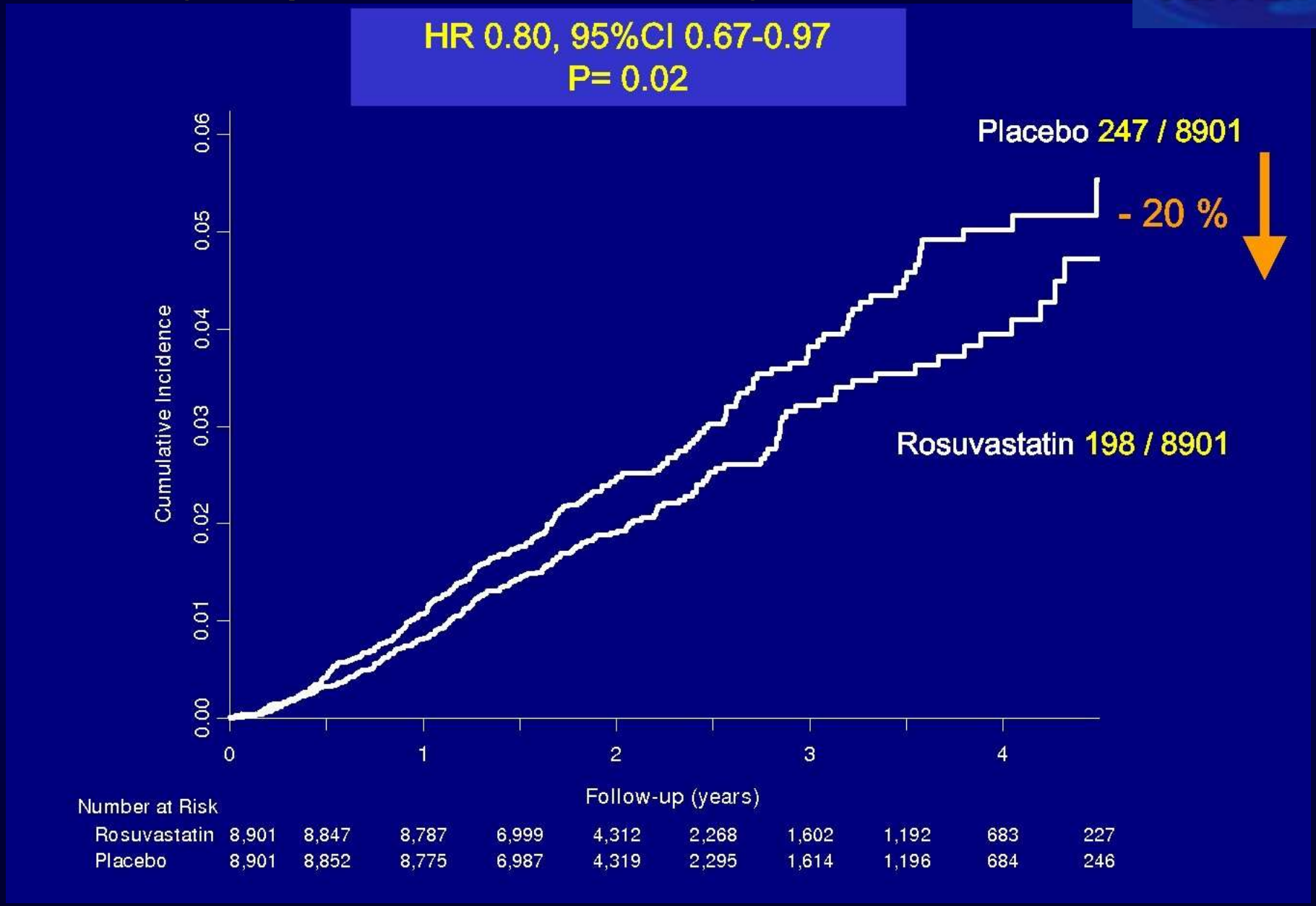
Grouped Components of the Primary Endpoint



JUPITER

Secondary Endpoint – All Cause Mortality



JUPITER
Conclusions

Among apparently healthy men and women with elevated hsCRP but low LDL, rosuvastatin reduced by 47 percent incident myocardial infarction, stroke, and cardiovascular death.

Despite evaluating a population with lipid levels widely considered to be “optimal” in almost all current prevention algorithms, the relative benefit observed in JUPITER was greater than in almost all prior statin trials.

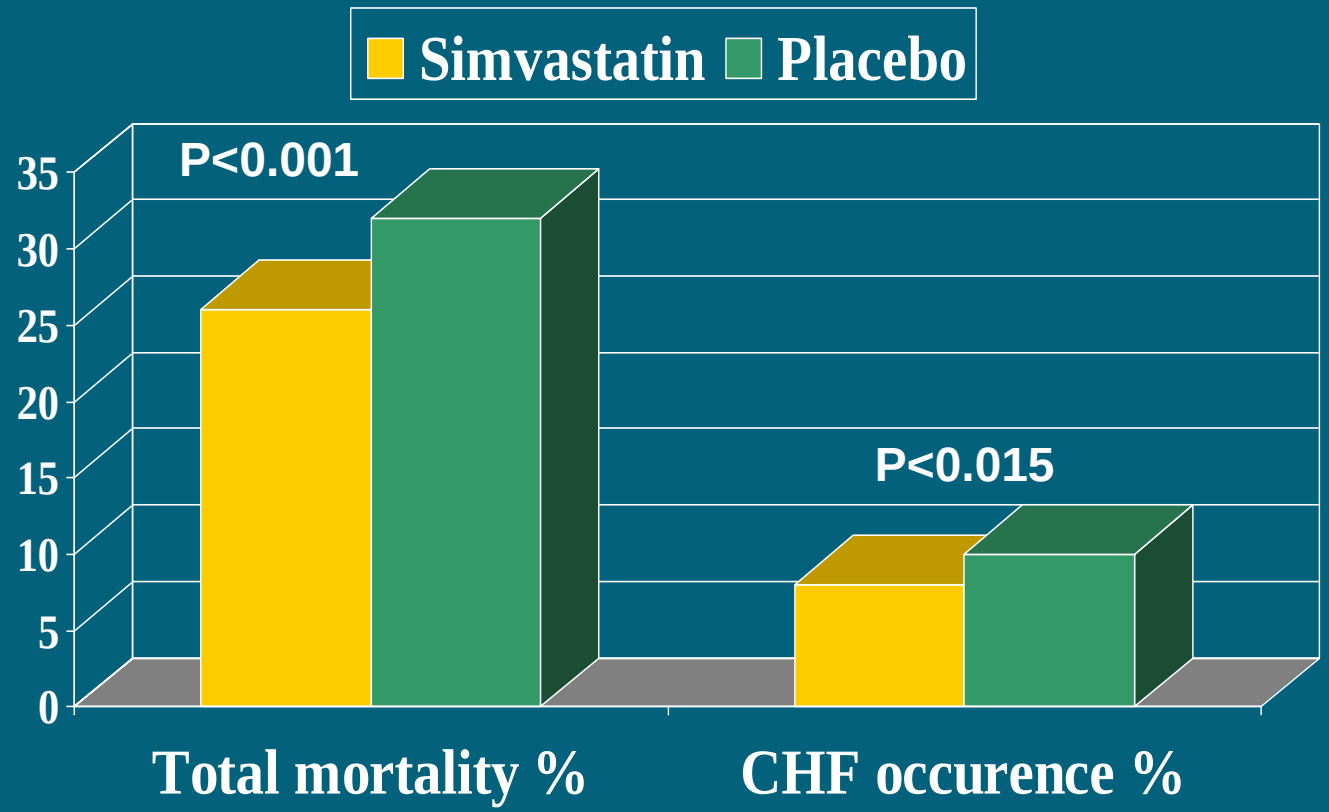
In this trial of low LDL/high hsCRP individuals who do not currently qualify for statin therapy, rosuvastatin significantly reduced all-cause mortality by 20 percent.

The role of statins after GISSI-HF

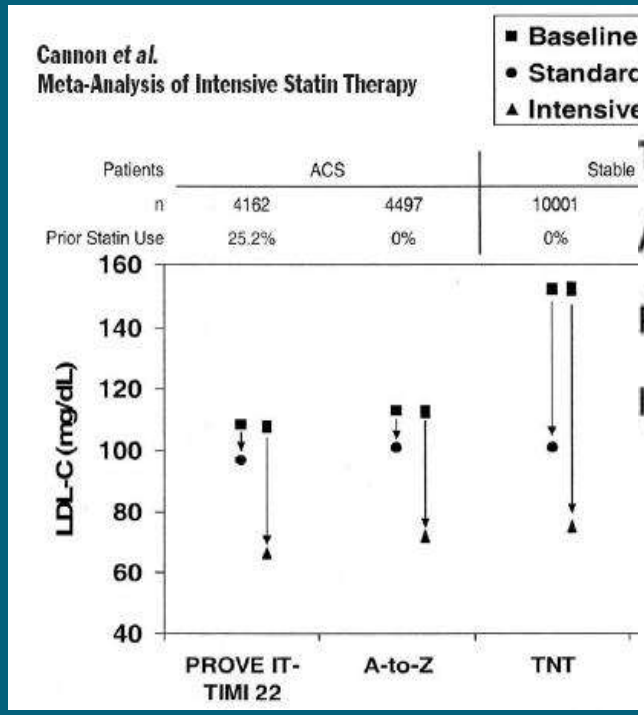
- The recommendations for primary and secondary prevention of CV events are not modified by the GISSI-HF results
- In patients with CHD and without HF/LVD, statins can prevent the occurrence of the first episode of overt HF

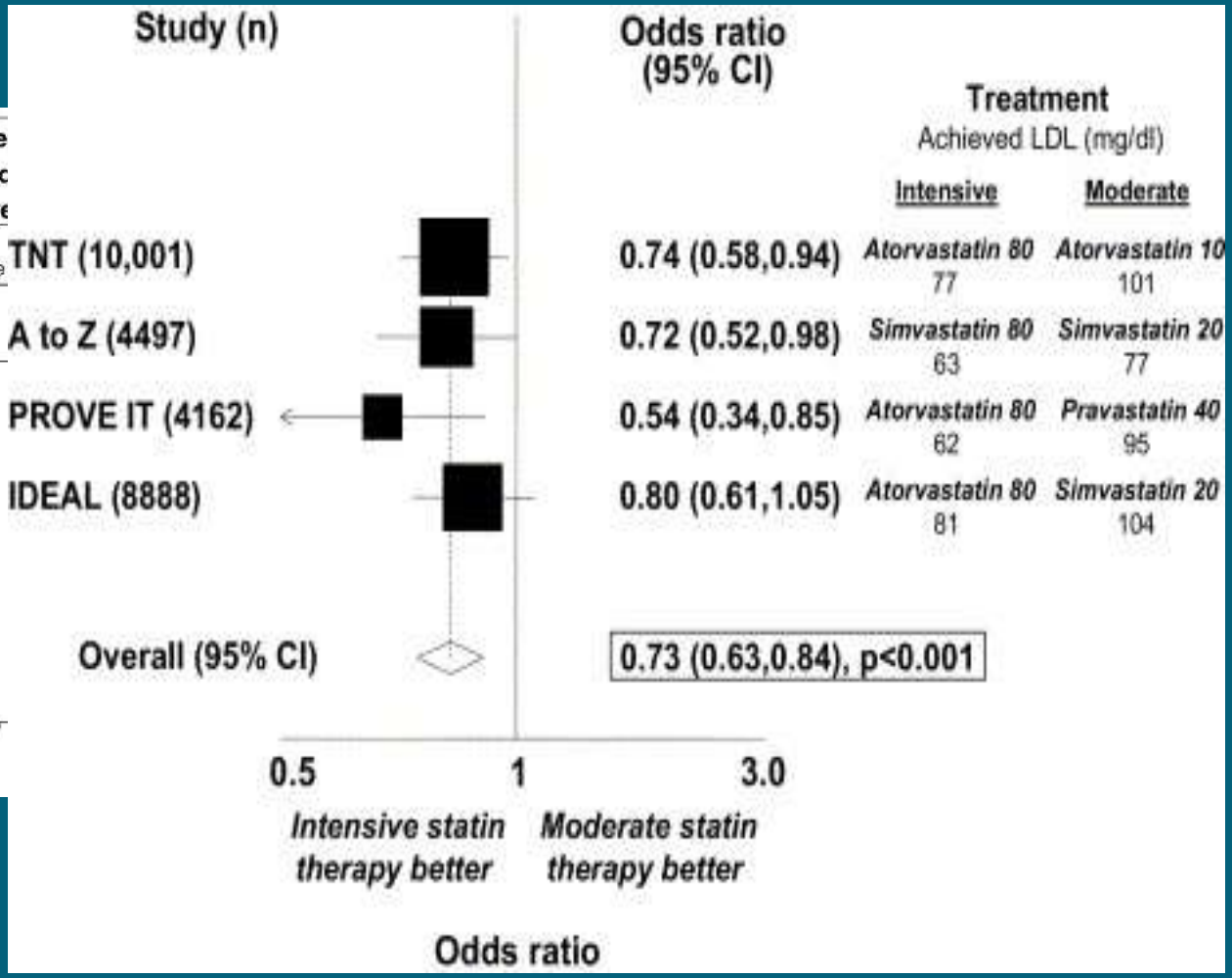
The effects of simvastatin on the incidence of HF in patients with CAD

J Card Fail 1997; 3:249-54



Hospitalization for HF (n.27,546 patients)





Scirica BM J Am Coll Cardiol 2006; 47: 2326-31

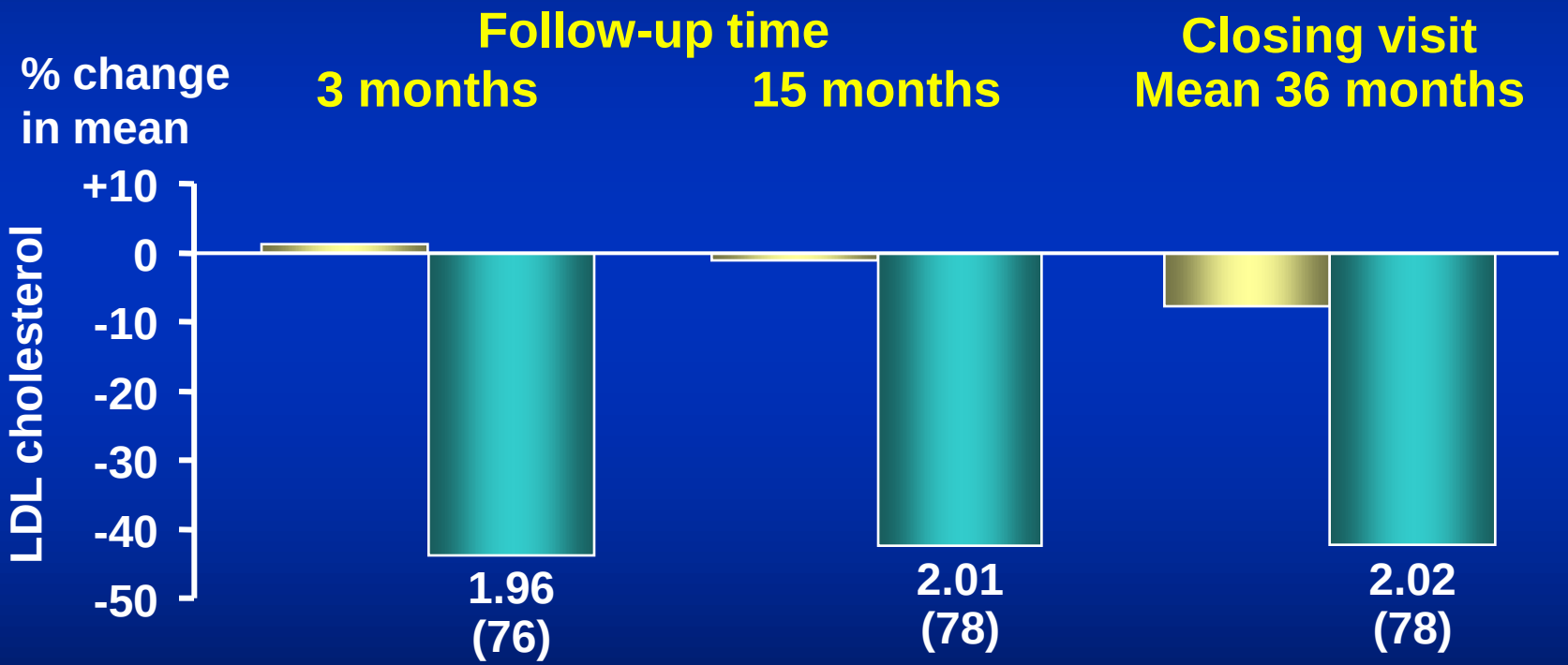
The role of statins after GISSI-HF

- The recommendations for primary and secondary prevention of CV events are not modified by the GISSI-HF results
- In patients with CHD and without HF/LVD, statins can prevent the occurrence of the first episode of overt HF
- In patients with chronic HF, LDL reduction with statins do not affect patients' outcomes

Mean LDL at Baseline and % Change During Follow-up

Baseline mean values

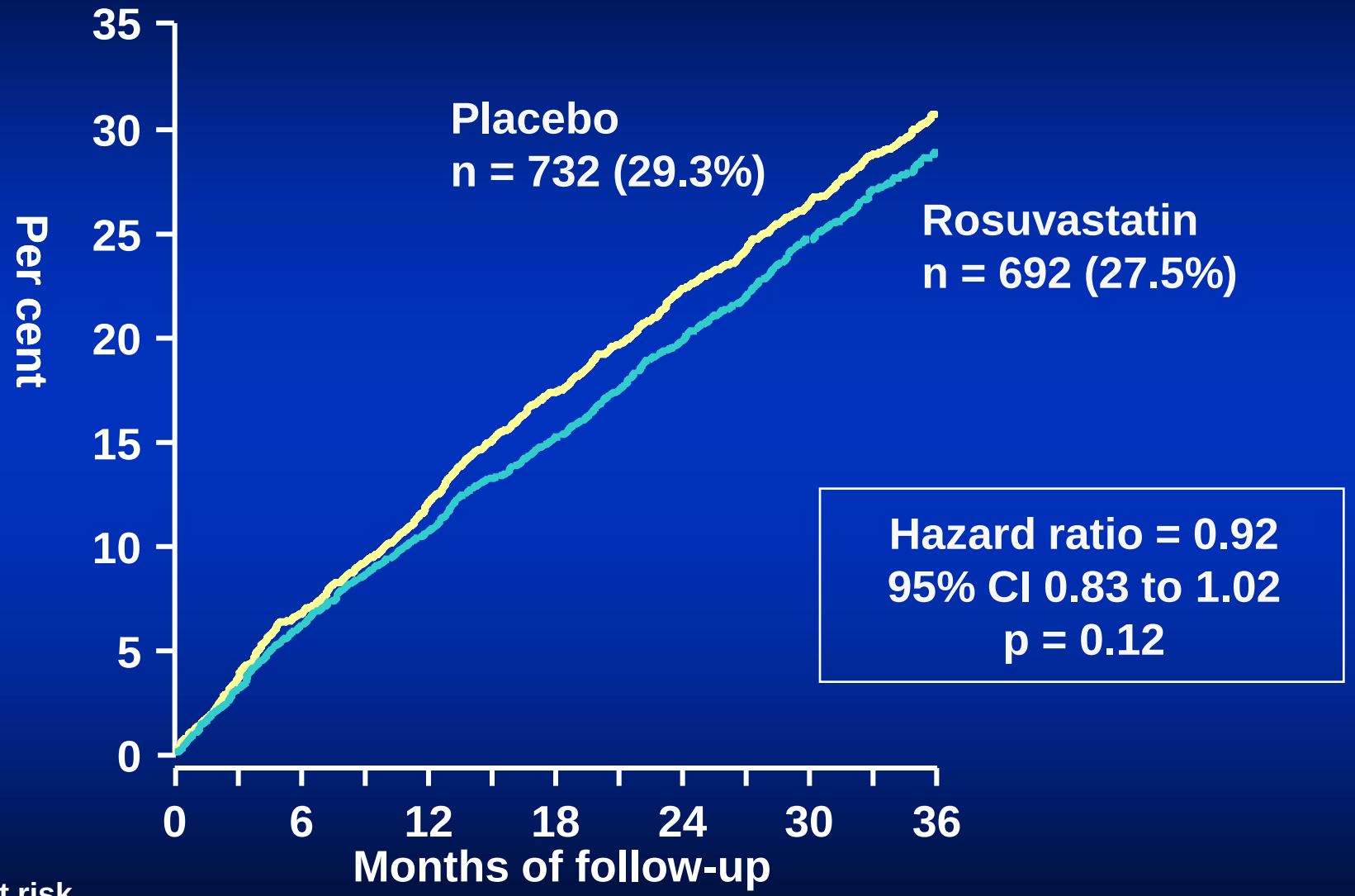
Placebo	3.56 mmol/L	(137 mg/dL)
Rosuvastatin	3.54 mmol/L	(137 mg/dL)



Kjekshus J et al. N Engl J Med 2007;357

Primary Endpoint

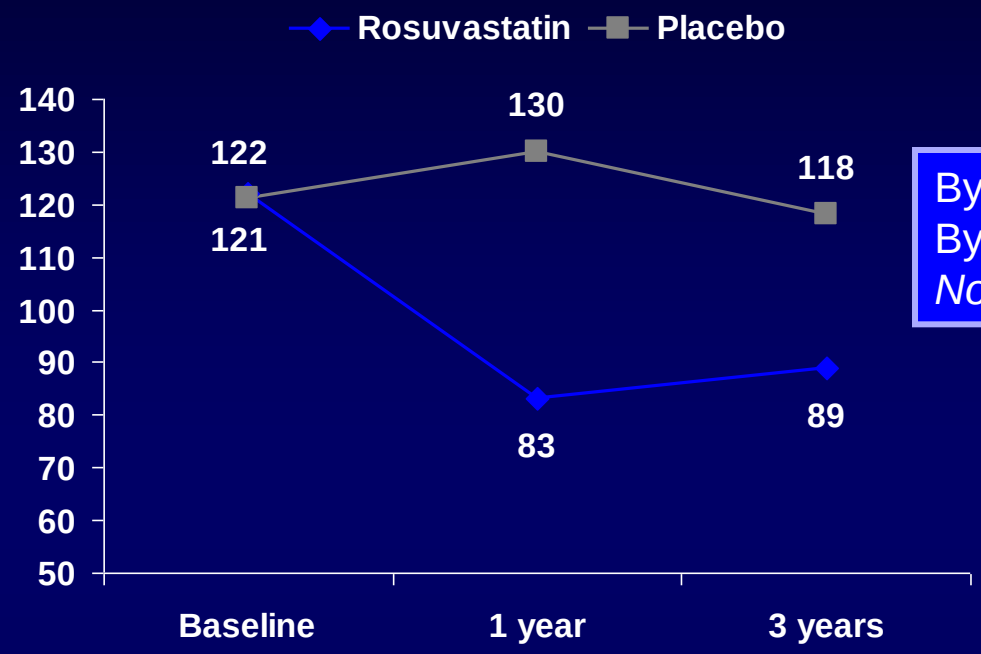
CV Death or Non-fatal MI or Non-fatal Stroke



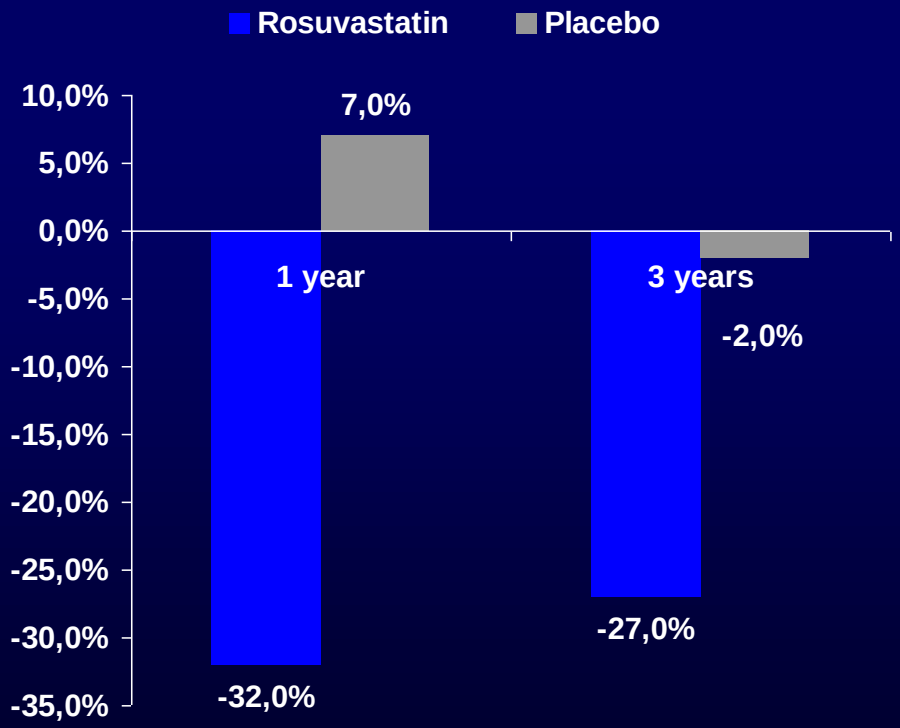
No. at risk							
Placebo	2497	2315	2156	2003	1851	1431	811
Rosuvastatin	2514	2345	2207	2068	1932	1484	855

Kjekshus J et al,
N Engl J Med 2007;357

LDL cholesterol (mg/dL) (2175 pts)



By time F=242.6, p<0.0001
By time and treatment F=390.7, p<0.001
No difference between Baseline Values, p=0.597



The rate of athero-thrombotic events in chronic HF is low

	Placebo	Rosuva	Follow-up
CORONA			**2.5 years**
MI %	6.0	5.2	
Stroke %	5.4	4.9	
GISSI-HF			**3.9 years**
MI %	3.1	2.7	
Stroke %	2.9	3.6	

Clinical implications

- No prescription of statins to patients with HF of non-ischemic etiology
- Discontinuation of statins in patients with HF without persistent signs/symptoms of ischemia, also to avoid multiple drug use or to not worsen compliance to other drugs proven to be effective in HF
- Maintainement of treatment in specific cases if the physician deems it useful, being reassured in doing so by the proven safety of the statins also in HF patients.