Effects of rosuvastatin in 4574 patients with chronic heart failure. The GISSI-HF trial

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on the behalf of the GISSI-HF Investigators

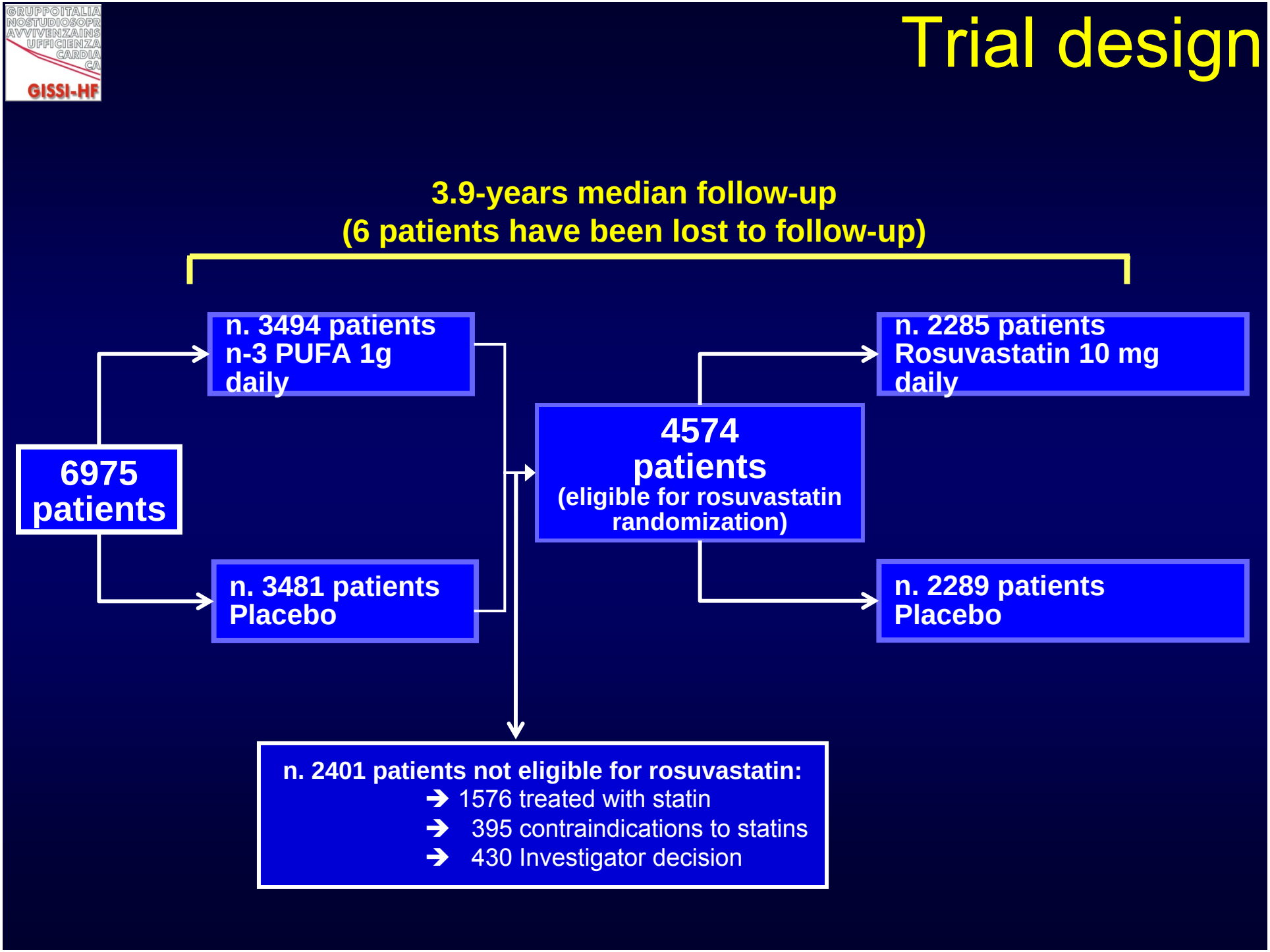
Rationale - 1

- “Pleiotropic” actions of statins - including anti-inflammatory, antihypertrophic, antifibrotic and antioxidant effects, improvement of endothelial dysfunction, inhibition of neurohormonal activation and prevention of cardiac arrhythmias - may target important components of the complex physiopathology of the HF syndrome

Rationale - 2

- Large observational studies, post-hoc analyses of RCTs, small RCTs (and their meta-analyses) suggesting a reduction in CV mortality in patients with HF of both ischemic and non-ischemic etiology
- Need of a large-scale RCT
  - to assess properly efficacy
  - to verify safety in a population at specific renal and hepatic risk
- Good opportunity of integrating the information expected from the CORONA trial in patients with systolic HF of ischemic etiology

Trial design



Patients' characteristics

	Rosuvastatin (n. 2285)	Placebo (n. 2289)
Age (years), mean±SD	68±11	68±11
Females, n. (%)	543 (23.8)	489 (21.4)
BMI (kg/m^2), mean±SD	27.1±4.6	27.1±4.4
SBP (mmHg), mean±SD	127±18	127±18
Heart rate (bpm), mean±SD	73±14	73±13

BMI=body mass index; SBP=systolic blood pressure

Medical history

	Rosuvastatin (n. 2285)	Placebo (n. 2289)
History of hypertension, n. (%)	1260 (55.1)	1224 (53.5)
Diabetes mellitus, n. (%)	625 (27.4)	571 (25.0)
Hospitalisation for HF in the previous year, n. (%)	1189 (52.0)	1131 (49.4)
Previous AMI, n. (%)	727 (31.8)	774 (33.8)
Previous stroke, n. (%)	99 (4.3)	109 (4.8)
History of atrial fibrillation, n. (%)	440 (19.3)	477 (20.8)
Peripheral vascular disease, n. (%)	184 (8.1)	160 (7.0)
COPD, n. (%)	538 (23.5)	522 (22.8)

HF=heart failure; AMI = acute myocardial infarction; COPD=chronic obstructive pulmonary disease

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

Concomitant medical treatment

	Rosuvastatin (n. 2285)	Placebo (n. 2289)
ACE-inhibitors/ARBs, n. (%)	2150 (94.1)	2126 (92.9)
Betablockers, n. (%)	1433 (62.7)	1420 (62.0)
Spironolactone, n. (%)	890 (39.0)	945 (41.3)
Diuretics, n. (%)	2057 (90.0)	2061 (90.0)
Digitalis, n. (%)	915 (40.0)	915 (40.0)
Oral anticoagulants, n. (%)	681 (29.8)	698 (30.5)
Aspirin, n. (%)	1020 (44.6)	1044 (45.6)
Other antiplatelet agents, n. (%)	179 (7.8)	188 (8.2)
Nitrates, n. (%)	729 (31.9)	761 (33.3)
Calcium-channel blockers, n. (%)	230 (10.1)	231 (10.1)
Amiodarone, n. (%)	464 (20.3)	421 (18.4)

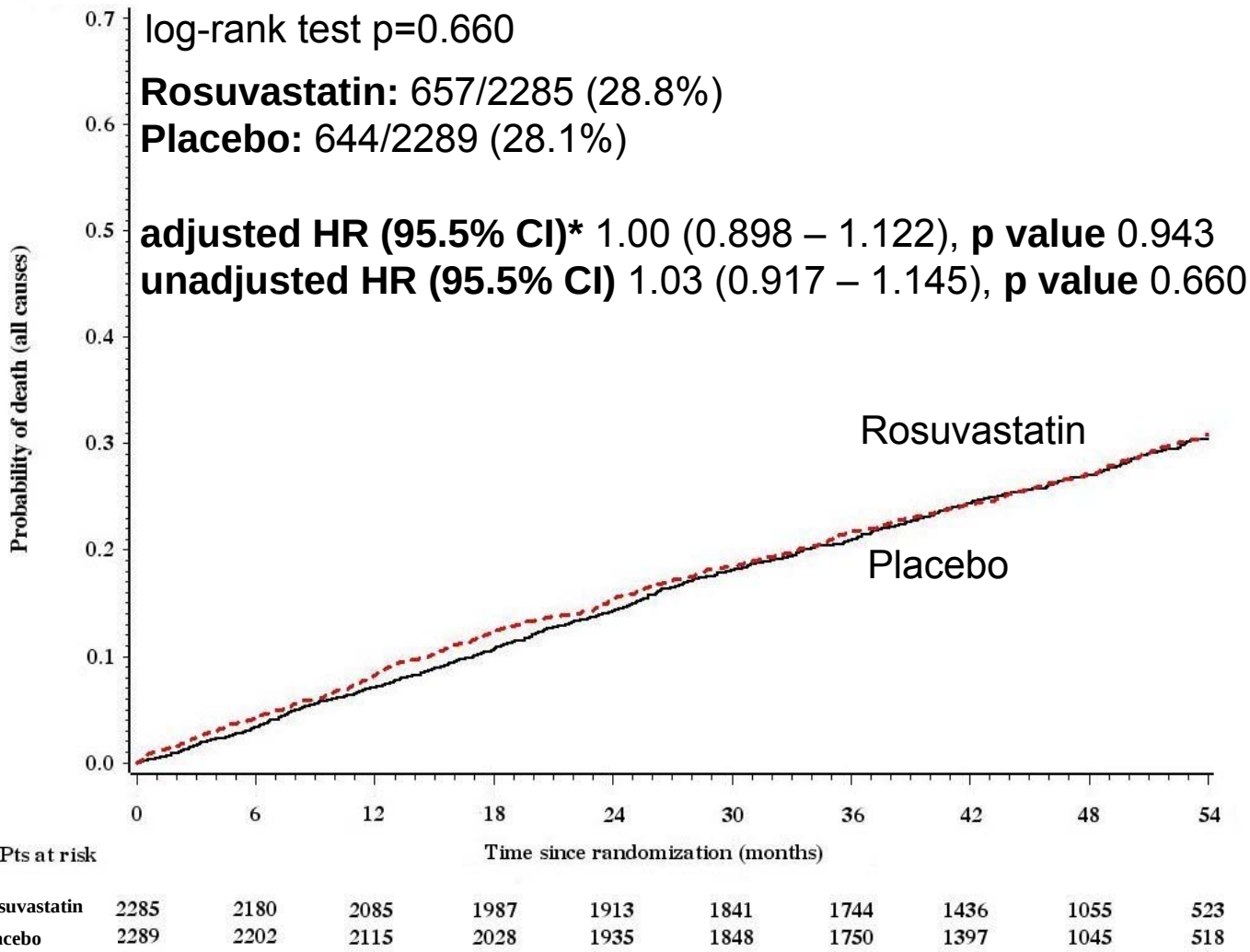
ARBs=angiotensin receptor blockers;

Time to all-cause death

log-rank test p=0.660

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

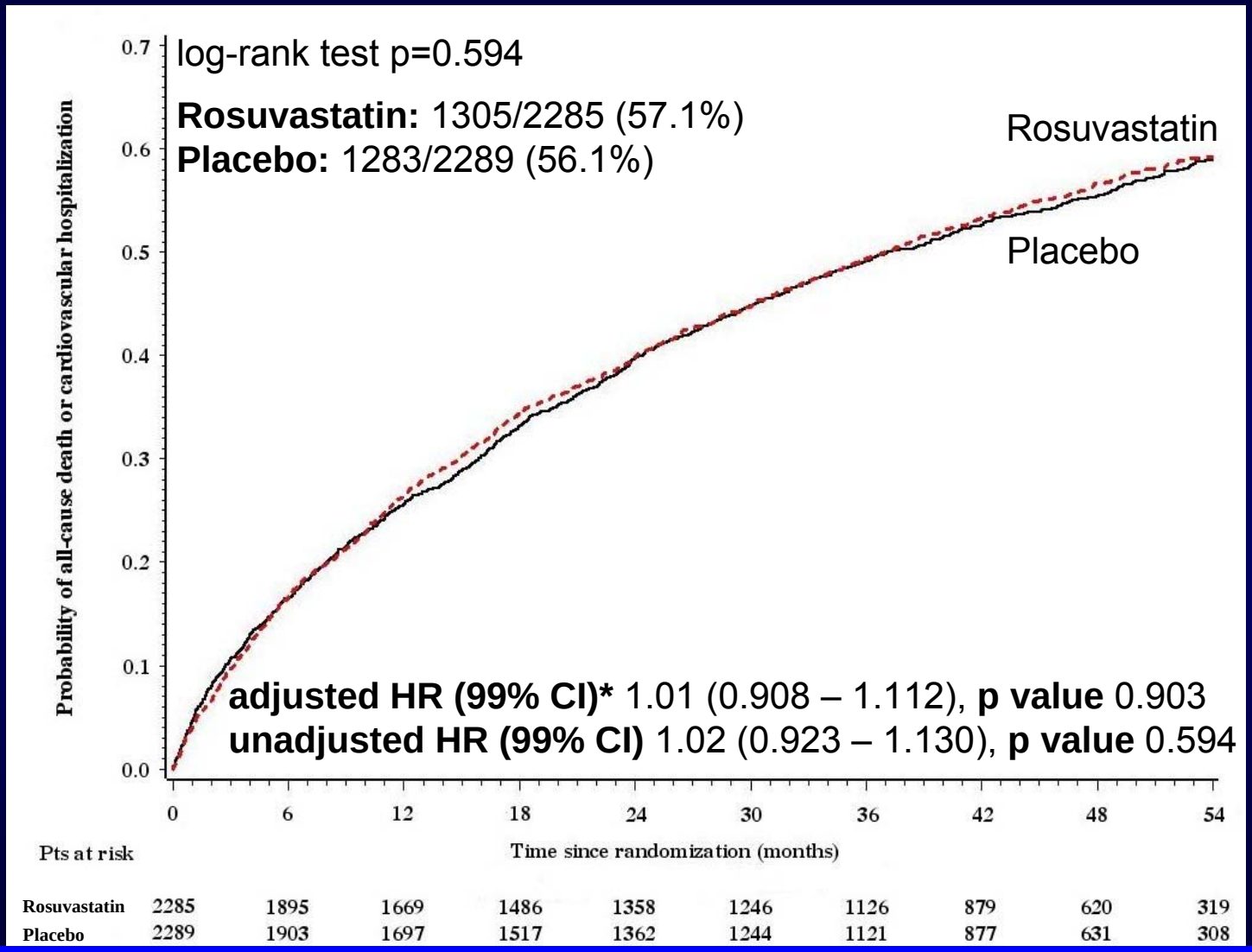
adjusted HR (95.5% CI)* 1.00 (0.898 – 1.122), **p value** 0.943
unadjusted HR (95.5% CI) 1.03 (0.917 – 1.145), **p value** 0.660



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.

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.

Secondary outcomes

	Rosuvastatin (n. 2285) n. (%)	Placebo (n. 2289) n. (%)	Adjusted		
			HR	95%CI*	p value
Patients who died of CV reasons	478 (20.9)	488 (21.3)	0.96	0.85-1.09	0.550
Patients who had a SCD	220 (9.6)	196 (8.6)	1.12	0.92-1.36	0.257
Patients hospitalised	1278 (55.9)	1286 (56.2)	0.99	0.92-1.07	0.776
Patients hospitalised for a CV reason	1033 (45.2)	1060 (46.3)	0.96	0.88-1.05	0.371
Patients hospitalised for HF	629 (27.5)	634 (27.7)	0.97	0.87-1.09	0.610
Patients who died of a CV cause or were hospitalised for any reason	1417 (62.0)	1385 (60.5)	1.02	0.95-1.10	0.626
Patients with fatal and not fatal MI	61 (2.7)	70 (3.1)	0.89	0.63-1.26	0.516
Patients with fatal and not fatal stroke	82 (3.6)	66 (2.9)	1.23	0.89-1.70	0.211

CV=cardiovascular; SCD=sudden cardiac death; HF=heart failure; MI=myocardial infarction

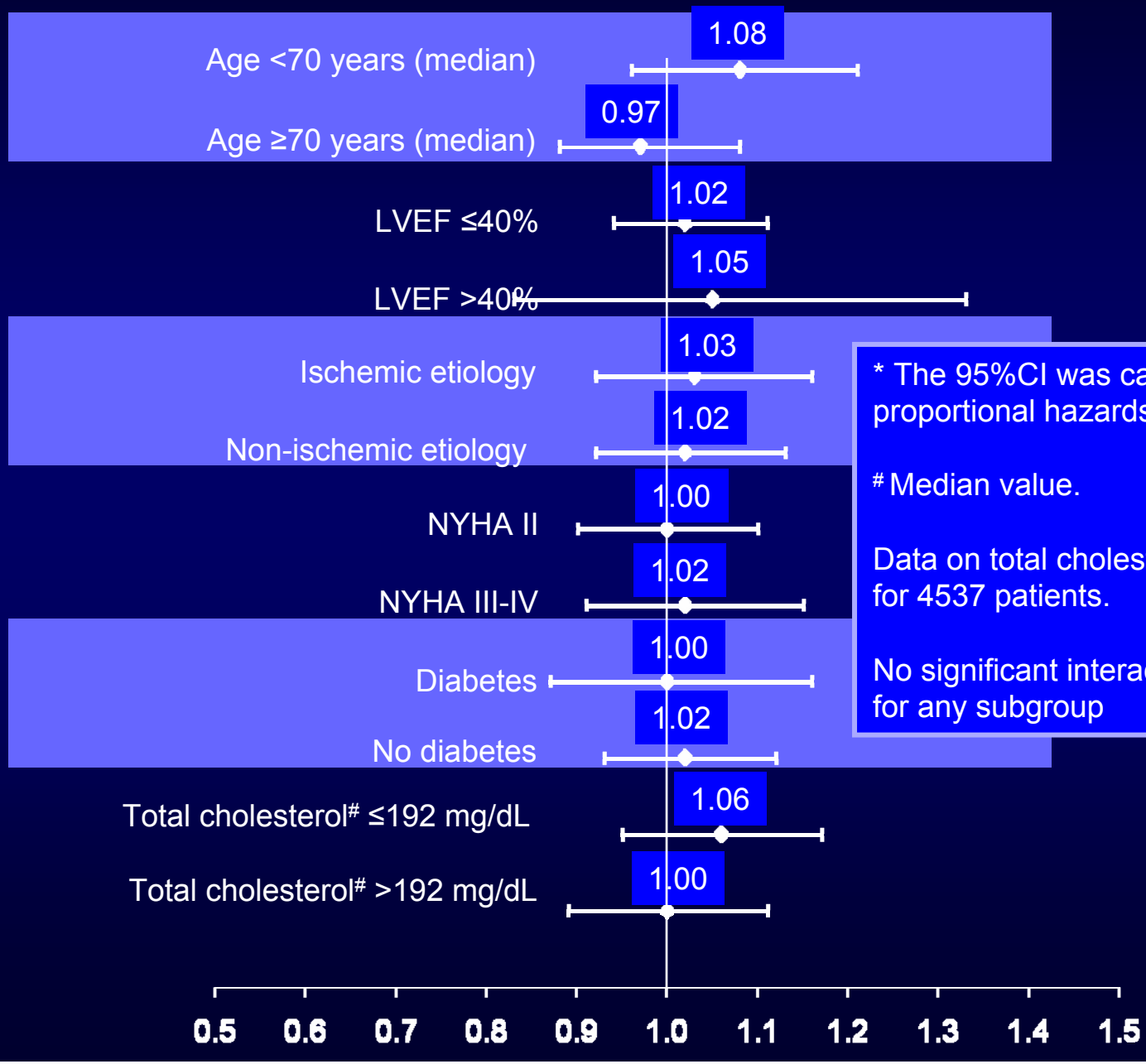
* The 95%CI was calculated using a Cox proportional hazards model adjusting for: hospitalisation for HF in the preceding year, prior pace-maker, gender, diabetes, pathological Q waves, ARBs.

Causes of death

	Rosuvastatin (n. 2285) n. (%)	Placebo (n. 2289) n. (%)
Total mortality	**657 (28.8)**	**644 (28.1)**
AMI	10 (0.4)	15 (0.7)
Worsening of HF	203 (8.9)	231 (10.1)
Presumed arrhythmic	198 (8.7)	182 (8.0)
Stroke	38 (1.7)	29 (1.3)
Other cardiovascular reasons	29 (1.3)	31 (1.4)
Neoplasia	81 (3.5)	75 (3.3)
Other non-cardiovascular reasons	75 (3.3)	55 (2.4)
Not known	23 (1.0)	26 (1.1)

AMI=acute myocardial infarction; HF=heart failure

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

Permanent treatment discontinuations

	Rosuvastatin (n. 2285)	Placebo (n. 2289)	p
Patients who permanently discontinued study treatment, n (%)	**790 (34.6)**	**831 (36.3)**	**0.22**
Adverse drug reaction	104	91	
Patients' decision	357	377	
Doctors' decision	30	39	
Investigators' decision	205	227	
Open label	10	22	
Other	84	75	

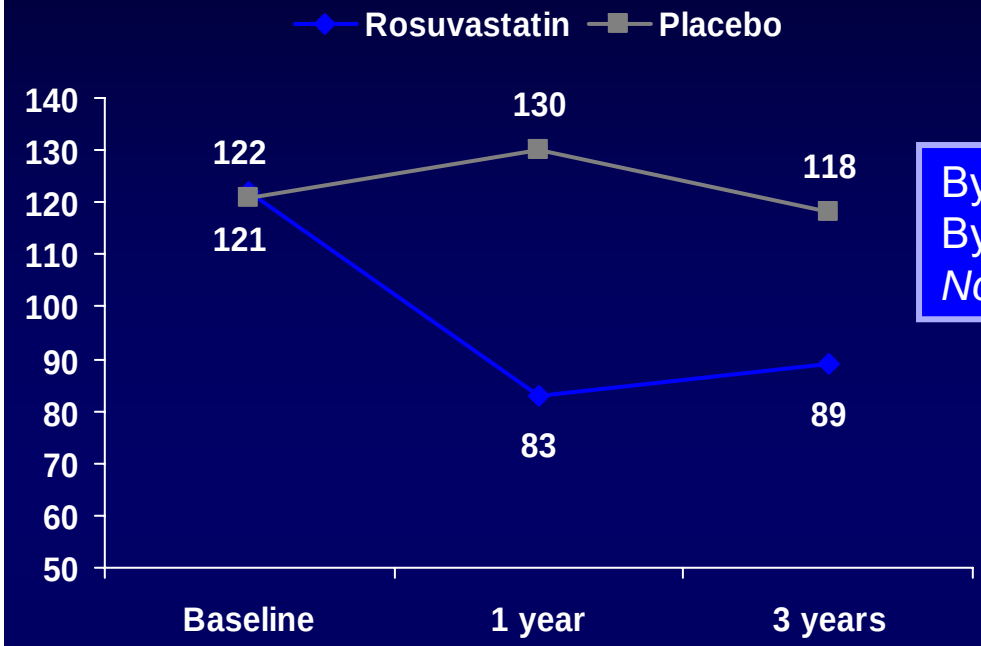
Adverse drug reactions

	Rosuvastatin (n. 2285)	Placebo (n. 2289)	p
Patients who permanently discontinued study treatment due to ADR, n (%)	**104 (4.6)**	**91 (4.0)**	**0.36**
Gastrointestinal disorders	34	44	
Astenia	1	-	
Allergic reaction	7	7	
Liver dysfunction	26	12	
Lipid abnormality	-	1	
Creatine phosphokinase increase	4	1	
Renal dysfunction	6	4	
Acute renal failure	2	-	
Hepatocellular jaundice	-	1	
Acute dermatitis*, Stevens-Johnson syndrome	1	-	
Muscle-related symptoms	23	21	
Patients who perrmanently discontinued study treatment due to serious ADR, n (%)	**2**	**-**	
Acute renal failure	1	-	
Acute dermatitis*, Stevens-Johnson syndrome	1	-	

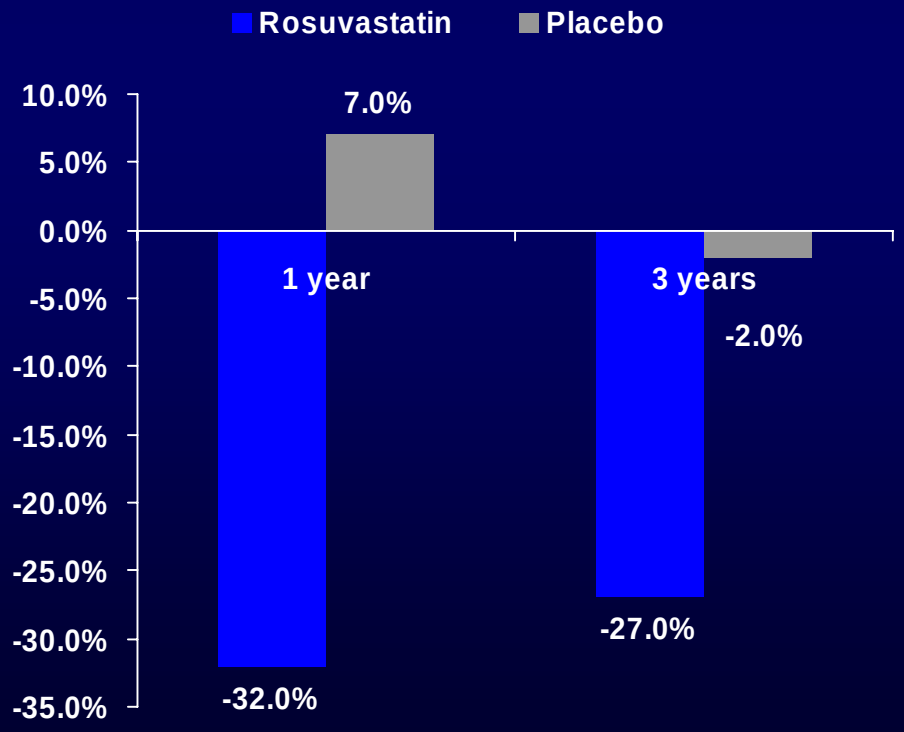
ADR=adverse drug reaction

* Diagnosed as Stevens Johnson Syndrome by the investigator, not confirmed by an expert adjudicator

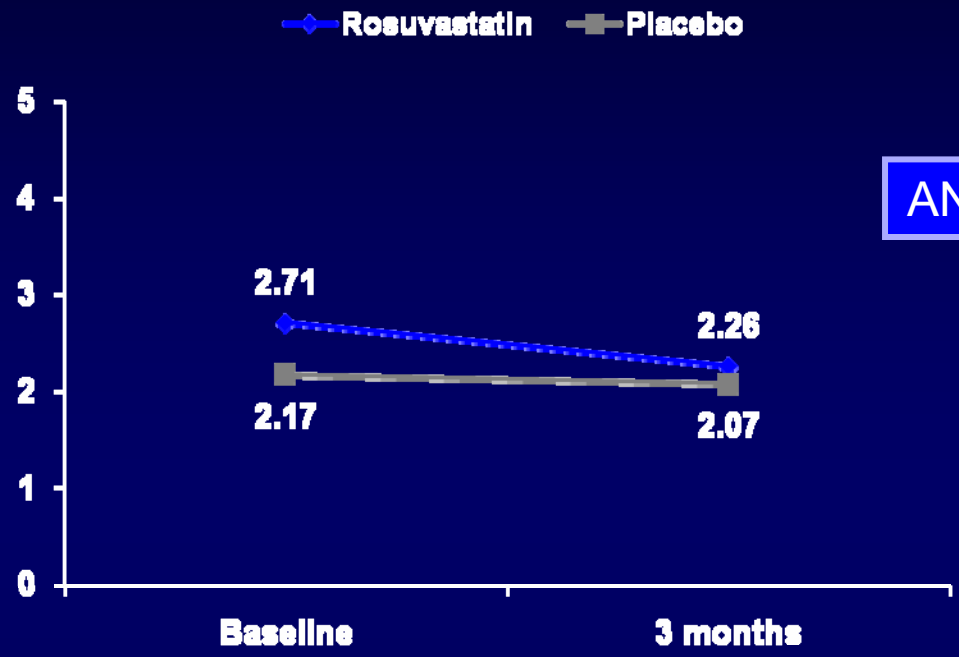
LDL cholesesterol (mg/dL)
(2175 pts)



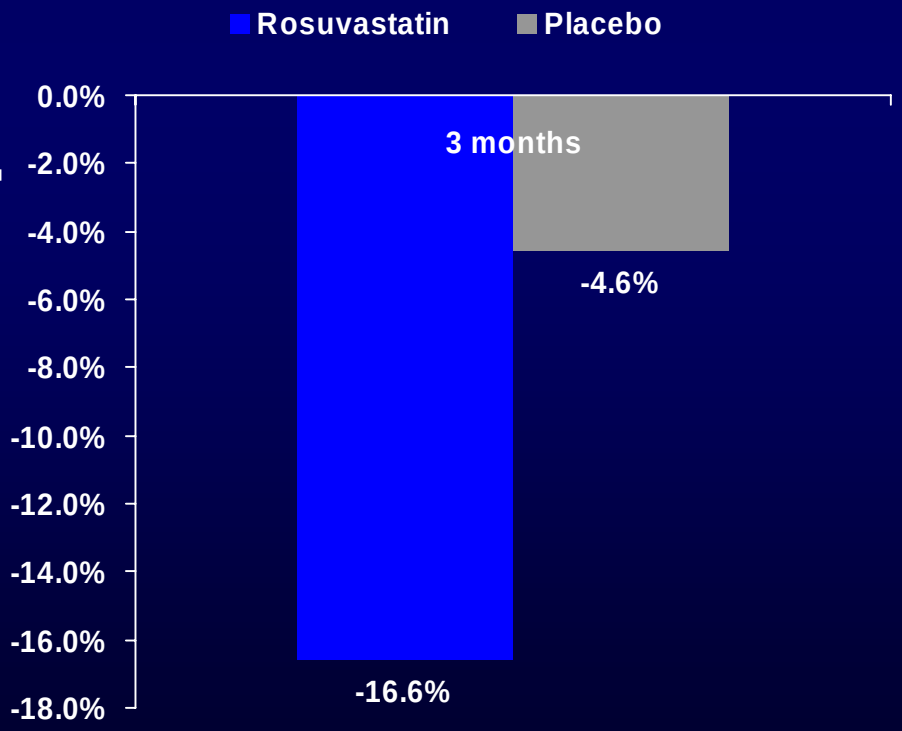
By time F=242.6, p<0.0001
By time and treatment F=390.7, p<0.001
No difference between Baseline Values, p=0.597



hsCRP (mg/L)
(626 pts)

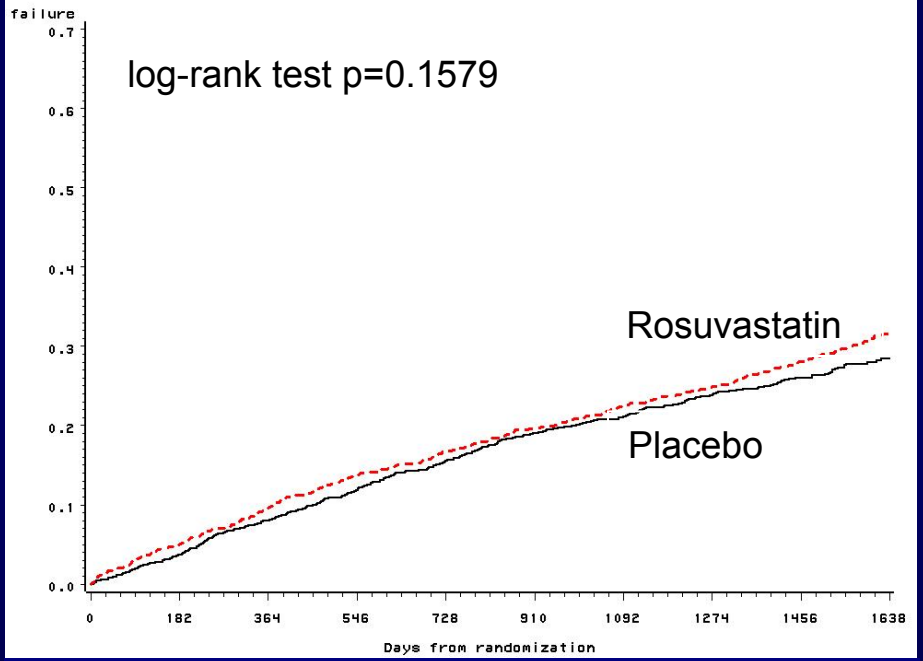


ANOVA p=0.0195



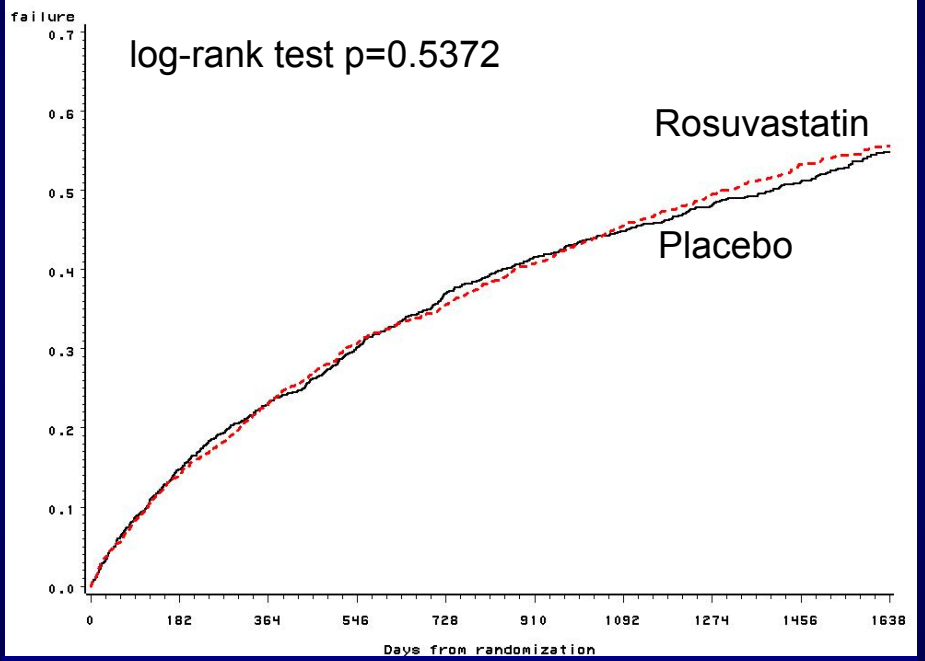
Per protocol analysis *(2874 patients)*

Time to all-cause death



Rosuvastatin: 429/1461 (29.4%)
Placebo: 377/1413 (26.7%)
unadjusted HR (95.5% CI) 1.11 (0.96–1.27), **p value** 0.159
adjusted HR (95.5% CI)* 1.12 (0.97–1.29), **p value** 0.116
*Estimates were calculated by Cox proportional hazards model, adjusting for: gender, prior by pass, patological Q waves, LVH, pulmonary whistle (p<0.1)

Time to Combined Endpoint = time to death or CV hospitalization, whichever comes first



Rosuvastatin: 784/1461 (53.7%)
Placebo: 731/1413 (51.7%)
unadjusted HR (99% CI) 1.03 (0.90–1.19), **p value** 0.537
adjusted HR (99% CI)* 1.05 (0.92–1.20), **p value** 0.364
*Estimates were calculated by Cox proportional hazards model, adjusting for: gender, prior by pass, patological Q waves, LVH, pulmonary whistle (p<0.1)

Total n. of hospitalizations and related causes

Causes	Rosuvastatin (2285 patients) n.	Placebo (2289 patients) n.
AMI	51	64
Angina	51	52
Worsening of HF	1153	1206
Atrial arrhythmia	79	103
Ventricular arrhythmia	99	94
Cardiovascular interventions	585	615
Stroke/TIA	94	77
Pulmonary/Peripheral embolism	5	8
Other vascular reasons	59	66
Total cardiovascular	**2176**	**2285**
Total not cardiovascular	**859**	**782**
Total	**3035**	**3067**

AMI = acute myocardial infarction; HF=heart failure; TIA=transient ischemic attack

Patients with hospitalizations and related causes

Patients with	Rosuvastatin (2285 patients)	Placebo (2289 patients)
AMI	46	59
Angina	44	33
Worsening of HF	629	634
Atrial arrhythmia	65	82
Ventricular arrhythmia	71	64
Cardiovascular interventions	540	564
Stroke/TIA	88	74
Pulmonary/Peripheral embolism	5	8
Other vascular reasons	50	64
Other not cardiovascular	593	560

AMI = acute myocardial infarction; HF=heart failure; TIA=transient ischemic attack

Conclusions

- The results of the GISSI-HF trial have proven that rosuvastatin 10 mg daily does not improve clinical outcomes in patients with chronic HF of any age, etiology and systolic function level
- The safety data were reassuring making the likelihood of causing harm, suggested in previous reports, at least remote

Clinical implications

- By definition, GISSI-HF results do not challenge the use of statins in all conditions for which they are currently recommended
- No prescription of statins to patients with HF of non-ischemic etiology
- The informed judgment of the treating physician is key for deciding on [dis]continuation of statins in pts with HF of ischemic etiology, for futility and/or to improve compliance with concurrent recommended treatments

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