

## Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF Trial

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The study was planned, conducted and analyzed by the GISSI group which has full ownership of the data, in complete independence from AstraZeneca that concurred to fund the study

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- AF is the most frequent form of arrhythmia in clinical practice, affecting 6% of people aged more than 65 years
- The traditional therapies (antiarrhythmic drugs and/or cardioversion) are often able to restore SR but relapses are very frequent
- The use of statins had been suggested to protect against AF in some clinical and experimental studies
- However, insufficient data are available at this time to allow recommendations for prevention of AF with statins in patients with HF

**Kannel WB et al. *N Engl J Med* 1982;306:1018-1022**

**Nattel S. *Nature* 2002;415:219-226**

**Crijns HJ et al. *Eur Heart J* 2000;21:1238-1245**

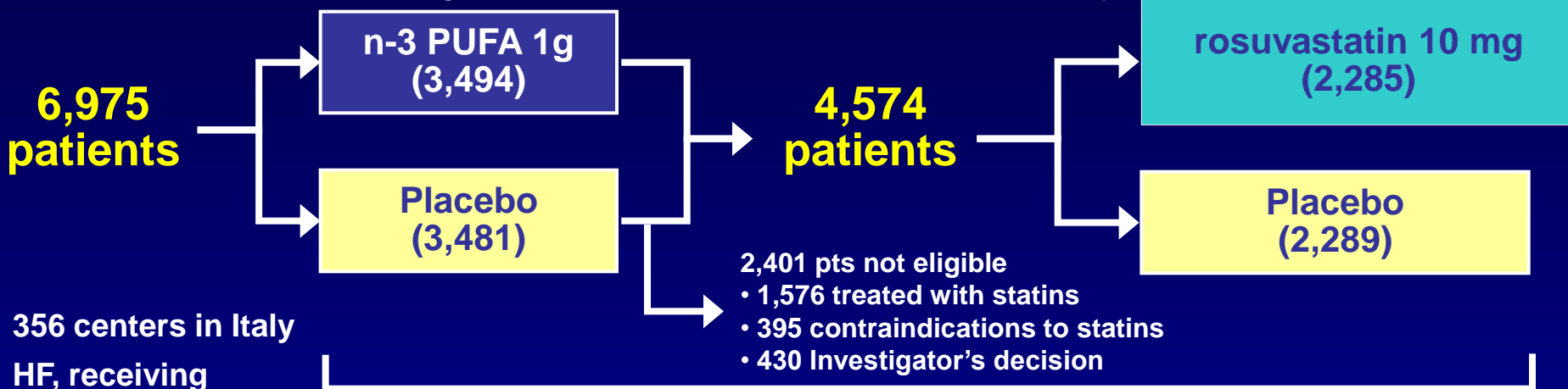
**Fauchier L et al. *J Am Coll Cardiol* 2008;51:828-835**

- The GISSI-HF study was aimed to assess the effect of n-3 PUFA and rosuvastatin compared with corresponding placebos in patients with chronic HF
  - GISSI-HF Investigators. *Eur J Heart Fail* 2004;6:635-641
  - GISSI-HF Investigators. *Lancet* 2008;372:1223-1230
  - GISSI-HF Investigators. *Lancet* 2008;372:1231-1239
- In the present report, we have analyzed the effect of rosuvastatin (10 mg daily) on the incidence of AF in the population of patients who were not in AF at the time of randomization

# 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  $\alpha = 0.045$**

## Primary end points

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

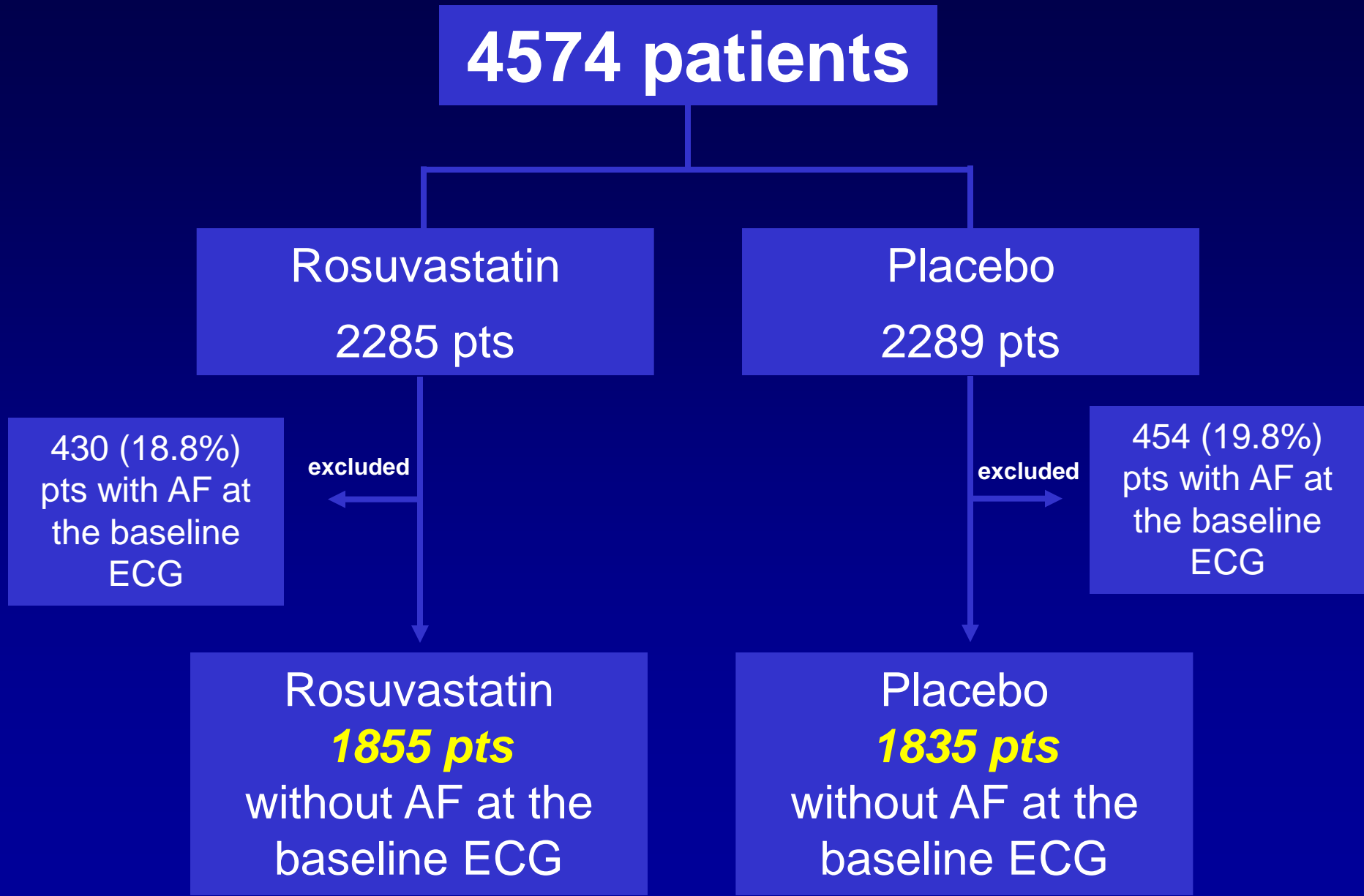
- Men and women aged 18 years or older
- Clinical evidence of HF of any cause classified according to the NYHA class II–IV
- LVEF measured within 3 months, if LVEF was greater than 40% a hospital admission for HF in the year before enrolment was needed
- Random allocation to rosuvastatin 10 mg daily or placebo
- Clinical visits planned at 1, 3, 6, and 12 months and then every 6 months until the end of the trial
- The institutional review committee at each participating center approved the study, and all patients gave informed consent

# Methods: *Definition of AF occurrence during the study*

- Patients with AF at the baseline ECG were excluded
- AF occurrence during the trial was defined as follows:
  - AF in the ECGs performed during the clinical visits
  - AF as a cause of worsening HF
  - AF as a cause of hospital admission
  - AF as an event occurring during a hospital admission

- Analyses were intention-to-treat
- Plots of the Kaplan-Meier estimates of the curves of AF occurrence presented along with the results of the log-rank tests
- Cox proportional hazards models were used in patients without AF at baseline, taking into account the effect of potential baseline confounding variables
- Different Cox proportional models were fitted
  1. adjusted for clinical variables
  2. adjusted for clinical variables and laboratory examinations
  3. adjusted for clinical variables, laboratory examinations and background therapy

# Patients' disposition



# Patients' characteristics

	AF during study (n. 552)	No AF during study (n. 3138)	p
<b>Patients' demographics</b>			
Age (years), mean±SD	70±10	66±11	<0.0001°
Age >70 years, n. (%)	286 (51.8)	1198 (38.2)	<0.0001*
Women, n. (%)	110 (19.9)	713 (22.7)	0.15*
<b>Clinical features</b>			
BMI (kg/m <sup>2</sup> ), mean±SD	27.3±4.6	26.8±4.4	0.01°
SBP (mmHg), mean±SD	129±19	126±18	0.003°
Heart rate (bpm), mean±SD	70±13	72±13	0.03°
NYHA class III-IV, n. (%)	217 (39.3)	1082 (34.5)	0.03*
LVEF (%), mean±SD	33.8±9.4	32.4±8.0	0.002°
Ischemic etiology, n. (%)	227 (41.1)	1328 (42.3)	0.60*

\* test Chi-square; ° t-test

# Medical history

	AF during study (n. 552)	No AF during study (n. 3138)	p
Prior admission for HF, n. (%)	313 (56.7)	1456 (46.4)	<0.0001*
Previous AMI, n. (%)	179 (32.4)	1127 (35.9)	0.11*
Previous stroke, n. (%)	30 (5.4)	114 (3.6)	0.044*
History of hypertension, n. (%)	328 (59.4)	1640 (52.3)	0.002*
Diabetes, n. (%)	140 (25.4)	840 (26.8)	0.49*
ICD, n. (%)	42 (7.6)	231 (7.4)	0.84*
Pacemaker, n. (%)	96 (17.4)	398 (12.7)	0.003*
History of paroxysmal AF, n. (%)	216 (39.1)	336 (10.7)	<0.0001*
Peripheral vascular disease, n. (%)	38 (6.9)	230 (7.3)	0.71*
COPD, n. (%)	160 (29.0)	655 (20.9)	<0.0001*
Neoplasia, n. (%)	26 (4.7)	111 (3.5)	0.18*

\* test Chi-square

# Laboratory examinations

	AF during study (n. 552)	No AF during study (n. 3138)	p
Hemoglobin (g/dL), mean±SD <i>available for 3666 patients</i>	13.6±1.6	13.7±1.6	0.09°
White cell count (mm <sup>3</sup> ), mean±SD <i>available for 3661 patients</i>	7314±2329	7328±2061	0.89°
Fibrinogen (mg/dL), mean±SD <i>available for 3375 patients</i>	378±114	364±111	0.008°
Glycemia (mg/dL), median [IQR] <i>available for 3646 patients</i>	102 [89-122]	103 [90-124]	0.23^
eGFR (ml/min/1.73m <sup>2</sup> ), mean±SD <i>available for 3671 patients</i>	66.1±22.5	70.8±22.2	<0.0001°
Sodium (mEq/L), mean±SD <i>available for 3666 patients</i>	140±4	140±4	0.06°
Bilirubin (mg/dL), median [IQR] <i>available for 3482 patients</i>	0.74 [0.56-1.00]	0.70 [0.50-0.93]	0.002^

° t-test; ^ Mann-U-Whithney test

	AF during study (n. 552)	No AF during study (n. 3138)	p
Total cholesterol (mg/dL), mean±SD <i>available for 3658 pts</i>	192±42	197±42	0.03°
LDL cholesterol (mg/dL), mean±SD <i>available for 3306 pts</i>	116±38	121±36	0.01°
HDL cholesterol (mg/dL), mean±SD <i>available for 3552 pts</i>	48±14	48±13	0.67°
Triglycerides (mg/dL), mean±SD <i>available for 3643 pts</i>	140±76	148±97	0.18°

° *t*-test

# Medical treatment

	AF during study (n. 552)	No AF during study (n. 3138)	p
ACE-inhibitors/ARBs, n. (%)	525 (95.1)	2940 (93.7)	0.20*
Betablockers, n. (%)	325 (58.9)	2059 (65.6)	0.002*
Spironolactone, n. (%)	252 (45.7)	1210 (38.6)	0.002*
Diuretics drugs, n. (%)	519 (94.0)	2757 (87.9)	<0.0001*
Digitalis, n. (%)	210 (38.0)	1007 (32.1)	0.006*
Oral anticoagulant drugs, n. (%)	202 (36.6)	516 (16.4)	<0.0001*
Aspirin/other antiplatelets, n. (%)	277 (50.2)	1904 (60.7)	<0.0001*
Nitrates, n. (%)	182 (33.0)	1032 (32.9)	0.97*
Amiodarone, n. (%)	158 (28.6)	584 (18.6)	<0.0001*

\* test Chi-square

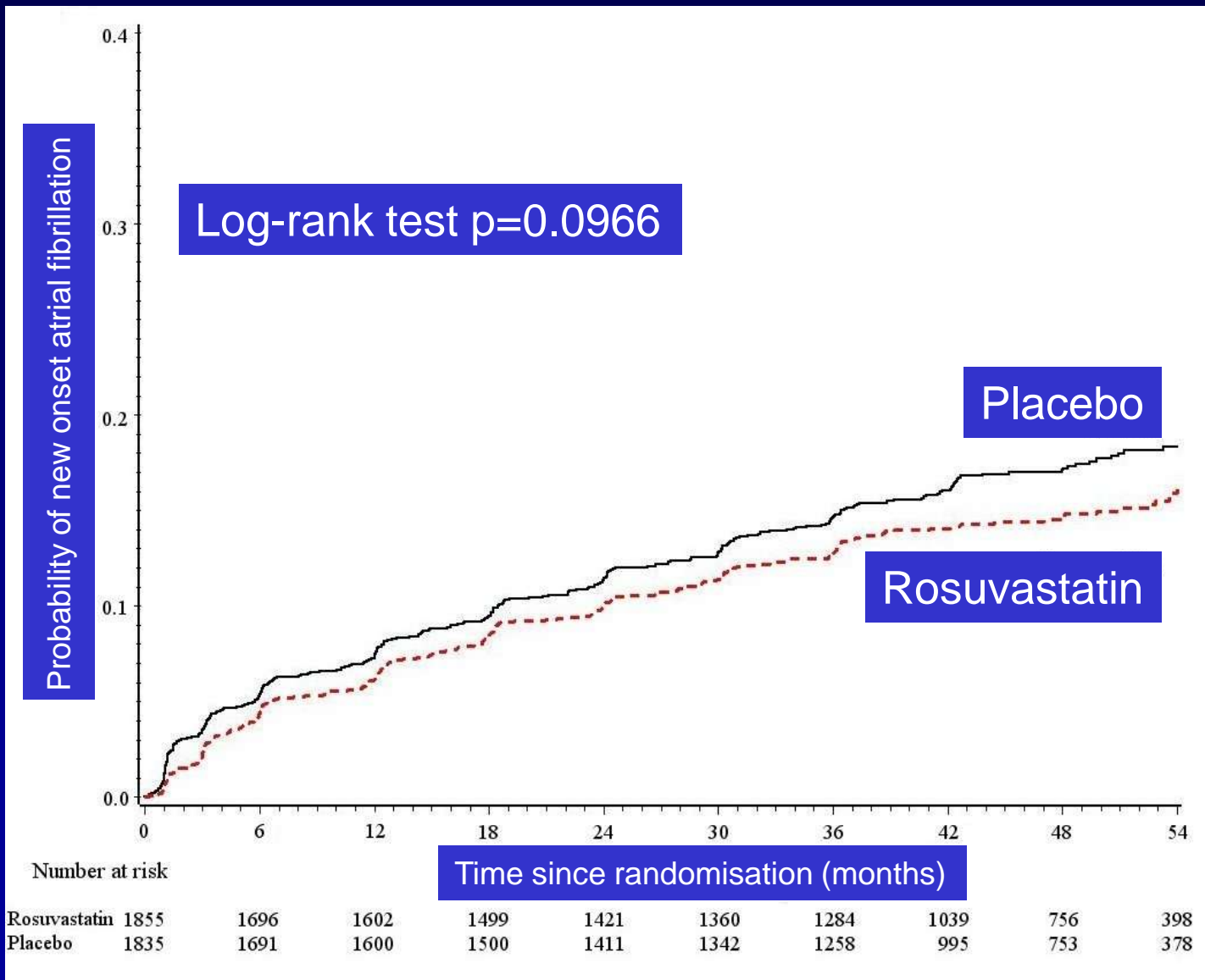
# RESULTS

# Effects of rosuvastatin on AF development

	Placebo	Rosuvastatin	Total
AF occurrence	294/1835 16.0%	258/1855 13.9%	552/3690 15.0%

- RRR = 13.2%
- ARR = 2.1%
- NNT to avoid 1 AF event = 47

# Kaplan-Meier curves for time to new onset of atrial fibrillation



# Effect of rosuvastatin on the occurrence of AF: unadjusted and multivariable analyses

	HR	95% CI	p
Unadjusted analysis	0.868	0.734-1.026	0.097
<b>Model 1</b>			
Adjusted for clinical variables*	0.855	0.722-1.011	0.067
<b>Model 2</b>			
Adjusted for clinical variables and laboratory examinations°	0.822	0.683-0.990	0.039
<b>Model 3</b>			
Adjusted for clinical variables, laboratory examinations and background therapy#	0.820	0.680-0.989	0.038

\* age (continuous), gender, BMI (continuous), SBP (continuous), heart rate (<60 vs ≥60 bpm), ischemic etiology, NYHA class (III-IV vs II), admission for HF in the previous year, prior stroke, history of hypertension, diabetes, history of paroxysmal AF, COPD, pulmonary congestion, pulmonary rales, third heart sound, mitral insufficiency, LVEF (>40 vs ≤40%), QRS (≥120 vs <120 msec), rhythm (pacemaker vs sinus), pathological Q waves, left ventricular hypertrophy.

° Hemoglobin (continuous), fibrinogen (continuous), glycemia (continuous), bilirubin (continuous), LDL cholesterol (continuous), HDL cholesterol (continuous), triglycerides (continuous), eGFR (<60 vs ≥60 ml/min/1.73m<sup>2</sup>), sodium (>140 vs ≤140 mEq/L, median value), white cell count (≤7047 vs >7047 mm<sup>3</sup>, median value).

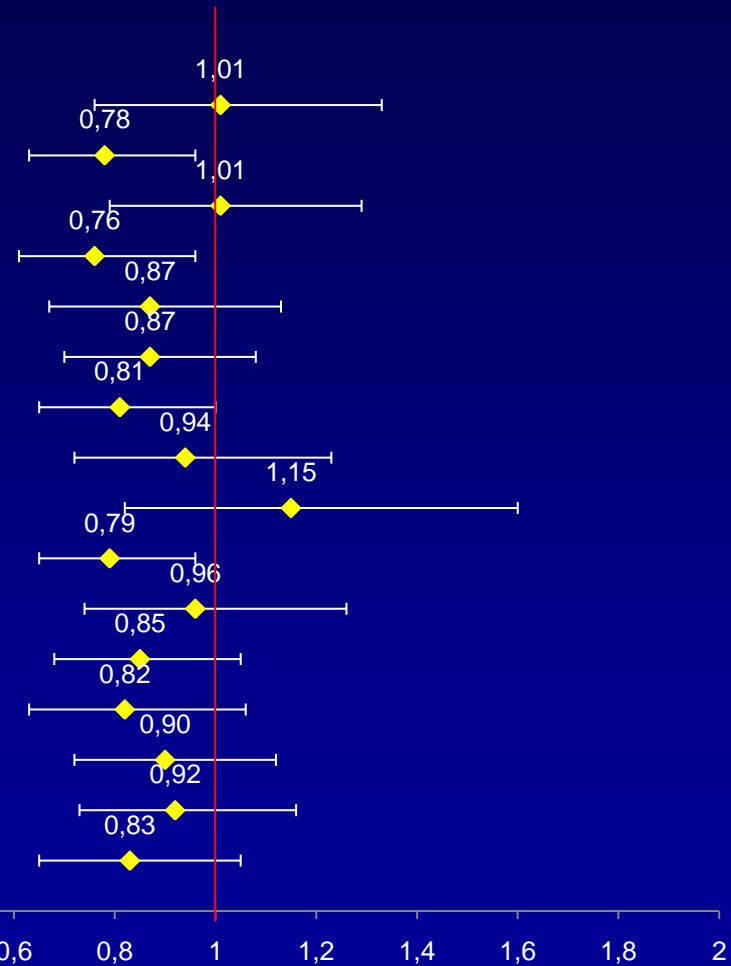
# Digitalis, spironolactone, diuretics, ACE-I/ARBs, betablockers, oral anticoagulant drugs, aspirin/other antiplatelet agents, nitrates, amiodarone.

# Relationship between LDL reduction and AF occurrence

- Irrespective of study treatment (rosuvastatin or placebo), patients with AF or without AF during the course of the study showed similar reduction of LDL cholesterol.
- From baseline to 6 months after study entry, the median decrease in patients with AF was 10 mg/dL (IQR -39/+14), in those without AF 13 mg/dL (IQR -47/+14),  $p=0.17$

# Predefined subgroup analysis

	Rosuvastatin Events/Patients (%)	Placebo Events/Patients (%)
Age ≤68 years <sup>#</sup>	100/937 (10.7)	102/952 (10.7)
Age >68 years <sup>#</sup>	158/918 (17.2)	192/883 (21.7)
LVEF <33%	123/905 (13.6)	126/917 (13.7)
LVEF ≥33%	135/950 (14.2)	168/918 (18.3)
Ischemic etiology	107/789 (13.6)	120/766 (15.7)
Non-ischemic etiology	151/1066 (14.2)	174/1069 (16.3)
NYHA II	147/1168 (12.6)	188/1223 (15.4)
NYHA III-IV	111/687 (16.2)	106/612 (17.3)
Diabetes	78/512 (15.2)	62/468 (13.3)
No diabetes	180/1343 (13.4)	232/1367 (17.0)
History of paroxysmal AF	102/267 (38.2)	114/285 (40.0)
No history of paroxysmal AF	156/1588 (9.8)	180/1550 (11.6)
eGFR <60 (ml/min/1.73m <sup>2</sup> )	106/633 (16.8)	123/599 (20.5)
eGFR ≥60 (ml/min/1.73m <sup>2</sup> )	152/1216 (12.5)	169/1223 (13.8)
Total cholesterol <sup>#</sup> ≤194 mg/dL	136/933 (14.6)	146/902 (16.2)
Total cholesterol <sup>#</sup> >194 mg/dL	120/906 (13.3)	144/917 (15.7)



Data on total cholesterol were available for 3658 patients. Data on eGFR were available for 3671 patients.

**No significant interactions were shown for any subgroup analysis**

<sup>#</sup> Median value

- Incidence of AF in patients with chronic HF treated according to the present evidence-based treatments remains relevantly high (15.0%)
- Rosuvastatin treatment was associated with a decreased risk of AF occurrence (13% relative risk reduction, 2.1% absolute risk reduction)
- The difference reached the conventional level of statistical significance just after adjustment for clinical variables, laboratory examinations and background pharmacological therapy
- This finding was homogeneous across the different subgroups, including patients with or without a history of previous episodes of AF

- Our study was not designed to test rosuvastatin on AF
  - A specific search for AF episodes was not planned (Holter or trans-telephonic monitoring)
  - Most cases of asymptomatic AF could not be detected
  - For this reason, the definition of AF used in our analysis has a limited sensitivity
  - The characteristics of the different types of AF are not available (paroxysmal, persistent, permanent, etc)
- Due to the progressively increasing divergence of the Kaplan-Meier curves , we can not exclude that a longer period of treatment could have produced more favorable results
- Being the trial not designed to assess the effect of rosuvastatin on AF occurrence, our ancillary analysis is likely underpowered

- In patients with chronic HF, presence and/or new onset AF are common complications which could have important clinical implications
- This post-hoc analysis of the GISSI-HF trial showed a weak evidence of a favorable effect of rosuvastatin in the prevention of AF occurrence
- Our study may not exclude that a treatment conducted for a longer period of time or in a larger population of patients could be associated with a favorable effect in terms of prevention of AF

# ***Acknowledgements***

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