Effects of n-3 PUFA in 6975 patients with chronic heart failure. The GISSI-HF trial

Luigi Tavazzi

on behalf of the GISSI-HF Investigators

GISSI-HF trial

Two nested studies to test:

- N-3 polyunsaturated fatty acids hypothesis

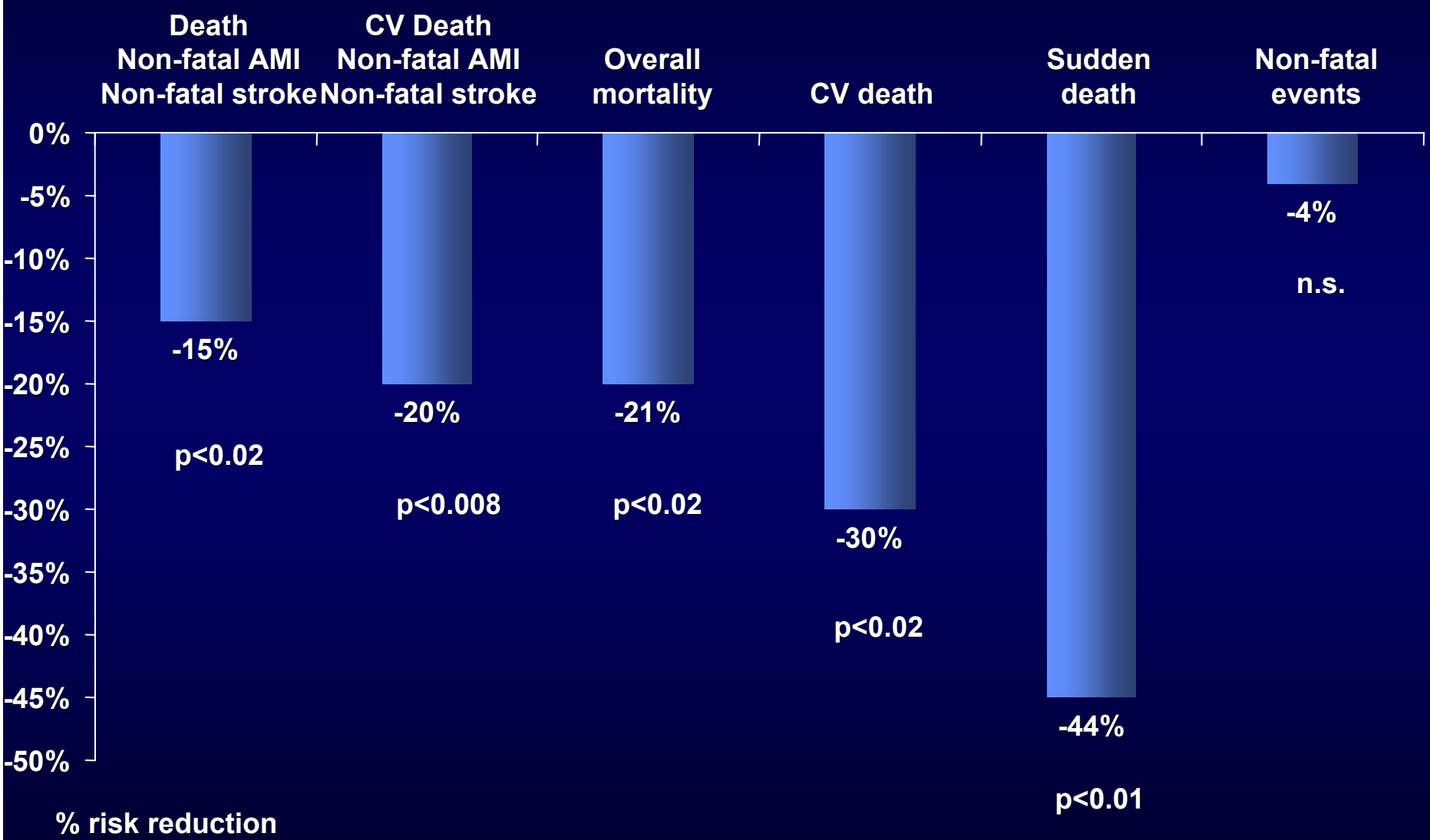
- Rosuvastatin hypothesis

in chronic HF patients

n-3 PUFA rationale

- **Experimental studies** extensively documented in cellular and animal models the favourable effects of n-3 PUFA on:
  - inflammatory processes (including reduction of endothelial activation and cytokine production)
  - platelet aggregation,
  - blood pressure and heart rate
  - ventricular function
  - autonomic tone
  - Arrhythmogenesis
- **Epidemiological studies** showed that fish consumption can be associated with a lower rate of cardiac death

Effect of n-3 PUFA treatment in GISSI-Prevenzione (11.323 post-MI pts)



(GISSI-Prevenzione Investigators, Lancet 1999; 354:447)

n-3 PUFA hypothesis

- n-3 PUFA could improve morbidity and mortality of patients with symptomatic HF of any etiology and any level of LVEF

GISSI-HF

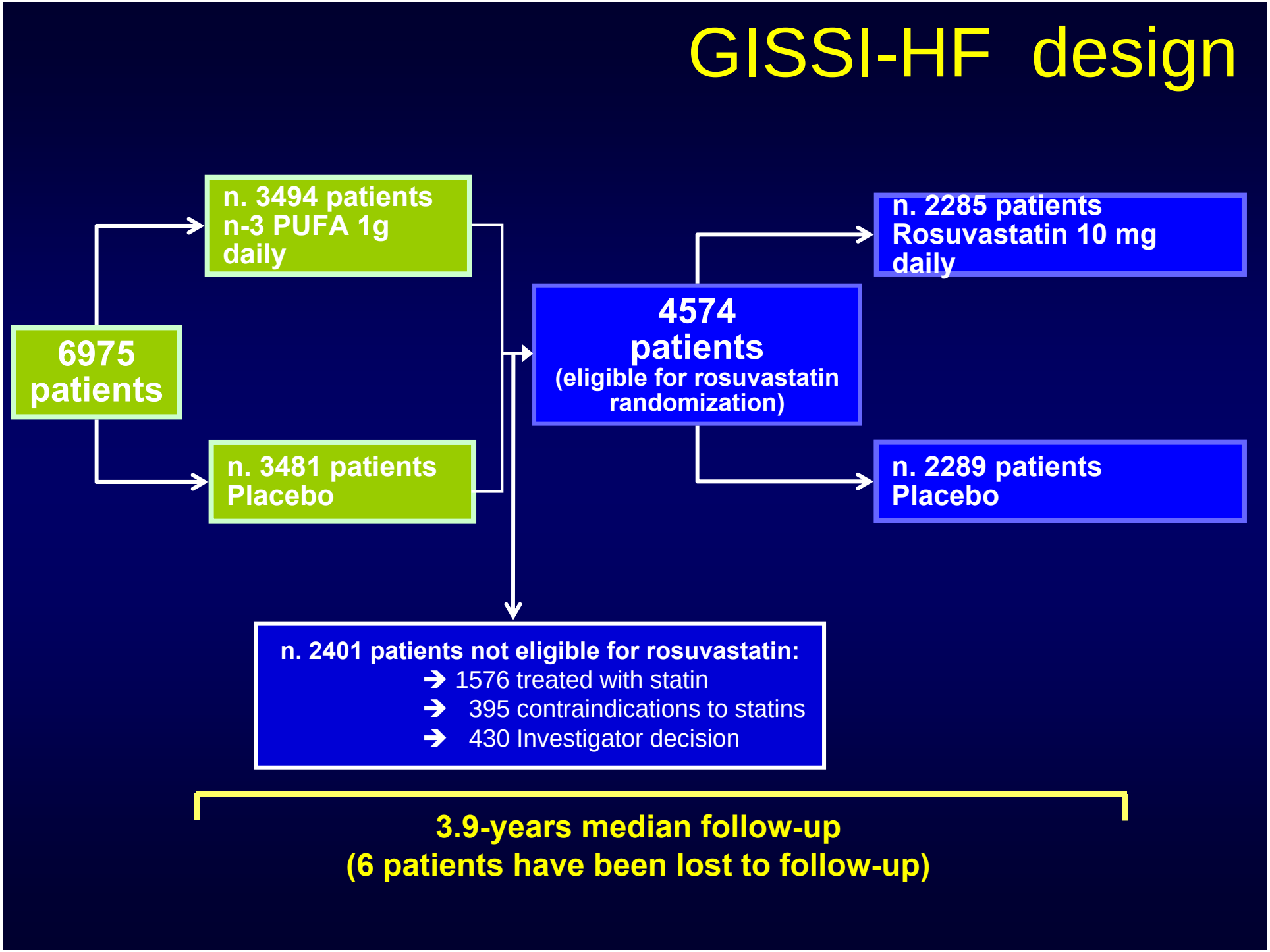
Inclusion criteria

- Patients ≥18 years old with chronic symptomatic heart failure (ESC Guidelines) of any etiology and with any LVEF

Exclusion criteria

- Indication, contraindication or known hypersensivity to the n-3 PUFA
- Severe comorbidities unlikely to be compatible with a long follow-up or requiring surgery
- Acute coronary syndrome or cardiac procedure within the preceding 1 month.

GISSI-HF design



Patients' characteristics
6975 pts enrolled in 357 centres in Italy

	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

Medical history

	n-3 PUFA (n. 3494)	Placebo (n. 3481)
History of hypertension (%)	54	55
Diabetes mellitus (%)	28	28
Hospitalisation for HF in the previous year (%)*	50	47
Previous AMI (%)	42	42
Previous stroke (%)	5	5
History of atrial fibrillation (%)	19	18
Peripheral vascular disease (%)	8	9
COPD (%)	21	23

*p 0.05

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;

RESULTS

Primary end-points

- All cause death
- All-cause death or hospitalization for CV reasons

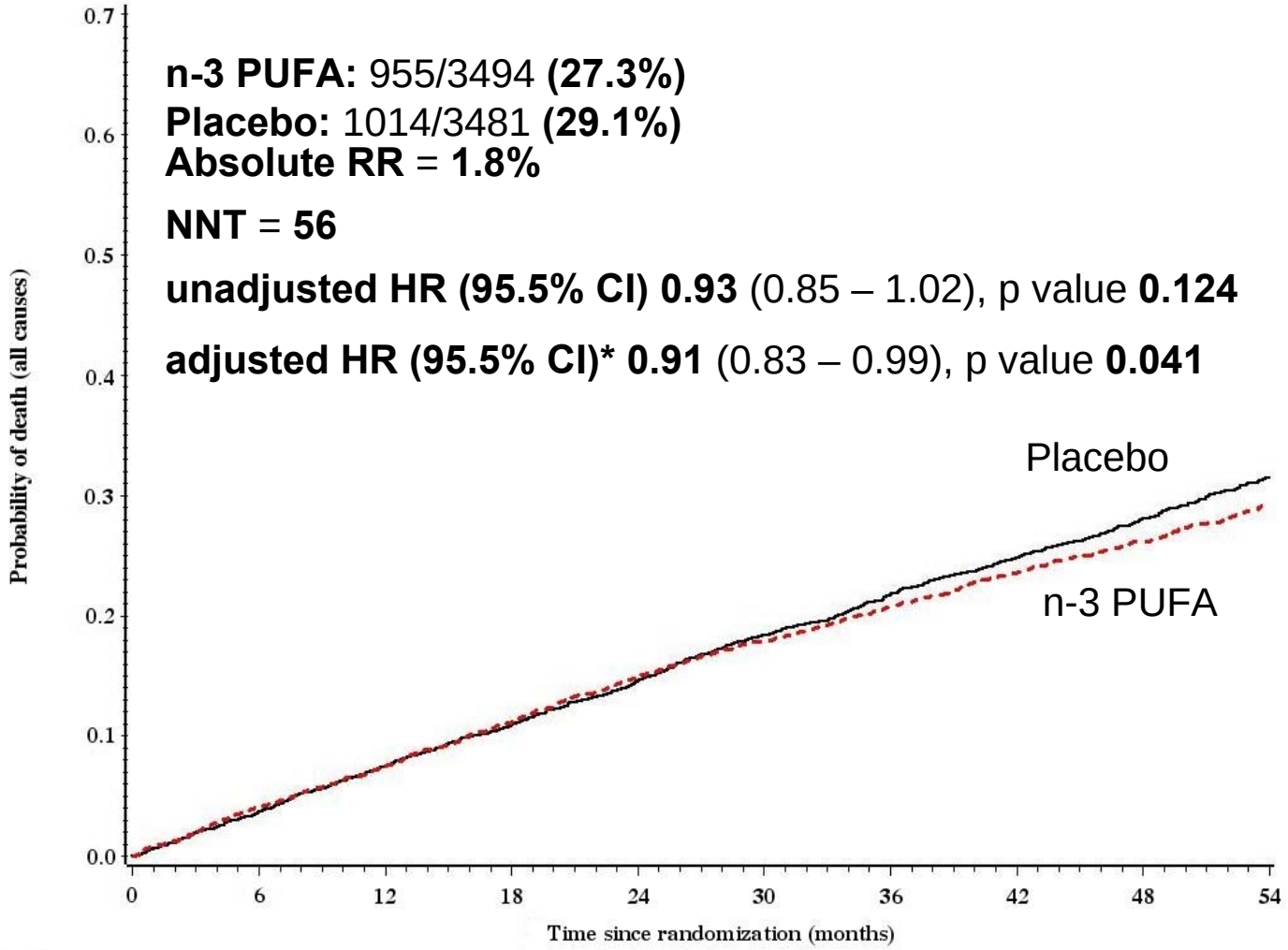
Time to all-cause death

n-3 PUFA: 955/3494 **(27.3%)**
Placebo: 1014/3481 **(29.1%)**
Absolute RR = **1.8%**

NNT = **56**

unadjusted HR (95.5% CI) 0.93 (0.85 – 1.02), p value **0.124**

adjusted HR (95.5% CI)* 0.91 (0.83 – 0.99), p value **0.041**

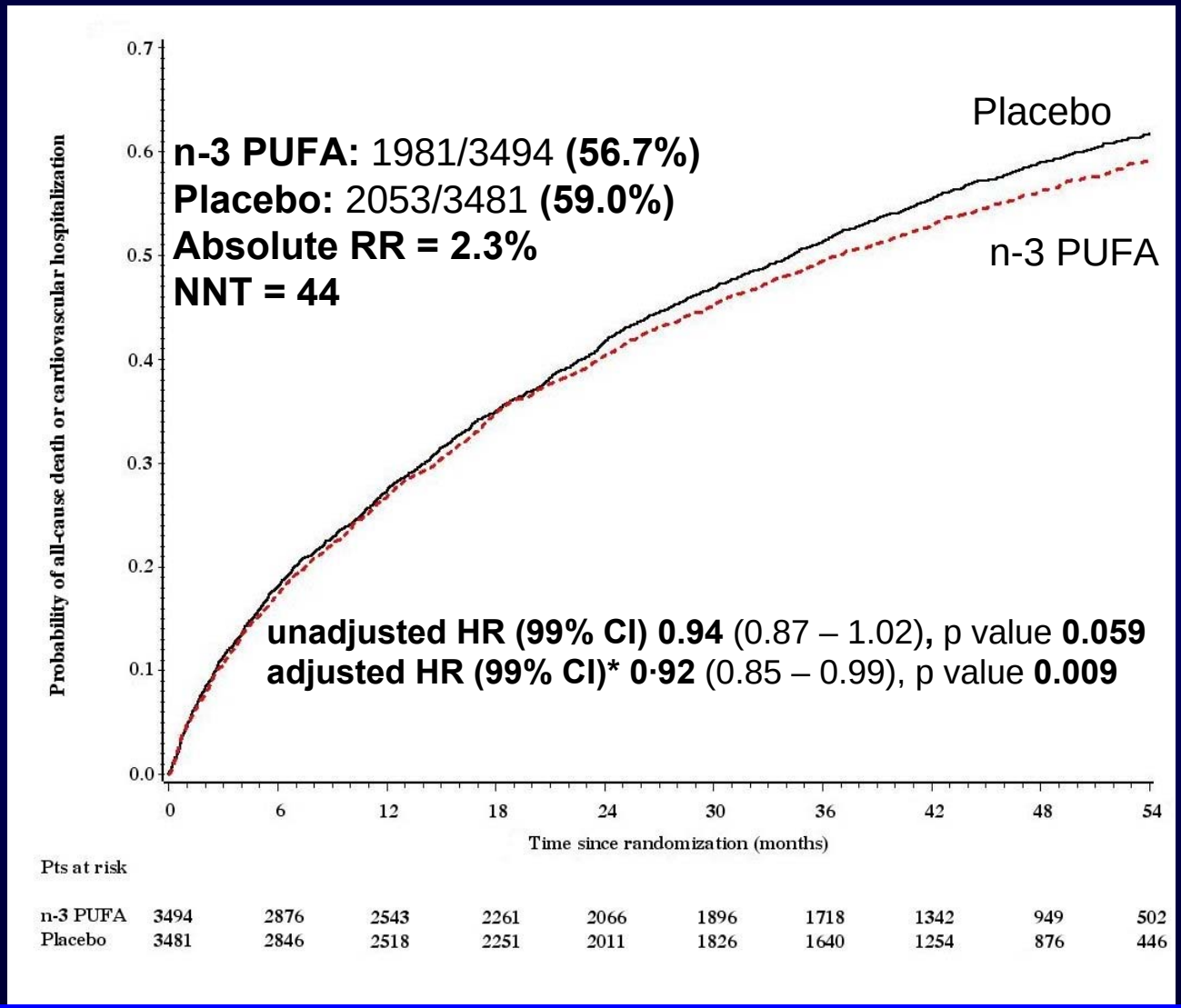


Pts at risk

n-3 PUFA	3494	3336	3215	3080	2947	2844	2680	2164	1588	844
Placebo	3481	3344	3209	3083	2941	2805	2631	2122	1558	816

*Cox proportional hazards model, adjusting for:
hospitalisation for HF in the previous year, prior pacemaker, aortic stenosis (p<0.1).

Time to all-cause death or hospitalisation for CV reasons



*Cox proportional hazards model, adjusting for:
hospitalisation for HF in the previous year, prior pacemaker, aortic stenosis (p<0.1).

Predefined Secondary Outcomes

	n-3 PUFA (n. 3494) %	Placebo (n. 3481) %	Adjusted		
			HR	95%CI*	p value
Patients who died of a CV cause	20.4	22.0	0.90	0.81-0.99	0.045
Patients who had a SCD	8.8	9.3	0.93	0.79-1.08	0.333
Patients hospitalized	56.8	58.3	0.94	0.88-1.00	0.049
Patients hospitalized for a CV reason	46.8	48.5	0.93	0.87-0.99	0.026
Patients hospitalized for HF	28.0	28.6	0.94	0.86-1.02	0.147
Patients who died of a CV cause or hospitalized for any reason	61.7	63.3	0.94	0.89-0.99	0.043

CV=cardiovascular; SCD=sudden cardiac death; HF=heart failure

* Cox proportional hazards model adjusting for: hospitalisation for HF in the previous year, prior pacemaker, and aortic stenosis ($p<0.1$).

Predefined Secondary Outcomes Vascular events

	n-3 PUFA (n. 3494) %	Placebo (n. 3481) %	Adjusted		
			HR	95%CI*	p
Patients with fatal and not fatal MI	3.1	3.7	0.82	0.63-1.06	0.12
Patients with fatal and not fatal stroke	3.5	3.0	1.16	0.89-1.51	0.27
Ischemic	*2.8*	*2.3*			
Hemorrhagic	*0.4*	*0.3*			
Not known	*0.3*	*0.4*			

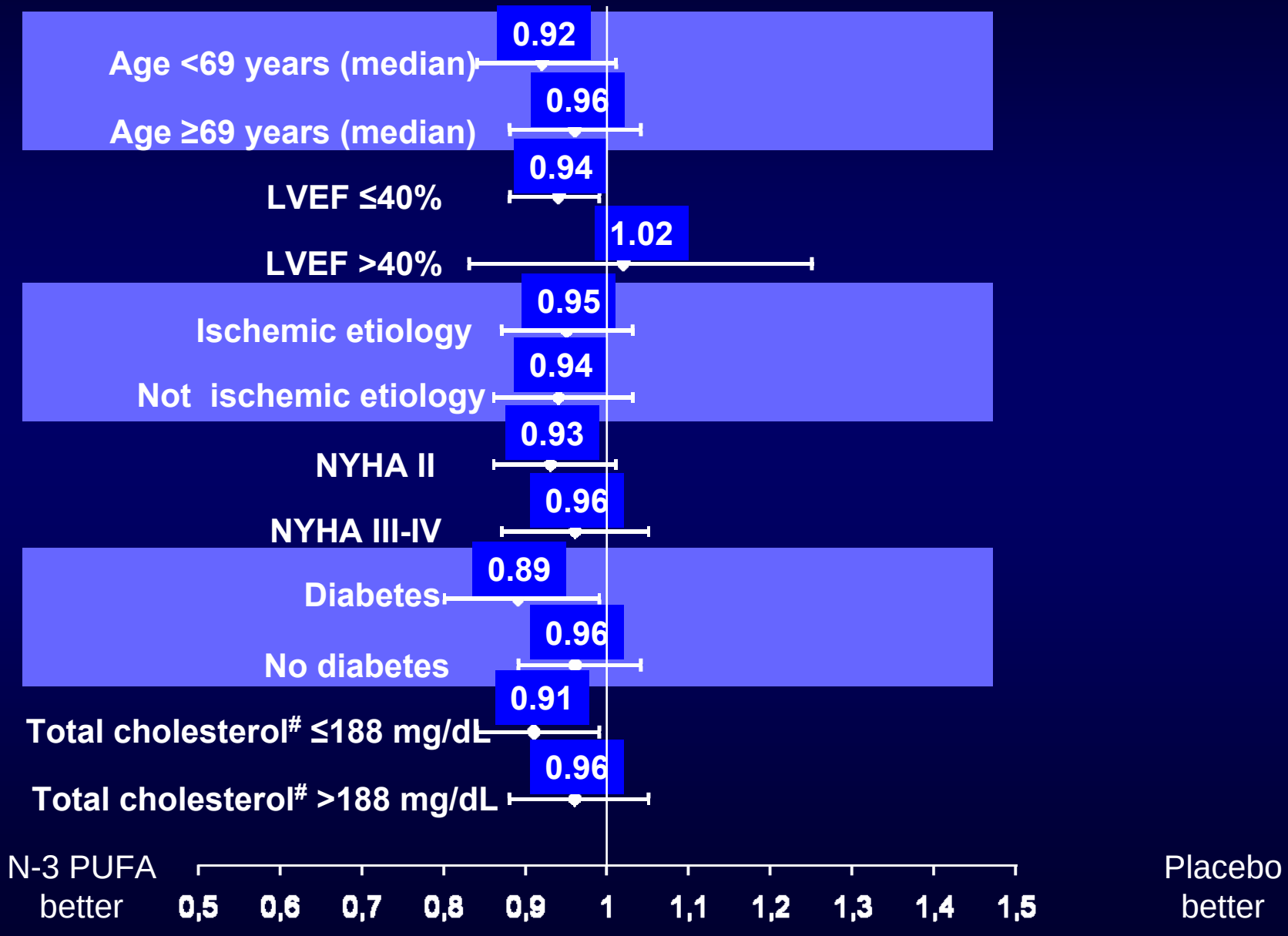
MI=myocardial infarction

* Cox proportional hazards model adjusting for: hospitalisation for HF in the previous year, prior pacemaker, and aortic stenosis ($p<0.1$).

Effects of n-3 PUFA on arrhythmic events

	n-3 PUFA (n. 3494) %	Placebo (n. 3481) %	HR	95%CI	p
Presumed arrhythmic deaths	7.8	8.7	0.88	0.75-1.04	0.14
Patients hospitalized for ventricular arrhythmias	2.8	3.8	0.72	0.55-0.93	0.01

Predefined Subgroup analysis

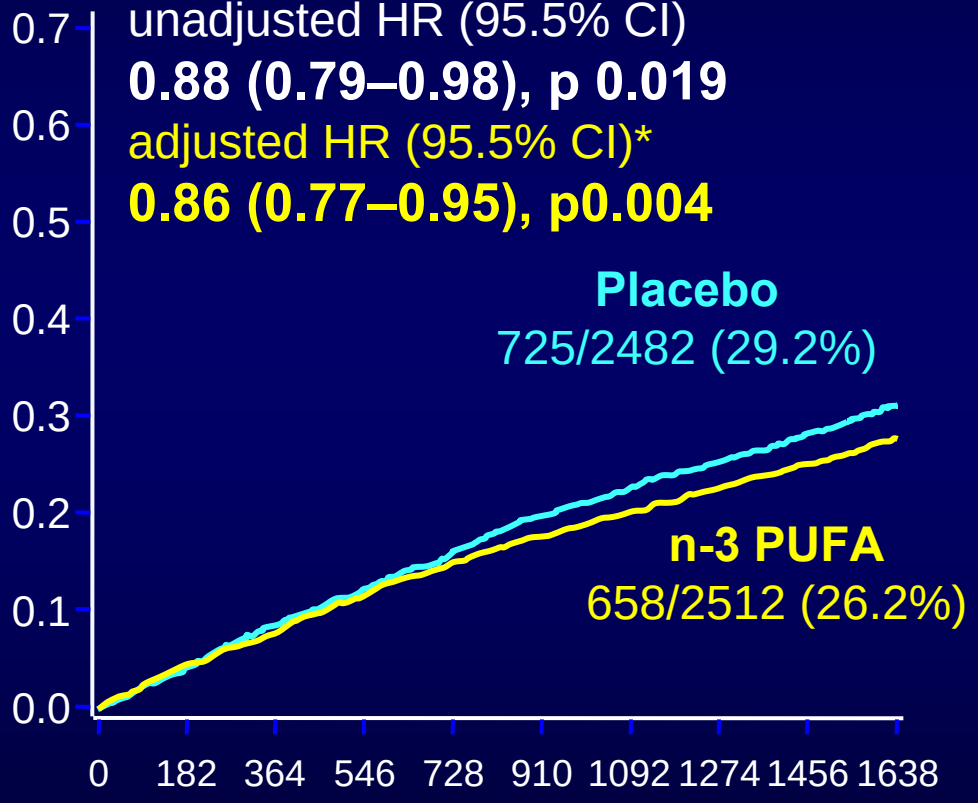


Permanent treatment discontinuations

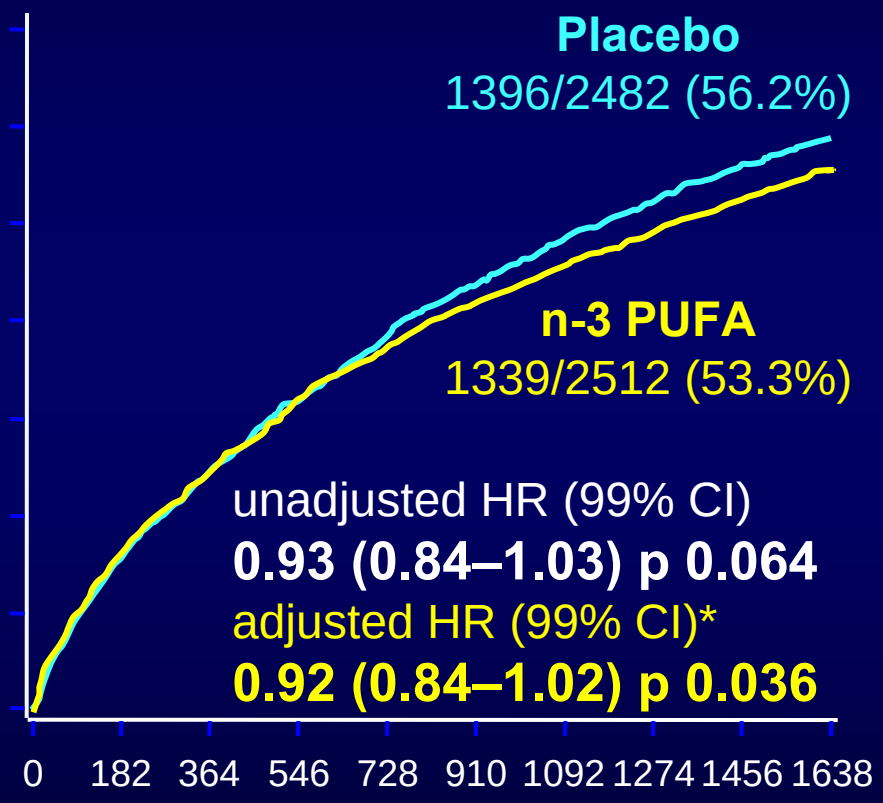
	n-3 PUFA (n. 3494)	Placebo (n. 3481)	p
Patients permanently discontinuing study treatment, n. (%)	**1004 (28.7)**	**1029 (29.6)**	**0.45**
Adverse drug reaction	102	104	
Patients' decision	478	500	
Doctor decision	299	298	
Other	125	127	

Per protocol analysis *(4,994 patients)*

Time to all-cause death



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



*Cox proportional hazards model, adjusted for: hospitalization for HF in the previous year, aortic stenosis, prior revascularization and history of paroxistical AF (p<0.1)

Adverse drug reactions

	n-3 PUFA (n. 3494)	Placebo (n. 3481)	p
Patients permanently discontinuing study treatment due to ADR, n. (%)	**102 (2.9)**	**104 (3.0)**	**0.87**
Gastro-intestinal disorder	96	92	
Allergic reaction	3	9	
Liver dysfunction	1	1	
Lipid abnormality	-	1	
Hepatocellular jaundice	-	1	
Subdural hematoma	1	-	
Muscle-related symptoms	1	-	

ADR=adverse drug reaction

GISSI-HF 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 pragmatic GISSI-HF trial , in a context of usual care.

GISSI-HF Conclusions

- 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 predefined subgroups
  - supported by per-protocol analysis (RRR 12%-14%)
- No adverse events were noted
- *In chronic heart failure patients the n-3 PUFA treatment is moderately effective, safe, simple (once daily) and cheap.*

Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial

*GISSI-HF investigators**

Lancet 2008; 372:

*Members listed at end of paper

Correspondence to:
GISSI-HF Coordinating Centre,
ANMCO Research Centre,
Via La Marmora 34,
50121 Florence, Italy
gissihf@anmco.it

Acknowledgements

The GISSI-HF trial was planned, conducted and analyzed by the GISSI group which has full ownership of the data.

SPA, Pfizer, Sigma Tau and AstraZeneca concurred to fund the study.

Acknowledgements

GISSI is endorsed by

- **Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO), Firenze, Italy;**
- **Ist.Ricerche Farmacologiche Mario Negri, Milan, Italy;**
- **Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy.**

Committees

Steering Committee

L Tavazzi (Chairman), G Tognoni (Co-Chairman), MG Franzosi, R Latini, AP Maggioni, R Marchioli, GL Nicolosi, M Porcu

Data and Safety Monitoring Board

S Yusuf (Chairman), F Camerini, JN. Cohn, A Decarli, B Pitt, PA. Poole-Wilson, Peter Sleight,

Clinical Endpoint Committee

E Geraci (Chairman), M Scherillo (Co-Chairman), G Fabbri (Coordinator), B Bartolomei (Secretary), D Bertoli, F Cobelli, CFresco, A Ledda, G Levantesi, C Opasich, F Rusconi, G Sinagra, F Turazza, A Volpi

Coordinating Centers

Clinical Monitoring

M Ceseri (coordinator), G Alongi, A Atzori, F Bambi, D Bastarolo, F Bianchini, I Cangioli, V Canu, C Caporusso, G Cenni, L Cintelli, M Cocchio, A Confente, E Fenicia, G Friso, M Gianfriddo, G Grilli, B Lazzaro, G Lonardo, A Luise, R Nota, M Orlando, R Petrolo, C Pierattini, V Pierota, A Provenzani, V Quartuccio, A Ragno, CSerio, A Spolaor, A Tafi, E Tellaroli

Database Management and Statistics

D Lucci, S Barlera, M Gorini, L Gonzini, V Milani, G Orsini

Regulatory, Administrative and Secretariat

E Bianchini, S Cabiddu, I Cangioli, L Cipressa, ML Cipressa, G Di Bitetto, B Ferri, L Galbiati, A Lorimer, C Pera, P Priami, A Vasamì

GISSI-HF Subprojects

*Ventricular Remodeling: Echo:*S Ghio, E Ghizzardi

Biohumoral:R Latini, S Masson

Genetic: M GFranzosi, L Crociati

*Arrhythmic/Autonomic :*MT La Rovere

*Exercise Capacity:*U Corrà

Quality of Life and Depression: P Di Giulio

*Implantable Cardiac Defibrillator:*A Finzi