Randomized, double blind, placebo-controlled, independent study to test the efficacy of n-3 PUFA for the maintenance of normal sinus rhythm in patients with previous atrial fibrillation.

FORωARD

(Fish Oil Research with ω-3 for Atrial fibrillation Recurrence Delaying)

ClinicalTrials.gov Identifier: NCT00597220

Alejandro Macchia, Hugo Grancelli, Sergio Varini, Daniel Nul, Nicolás Laffaye, Javier Mariani, Daniel Ferrante, Raúl Badra, Julio Figal, Silvina Ramos, Gianni Tognoni, Hernán C Doval on behalf of the GESICA Investigators.

GESICA Foundation, Buenos Aires, Argentina.

FORωARD - Disclosures

- This was an independent clinical trial. Funding was through unrestricted grants provided by the companies that supplied the study drugs - SPA Società Prodotti Antibiotici - Milan, Italy and Sigma Tau (Rome, Italy) - but these companies did not have representatives on the Steering Committee.

FORωARD - Background

- ✓ Current medical strategies for avoidance of atrial fibrillation (AF) are of limited value.
- ✓ Antiarrhythmic agents faced major challenges related to their limited efficacy and their serious and frequent side effects.
- ✓ Epidemiological studies, clinical trials and basic science support the role of Omega-3 fatty acids (n-3 PUFA) in reducing all cause mortality among patients with previous MI, mostly by reducing ventricular arrhythmias.
- ✓ However their effects regarding supraventricular arrhythmia are scarce and provided mixed results.

FORωARD - Background

PREVIOUS CLINICAL TRIALS

Dato	Year	N	N-3 PUFA	Control	RR (95% CI)
Margos et al.	2007	40	7/20	8/20	0.88 (0.39-1.95)
Nodari et al.	2011	199	37/100	56/99	0.65 (0.48-0.89)
Kumar et al.	2011	188	61/91	78/87	0.75 (0.64-0.88)
Kowey et al.	2010	645	167/322	147/323	1.14 (0.97-1.34)
Erdogan et al.	2007	108	41/54	46/54	0.89 (0.74-1.07)
Ozaydin et al.	2011	47	9/23	9/24	1.04 (0.51-2.16)
Bianconi et al.	2011	187	56/95	47/92	1.15 (0.89-1.50)

Mariani J.2012; Submitted

FORωARD – Study Objective

- The FORωARD was a randomized, double-blind, placebo-controlled trial testing the efficacy of pharmacologic supplementation with 1 gram daily of n-3 PUFA (which provide 850-882 mg eicosapentaenoic acid (EPA) / docosahexaenoic acid (DHA) ethyl esters) for the maintenance of normal sinus rhythm in patients with previous AF.

FORωARD – eligibility

- Males and females ≥21 years, diagnosed in an outpatient setting with previous symptomatic AF, who had recovered normal sinus rhythm.

- Patients must have either:

a) at least two symptomatic episodes of documented AF in the previous 6 months before randomization, with the last episode occurring in the 3 to 90 days prior to randomization (paroxysmal AF)

b) Successful electrical or pharmacologic cardioversion for persistent AF performed in the 3 to 90 days prior to randomization.

FORωARD – eligibility (II)

- To avoid the inclusion of patients with lone AF, all subjects <65 years of age must present with at least one characteristics of moderate-to-high risk of stroke: CHF or documented EF <40%, T2DM, CAD, PVD, HT, previous Stroke or TIA.

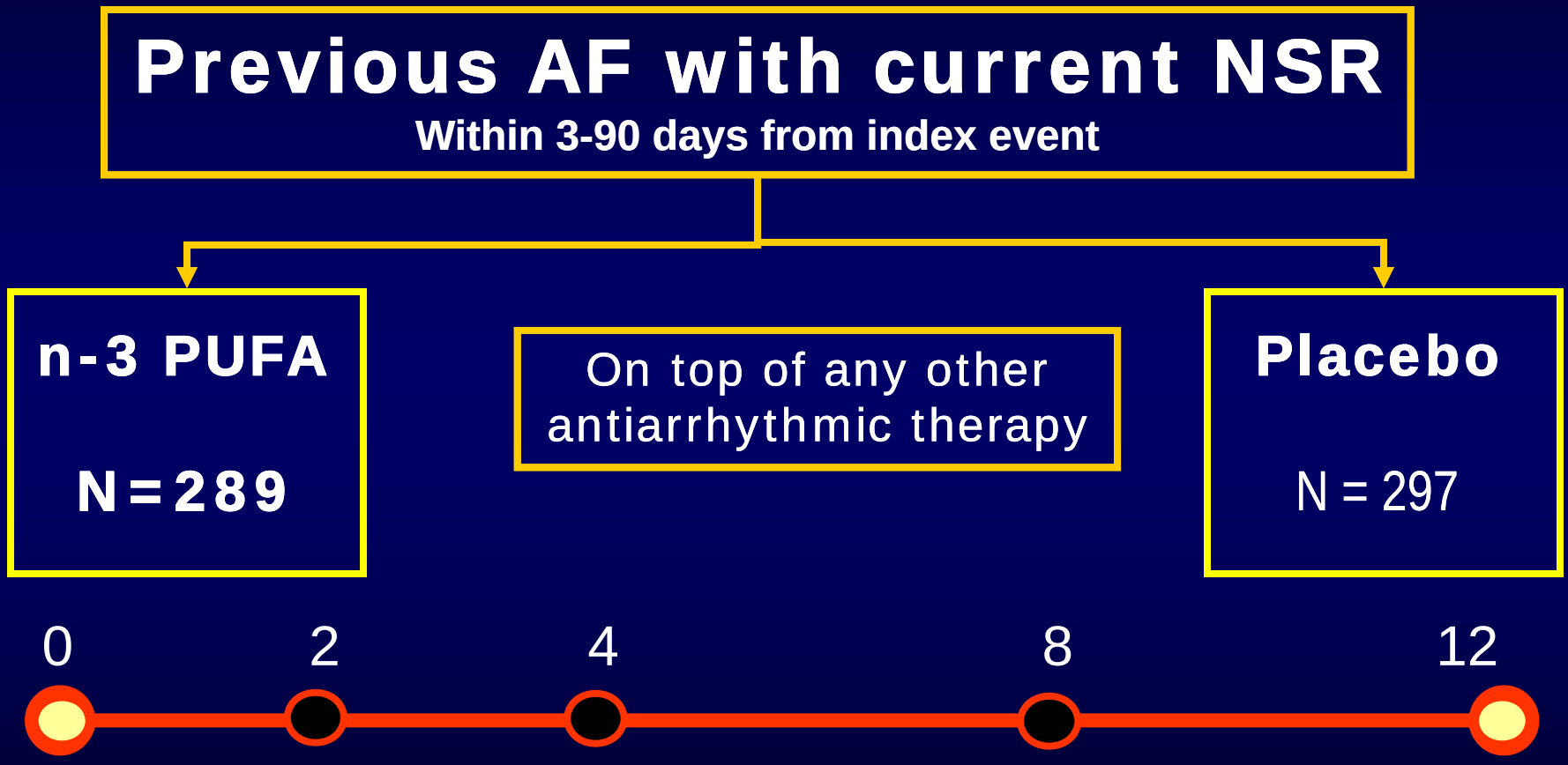
- Exclusion Criteria

CHF (class IV); acute coronary syndromes; Cardiac Surgery within the past 3 months; significant valvular disease; Wolff-Parkinson-White; planned or recent (<6 months) implantation of cardiac devices or ablative treatment for AF; any arrhythmia associated with an acute reversible condition; COPD; pregnancy or lactation.

FORωARD – follow up visits

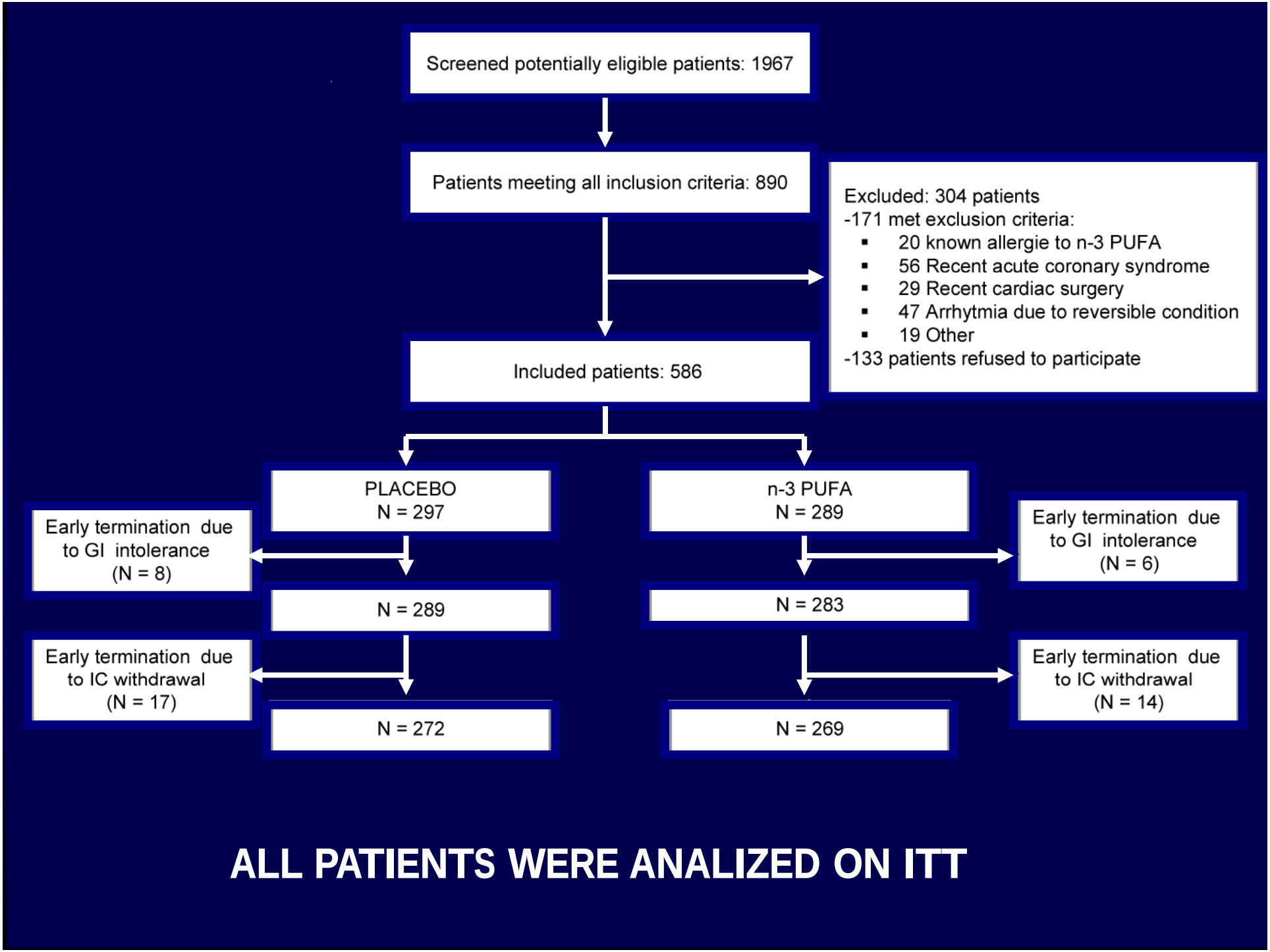
- The primary efficacy end point is the time to first recurrence of symptomatic or asymptomatic AF documented by a 12-lead ECG. All other sources of data suggesting or showing the presence of AF was used as triggers to obtain a 12-lead ECG.
- Secondary outcomes include
- a) the hierarchical composite of all-cause mortality, non-fatal stroke, non-fatal AMI, systemic embolism, CHF development, severe bleeding; b) all-cause hospitalizations;
- c) survival free of thromboembolic events and
- d) hospitalizations for cardiovascular reasons.

FORωARD – follow up visits



FORωARD – Baseline characteristics

Characteristic	N-3 PUFA (n=289)	PLACEBO (n=297)
Age, mean years ± SD	66 ± 12	66 ± 11
Male gender, n (%)	167 (57.8)	154 (51.9)
Recruitment criteria		
Cardioversion	216 (74.7)	212 (71.4)
2 episodes ≤6 months	23 (8)	32 (11)
Both	50 (17.3)	53 (17.8)
Hypertension, n (%)	259 (92)	265 (91)
Diabetes, n (%)	31 (11)	43 (15)
CHF, n (%)	39 (14)	42 (14)
CHD, n (%)	36 (13)	31 (11)
Amiodarone	183 (63)	189 (64)
B-blocker	177 (62)	176 (60)


Screened potentially eligible patients: 1967
Patients meeting all inclusion criteria: 890
Excluded: 304 patients
-171 met exclusion criteria:
20 known allergie to n-3 PUFA
56 Recent acute coronary syndrome
29 Recent cardiac surgery
47 Arrhytmia due to reversible condition
19 Other
-133 patients refused to participate
Included patients: 586
PLACEBO
N = 297
n-3 PUFA
N = 289
Early termination due to GI intolerance (N = 8)
Early termination due to GI intolerance (N = 6)
N = 289
N = 283
Early termination due to IC withdrawal (N = 17)
Early termination due to IC withdrawal (N = 14)
N = 272
N = 269
ALL PATIENTS WERE ANALIZED ON ITT

FORωARD – Results

Outcome	N-3 PUFA	Placebo	HR (95% CI)
Recurrent AF, n (%)	69 (23.9)	56 (18.9)	1.28 (0.90 – 1.83)
Death, n (%)	4 (1.4)	5 (1.7)	0.80 (0.21 – 3.00)
Composite end point , n (%)	16 (5.5)	20 (6.7)	0.86 (0.44 – 1.66)
All-cause hospitalization, n (%)	48 (16.6)	42 (14.1)	1.22 (0.81 – 1.85)

FORωARD – Conclusions

Pharmacological supplementation with 1 gram of n-3 PUFA for 1 year did not reduce recurrent AF.