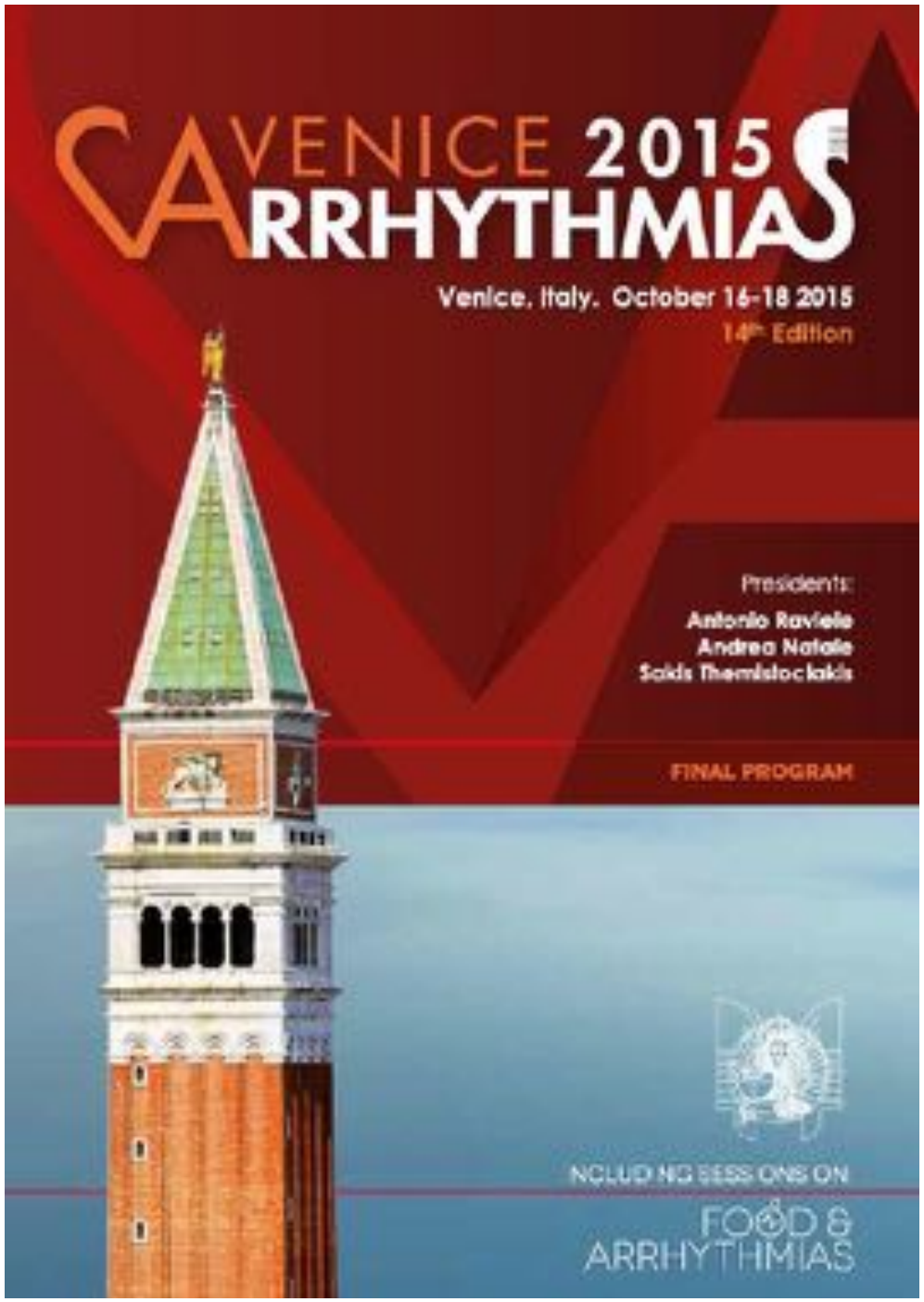


Featured Symposium

Food and arrhythmias

Program Chairmen: Andrea Natale – Antonio Raviele – Sakis Themistoclakis

DIET / BEVERAGE HABITS & AF: WHICH RELATIONSHIP?

Does fish oil reduce the incidence of AF?

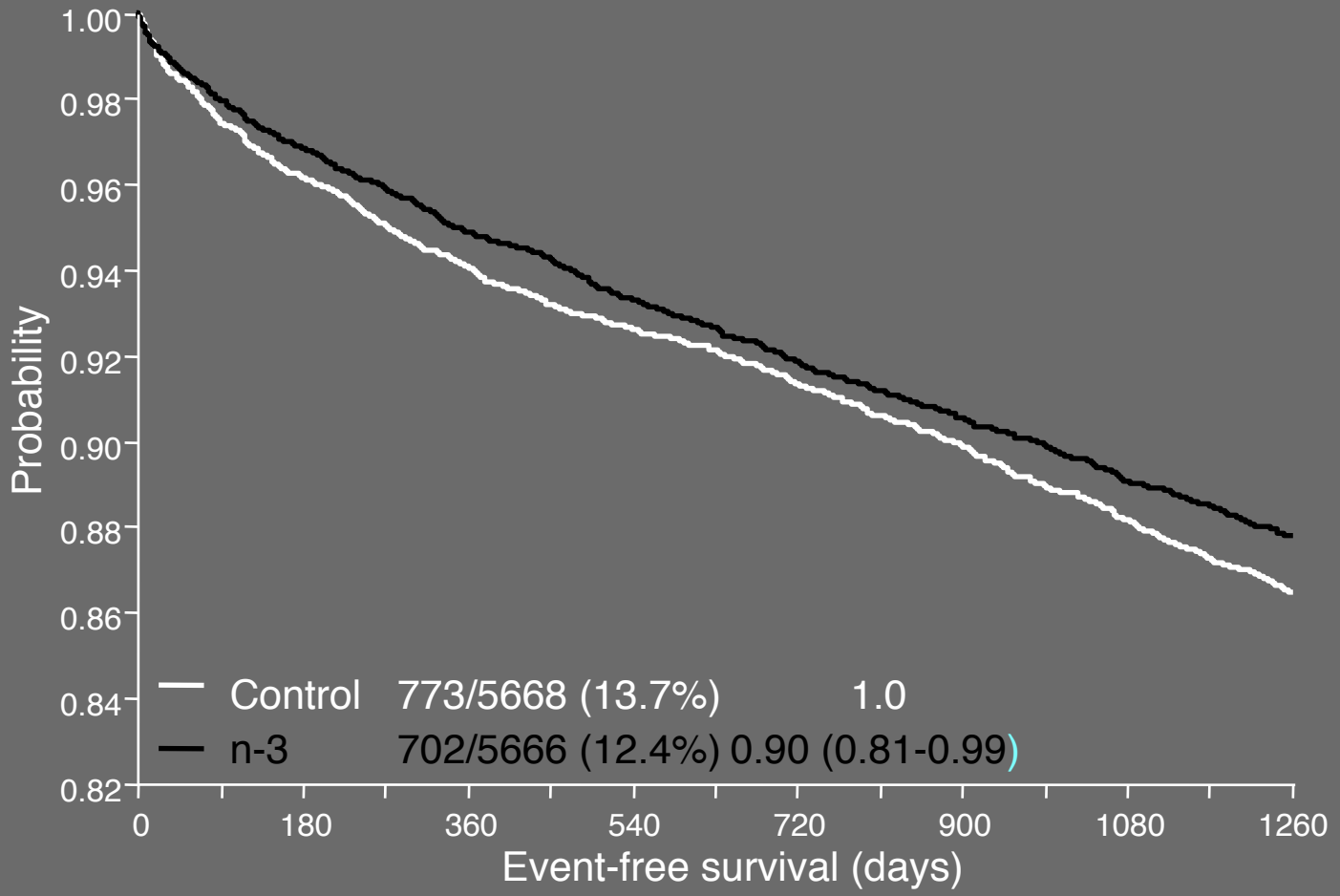
Federico Lombardi, MD, FESC.
UOC Malattie Cardiovascolari
Fondazione IRCCS, Ospedale Maggiore Policlinico, Università degli Studi di Milano, Italy.

October 16 - 18
14th EDITION 2015

NO CONFLICT OF INTEREST TO DECLARE

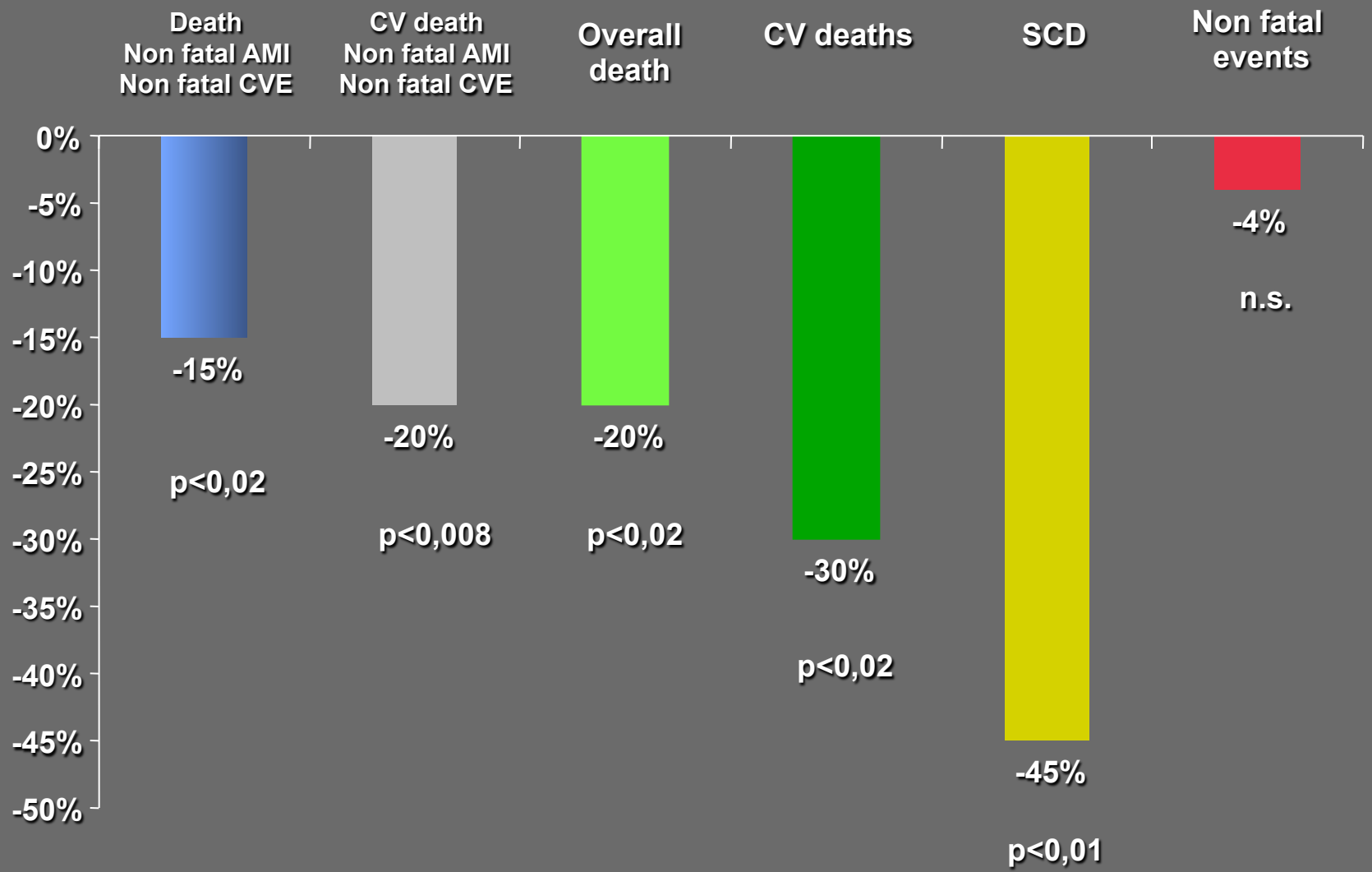
GISSI-Prevenzione

Event-free survival n-3 PUFA



Lancet, 1999.

Major findings of GISSI Prevenzione TRIAL



Modified from lancet 1999

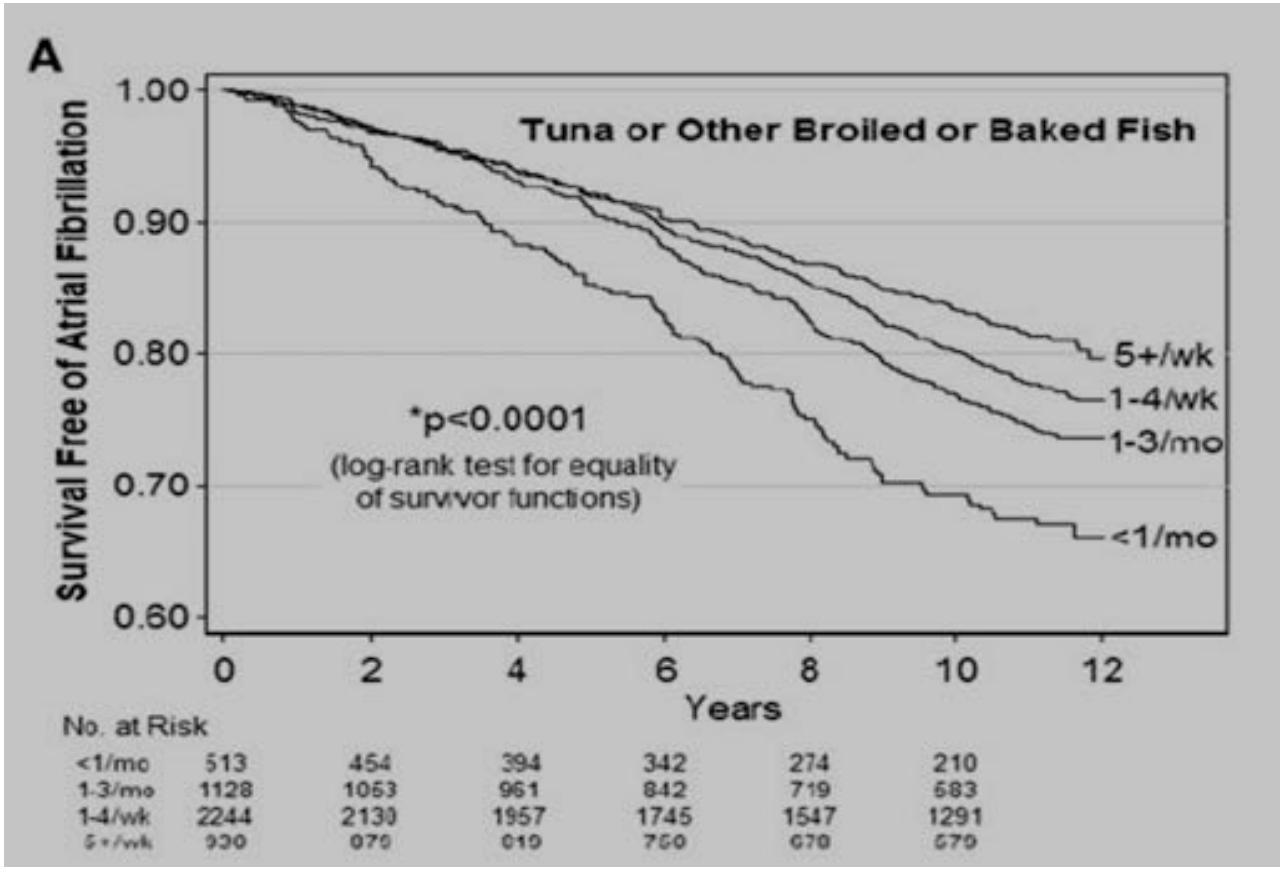
Does fish oil reduce the incidence of AF?

1) Epidemiologic studies
   (uncontrolled, AF definition, AF incidence assessment)
1) Effects of n-3 PUFA in pts with paroxysmal or persistent atrial fibrillation (limited data)
2) Effects of n-3 PUFA on atrial fibrillation after cardia surgery
   (good size data).

Fish Intake and Risk of Incident Atrial Fibrillation

Dariush Mozaffarian, MD, MPH; Bruce M. Psaty, MD, PhD; Eric B. Rimm, ScD; Rozenn N. Lemaitre, PhD, MPH; Gregory L. Burke, MD, MS; Mary F. Lyles, MD; David Lefkowitz, MD; David S. Siscovick, MD, MPH

Cardiovascular Health Study; N°= 4815 subjects >65 yrs, 12 yrs follow-up



Circulation 2004

Controversial results of fish intake

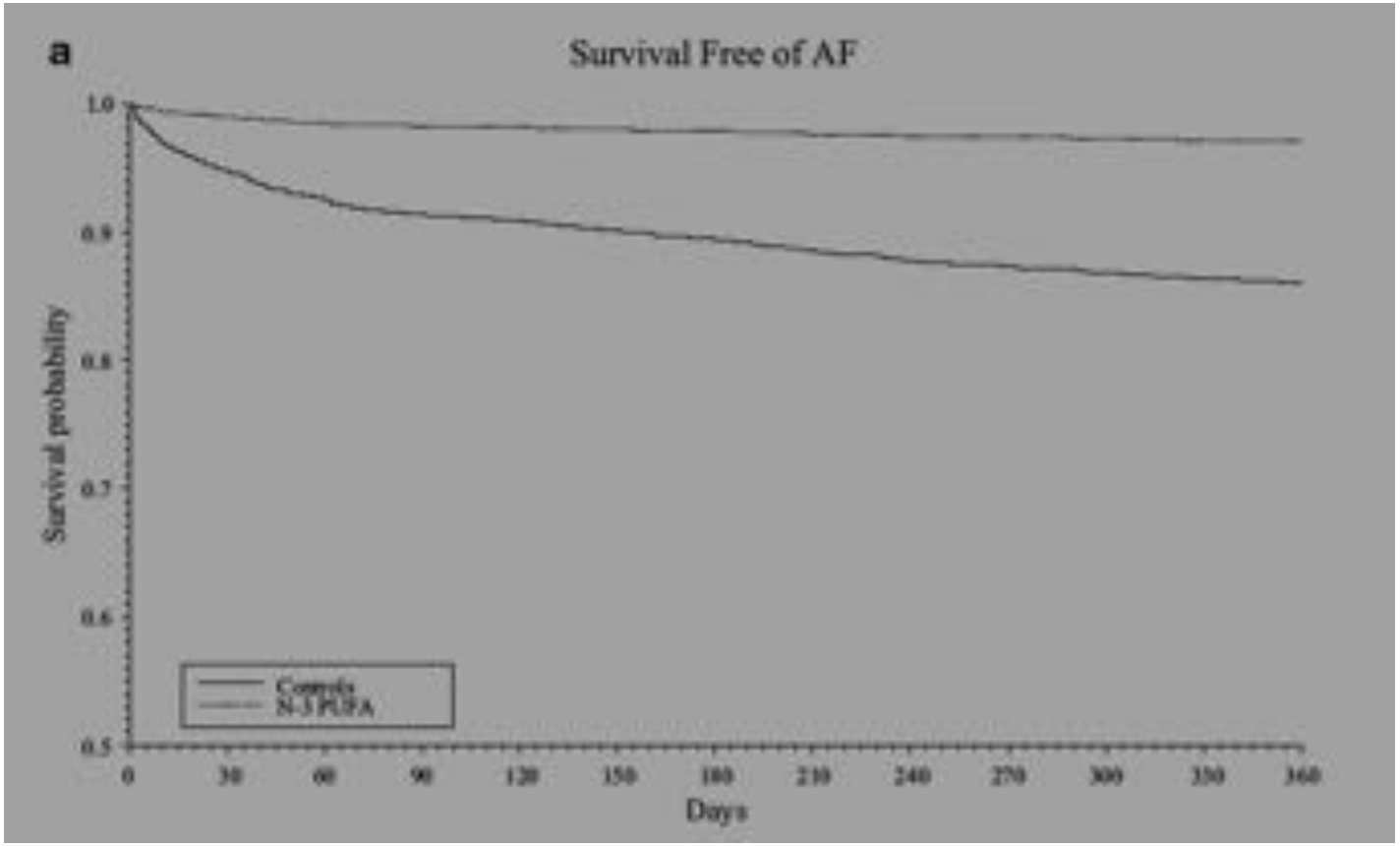
\+ **Fish Intake and Risk of Incident Atrial Fibrillation**

\- n−3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study[1–3]

\- **Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study**

Omega-3 fatty acid supplementation reduces one-year risk of atrial fibrillation in patients hospitalized with myocardial infarction

3246 pts discharged with a primary diagnosis of acute myocardial infarction were included.

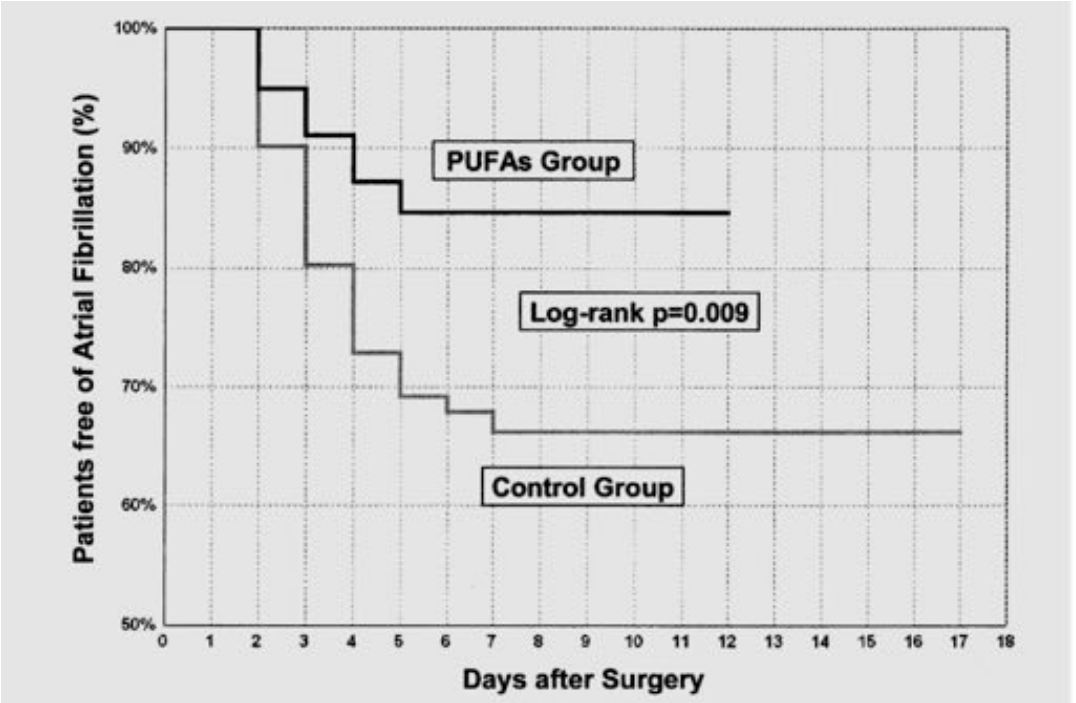


Macchia et al, Eur J Clin Pharm 2008

N-3 Fatty Acids for the Prevention of Atrial Fibrillation After Coronary Artery Bypass Surgery

A Randomized, Controlled Trial

160 pts were prospectively randomized to a control group or PUFA 2 g/day for at least 5 days before elective CABG. Valvular and patients with a history of AF were excluded. PoAF developed in 27 pts of the control group (33%) and in 12 pts of the PUFA group (15%; p= 0.013).



Calò et al, JACC 2005.

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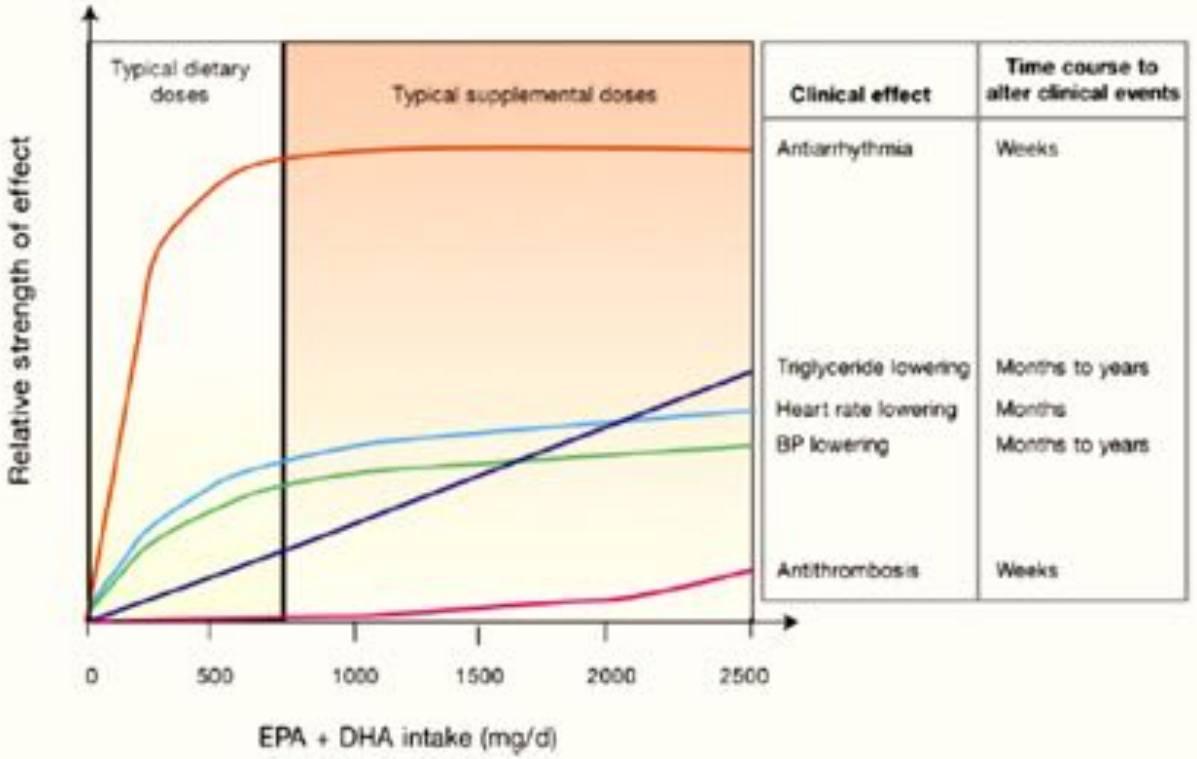
Vol. 54, No. 7, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.02.084

STATE-OF-THE-ART PAPER

Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Diseases

Carl J. Lavie, MD,* Richard V. Milani, MD,* Mandeep R. Mehra, MD,† Hector O. Ventura, MD*

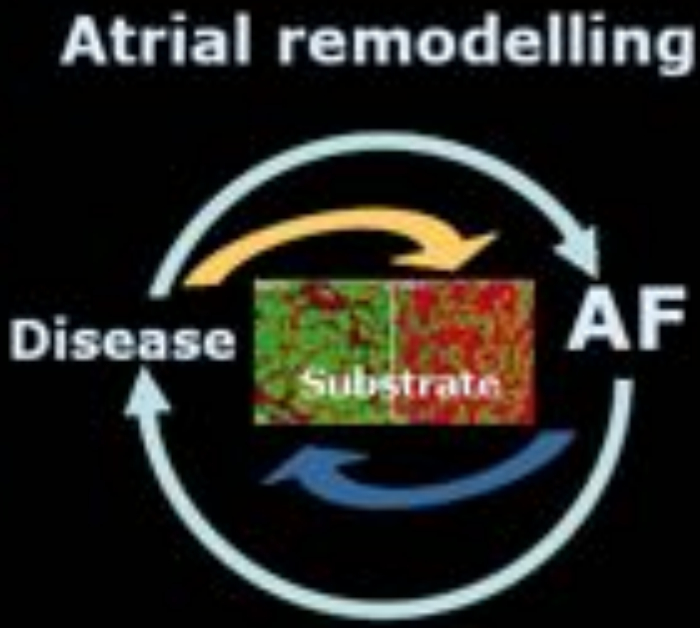
New Orleans, Louisiana; and Baltimore, Maryland



Fish Oil Dosing and Cardiovascular Impact

"Upstream" Therapies in AF

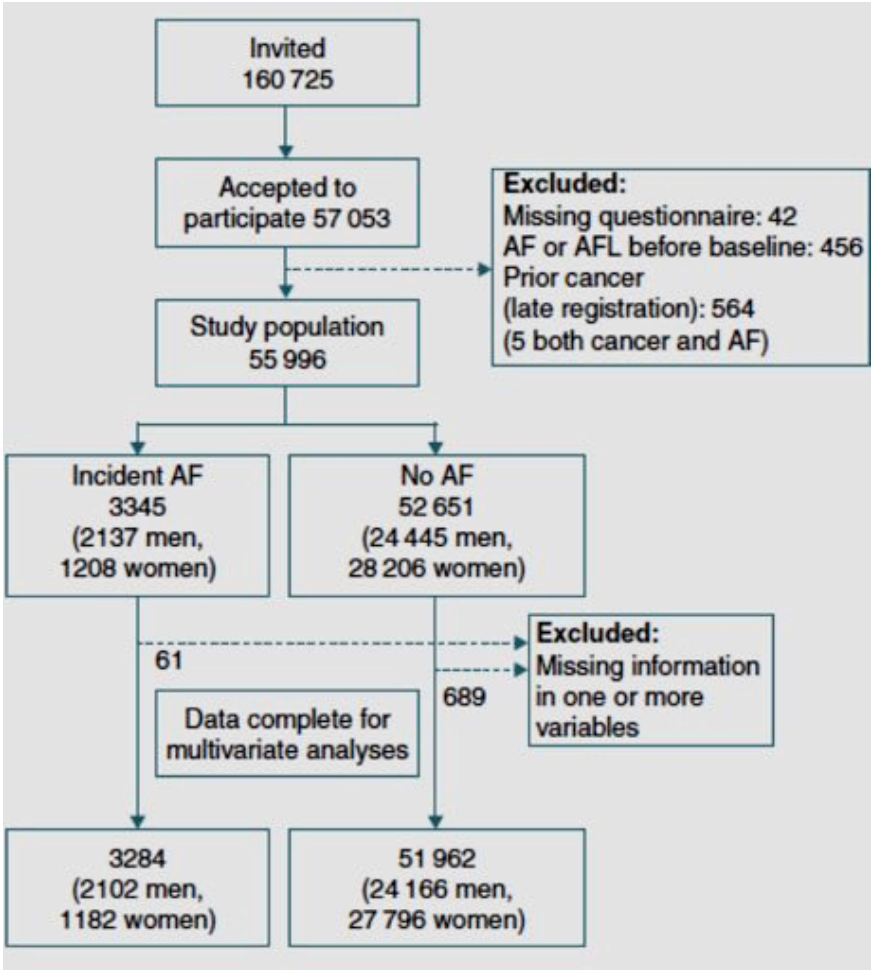
Therapies	Possible target
ACE inh and ARBs	· HT, CHF · Antifibrotic, antiarrhythmic?
Aldosterone antagonists	· HT, CHF · Antifibrotic, antiarrhythmic?
Statins	· CAD, systemic atherosclerosis · Antiinflammatory, antioxidant
Corticosteroid	· Antiinflammatory
n-3 PUFA (fish oil)	· Lipid-lowering · Antiarrhythmic
Beta blockers	· HT, CHF, CAD, etc · Antiarrhythmic effect



Salieva and Camm, Europace 2009

A U-shaped association between consumption of marine n-3 fatty acids and development of atrial fibrillation/atrial flutter—a Danish cohort study

Follow-up: 13.6 yrs



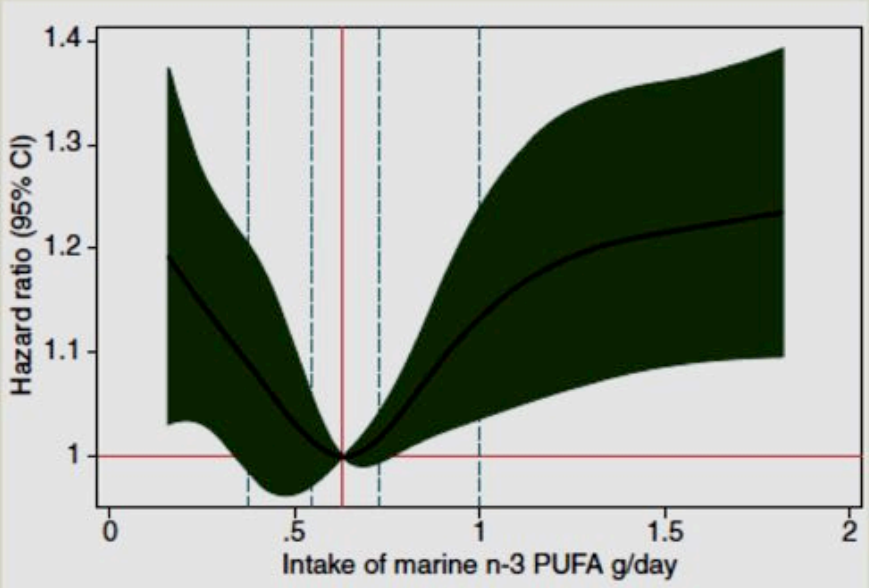
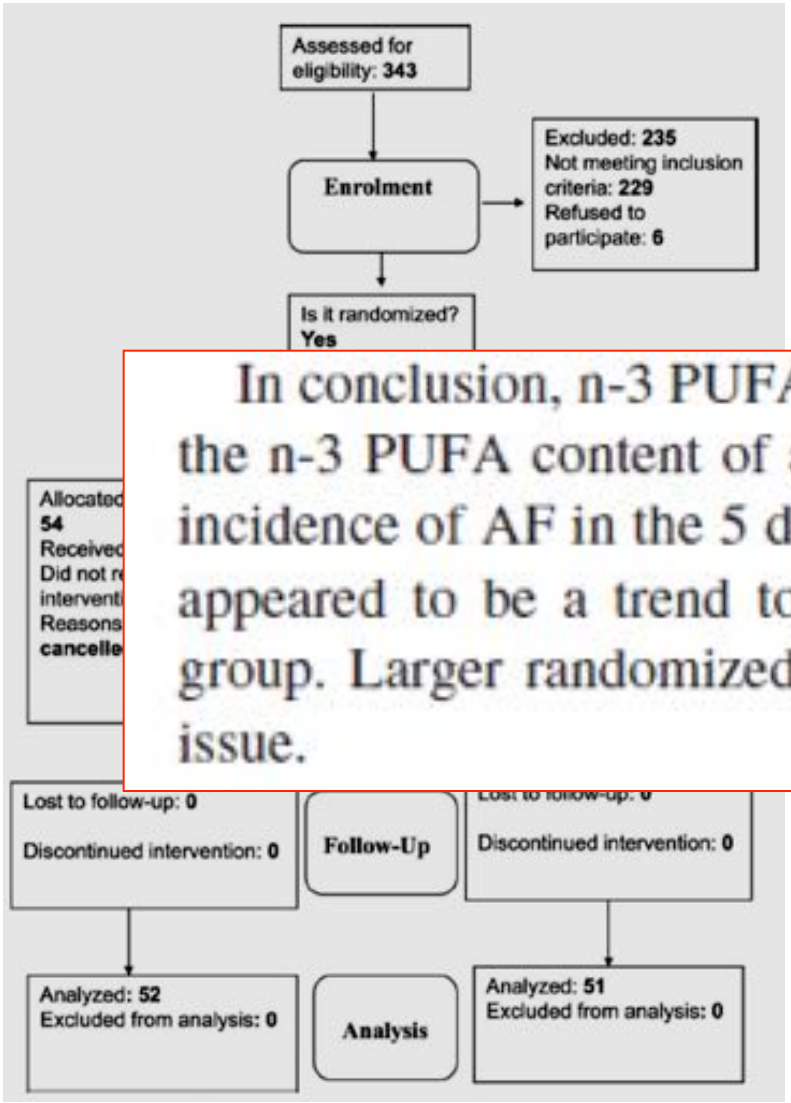


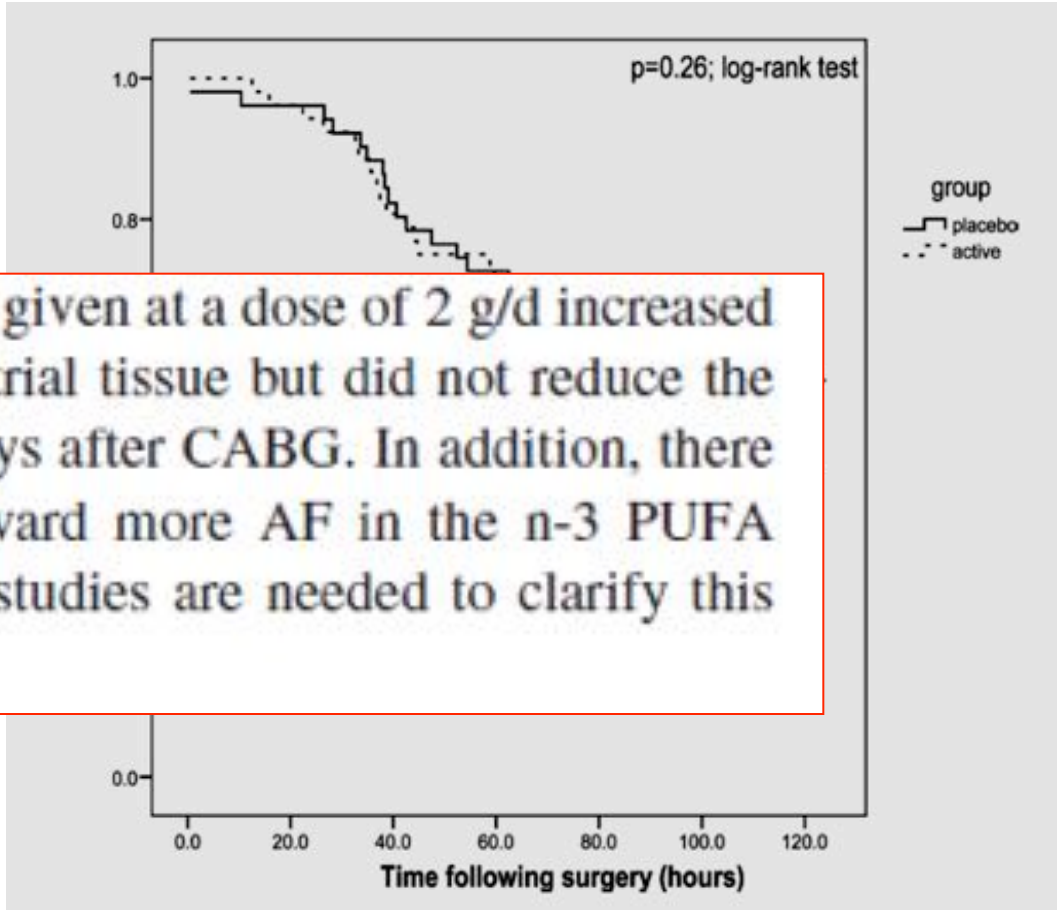
Figure 2 Dietary consumption of total marine n-3 polyunsaturated fatty acids (PUFAs) and risk of incident AF. Median intake as reference (red vertical line). The 20, 40, 60, and 80 percentiles of intake are marked by dashed lines. Shaded green area shows the 95% CI for the hazard ratio for AF (black curve). Only the 2.5–97.5 percentile of exposure is shown.

Rix et al, Europace 2014

Omega-3 Fatty Acid Supplementation Does Not Reduce Risk of Atrial Fibrillation After Coronary Artery Bypass Surgery

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial





In conclusion, n-3 PUFA given at a dose of 2 g/d increased the n-3 PUFA content of atrial tissue but did not reduce the incidence of AF in the 5 days after CABG. In addition, there appeared to be a trend toward more AF in the n-3 PUFA group. Larger randomized studies are needed to clarify this issue.

Saravan et al, Circ Arr Electrophysiol 2010

The ω-3 fatty acids for Prevention of Post-Operative Atrial Fibrillation trial—rationale and design

Dariush Mozaffarian, MD, DrPH,[a,m,*] Roberto Marchioli, MD,[b,m,*] Tim Gardner, MD,[c,m] Paolo Ferrazzi, MD,[d,m] Patrick O'Gara, MD,[e,m] Roberto Latini, MD,[f,m] Peter Libby, MD,[e,m] Federico Lombardi, MD,[g,m] Alejandro Macchia, MD,[h,m] Richard Page, MD,[i,m] Massimo Santini, MD,[j,m] Luigi Tavazzi, MD,[k,m] and Gianni Tognoni, MD[l,m] *Boston, MA; Madison, WI; Newark, DE; Santa Maria Imbaro, Milano, Bergamo, Cotignola, Rome, and Milan, Italy; and Buenos Aires, Argentina*

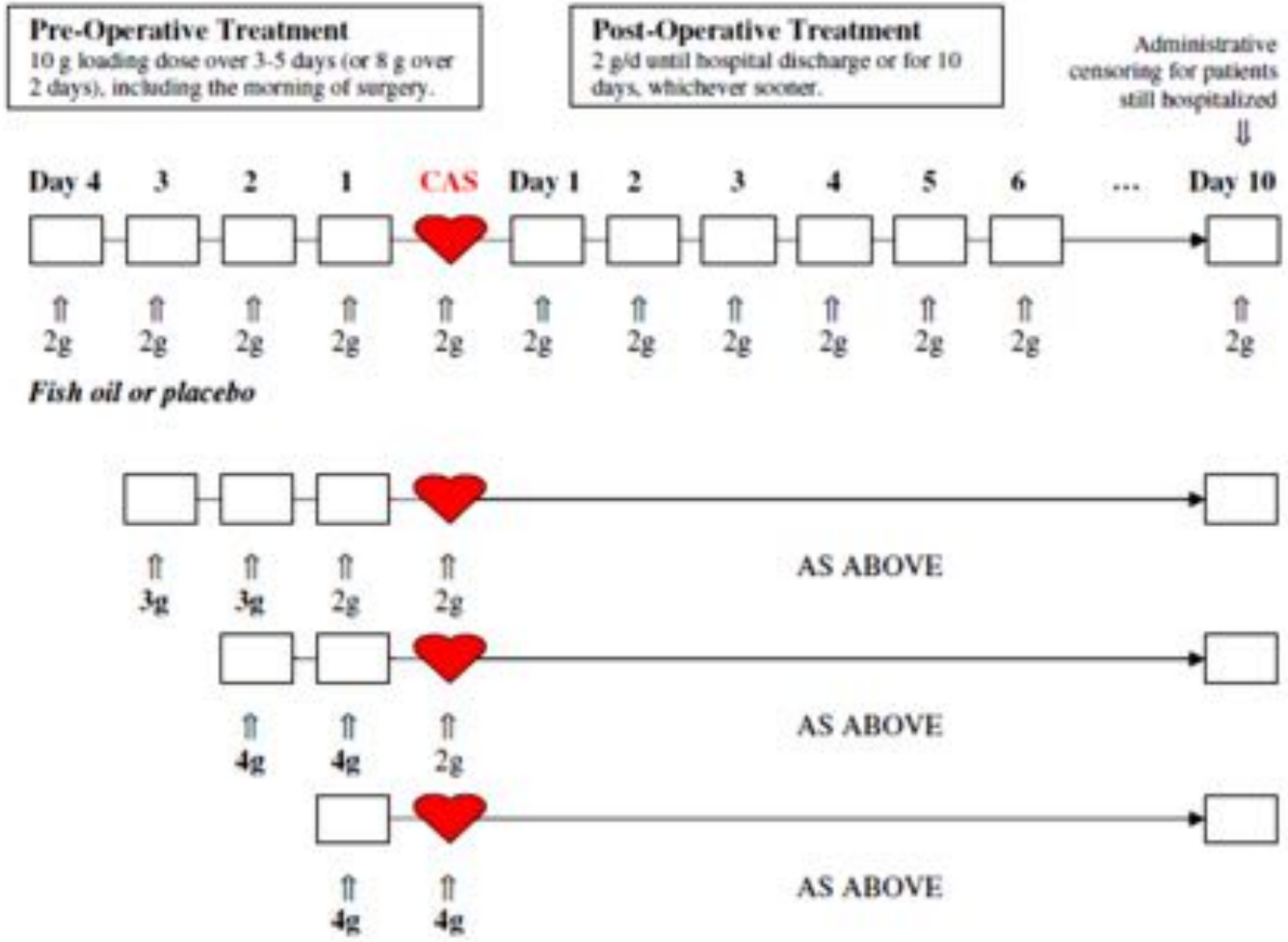
Table I. OPERA inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age ≥18 y	Regular use (≥3 d/wk) of fish oil during the past 4 wk
Scheduled for cardiac surgery on the following day or later*	Known allergy or intolerance to fish oil or olive oil
Sinus rhythm on ECG at enrollment.†	Currently pregnant
	Planned or existing cardiac transplant or left ventricular assist device
	Unable or unwilling to provide informed written consent

*Cardiac surgery may include surgical coronary artery bypass, surgical valve repair or replacement, or any other open cardiac surgery that includes opening of the pericardium, including any combination of the above.

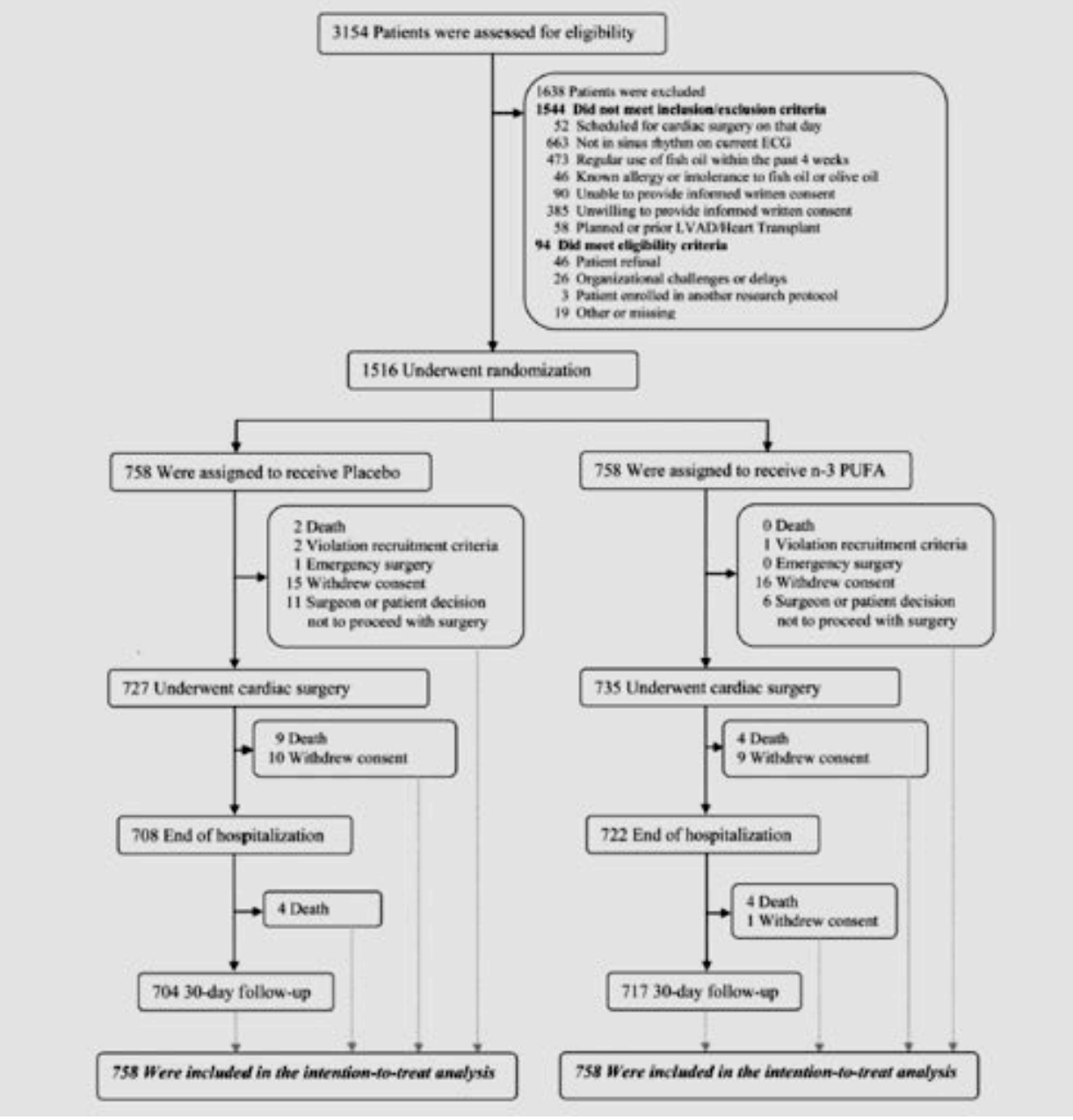
Endpoint	Definition
Atrial fibrillation* (primary endpoint)	Any documented AF or AFL of at least 30 s duration and documented by rhythm strip or 12-lead ECG. If only a shorter duration ECG is available, then the diagnosis of AF/AFL is based on the arrhythmia being present at onset or termination.

Am Heart J, 2011

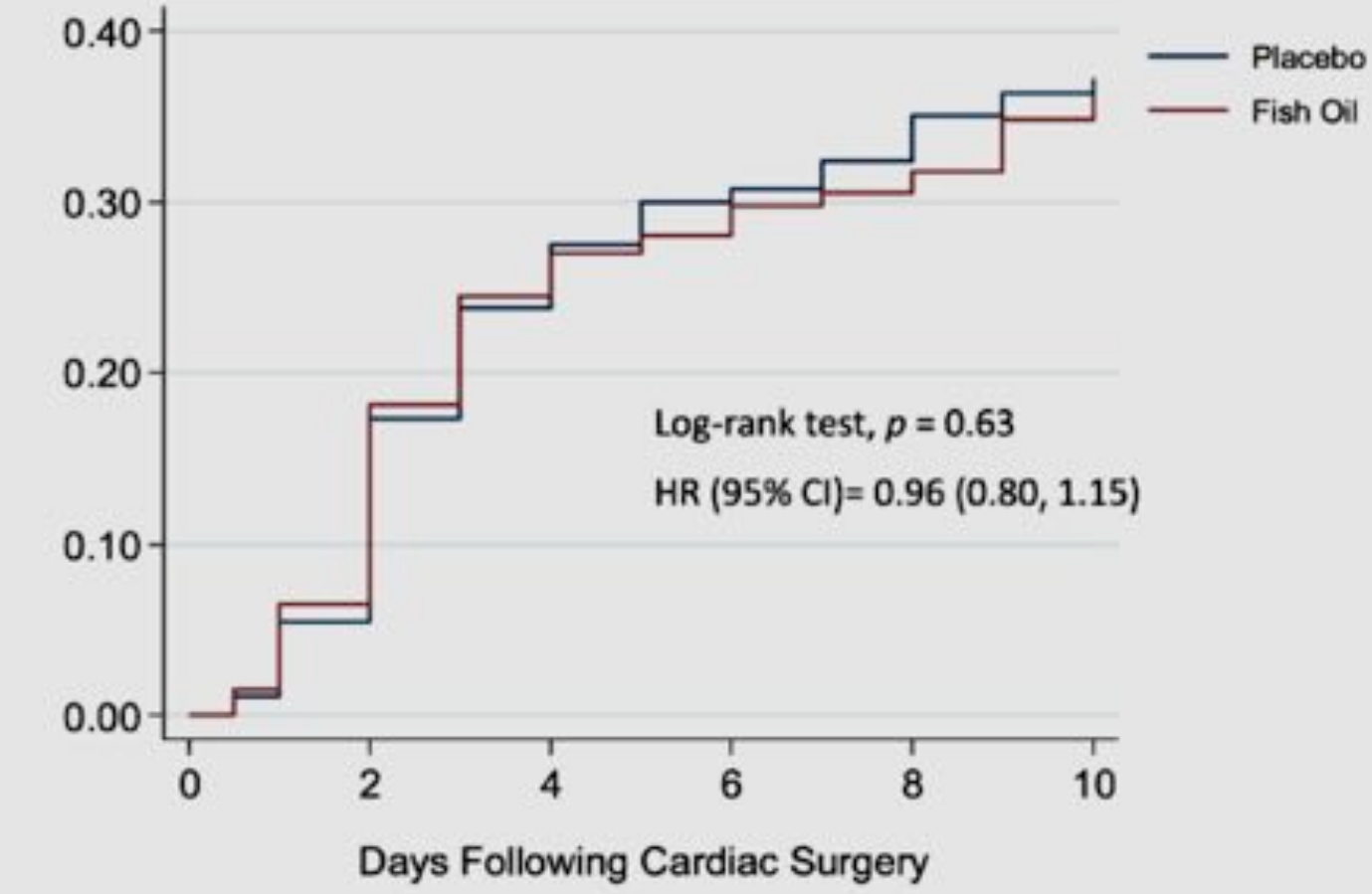


Dosing of study drug in the OPERA trial.

Fish Oil and Post-Operative Atrial Fibrillation – Results of the Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation (OPERA) Trial



JAMA 2012

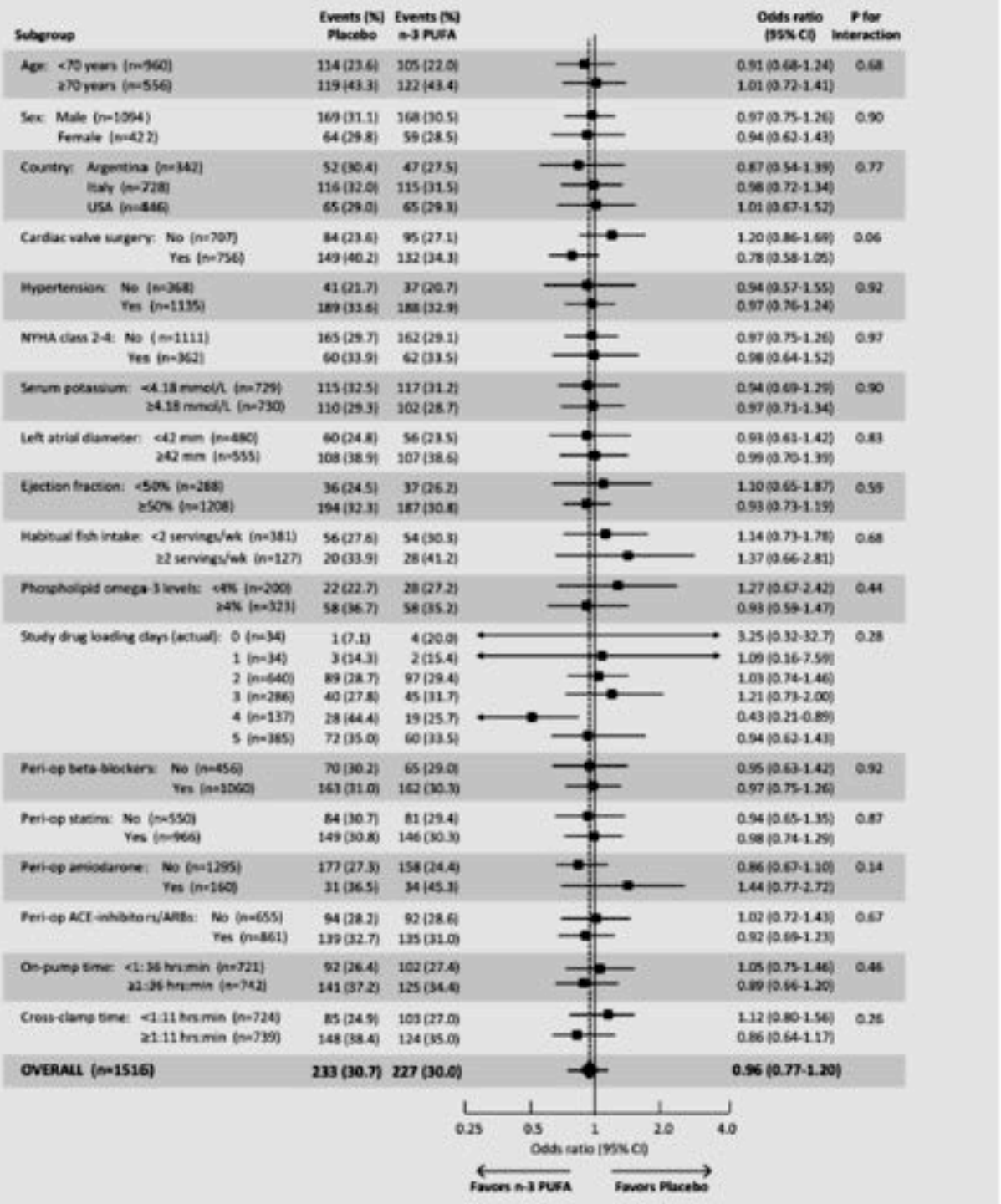


Number at risk

Placebo	758	684	532	354	153	74
Fish oil	758	688	543	378	162	91

Figure 2. Kaplan Meier Incidence of Post-Operative Atrial Fibrillation, According to Treatment Group

JAMA 2012


Subgroup
Events (%) Placebo
Events (%) n-3 PUFA
Odds ratio (95% CI)
P for interaction
Age: <70 years (n=960) 114 (23.6) 105 (22.0) 0.91 (0.68-1.24) 0.68
≥70 years (n=556) 119 (43.3) 122 (43.4) 1.01 (0.72-1.41)
Sex: Male (n=1094) 169 (31.1) 168 (30.5) 0.97 (0.75-1.26) 0.90
Female (n=422) 64 (29.8) 59 (28.5) 0.94 (0.62-1.43)
Country: Argentina (n=342) 52 (30.4) 47 (27.5) 0.87 (0.54-1.39) 0.77
Italy (n=728) 116 (32.0) 115 (31.5) 0.98 (0.72-1.34)
USA (n=446) 65 (29.0) 65 (29.3) 1.01 (0.67-1.52)
Cardiac valve surgery: No (n=707) 84 (23.6) 95 (27.1) 1.20 (0.86-1.69) 0.06
Yes (n=756) 149 (40.2) 132 (34.3) 0.78 (0.58-1.05)
Hypertension: No (n=368) 41 (21.7) 37 (20.7) 0.94 (0.57-1.55) 0.92
Yes (n=1135) 189 (33.6) 188 (32.9) 0.97 (0.76-1.24)
NYHA class 2-4: No (n=1111) 165 (29.7) 162 (29.1) 0.97 (0.75-1.26) 0.97
Yes (n=362) 60 (33.9) 62 (33.5) 0.98 (0.64-1.52)
Serum potassium: <4.18 mmol/L (n=729) 115 (32.5) 117 (31.2) 0.94 (0.69-1.29) 0.90
≥4.18 mmol/L (n=730) 110 (29.3) 102 (28.7) 0.97 (0.71-1.34)
Left atrial diameter: <42 mm (n=480) 60 (24.8) 56 (23.5) 0.93 (0.61-1.42) 0.83
≥42 mm (n=555) 108 (38.9) 107 (38.6) 0.99 (0.70-1.39)
Ejection fraction: <50% (n=288) 36 (24.5) 37 (26.2) 1.10 (0.65-1.87) 0.59
≥50% (n=1208) 194 (32.3) 187 (30.8) 0.93 (0.73-1.19)
Habitual fish intake: <2 servings/wk (n=381) 56 (27.6) 54 (30.3) 1.14 (0.73-1.78) 0.68
≥2 servings/wk (n=127) 20 (33.9) 28 (41.2) 1.37 (0.66-2.81)
Phospholipid omega-3 levels: <4% (n=200) 22 (22.7) 28 (27.2) 1.27 (0.67-2.42) 0.44
≥4% (n=323) 58 (36.7) 58 (35.2) 0.93 (0.59-1.47)
Study drug loading days (actual): 0 (n=34) 1 (7.1) 4 (20.0) 3.25 (0.32-32.7) 0.28
1 (n=34) 3 (14.3) 2 (15.4) 1.09 (0.16-7.59)
2 (n=640) 89 (28.7) 97 (29.4) 1.03 (0.74-1.46)
3 (n=286) 40 (27.8) 45 (31.7) 1.21 (0.73-2.00)
4 (n=137) 28 (44.4) 19 (25.7) 0.43 (0.21-0.89)
5 (n=385) 72 (35.0) 60 (33.5) 0.94 (0.62-1.43)
Peri-op beta-blockers: No (n=456) 70 (30.2) 65 (29.0) 0.95 (0.63-1.42) 0.92
Yes (n=1060) 163 (31.0) 162 (30.3) 0.97 (0.75-1.26)
Peri-op statins: No (n=550) 84 (30.7) 81 (29.4) 0.94 (0.65-1.35) 0.87
Yes (n=966) 149 (30.8) 146 (30.3) 0.98 (0.74-1.29)
Peri-op amiodarone: No (n=1295) 177 (27.3) 158 (24.4) 0.86 (0.67-1.10) 0.14
Yes (n=160) 31 (36.5) 34 (45.3) 1.44 (0.77-2.72)
Peri-op ACE-inhibitors/ARBs: No (n=655) 94 (28.2) 92 (28.6) 1.02 (0.72-1.43) 0.67
Yes (n=861) 139 (32.7) 135 (31.0) 0.92 (0.69-1.23)
On-pump time: <1:36 hrs:min (n=721) 92 (26.4) 102 (27.4) 1.05 (0.75-1.46) 0.46
≥1:36 hrs:min (n=742) 141 (37.2) 125 (34.4) 0.89 (0.66-1.20)
Cross-clamp time: <1:11 hrs:min (n=724) 85 (24.9) 103 (27.0) 1.12 (0.80-1.56) 0.26
≥1:11 hrs:min (n=739) 148 (38.4) 124 (35.0) 0.86 (0.64-1.17)
OVERALL (n=1516) 233 (30.7) 227 (30.0) 0.96 (0.77-1.20)
0.25
0.5
1
2.0
4.0
Odds ratio (95% CI)
Favors n-3 PUFA
Favors Placebo

JAMA 2012

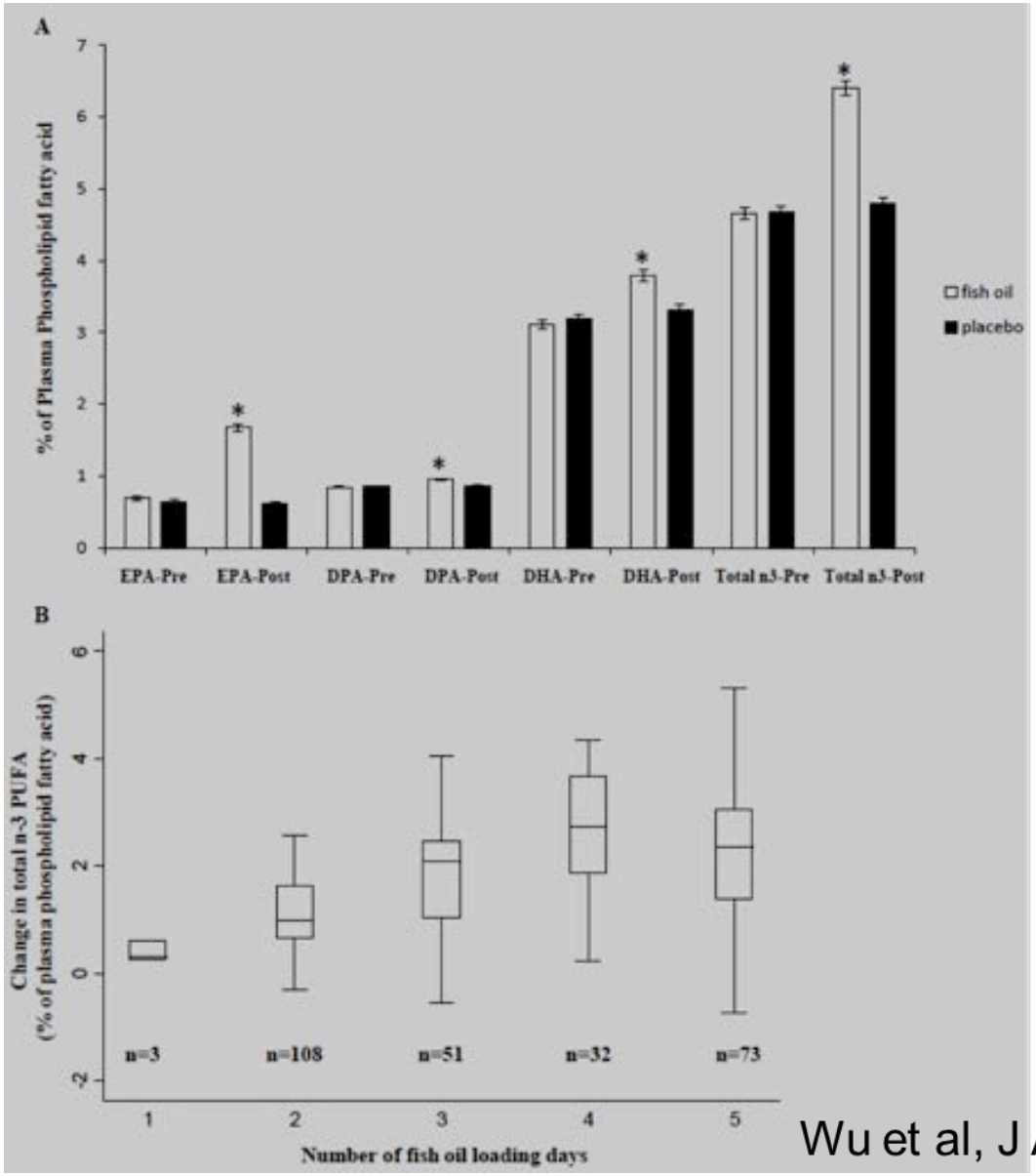
Table 2

Primary and Secondary Study Outcomes in OPERA, According to Treatment Assignment

Outcome		Placebo (n=758)	n-3-PUFA (n=758)	Odds Ratio or Hazard Ratio* (95% CI)	P value†
Any first post-op AF, primary endpoint, n (%) ‡		233 (30.7)	227 (30.0)	0.96 (0.77, 1.20)	0.74
Post-op AF, secondary endpoints					
Sustained, symptomatic, or treated post-op AF, n (%) §		231 (30.5)	224 (29.6)	0.96 (0.77, 1.19)	0.70
Post-op AF excluding flutter, n (%) ‖		220 (29.0)	217 (28.6)	0.98 (0.79, 1.23)	0.87
No. of post-op AF episodes, n (%)	1	156 (20.6)	157 (20.7)		
	2	59 (7.8)	49 (6.5)	n/a	0.73
	3+	18 (2.4)	21 (2.8)		
Total in-hospital days with any post-op AF, mean (SD) ¶		2.75 (2.1)	2.84 (2.1)	n/a	0.58
Proportion of in-hospital days free of any post-op AF, percent		89.0	88.7	n/a	0.88
Other arrhythmias, n (%)					
Other supraventricular tachycardia		6 (0.8)	11 (1.5)	1.85 (0.68, 5.02)	0.33
Ventricular tachycardia or fibrillation		9 (1.2)	5 (0.7)	0.55 (0.18, 1.66)	0.42
Other endpoints, n (%)					
MACE, in-hospital #		20 (2.6)	13 (1.7)	0.62 (0.31, 1.25)	0.18
Myocardial infarction		10 (1.3)	10 (1.3)	0.99 (0.41, 2.39)	1.00
Stroke		8 (1.1)	4 (0.5)	0.45 (0.13, 1.51)	0.18
Cardiovascular death		3 (0.4)	0 (0.0)	n/a	0.08
Arterial thromboembolism, 30 days		13 (1.7)	5 (0.7)	0.37 (0.13-1.03)	0.047
Arterial thromboembolism or death, 30 days		27 (3.6)	13 (1.7)	0.43 (0.22-0.84)	0.01
Total mortality, 30 days		15 (2.0)	8 (1.1)	0.53 (0.23-1.26)	0.14
- Cardiac arrhythmic		0 (0.0)	1 (0.1)	–	0.32
- Cardiac nonarrhythmic		2 (0.3)	0 (0.0)	–	0.16
- Vascular		3 (0.4)	0 (0.0)	–	0.08

JAMA 2012

Plasma Phospholipid Omega-3 Fatty Acids and Incidence of Postoperative Atrial Fibrillation in the OPERA Trial



Wu et al, J Am Heart Ass 2013

Enrollment n-3 PUFA concentrations

	Quartiles of Fatty Acid Levels (Odds Ratios)				P Value for Trend[a]	P Value for Interaction[a]
	1st	2nd	3rd	4th		
Enrollment n-3 PUFA concentrations						
Country[b]						
Italy (n=179)	1.0 (reference)	2.25 (0.84 to 6.04)	0.96 (0.35 to 2.64)	2.32 (0.86 to 6.26)	0.16	0.61
US (n=324)	1.0 (reference)	2.46 (1.11 to 5.48)	1.71 (0.74 to 3.94)	1.92 (0.83 to 4.45)	0.36	
Age, y						
<64 (n=272)	1.0 (reference)	1.93 (0.73 to 5.07)	2.70 (1.02 to 7.13)	3.27 (1.15 to 9.34)	0.04	0.35
≥64 (n=292)	1.0 (reference)	0.91 (0.45 to 1.87)	0.88 (0.42 to 1.82)	0.77 (0.35 to 1.65)	0.50	
Sex						
Women (n=158)	1.0 (reference)	2.59 (0.74 to 9.14)	2.28 (0.66 to 7.84)	1.17 (0.31 to 4.34)	0.68	0.65
Men (n=406)	1.0 (reference)	0.95 (0.48 to 1.89)	1.32 (0.68 to 2.57)	1.31 (0.63 to 2.71)	0.34	
Statins						
No (n=247)	1.0 (reference)	2.14 (0.81 to 5.66)	3.02 (1.10 to 8.29)	2.97 (1.02 to 8.60)	0.10	0.06
Yes (n=317)	1.0 (reference)	0.68 (0.32 to 1.47)	0.77 (0.36 to 1.64)	0.51 (0.22 to 1.17)	0.15	
β-blockers						
No (n=263)	1.0 (reference)	0.98 (0.40 to 2.39)	1.33 (0.57 to 3.14)	1.75 (0.69 to 4.41)	0.16	0.13
Yes (n=301)	1.0 (reference)	0.93 (0.42 to 2.09)	1.27 (0.57 to 2.80)	0.69 (0.29 to 1.65)	0.41	
Ejection fraction, %						
<60 (n=270)	1.0 (reference)	1.69 (0.70 to 4.08)	2.31 (0.98 to 5.42)	1.91 (0.75 to 4.87)	0.25	0.35
≥60 (n=294)	1.0 (reference)	0.80 (0.36 to 1.78)	0.98 (0.43 to 2.24)	0.83 (0.35 to 1.94)	0.75	
LA diameter, mm						
<42 (n=166)	1.0 (reference)	4.87 (1.23 to 19.3)	7.02 (1.73 to 28.5)	3.30 (0.67 to 16.2)	0.63	0.24
≥42 (n=218)	1.0 (reference)	0.59 (0.23 to 1.53)	1.26 (0.50 to 3.15)	1.09 (0.41 to 2.94)	0.57	

Wu et al, J Am Heart Ass 2013

Change in total n-3PUFA concentrations

Change in total n-3 PUFA concentrations						
Country[b]						
Italy (n=167)	1.0 (reference)	1.35 (0.50 to 3.62)	1.12 (0.42 to 2.97)	1.13 (0.43 to 2.99)	0.96	0.99
US (n=301)	1.0 (reference)	0.72 (0.33 to 1.57)	0.52 (0.23 to 1.15)	0.98 (0.47 to 2.08)	0.81	
Age, y						
<64 (n=256)	1.0 (reference)	1.45 (0.59 to 3.56)	1.06 (0.43 to 2.63)	1.51 (0.62 to 3.65)	0.51	0.62
≥64 (n=267)	1.0 (reference)	0.81 (0.38 to 1.74)	1.17 (0.56 to 2.45)	0.82 (0.39 to 1.75)	0.74	
Sex						
Women (n=144)	1.0 (reference)	0.67 (0.20 to 2.27)	1.03 (0.30 to 3.49)	0.85 (0.26 to 2.86)	0.99	0.98
Men (n=379)	1.0 (reference)	0.84 (0.43 to 1.65)	1.03 (0.54 to 1.98)	0.94 (0.49 to 1.82)	0.97	
Statins						
No (n=226)	1.0 (reference)	1.44 (0.55 to 3.74)	1.13 (0.44 to 2.96)	1.49 (0.59 to 3.74)	0.53	0.64
Yes (n=297)	1.0 (reference)	0.58 (0.26 to 1.30)	0.92 (0.43 to 1.97)	0.98 (0.46 to 2.11)	0.56	
β-blockers						
No (n=242)	1.0 (reference)	0.95 (0.39 to 2.29)	1.03 (0.42 to 2.51)	1.23 (0.52 to 2.93)	0.55	0.66
Yes (n=281)	1.0 (reference)	0.68 (0.30 to 1.52)	0.74 (0.34 to 1.60)	0.89 (0.42 to 1.91)	0.94	
Ejection fraction, %						
<60 (n=246)	1.0 (reference)	0.52 (0.22 to 1.22)	0.77 (0.34 to 1.76)	0.64 (0.28 to 1.48)	0.61	0.24
≥60 (n=277)	1.0 (reference)	1.39 (0.60 to 3.21)	1.07 (0.46 to 2.52)	1.58 (0.70 to 3.58)	0.35	
LA, mm						
<42 (n=151)	1.0 (reference)	0.74 (0.22 to 2.51)	0.65 (0.19 to 2.26)	1.31 (0.40 to 4.27)	0.44	0.63
≥42 (n=204)	1.0 (reference)	0.79 (0.32 to 1.97)	0.97 (0.38 to 2.46)	0.95 (0.38 to 2.36)	0.93	

Wu et al, J Am Heart Ass 2013

Oxidative Stress Biomarkers and Incidence of Postoperative Atrial Fibrillation in the Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation (OPERA) Trial

Jason H. Y. Wu, PhD; Roberto Marchioli, MD; Maria G. Silletta, MS; Serge Masson, PhD; Frank W. Sellke, MD; Peter Libby, MD; Ginger L. Milne, PhD; Nancy J. Brown, MD; Federico Lombardi, MD, FESC; Ralph J. Damiano, Jr, MD; Joann Marsala, RN; Mauro Rinaldi, MD; Alberto Domenech, MD; Caterina Simon, MD; Luigi Tavazzi, MD; Dariush Mozaffarian, MD, DrPH

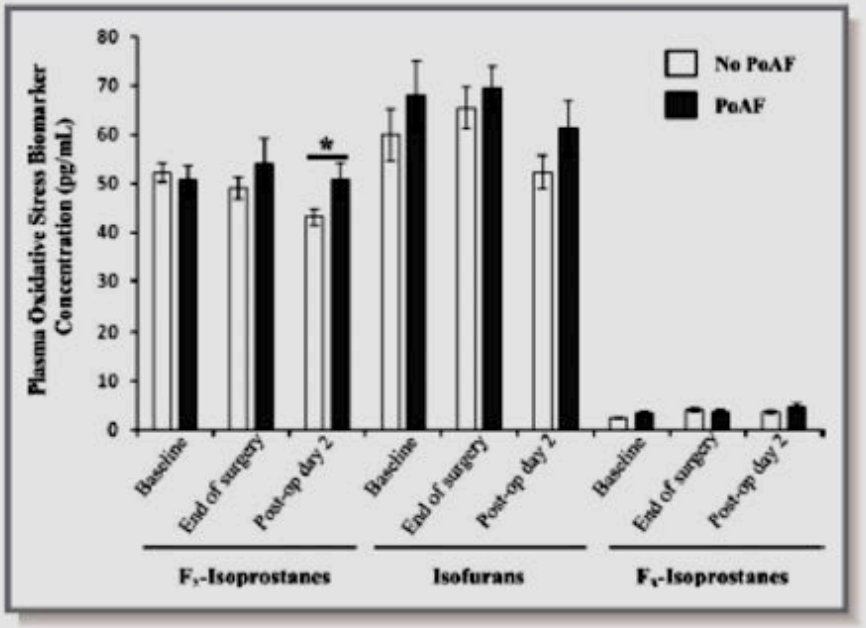


Figure 1. Plasma oxidative stress biomarkers concentration (pg/mL) at baseline (recruitment), end of surgery (at time of closure), and postoperative day 2. Data shown are mean±SE. The white and gray bars represent subjects without and with incident postoperative atrial fibrillation (PoAF), respectively. *Mean plasma level of F_2-isoprostanes were ≈20% higher in patients who developed PoAF than in those who did not (P=0.05, adjusted for end of surgery F_2-isoprostane concentrations).

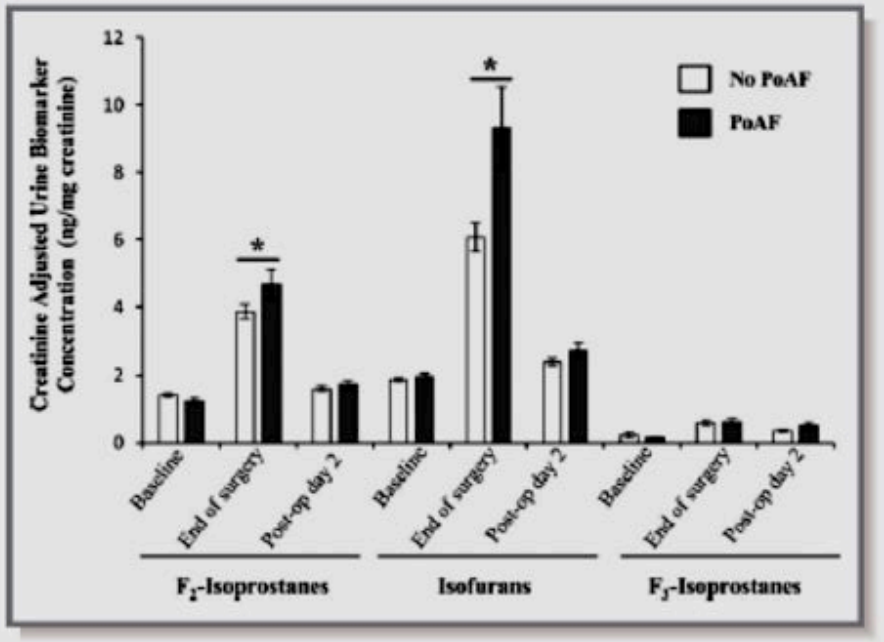
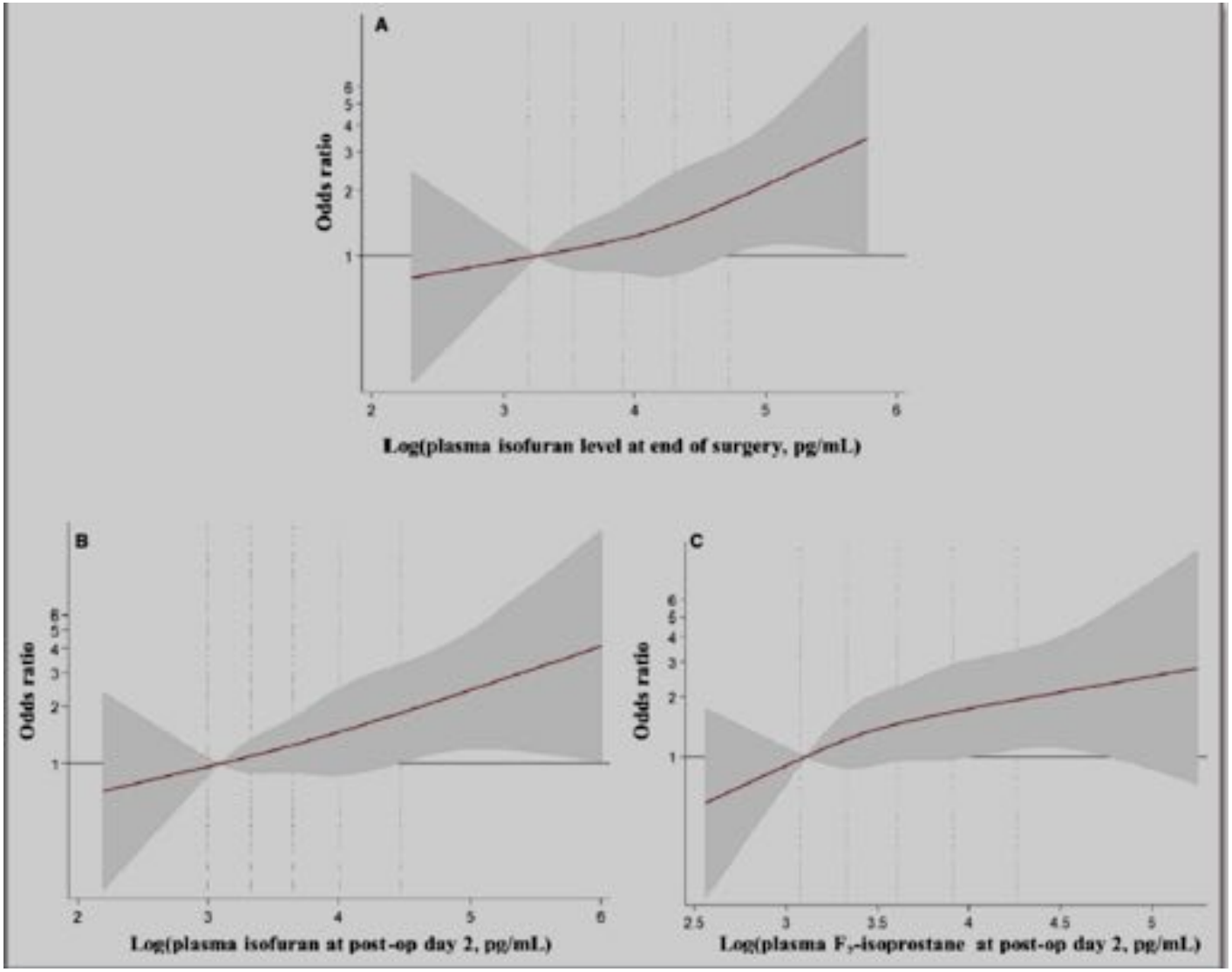


Figure 2. Urine creatinine-adjusted concentration of oxidative stress biomarkers (ng/mg) at baseline (recruitment), end of surgery (at time of closure), and postoperative day 2. Data shown are mean±SE. The white and gray bars represent subjects without and with incident postoperative atrial fibrillation (PoAF), respectively. *Mean urine F_2-isoprostane and isofuran levels were ≈20% and ≈50% higher in subjects who subsequently developed PoAF (P≤0.009, adjusted for baseline concentrations).

J Am Heart Ass, 2015

Multivariable-adjusted association of plasma (A) isofuran at the end of surgery, (B) isofuran and (C)isoprostanes at post-operative day 2 with POAF



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n-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial

6975 pts randomized to 1 g daily of n-3 PUFA or placebo on top of best medical therapy
16.3% had AF at baseline ecg.
Among 5835 pts without AF at baseline, 444 randomized to n-3 PUFA and 408 to placebo developed AF. HR 1.10, p= 0.19

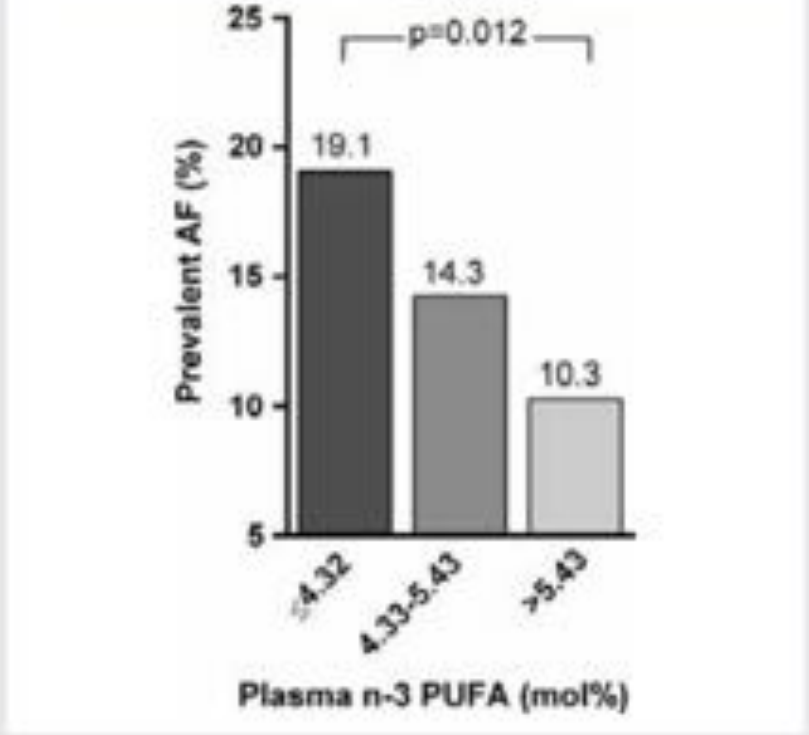

Figure 1 Prevalence of AF at study entry by circulating levels of *n*-3 polyunsturated fatty acids (PUFAs) in 1203 patients of the GISSI-HF trail. Plasma levels of *n*-3 PUFAs were measured at study entry and divided into tertiles. Logistic analysis were adjusted as described in the Methods.

Aleksova et al, Eur J Heart Fail 2013

Despite an inverse relationship between plasma *n*-3 PUFA levels and prevalent AF, this study found no evidence that 1 g daily *n*-3 PUFA supplementation in patients with chronic HF reduces incident AF.

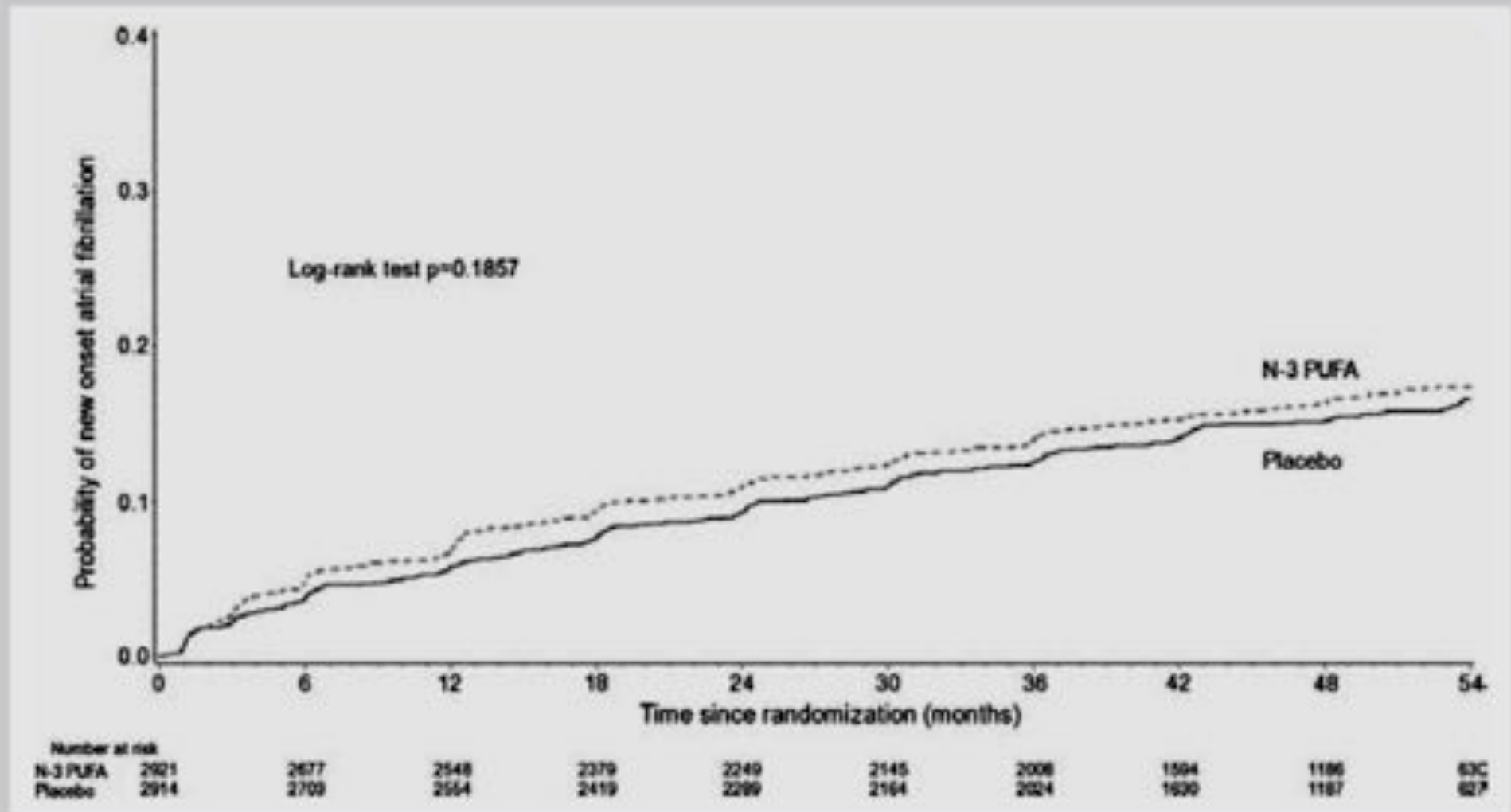

Figure 2 Kaplan–Meier curves for time to new onset of AF in the *n*-3 polyunsturated fatty acid (PUFA) and placebo groups.

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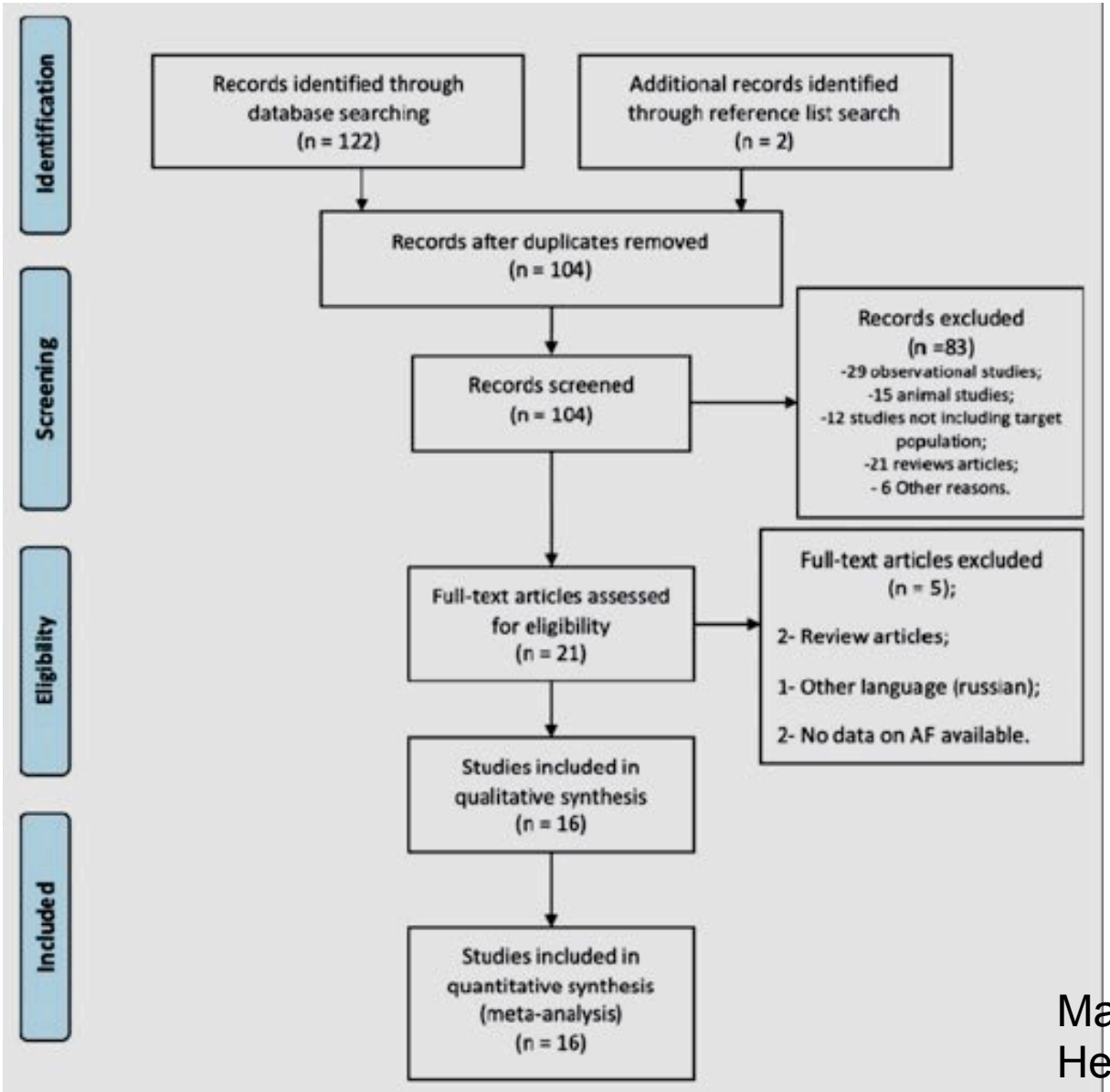
N-3 Polyunsaturated Fatty Acids to Prevent Atrial Fibrillation: Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

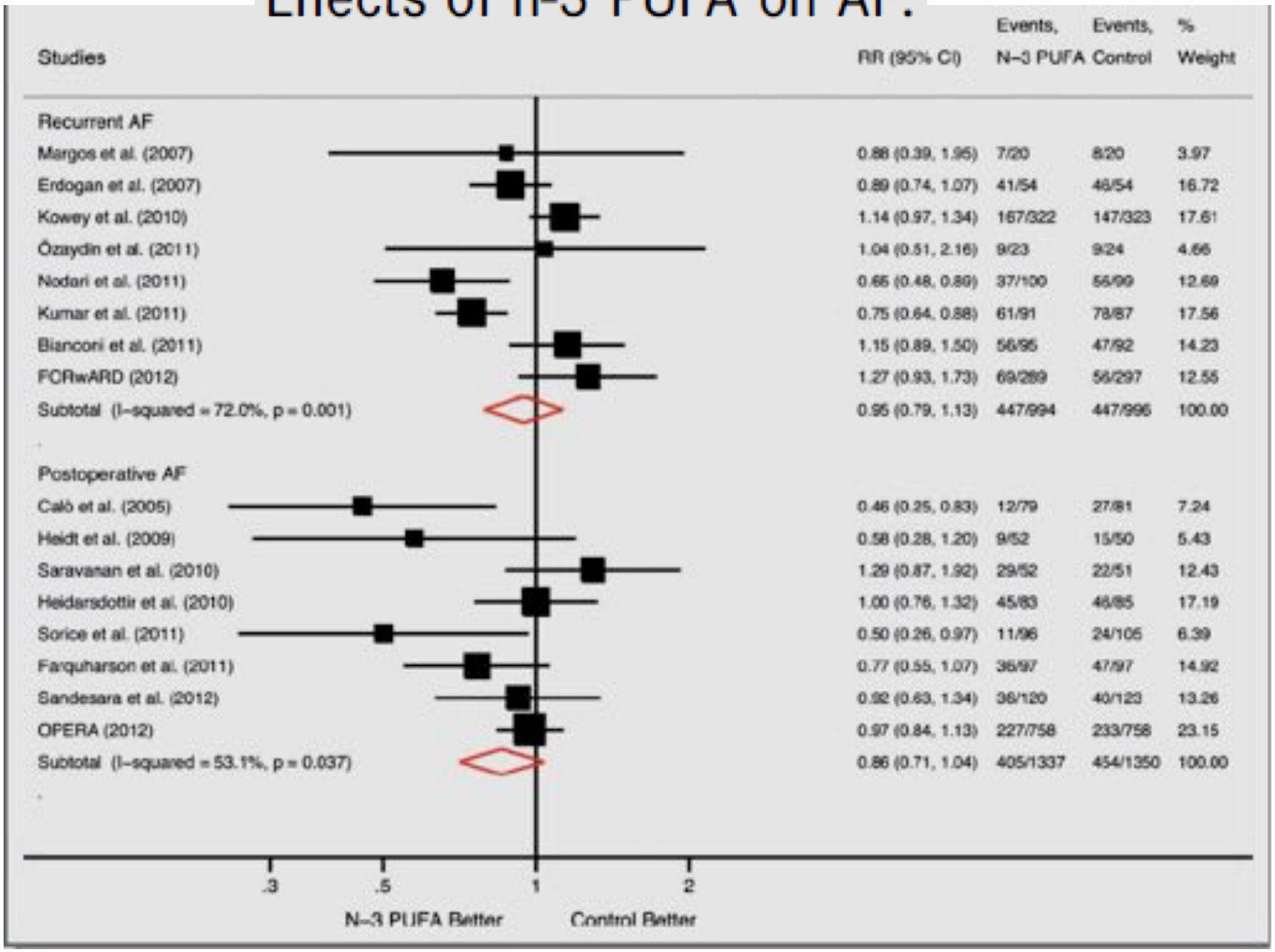


Mariani et al, J Am Heart Ass 2013

Study	N	Age,* Mean	Male Sex, n (%)	Hypertension, n (%)	Previous MI, n (%)	Diabetes, n (%)	β-Blockers, n (%)	Amiodarone, n (%)	LA mm*, Mean	LVEF,* %
Persistent or paroxysmal atrial fibrillation										
Erdogan et al[32]	108	65.0	78 (72.2)	NA	NA	NA	NA	NA	NA	NA
Margos et al[33]	40	55.5	28 (70)	NA	NA	NA	NA	23 (57.5)	44.9	57.3
Kowey et al[36]	663†	60.5	373 (56)	NA	NA	NA	NA	0 (0)	NA‡	NA‡
Bianconi et al[35]	214§	69.2	129 (70)	134 (71.7)	18 (9.6)	34 (18.2)	84 (44.9)	52 (27.8)	44.9	57.7
Özaydin et al[37]	47	61.5	20 (42.6)	25 (53.2)	0 (0)	8 (17.0)	12 (25.5)	47 (100)	44	60.5
Nodari et al[34]	205¶	69.5	133 (66.8)	87 (43.7)	68 (34.2)	69 (34.7)	123 (61.8)	199 (100)	46	49.5
Kumar et al[38]	182‖	62.0	138 (77.5)	92 (51.7)	31 (17.4)	27 (15.2)	NA	59 (33.2)	45.8	58.4
FORWARD[39]	586	66.1	321 (54.8)	524 (91.4)	67 (11.7)	74 (12.9)	353 (60.2)	372 (63.5)	29.1#	60
Postoperative atrial fibrillation										
Caló et al[40]	160	65.6	136 (85)	128 (80)	84 (52.5)	52 (32.5)	92 (57.5)	0 (0)	39.7	55.8
Heidt et al[41]	102	64.4	70 (68.6)	NA	NA	NA	NA	0 (0)	40.3	52.2
Heidarsdottir et al[42]	168	67.0	133 (79.2)	106 (63.1)	26 (15.5)	26 (15.5)	126 (75)	0 (0)	NA	60
Saravanan et al[43]	103	66.0	82 (79.6)	33 (32)	26 (25.2)	15 (14.6)	88 (85.4)	0 (0)	NA**	NA**
Sandesara et al[44]	243	62.8	196 (80.7)	215 (88.5)	101 (41.6)	88 (36.2)	194 (80.0)	0 (0)	39.0	52.7
Sorice et al[45]	201	63.2	164 (81.6)	129 (64.2)	NA	85 (42.3)	121 (60.2)	0 (0)	40.6	52.5
Farquharson et al[46]	194	64.0	142 (73.2)	151 (77.8)	68 (35)	61 (31.4)	80 (41.2)	0 (0)	NA	64.5
OPERA[47]	1516	63.7	1094 (72.2)	1135 (74.9)	366 (24.1)	393 (25.9)	877 (57.9)	58 (3.8)	42.2	56.7

Mariani et al, J Am Heart Ass 2013

Effects of n-3 PUFA on AF.



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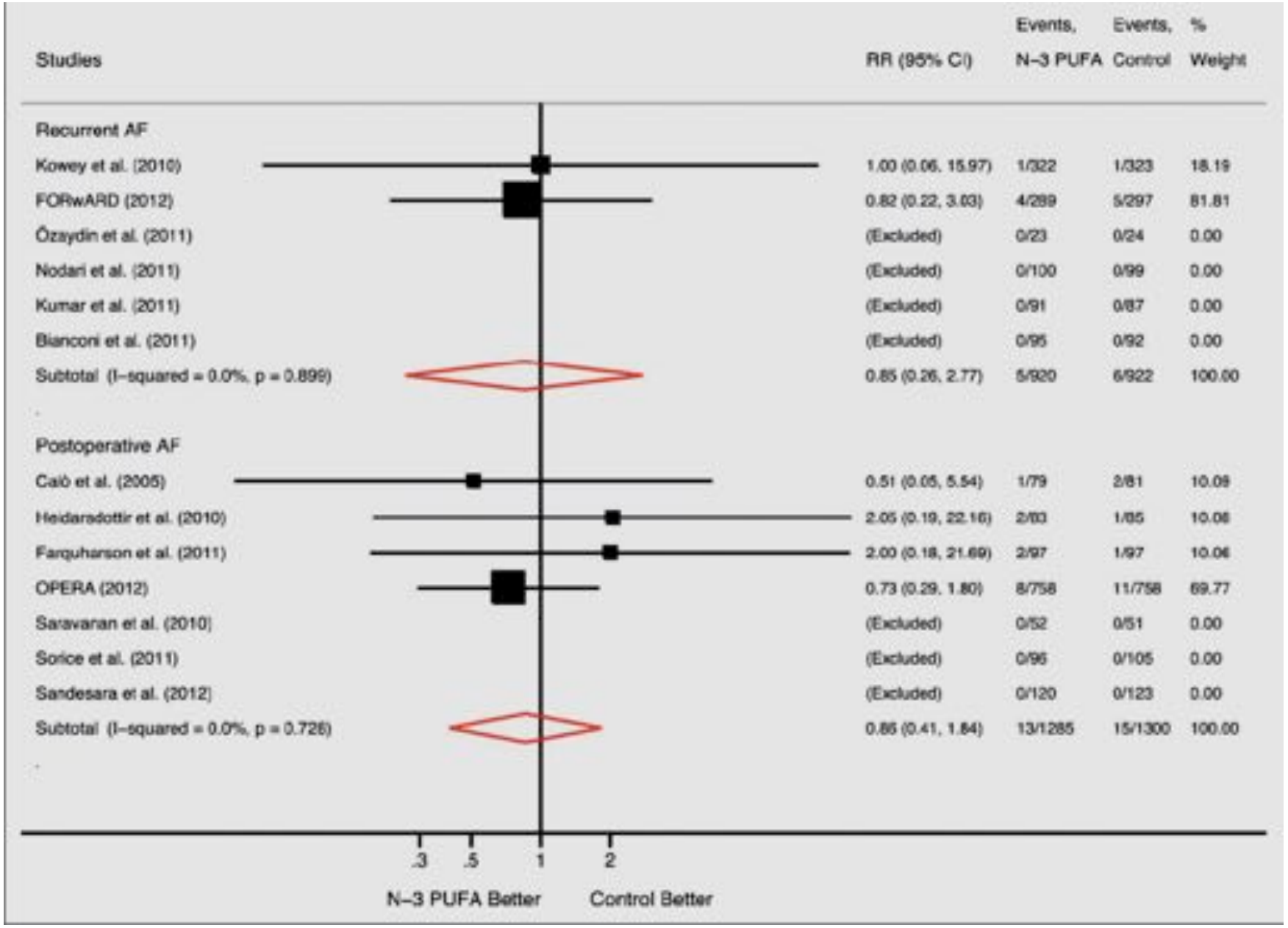
Effects of n-3 PUFA on mortality.



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Meta-regression analyses

Covariates	Recurrent AF			Postoperative AF		
	Coefficient (95% CI)*	*P* Value	Residual I^2 (%)	Coefficient (95% CI)*	*P* Value	Residual I^2 (%)
n-3 PUFA dose	1.02 (0.67 to 1.57)	0.891	80.7	0.96 (0.68 to 1.36)	0.782	59.4
AF rate in control group	0.53 (0.31 to 1.04)	0.070	40.2	3.73 (0.23 to 60.60)	0.292	58.5
Quality score	1.07 (0.86 to 1.33)	0.433	69.7	1.10 (0.85 to 1.43)	0.385	56.4
Mean age	1.00 (0.94 to 1.06)	0.877	75.8	1.05 (0.86 to 1.28)	0.572	58.4

In conclusion, the present meta-analysis provides confident evidence of the lack of usefulness of oral supplementation of n-3 PUFAs for the secondary prevention of AF and for the incidence of new AF in patients undergoing cardiovascular surgery.

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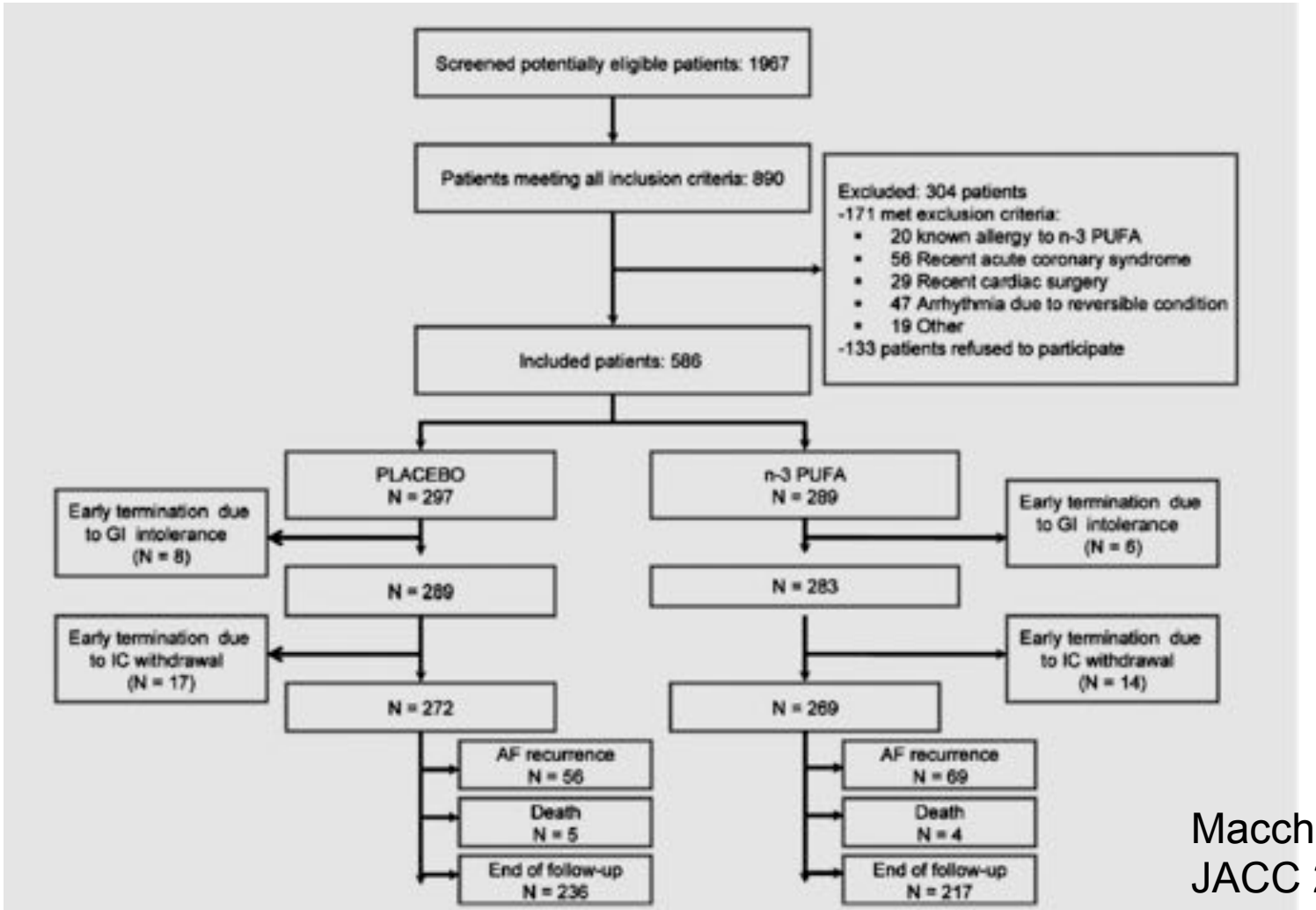
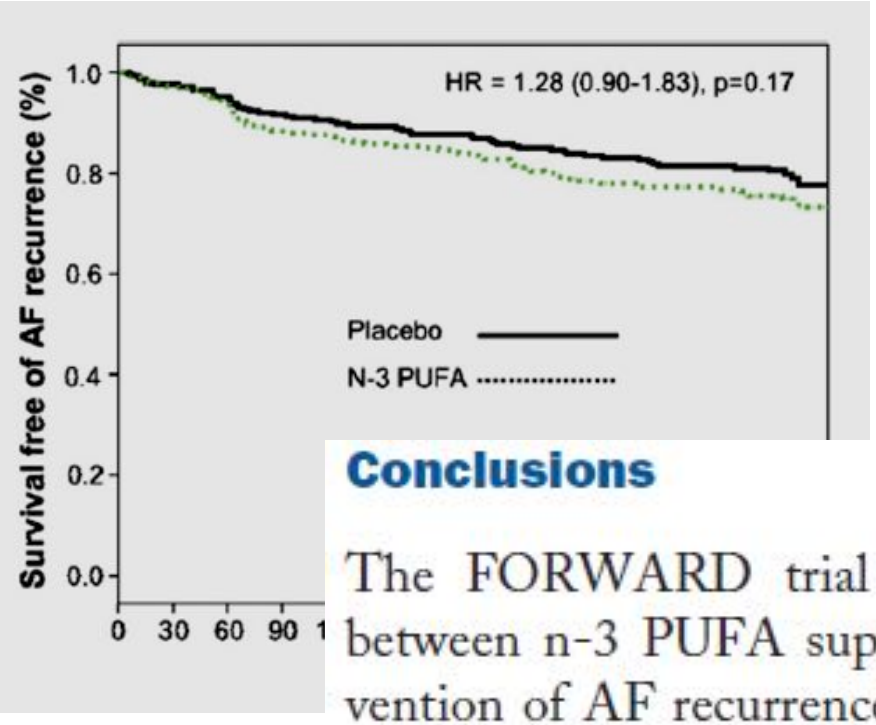
Omega-3 Fatty Acids for the Prevention of Recurrent Symptomatic Atrial Fibrillation

Results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) Trial

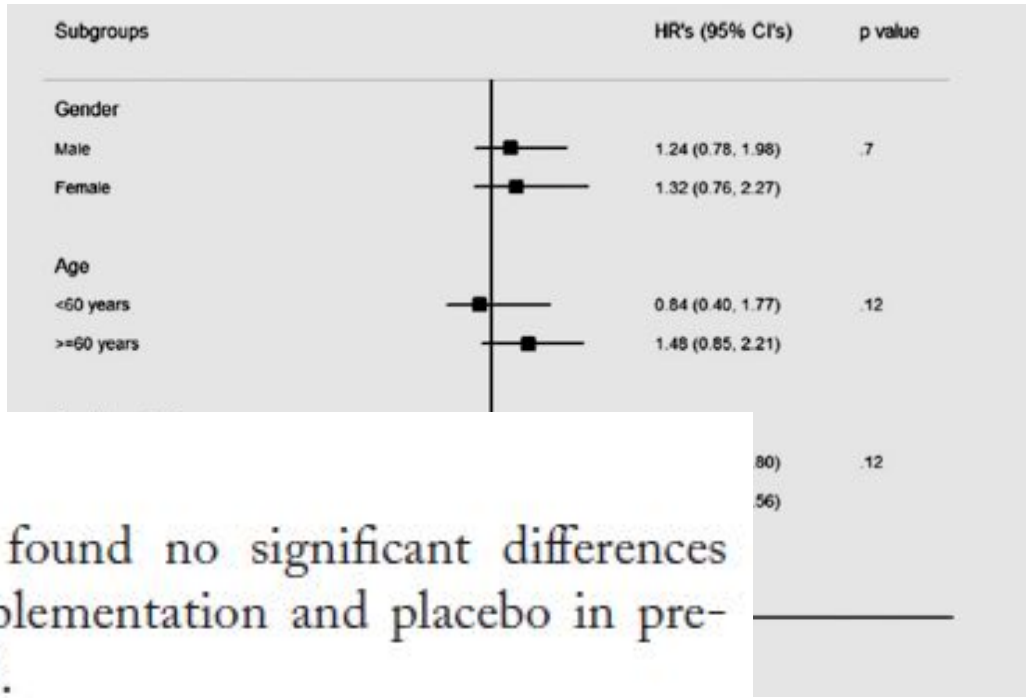


Macchia et al, JACC 2013

Time to first AF recurrence



Sub-groups analysis



Conclusions

The FORWARD trial found no significant differences between n-3 PUFA supplementation and placebo in prevention of AF recurrence.

Macchia et al, JACC 2013

The Current Role of Omega-3 Fatty Acids in the Management of Atrial Fibrillation

3. Conclusions

n-3 PUFA supplementation has been reported to attenuate structural atrial remodeling, exert beneficial electrophysiological effects on the atria and reduce the incidence as well as the duration of AF episodes in various settings, such as after cardiac surgery or after cardioversion of AF. However, the results of the relevant studies were, to some extent, conflicting regarding the efficacy of n-3 PUFA to prevent AF. This discrepancy could be attributed at least in part to important methodological limitations of these studies. Therefore, further large-scale, well-designed randomized controlled studies are needed, including subjects with low dietary fish intake, adequate pretreatment with n-3 PUFA for at least one month and using formulations with a high content of DHA. At present, firm conclusions about the clinical utility of n-3 PUFA in the management of AF cannot be reached based on the existing data.

Christou et al Int J Mol Med 2015