Atrial Fibrillation and Omega-3 fatty acids: Present situation & Future outlooks

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Agenda

- Atrial fibrillation (AF) background
- Clinical studies with Omega-3 fatty acids on AF
- Ongoing trials with Omacor
- Discussion

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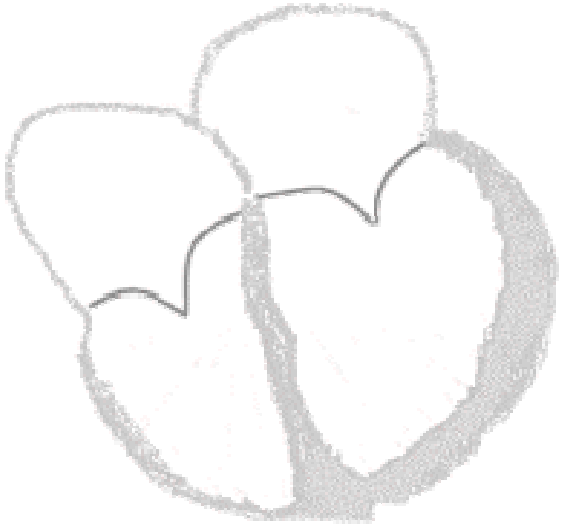
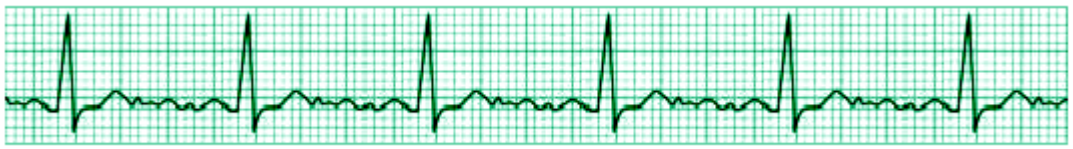
A little background on AF

In atrial fibrillation, the regular impulses produced by the sinus node to provide rhythmic contraction of the heart are overwhelmed by the rapid randomly generated electrical discharges produced by larger areas of atrial tissue. It can be distinguished from atrial flutter, which is a more organized electrical circuit usually in the right atrium that produces characteristic saw toothed p-waves on the electrocardiogram.

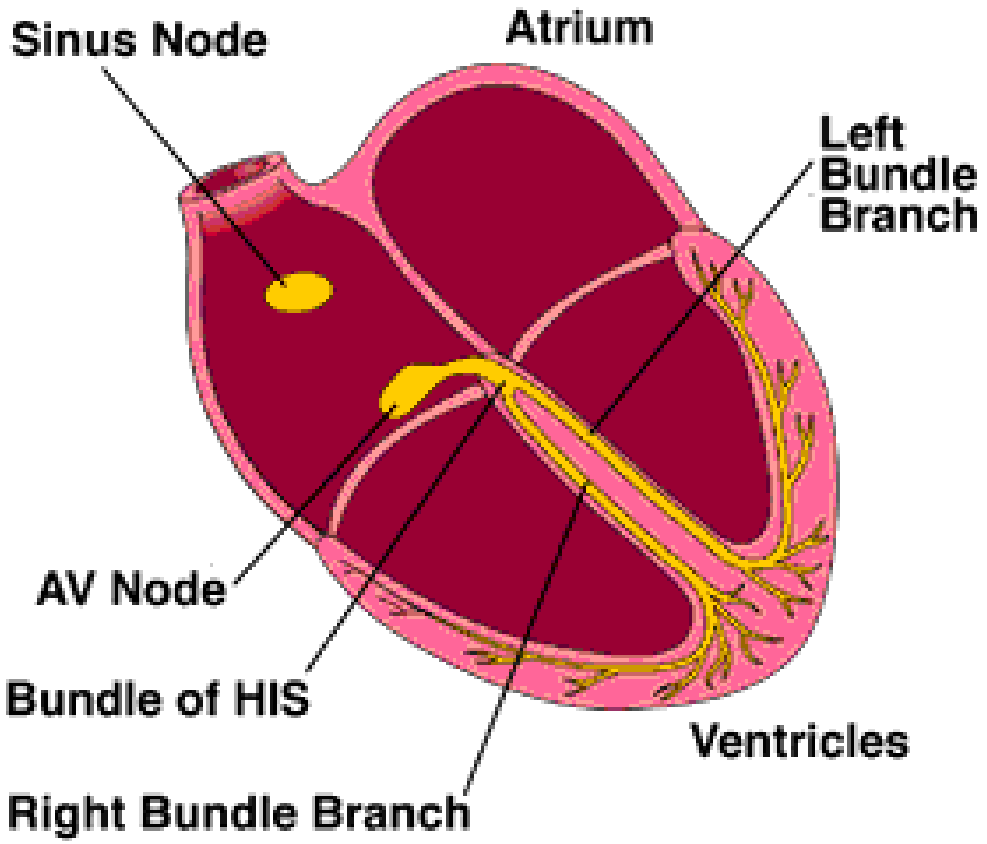


Sinus rhythm

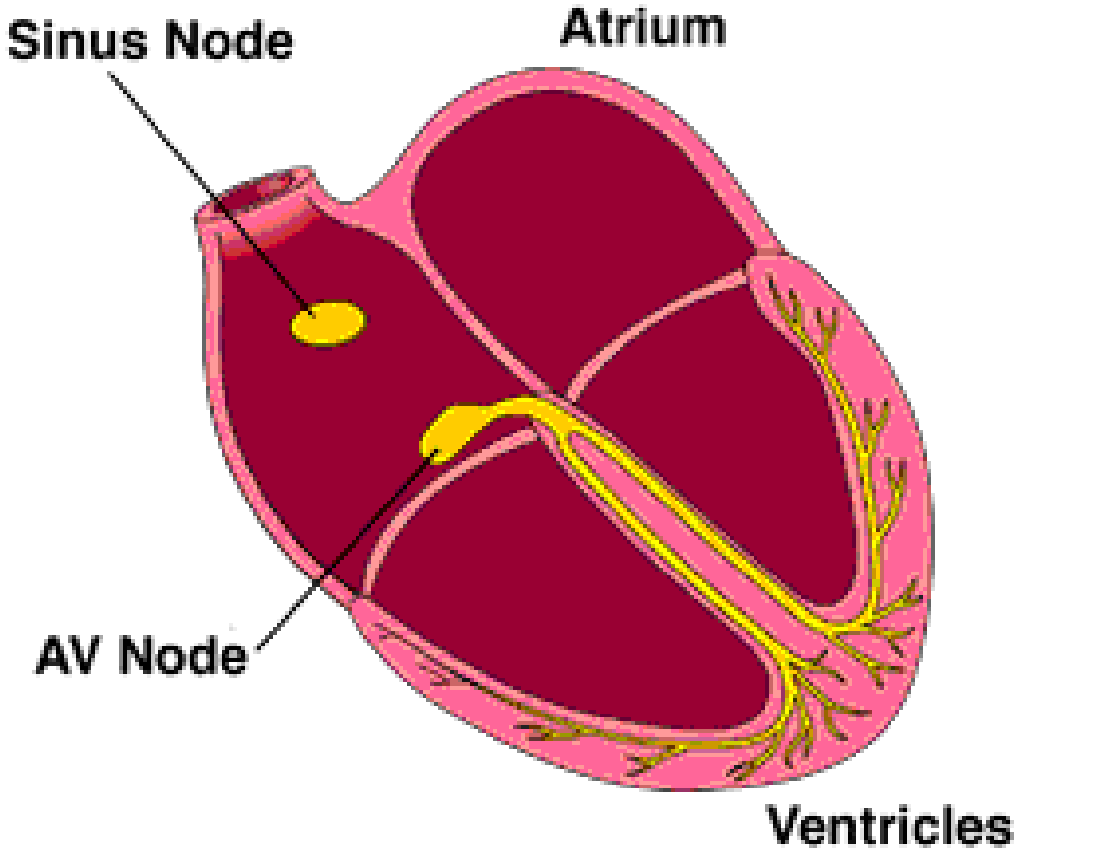
Atrial fibrillation



Normal Sinus rhythm



Atrial Fibrillation



Ventricular arhythmias

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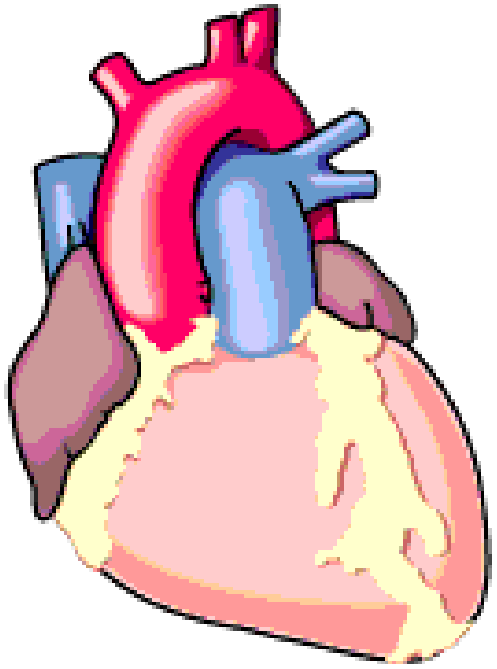
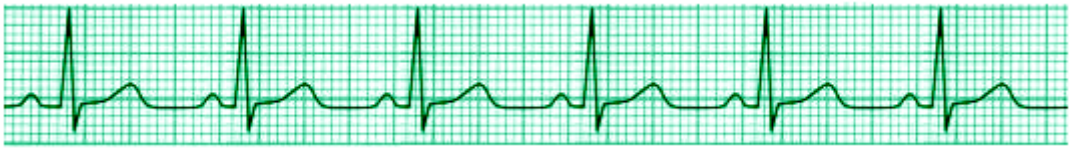


Sinus rhythm



Ventricular fibrillation

What are some types of ventricular arrhythmias?

- Premature ventricular contractions (PVC's) - these early depolarizations begin in the ventricle instead of the usual place, the sinus node. They are very common, and are sometimes perceived as a palpitation. They often occur without the patient being aware of it at all. By themselves, PVC's do not present any problem.
- Bigeminy, Trigeminy, Quadrigeminy, etc. - ventricular bigeminy is the occurrence of a PVC every other beat, trigeminy is every third beat, quadrigeminy every fourth beat. The main point with these types is that the PVC's are more frequent in these circumstances. They are otherwise little different from PVC's.
- Ventricular tachycardia - is defined as three or more consecutive PVC's. This may extend for hours. If it is prolonged and at a high enough rate, patients will become symptomatic. This is often a very serious arrhythmia, although on the other hand, there are some people who have it frequently and tolerate it for years.
- Ventricular fibrillation - is a rhythm that cannot sustain life. Like atrial fibrillation, there is no coordinated contraction of the heart muscle possible when this disorganized activity takes place. While this may be tolerable in the atrium, it does not allow any significant output from the heart when it occurs in the ventricle.

What's the relationship between all of these?

- An increased frequency of PVC's in patients with heart disease is STATISTICALLY predictive of ventricular fibrillation and sudden death. This does not mean that every patient with PVC's, even when frequent, is at high risk of sudden death. In fact, more cases of sudden death occur in people who do not have frequent PVC's. There are many people who have literally millions of PVC's throughout their lives, and never have a lick of trouble from their hearts.
- In patients with some types of heart disease, PVC's or ventricular tachycardia do indicate an increased risk of serious arrhythmias.

Causes of ventricular arrhythmias?

- Some cases are simply "normal variants", occurring in otherwise normal individuals.
- Other causes include:
- A variety of underlying cardiac conditions, including coronary artery disease, cardiomyopathy, mitral valve prolapse, etc.
- Abnormal levels of "electrolytes" (minerals) in the blood. Decreased potassium and/or magnesium are the most common associated abnormalities of electrolytes. Both may be caused by the use of diuretics (water pills), among other reasons.
- There are unusual congenital (familial) causes of ventricular arrhythmias.
- Abnormal conditions such as increased thyroid hormones, and others.
- Toxins, including alcohol.
- Stimulants
  - Caffeine
  - Nicotine
  - Cocaine can cause serious ventricular arrhythmias.
  - Some over-the-counter medications and herbal/natural formulations contain important stimulants
  - Infection, inflammation or degeneration of the heart muscle.
  - Infections at other sites in the body.
  - They are often worse with lack of sleep, or stress.
  - There are also other causes.

Consequences of Atrial Fibrillation

- Shortness of breath
- Nausea, dizziness
- Fatigue
- Palpitations
- Congestive heart failure
- Stroke

Definition

Atrial Fibrillation

Classification:

- **ACC,AHA, ESC, in collaboration with the Heart Rhythm Society have established guidelines for the classification of AF[i]**

General:

Lone AF: AF without any underlying CVD. 10% of whole AF population [ii]

1. **Recent onset AF: AF within 72 hours of onset**

2. **Chronic AF: More sustained or recurrent forms of AF, which can be subdivided into paroxysmal, persistent, or permanent AF**
   - ***Paroxysmal AF:*** *If the atrial fibrillation recurs intermittently with sinus rhythm, with spontaneous recurrences or termination, it is designated as "paroxysmal", and the objective of management is suppression of paroxysms and maintenance of sinus rhythm. Self-terminating, spontaneously converts to sinus rhythm*
   - ***Persistent AF*** *When atrial fibrillation is more sustained than paroxysmal, atrial fibrillation is designated "persistent" and needs termination with pharmacological treatment or electrical cardioversion. Lasts longer than 7 days, is not self-terminating and usually requires medical intervention*
   - ***Permanent AF*** *If cardioversion is inappropriate, and has not been indicated or attempted, atrial fibrillation is designated as "permanent", where the objective of management is rate control and antithrombotic treatment. Refractory to cardioversion or has persisted for a long period of time (greater than 1 year)*

[i] Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48:e149-246.

[ii] Camm AJ, Obel OA. Epidemiology and mechanism of atrial fibrillation and atrial flutter. Am J Cardiol 1996;78(suppl 8A):3-11

Atrial Fibrillation Begets Atrial Fibrillation

- **One of the main challenges of atrial fibrillation is the tendency of the disease to become chronic over time, during which a combination of molecular and structural changes make it difficult to achieve and maintain sinus rhythm[i]**

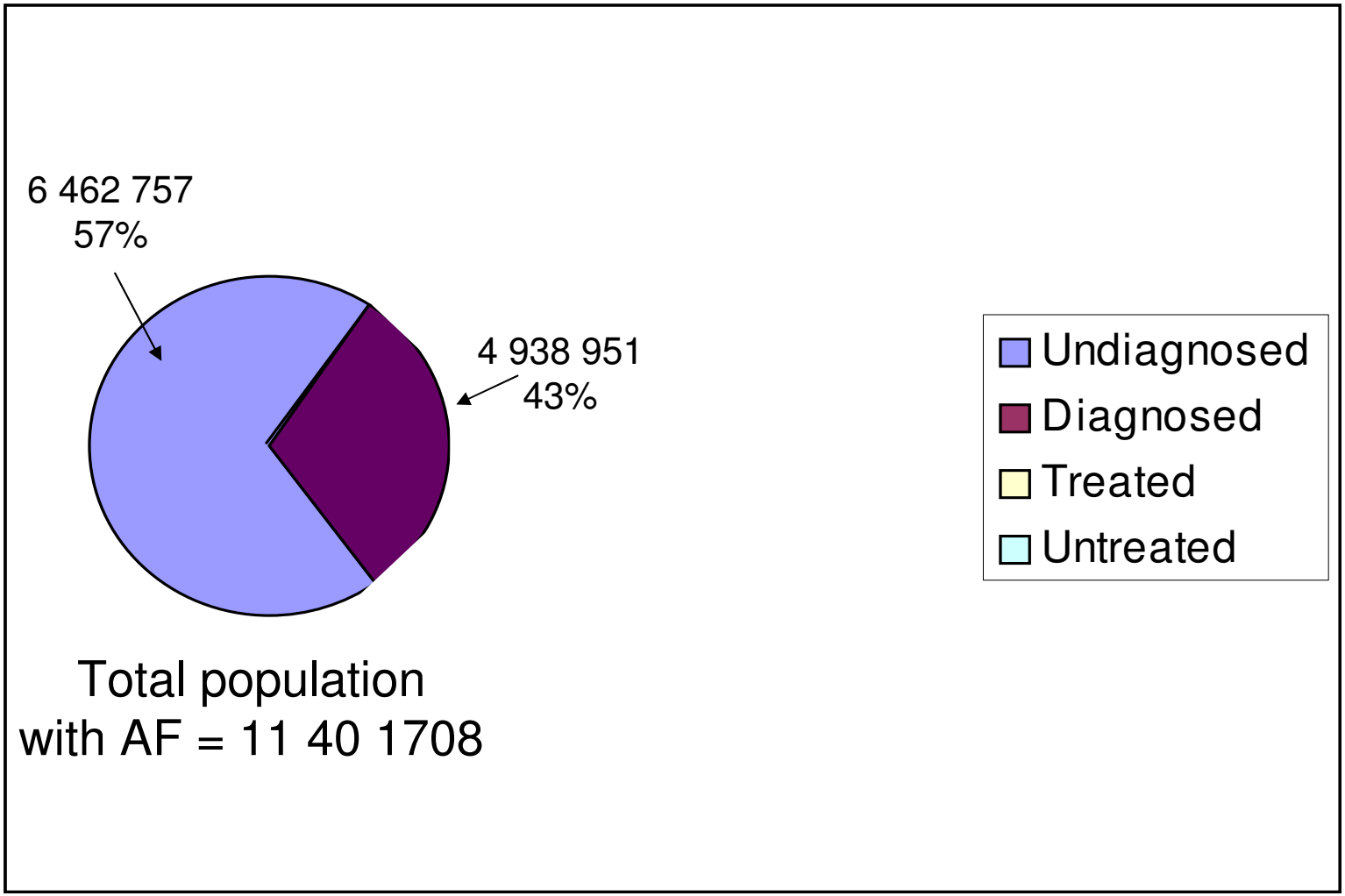
[i] Van Wagoner DR, Nerbonne JM. Molecular basis of electrical remodeling in atrial fibrillation. *J Mol Cell Cardiol*. 2000;32:1101-1117.

Atrial Fibrillation Begets Atrial Fibrillation *(cont)*

- A retrospective analysis demonstrated that 20% of patients with intermittent AF were in permanent AF after 4 years[i]
- 77% of patients with paroxysmal AF were in permanent AF after a mean of 14 years10. Independent risk factors for early progression to permanent AF included age, dilated left atrium, MI, and valvular disease10
- The longer one waits to initiate a rhythm treatment strategy, the harder it is to regain sinus rhythm. Patients who converted to sinus rhythm within 3 months of onset of AF were more likely to remain in sinus rhythm at 6 months than patients who converted more than 12 months after onset of AF (67% versus 27%)[ii]
- By shortening the atrial refractory period, reducing conduction velocity and provoking contractile and structural remodeling, AF sets the stage for self-perturbation

[i] Van Gelder IC, Hemels MEW. The progressive nature of atrial fibrillation: a rationale for early restoration of sinus rhythm and maintenance of sinus rhythm. *Europace*. 2006;8:943-949.
[ii] Dittrich HC, Erickson JS, Schneiderman T, et al. Echocardiographic and clinical predictors of outcome of elective cardioversion of atrial fibrillation. *Am J Cardiol.* 1989;63:193-197.

Breakdown of AF population: 7 major countries



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Studies on AF with Omega-3 fatty acids

Studies on Atrial Fibrillation with Ω-3s

Mozaffarian et al [i]	Fish trial
Mavrakis et al. [vii]	Other fish oil
Calò et al [v]	Omacor
Biscione	Omacor
Nodari [iii]	Omacor
Macchia et al [ix]	Omacor

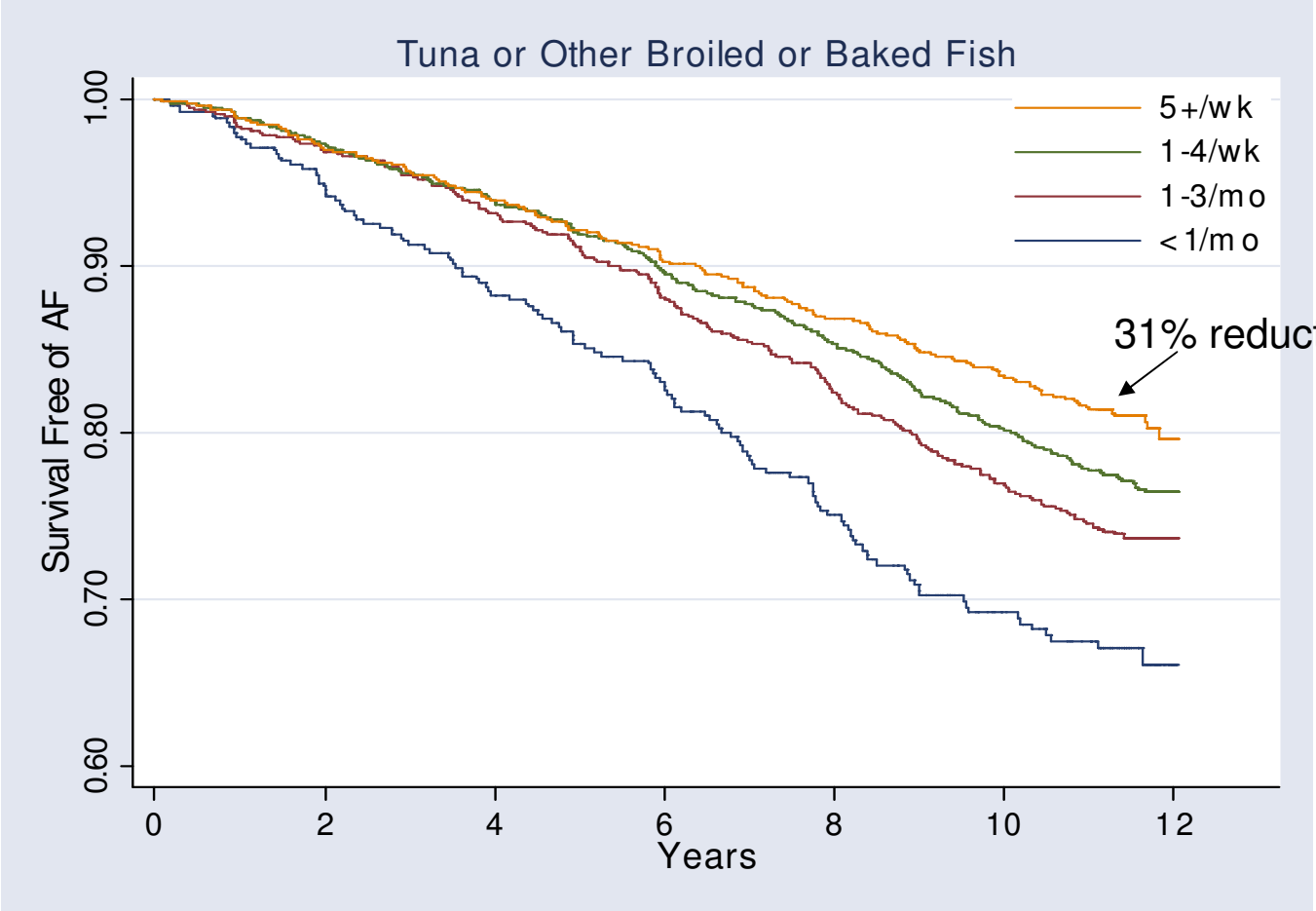
[i] Dariush Mozaffarian et al. *Circulation*. 2004 July 27; 110(4): 368–373.
(iii) Nodari et al. Eur Heart J 2006, 27 (Abstract Suppl), 887
[vi] Roberto Marchioli. *Circulation*. 2002;105: 1897-1903.
[v] Calo et al. JACC 2005; 45(10):1723-8
(vii) Mavrakis et al. European Heart Journal (2007) 28 (Abstract Supplement), 643
(ix) Macchia A. et al. Circulation 2007;116:II_518-II_519

Mozaffarian et al.

Observational study

Survival free of AF among 4,815 older adults according to intake of tuna or other broiled or baked fish. P<0.001 for survival differences according to fish intake.

Observational study

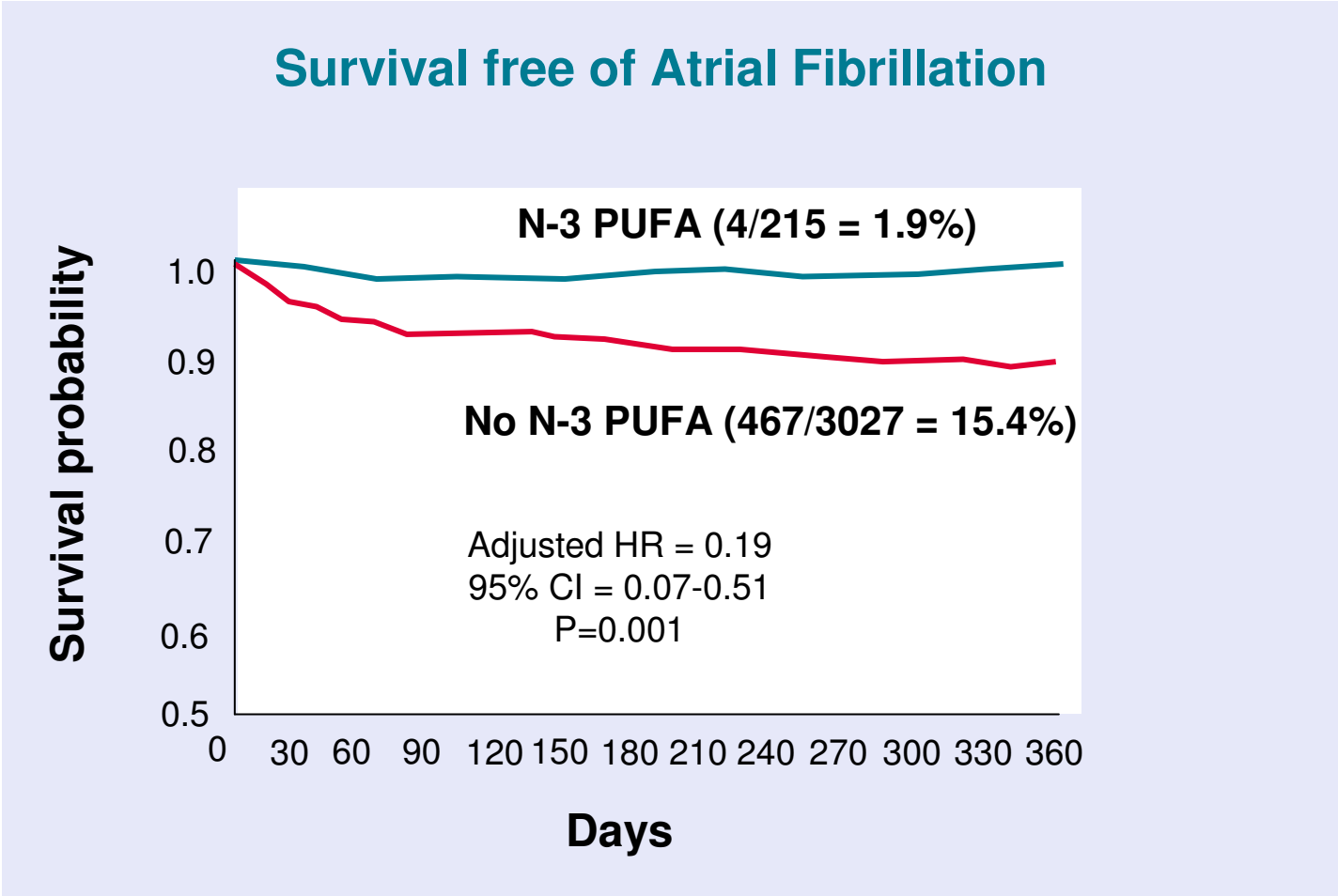


Reference: Mozaffarian D et al. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004;110:368-373.

Macchia et al.

Observational study

Omega 3 Fatty Acid Supplementation Reduces One-Year Risk of Atrial Fibrillation in Patients Hospitalized with Myocardial Infarction (Macchia, 2007- AHA presentation)



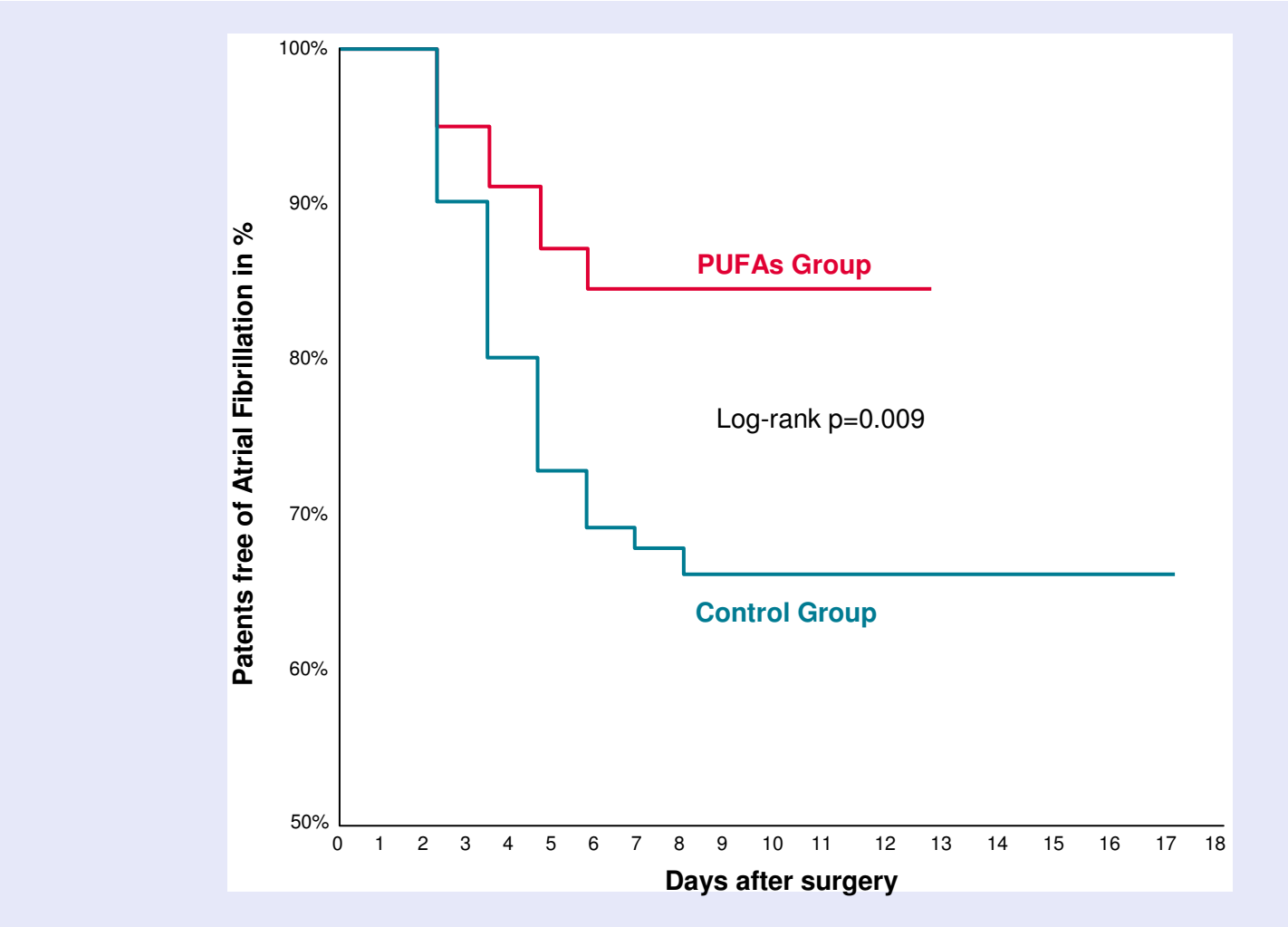
Reference: Macchia A. et al. Circulation 2007;116:II_518-II_519

Calo et al.

Post-Bypass sugery Atrial Fibrillation

Post Bypass Operation Atrial Fibrillation reduced by Omacor®

Omacor reduces incidence of post operative atrial fibrillation, n=160 (Calo, 2005)



Note: The Kaplan-Meier acturial estimates of occurrence postoperative atrial fibrillation in the study group. PUFA= n-3 polyunsaturated fatty acids

Reference: Calo L et al, J Am Coll Cardiol 2005;45:1723-8

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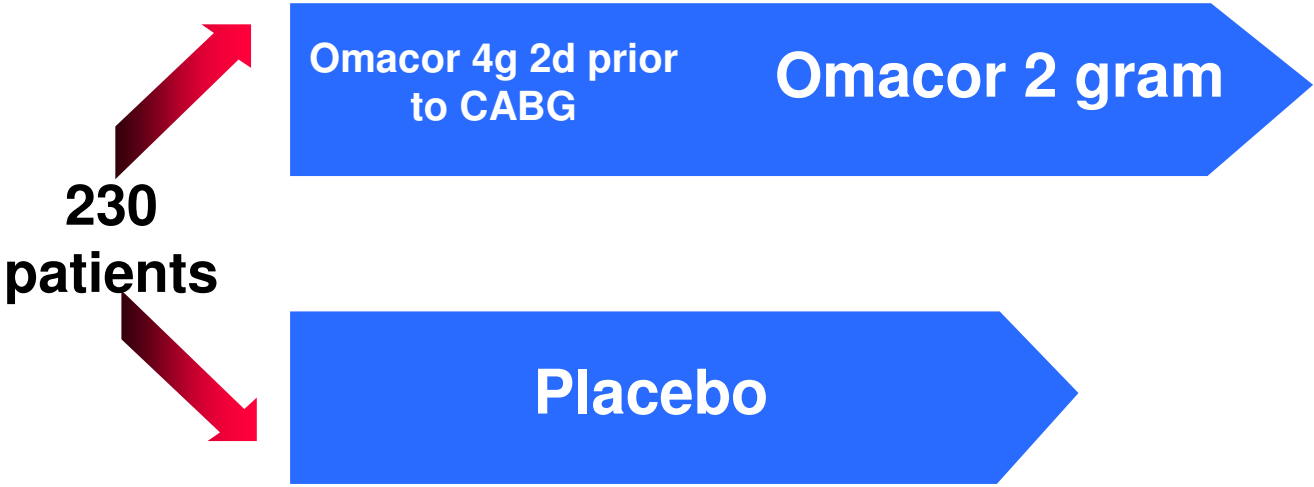
Ongoing AF trials with Omacor®

1. AF after a bypass operation-US

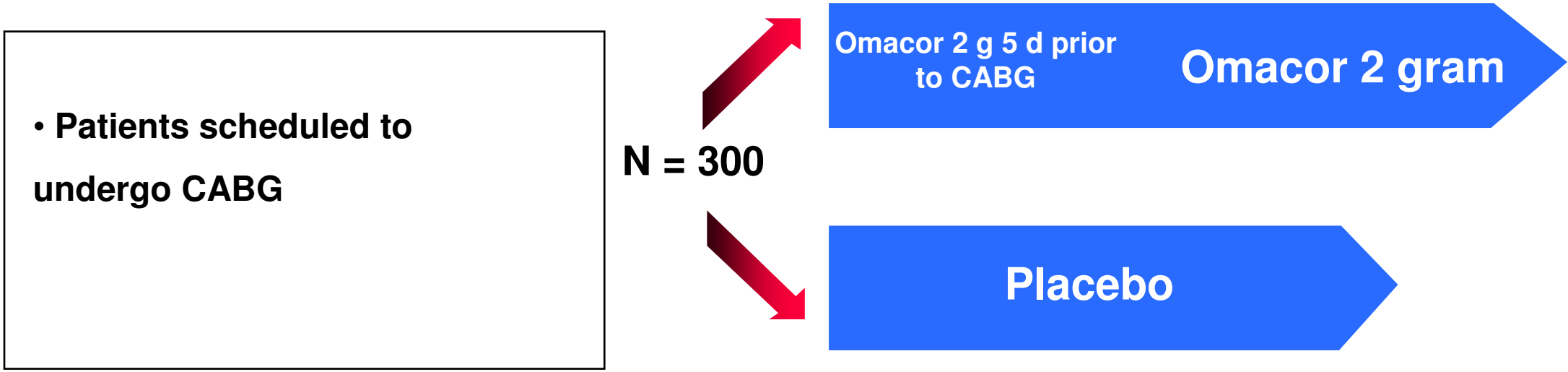
- **Patients > 65 years to be submitted for Coronary Artery Bypass Graft (CABG)**
- **14 day post-CABG treatment**



- **Estimated finished: 2008 ???**

Randomized, double blind, parallel group placebo controlled run in the US

2. AF after a bypass operation CABG – UK



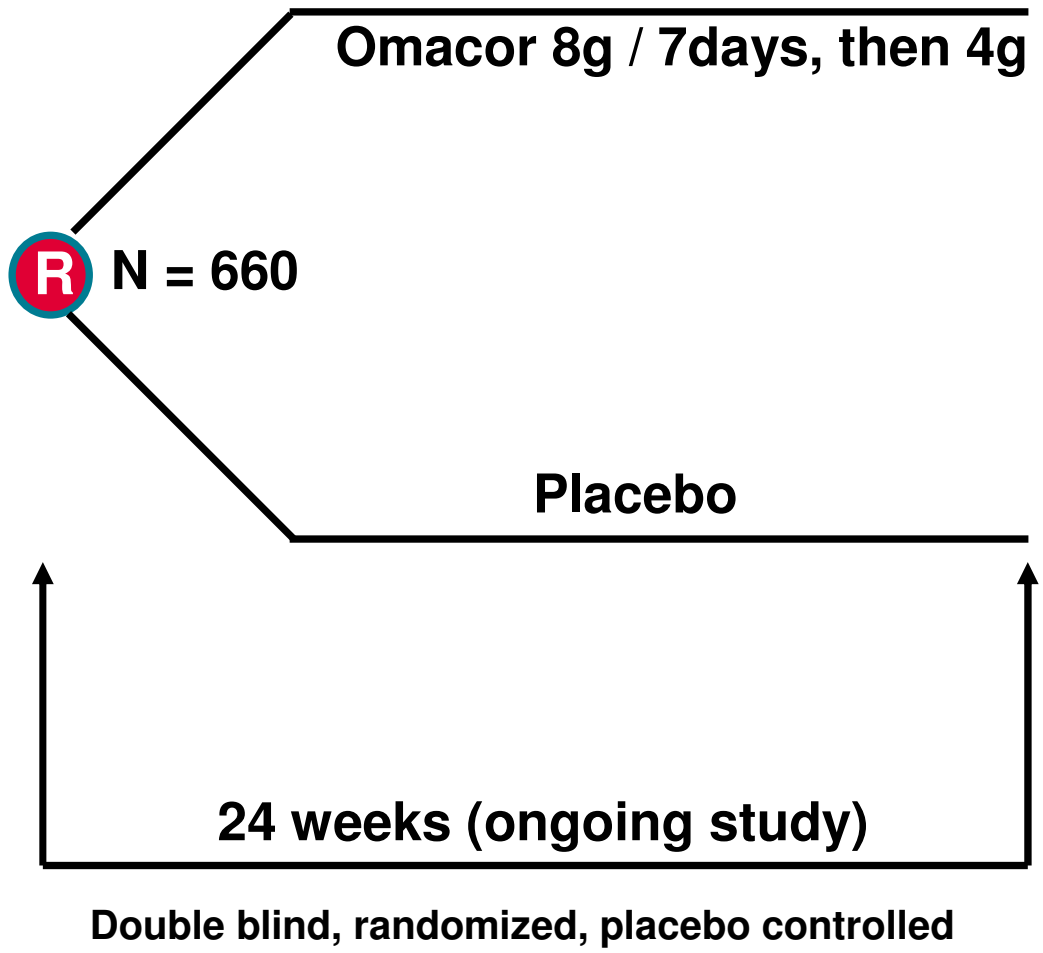
- **Primary endpoint: AF lasting more than 5 minutes**
- **Secondary endpoints: Any AF, any atrial arrhythmia**

- **Treatment time: ?**
- **Status: Planned**

Phase III, single center, double blind, randomized, placebo controlled

3. Paroxysomal Atrial Fibrillation – OM8 (US)

Inclusion: ECG evidence of paroxysmal or persistent atrial fibrillation and older than 18 years



Endpoint: Prevention of atrial fibrillation relapse

Double blind, randomized, placebo controlled

4. Post-DC-cardioversion trial -Italy (SPA-S-891/051)

A controlled study of Omacor vs. Placebo to evaluate the efficiency of Omacor in maintaining sinus rhythm after electroversion in patients with persistent atrial fibrillation

AF after electroversion – Italy

- **Patients with persistent AF requiring electroversion**

N = 144

Omacor 3 g 7 d prior to conversion → **Omacor 2 gram**

Placebo

- **Primary endpoint: # of patients at sinus rhythm at 6 months**
- **Secondary endpoint: Number of AF episodes during follow-up**
- **Treatment time: 6 months**
- **Number of visits: 6**
- **Study report: Q3 2008**

Multicenter, Double blind, randomized, placebo controlled, parallel groups, adaptive design

Conclusion

- Omega-3 trials on AF, inconclusive
- Currently limited data on Omacor®, but, Omacor® studies have been encouraging and there are several trials ongoing

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Thank you for your attention

Discussion/Questions