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Effects of long-term omega-3 polyunsaturated fatty acid supplementation on paroxysmal atrial tachyarrhythmia burden in patients with implanted pacemakers: Results from a prospective randomised study☆,☆☆

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ABSTRACT

Background: Sino-atrial node disease and aging increase AF risk. We investigated if long-term fish oil supplementation reduces paroxysmal atrial tachycardia/fibrillation (AT/AF) burden in patients aged ≥60 years with sinoatrial node disease and dual chamber pacemakers.

Methods: Following a run-in period of 6 months (p1) where AT/AF burden was logged,78 patients were randomised to control or fish oil group(total omega-3 6 g/d) and AT/AF burden evaluated after 6 months(p2; 39 controls, 39 fish oil) and 12 months (p3; 39 controls; 18 fish oil). A subset of 21 fish oil patients crossed over to controls in the final 6 months (crossover group).

Results: Median AT/AF burden increased significantly in controls (1.5%, 3.2%, 4.3%, $P < .001$) but not in fish oil patients at 6 months (1.4% to 2%, $P = .46$) or those continuing for 12 months (1.5%, 0.98%, 1%, $P = .16$). Time to first episode of AT/AF >1 min was not significantly different between the groups ($P = .9$). There was a rebound increase in AT/AF burden in p3 in cross over patients (2.2% to 5.8%, $P = .01$) reaching a level similar to controls (crossover vs. controls, 5.8% vs. 4.3%, $P = .63$) and higher than those who continued fish oil for 12 months (crossover vs. continued intake 5.8% vs. 1.2%, $P = .02$). Fish oil patients had shorter duration episodes of AT/AF with no difference in frequency compared to controls.

Conclusion: Long-term fish oil supplementation did not suppress AT/AF burden but may have attenuated its temporal progression related to aging and sinus node disease.

1. Introduction

Aging and sinoatrial node disease are associated with progressive electrical and structural remodeling of the atria and the pulmonary veins that result in heightened propensity to atrial fibrillation (AF) [1–3]. Current anti-arrhythmic drugs are limited in their efficacy and tolerability in AF management. A concordance of animal studies suggest that omega-3 polyunsaturated fatty acids found in fish oils may be anti-fibrillatory via electrophysiological, autonomic, anti-inflammatory and anti-remodeling effects on the atria [4–9]. Increased fish consumption is associated with a lower risk of incident AF in older adults in long-term epidemiological studies [10,11]. We therefore sought to determine if *long-term* fish oil supplementation in a high-risk population ≥60 years of age with sinus node dysfunction and permanent pacemakers reduces paroxysmal atrial arrhythmia burden. We also evaluated if the effects were mediated by suppression of arrhythmia triggers or reduction in duration of arrhythmia episodes.

2. Methods

2.1. Study population

Inclusion criteria were: (i) age ≥60 years; (ii) dual chamber permanent pacemaker for the treatment of sinus node dysfunction; (iii) ≥2 episodes of paroxysmal atrial tachycardia or fibrillation (AT/AF) per month over the past 1 year; (iv) paroxysmal AT/AF documented on atrial electrograms (EGMs) on pacemaker interrogation and/or ECG and (v) oily fish intake ≤1 portion per week (Fig. 1). Only patients with St. Jude Medical or Medtronic dual chamber pacemakers with advanced capabilities for mode switching and EGM recording were recruited (Supplementary Table 1). All St. Jude devices used the "running atrial average algorithm" which detects AT/AF based on a comparison of

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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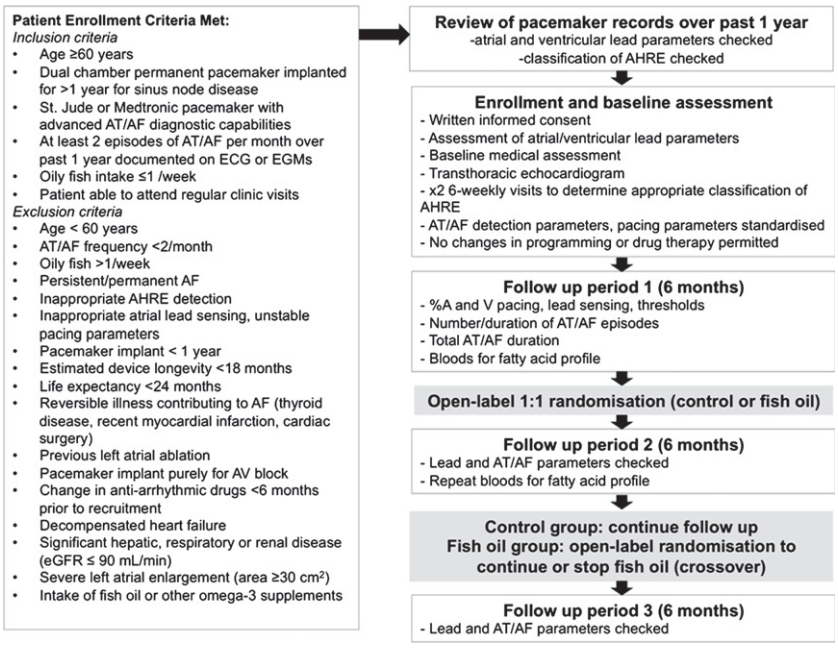

Fig. 1. Study design.

continuously updated filtered atrial rate interval with the programmable maximal atrial tachycardia detection rate [12]. AT/AF detection in all Medtronic devices was based on 4/7 consecutive A–A intervals that are shorter than the programmable detect rate interval for a programmable detect duration [13]. Both algorithms have excellent accuracy for detection of atrial tachyarrhythmias [12,13].

2.2. Study design

This was a prospective, open-label randomised study with patients assigned to control or fish oil groups in a 1:1 fashion. Randomisation was performed using sequentially numbered, opaque, sealed envelopes. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki which was approved by the Melbourne Health Human Research Ethics Committee.

2.2.1. Patient selection

Before recruitment, records of both lead parameters and all atrial high rate episodes (AHRE) over the past 1-yearwere reviewed. These parameters were then prospectively tested in two consecutive clinic visits at least 6 weeks apart (Fig. 1). AHRE were evaluated for appropriate sensing and classified as AT, AF, atrial flutter (AFL), pacemaker-mediated tachycardia, repetitive non-re-entrant atrio-ventricular synchrony or lead noise. Patients with events other than AT or AF were excluded. Recruitment was performed after the second screening visit, where a medical history, physical examination, 12-lead ECG, baseline bloods, transthoracic echocardiogram and pacemaker interrogation was performed (Fig. 1).

All patients included in the study had device implantation at the recruitment center. Bipolar atrial lead implantation was at the right atrial appendage ensuring that P wave amplitude was ≥ 2 millivolts (mV) and atrial capture threshold was ≤1 milliamps (mA) at 0.5 milliseconds (ms) pulse width. Atrial sensitivity was programmed to ≥4 times the threshold value in the bipolar mode after excluding myopotential oversensing (0.1–0.5 mV). Devices used in the study and programming parameters are shown in Supplementary Table 1. No changes in device programming or anti-arrhythmic drugs were permitted during follow up. AT/AF detection rate was set to 180 beats per minute. AF suppression algorithm was programmed 'off' (Supplementary Table 1).

2.3. Follow up

The first six months constituted the run-in period (period 1, p1) at the end of which AT/AF burden was logged (Fig. 2). Patients were then randomised to fish oil or control groups. Fish oil supplementation occurred over the next 6 months (period 2, p2) and the AT/AF burden was logged at the end of p2 in both groups. In the final 6 months (period 3, p3), one half of the fish oil patients were randomly assigned to cross over to the control group (crossover group) and the other half continued fish oil. AT/AF burden was logged in the control, fish oil and crossover groups at the end of p3.

2.3.1. Fish oil supplementation

Fish oil patients were *prescribed* and *dispensed* a triglyceride preparation containing a total of 6 g/day of omega-3 polyunsaturated fatty acids of which 1.8 g/day were eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA), the active components of fish oil (1.02 g EPA and 0.72 g DHA). This dose was chosen to maximise treatment effects, whilst maintaining patient tolerability [15–18]. The duration of supplementation was chosen to maximise myocardial membrane incorporation of EPA and DHA, which is known to occur after 30 days of supplementation [19].

The control groups were not given placebo however were given strict instructions not to commence omega-3 supplements and maintain a stable omega-3 intake. The open-label design was undertaken as the triglyceride preparation had a distinct aftertaste and no placebo with an identical aftertaste was available to us at study initiation.

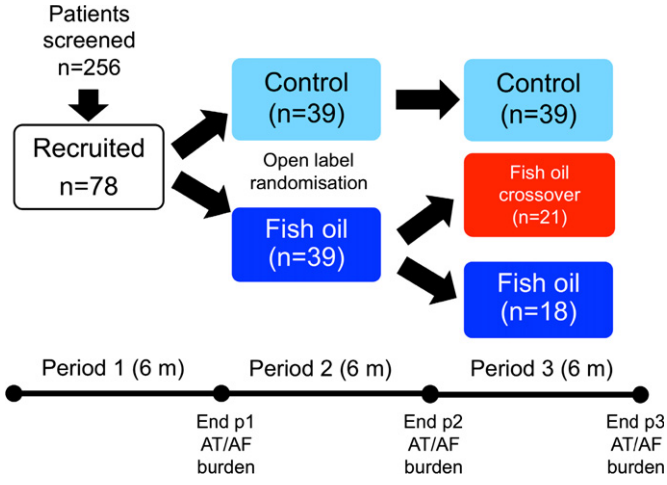

Fig. 2. Patient recruitment and follow up.