N-3 polyunsaturated fatty acids administration does not reduce the recurrence rates of atrial fibrillation and inflammation after electrical cardioversion: a prospective randomized study

N-3 çoklu doymamış yağ asitlerinin kullanımı elektriksel kardiyoversiyon sonrası inflamasyon ve atriyal fibrilasyon nüks oranlarını azaltmaz: Prospektif randomize bir çalışma

Mehmet Özaydın, Doğan Erdoğan, Şenol Tayyar, Bayram Ali Uysal, Abdullah Doğan, Atilla İçli, Emel Özkan[1], Ercan Varol, Yasin Türker[1], Akif Arslan

Department of Cardiology, Faculty of Medicine, Süleyman Demirel University, Isparta
[1]Department of Cardiology, Gülkent State Hospital, Isparta-*Turkey*

ABSTRACT

Objective: The purpose of the present prospective randomized study was to evaluate the effects of n-3 polyunsaturated fatty acids on recurrence rates of atrial fibrillation (AF) and inflammation after electrical cardioversion.
Methods: Calculation of the number of patients needed was based on the assumption of 20% and 65% chance of maintaining sinus rhythm with amiodarone and with polyunsaturated fatty acids, respectively. To observe a significant difference with an alpha level of 0.05 and a power of 0.80 it was necessary to include 22 patients in each group. A total of 47 patients were randomized to amiodarone (n=24) and amiodarone plus n-3 polyunsaturated fatty acids (n=23) groups before scheduled electrical cardioversion. The end-point was the recurrence of AF during 12-month follow-up. Effect of n-3 polyunsaturated fatty acids on inflammation was evaluated with high sensitivity C-reactive protein level measurements. Statistical analysis was performed using unpaired Student' t, Mann Whitney U and Chi-square tests. We analyzed the recurrence of AF using the Cox proportional hazards regression model to control for potentially confounding factors.
Results: Nine patients in the amiodarone group (37.5%), and 9 patients in the amiodarone plus n-3 polyunsaturated fatty acids group (39.1%) had recurrence of AF during follow-up (p=1). With the Cox proportional model, risk factors for the recurrence of AF were previous electrical cardioversion (HR 10.33, 95% CI 1.74 to 61.10, p=0.01) and high sensitivity C-reactive protein levels (HR 1.07, 95% CI 1.02 to 1.38, p=0.007). High sensitivity C-reactive protein levels at baseline, at day 15 and during AF recurrence were similar between two groups (p > 0.05 for all).
Conclusion: N-3 polyunsaturated fatty acids administration does not reduce the recurrence rates of atrial fibrillation and inflammation.
(Anadolu Kardiyol Derg 2011; 11: 305-9)
Key words: Atrial fibrillation, recurrence, polyunsaturated fatty acids, Cox proportional regression analysis

ÖZET

Amaç: Bu prospektif randomize çalışmanın amacı, n-3 çoklu doymamış yağ asitlerinin elektriksel kardiyoversiyon sonrası atriyal fibrilasyon (AF) nüksü üzerine olan etkilerini araştırmaktır.
Yöntemler: Gerekli hasta sayısı, sinüs ritmi idamesinin amiyodaron grubunda %20, yağ asidi grubunda %65 olacağı tahmin edilerek hesaplandı. Alfa değeri 0.05 ve güç %80 olacak şekilde anlamlı sonuç elde etmek için her bir grupta 22 hastanın gerekli olduğu bulundu. Toplam 47 hasta elektriksel kardiyoversiyon öncesi amiyodaron (n=24) ve amiyodaron+n-3 çoklu doymamış yağ asidi (n=23) gruplarına randomize edildiler. Sonlanım noktası 12 aylık takipte AF nüksü olarak belirlendi. N-3 çoklu doymamış yağ asitlerinin inflamasyon üzerine olan etkisi C-reaktif protein düzeylerinin ölçülmesi ile değerlendirildi. İstatistiksel analiz eşleştirilmemiş Student t-testi, Mann-Whitney U testi Ki-kare testi ile yapıldı. Atriyal fibrilasyon nüksü, potansiyel etkili faktörleri kontrol ederek Cox oransal regresyon modeli ile değerlendirildi.
Bulgular: Amiyodaron grubundaki 9 hastada (%37.5) ve amiyodaron+n-3 çoklu doymamış yağ asidi grubundaki 9 hastada (%39.1) nüks gözlendi (p=1). Cox regresyon analizinde, nüks için risk faktörleri önceden elektriksel kardiyoversiyon yapılmış olması (izafi risk 10.33; %95 GA 1.74-61.10;

Address for Correspondence/Yazışma Adresi: Dr. Mehmet Özaydın, Department of Cardiology, Faculty of Medicine, Süleyman Demirel University, Isparta-*Turkey* Phone: +90 246 232 44 79 Fax: +90 246 218 01 63 E-mail: mehmetozaydin@hotmail.com
Accepted Date/Kabul Tarihi: 29.12.2010 **Available Online Date/Çevrimiçi Yayın Tarihi:** 05.05.2011

doi:10.5152/akd.2011.080

p=0.01) ve yüksek duyarlıklı C-reaktif protein düzeyleri (izafi risk 1.07, %95 GA 1.02-1.38, p=0.007) olarak bulundu. Bazal, 15.günde ve nüks sırasında bakılan çok duyarlı C-reaktif protein düzeyleri iki grupta benzerdi (tümü için p>0.05).
Sonuç: Çoklu doymamış yağ asidi kullanılmasının atriyal fibrilasyon nüksü ve inflamasyon üzerine bir etkisi tespit edilmemiştir.
(Anadolu Kardiyol Derg 2011; 11: 305-9)
Anahtar kelimeler: Atriyal fibrilasyon, nüks, çoklu doymamış yağ asidi, Cox oransal regresyon analizi

Introduction

Previous studies indicated that atrial fibrillation (AF) is associated with inflammation (1-3). Statins, which have anti-inflammatory actions, have been shown to be effective in preventing AF in different patient populations (4-9), including recurrence of AF after electrical cardioversion (EC) (10, 11). N-3 polyunsaturated fatty acids (PUFAs) also have anti-inflammatory actions (12).

However, conflicting results on the effects on the development of AF have been obtained with the use of these agents (13-16).

The aim of the present study was to evaluate the effects of n-3 PUFAs on recurrence of AF after EC.

Methods

Patient population, and study design

The population of the present prospective randomized study was chosen from a group of 67 patients with persistent AF referred to cardioversion between April 2006 and May 2009. From this group, patients with hyperthyroidism (n=3), left atrial thrombi (n=10), unsuccessful cardioversion attempts (n=5), and spontaneous conversion into the sinus rhythm (n=2) were excluded and remaining 47 patients constituted the study population. Therefore, 47 patients (27 women; mean age: 61±11 years; range: 37-81) with persistent AF were enrolled for the study with the aim of EC and were randomized in 1:1 fashion to amiodarone (n=24) and amiodarone plus PUFAs (n=23) groups.

In all the patients, the duration of AF was >48 h. Exclusion criteria included paroxysmal AF episodes; a left atrium size >5.5 cm; moderate to severe heart valve disease; coronary artery disease; unsuccessful cardioversion; New York Heart Association class 3, 4 heart failure; a history of cardiac surgery; acute reversible condition; contraindications to treatment with amiodarone; significant impairment of renal function; pregnancy; lactation; fertile female; age <18 years old; and an ejection fraction <0.30.

The local Ethics Committee approved the study protocol, and all subjects gave written informed consent.

Study protocol

Transthoracic echocardiography and baseline laboratory analysis were performed and electrocardiography was taken before the randomization. Patients were randomized to amiodarone (n=24) and amiodarone plus n-3 PUFAs (n=23) groups. N-3 polyunsaturated fatty acids treatment and amiodarone were started after the cardioversion and both were given during 12-month follow-up or until the recurrence. Amiodarone was given intravenously 1 g/d for the first day, followed by 800 mg/d for the first week, 600 mg/d for the second week, 400 mg/d for the third week and 200 mg/d thereafter. The dose of commercially available n-3 PUFAs was 2 g/d (Marincap, Koçak, Turkey). One capsule of this product is 500 mg (Eicosapentaenoic acid [EPA], 18%; Docosahexaenoic acid [DHA], 12%). All the patients underwent transesophageal echocardiography to rule out the possibility of intracardiac thrombi and patients with detected intracardiac thrombi were excluded from the study. After the EC, anticoagulation with warfarin to achieve an international normalized ratio of 2.0 to 3.0 for at least four weeks was done in all the patients. The dose of warfarin was arranged based on the strict international normalized ratio measurements. EC was performed in the fasting state. Propofol was administered for sedation. R wave-synchronized monophasic direct-current shocks (Zoll) were delivered in all patients with the step-up protocol of 200, 300, and 360 J with anterolateral approach. Successful cardioversion was defined as the presence of sinus rhythm lasting ≥1 minute after the shock. If unsuccessful, 2 anteroposterior shocks of 200 and 360 J were applied. Patients with unsuccessful cardioversion attempts were excluded from the study.

High sensitivity C-reactive protein measurement

High sensitivity C-reactive protein (hsCRP) levels were determined by Immulite 2000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA, US) before the randomization, at day 15 and during recurrence. Normal reference values for hsCRP were 0-1.1 mg/L.

Follow-up

All the patients were seen at each week in the first month, then at each month thereafter, and at any time the patient complained of any symptoms. A 24-hour Holter recording was performed at 1 and 3 months. Electrocardiography and 24-hour Holter recording were also performed at any time the patient had any symptoms. The duration of follow-up was 12 months and the end point of the study was electrocardiographically confirmed recurrence of AF lasting >10 minutes. When recurrence was documented, amiodarone and n-3 PUFAs were discontinued.

Statistical analysis

Statistical analyses were performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 (two-tailed) was considered significant. Continuous variables are expressed as mean±1 SD and categorical variables are presented as percentages. Kolmogorov-Smirnov test was used to test the distribution of numeric variables and variables with normal distribution were compared with unpaired Student t-test (age and body mass index) and those without normal distribution was compared with Mann-Whitney U test (AF duration, ejection fraction, left atrial diameter and baseline hsCRP). Categorical variables were compared with Chi-square test. Serial measurements of hsCRP in each group were compared with Friedman's test.

We analyzed the recurrence of AF using the Cox proportional hazards regression model to control for potentially con-

founding factors. The strength of the association between N-3 PUFAs treatment and the occurrence of AF was represented by hazard ratios (HRs) and accompanying 95% confidence interval (CI). We employed an epidemiological approach and factors that have been shown to be multivariate predictors of AF recurrence in the previous studies (10, 17-19) have been accepted as potential risk factors for the recurrence of AF. Therefore, age, left atrial diameter, treatment with beta-blockers, treatment with statins, body mass index, AF duration, previous EC and hsCRP have been included in the Cox proportional hazards regression model. A p value of <0.05 was considered significant.

Sample size calculation

Calculation of the sample size was performed using InStat (GraphPad Software, Inc. La Jolla, CA, USA) software.

Calculation of the number of patients needed was based on the assumption of 20% and 65% chance of maintaining sinus rhythm at 12 months with amiodarone and with amiodarone plus n-3 PUFAs, respectively. To observe a significant difference with an alpha level of 0.05 and a power of 0.80 it was necessary to include 22 patients in each group.

Results

Baseline characteristics

A total of 47 patients were randomized to amiodarone and amiodarone plus n-3 PUFAs groups before scheduled EC. The baseline characteristics (Table 1) were similar between two groups (p>0.05 for all).

Laboratory findings

HsCRP levels at baseline, at day 15 and during recurrence (Table 2) all were similar in the both groups (p>0.05 for all).

Follow-up findings

Nine patients in the amiodarone group (37.5%), and 9 patients in the amiodarone plus PUFAs group (39.1%) had recurrence during follow-up (p=1). The duration of follow-up was 12 months. One patient in each group lost to follow-up. Three patients in the amiodarone group (12.5%) and 5 patients in the amiodarone plus n-3 PUFAs group (21.7%) developed hyperthyroidism requiring cessation of amiodarone (p=0.46). One patient in the combination group had liver enzyme elevation and amiodarone was also stopped in this patient. One patient in the amiodarone group (4.2%) had transient ischemic attack and one patient in the combination group (4.3%) had ischemic stroke during follow-up (p=1). Hospitalization rates were also similar in the both groups (p=0.7; Table 3).

With the Cox proportional model, risk factors for the recurrence of AF were previous electrical cardioversion (HR 10.33, 95% CI 1.74 to 61.10, p=0.01) and hsCRP levels (HR 1.07, 95% CI 1.02 to 1.38, p=0.007; Table 4).

Discussion

The main finding of the current study is that n-3 PUFAs administration does not reduce the recurrence rates of AF and inflammation after EC.

Conflicting results have been obtained about the effects of fish oil on AF. Data from experimental, epidemiological and randomized studies are controversial.

Hearts from rabbits fed a PUFA-rich diet have demonstrated an increased resistance to stretch-mediated changes in atrial electrophysiological properties. AF episode duration was shorter in rabbits with a high PUFA content in the atrial myocyte membranes (20).

There are two positive epidemiological studies showing antiarrhythmic effects of PUFAs on AF. Mozaffarian et al. (14) conducted a prospective study in 4.815 adults aged ≥65 years. They reported that there was a negative correlation between the consumption of fish oil and the risk of AF. AF risk at hospital discharge records and annual ECGs at 12-year follow-up was 31% lower when fish was consumed ≥5 times weekly. A lower AF incidence was associated with consumption of broiled or baked fish but not fried fish. They noted that frying can increase the content of n-6 and trans fatty acids, and oxidation species. Another study supported the findings of Mozaffarian et al. (14); n-3 PUFA reduced the risk of the hospitalization for AF.

Table 1. Clinical characteristics

Variables	Amiodarone (n=24)	Amiodarone plus PUFAs (n=23)	p*
Age, years	61±11	62±12	0.8
Male gender, n (%)	9 (37.5)	11 (47.8)	0.56
Diabetes mellitus, n (%	5 (20.8)	3 (13)	0.7
Hypertension, n (%)	12 (50)	13 (56.5)	0.77
Ejection fraction, %	60±8 (40-70)	61±7 (40-70)	0.89
Left atrial diameter, mm	44±4 (36-51)	44±4 (34-54)	0.75
Body mass index, kg/m^2	28±4	28.8±5.7	0.7
Duration of atrial fibrillation, day	58±97 (2-365)	103±179 (2-730)	0.86
Previous electrical cardioversion, n (%)	4 (16.7)	8 (34.8)	0.19
Medications use, n (%)			
Beta- blockers	6 (25)	6 (26.1)	1
Calcium antagonists	3 (12.5)	3 (13)	1
Statins	5 (20.8)	7 (30.4)	0.51
ACEIs/ARBs	11 (45.8)	17 (73.9)	0.07

Values are presented as mean±SD (range) or number (percentage)
*Student t- test, Mann-Whitney U test and Chi-square test
ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin receptor blockers, PUFAs - N-3 polyunsaturated fatty acids

Table 2. Laboratory findings

Variables	CRP-baseline	CRP-15th day	CRP recurrence	p*
Amiodarone (n=24)	6.7±11	5.1±7.4	6.5±10.9	0.16
Amiodarone plus PUFAs (n=23)	9.9±16	7.9±22	14±16	0.25

Data are presented as mean±SD
*Friedman's test
CRP - C-reactive protein, PUFAs - N-3 polyunsaturated fatty acids

Table 3. Follow-up findings

Variables	Amiodarone (n=24)	Amiodarone plus PUFAs (n=23)	p*
AF recurrence	9 (37.5%)	9 (39.1%)	1
Hyperthyroidism	3 (12.5%)	5 (21.7%)	0.46
Liver enzyme elevation	-	1 (4.3%)	0.48
Thromboembolism	1 (4.2%)	1 (4.3%)	1
Hospitalization	4 (16.7%)	5 (21.7%)	0.7

Values are presented as mean±SD (range) or number (percentage)
*Chi-square test
AF - atrial fibrillation, PUFAs - N-3 polyunsaturated fatty acids

Table 4. Multivariable predictors of recurrence with Cox proportional regression analysis

Variable	Hazard ratio	95% Confidence intervals	p
Previous electrical cardioversion	10.33	1.74 to 61.10	0.01
HsCRP levels	1.07	1.02 to 1.38	0.007

HsCRP - high sensitivity C-reactive protein

Danish Diet, Health, and Cancer Study (15), Physicians' Health Study (21) Rotterdam study (22), Women's Health Initiative Study (23) and small randomized study (24) were unable to indicate any beneficial effects of fish consumption or PUFAs treatment on AF. Danish Study (15) was a prospective cohort study performed in 47.949 adults aged 50 to 64 years who were free of coronary artery disease at baseline. At a mean follow-up of 5.7 years, there was no benefit on AF with the consumption of fish. Interestingly, the Danish Study (15) and the Physicians' Health Study (21) actually reported a trend toward increased risk of developing AF in those with greater fish intake.

No association was found between fish or omega-3 acid intake and incident AF in a large epidemiological study that included 44.720 participants from the Women's Health Initiative clinical trials who were not enrolled in the dietary modification intervention arm and without AF at baseline (23).

There is only one study that evaluated the effects of PUFAs on AF recurrence after EC: In a placebo-controlled study that enrolled 108 patients with persistent AF, Erdoğan et al. (24) have shown that PUFAs treatment had no effect on the recurrence rate of AF, which is in agreement with the result of the current study.

There is only one positive randomized study indicating beneficial effects of PUFAs on AF: Calo et al. (13) randomized 160 patients undergoing coronary artery bypass surgery to receive PUFAs (fish oil capsules containing 850-882 mg EPA and DHA in a ratio of 1:2, with a dose: 2 g/day) or placebo control, starting 5 days before surgery and continuing until hospital discharge. They reported that the incidence of AF was reduced by PUFAs (p=0.013).

Although previous studies have shown that PUFAs have anti-inflammatory actions (12, 25), however, current study indicated that hsCRP levels, an indicator of inflammation, were similar between PUFAs group and control group.

Mechanisms of action of n-3 PUFAs

Eicosapentaenoic acid and DHA are found in varying proportions in PUFAs extracted from fish oil. N-3 polyunsaturated fatty acids inhibit Na and Ca current and Na^+H^+ exchanger and at higher concentrations, K currents. Thus, may prevent electrical remodeling. They have also anti-inflammatory and anti-oxidant effects and thus may prevent structural remodeling (25). Li et al. (26) have shown that omega-3 fatty acids inhibit I(to), I(Kur) and I(Na) in human atrial patch clamp preparation.

Possible mechanism of negative results obtained in the present study

We used fish oil with a dose of 2 g/d in the present study. One capsule of the commercially available fish oil product used the present study is 500 mg and EPA and DHA ratios are 18% and 12%, respectively. However, fish oil capsules containing 850-882 mg EPA and DHA in a ratio of 1:2, with a dose: 2 g/d were used in the study of Calo et al. (13) the difference in this ratio might be a reason of the negative result. Calo et al. (13) started the fish oil 5 days before the operation and we started it after the EC. We used amiodarone in the both group. These differences might also affect the results. Dietary intake of fish oil might have been higher in the amiodarone group, causing us not to obtain beneficial effect in the combination group. As shown in a previous study (14) more patients in the amiodarone group might have eaten broiled or baked fish and/or more patients in the combination group might have eaten fried fish. Baseline left atrial diameters were higher in the both group (about 45 mm), this might be one of the reasons of the negative results of PUFAs. Follow-up duration is relatively short in the current study. Larger randomized studies with longer duration of follow-up could show positive effect of PUFAs on AF. The results of ongoing prospective randomized studies would be very helpful in this issue (27, 28). Although statistically insignificant compared with amiodarone group, follow-up period was shorter in combination group. Last possible mechanism is that, epidemiological studies that demonstrated no benefit of PUFAs on AF generally enrolled younger patients than studies showing benefit (15, 21); the mean age in negative studies was 56 and 60 years, however, the mean age in CHS study, which showed beneficial effects of PUFAs was 73 years (14). The mean age in the present study is 61 therefore this might also be another mechanism of the negative result in the present study.

Study limitations

The sample size was small. We did not evaluate plasma phospholipid EPA and DHA concentrations. Therefore, the dose of fish oil in the combination group might not be high enough to show a positive effect on AF and inflammation. Atrial fibrillation recurrence represent periodic and widely spaced snapshots of rhythm status, so the information that comes from these periodic assessments addresses prevalence of AF in the population at these time points, not the time when AF may have occurred. This is a continuous variable; it has far more statistical power as a continuous longitudinal repeated measure than a binary variable. However, to overcome this problem, instead of the employed multivariable regression analysis, we employed a Cox analysis. The duration of n-3 PUFAs treatment was too short to have an effect on structural remodeling. It remains controversial as to whether elevated CRP in itself results in electrical remodeling or is a marker of ongoing electrical disturbance. So remodeling

may not be relevant to be dependent on CRP alone. The duration of follow-up was short. It is not a placebo-controlled double-blind trial. We might have missed short-lived asymptomatic paroxysmal AF recurrences between scheduled follow-up visits. However, we did not include patients with paroxysmal and self-terminating AF, the follow-up visits were relatively frequent and we used Holter ECG recording to detect recurrence. The two groups were not perfectly balanced concerning pre-procedural ACEIs/ARBs. However, this variable was inserted in the regression analysis. The study was underpowered because of different patients had to be discontinued amiodarone/PUFA therapy during follow-up. Another potential limitation is that the n-3 PUFAs administration started after the cardioversion. Finally, we did not evaluate possible mechanisms other than inflammation.

Conclusion

N-3 PUFAs administration does not reduce the recurrence rates of AF and inflammation after EC.

Conflict of interest: None declared.

References

1. Kumagai K, Nakashima H, Saku K. The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. Cardiovasc Res 2004; 62: 105-11.
2. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001; 104: 2886-91.
3. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997; 96: 1180-4.
4. Patti G, Chello M, Candura D, Pasceri V, D'Ambrosio A, Covino E, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. Circulation 2006; 114: 1455-61.
5. Özaydın M, Doğan A, Varol E, Kapan S, Tüzün N, Peker O, et al. Statin use before by-pass surgery decreases the incidence and shortens the duration of postoperative atrial fibrillation. Cardiology 2007; 107: 117-21.
6. Marin F, Pascual DA, Roldan V, Arribas JM, Ahumada M, Tornel PL, et al. Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. Am J Cardiol 2006; 97: 55-60.
7. Young-Xu Y, Jabbour S, Goldberg R, Blatt CM, Graboys T, Bilchik B, et al. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. Am J Cardiol 2003; 92: 1379-83.
8. Hanna IR, Heeke B, Bush H, Brosius L, King-Hageman D, Dudley SC Jr, et al. Lipid-lowering drug use is associated with reduced prevalence of atrial fibrillation in patients with left ventricular systolic dysfunction. Heart Rhythm 2006; 3: 881-6.
9. Özaydın M, Türker Y, Erdoğan D, Karabacak M, Doğan A, Varol E, et al. The association between previous statin use and development of atrial fibrillation in patients presenting with acute coronary syndrome. Int J Cardiol 2010; 141: 147-50.
10. Özaydın M, Varol E, Aslan SM, Küçüktepe Z, Doğan A, Öztürk M, et al. Effect of atorvastatin on the recurrence rates of atrial fibrillation after electrical cardioversion. Am J Cardiol 2006; 97: 1490-3.
11. Siu CW, Lau CP, Tse HF. Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. Am J Cardiol 2003; 92: 1343-5.
12. Micallef MA, Garg ML. Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals. Atherosclerosis 2008; 204: 476-82.
13. Calo L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. J Am Coll Cardiol 2005; 45: 1723-8.
14. Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, et al. Fish intake and risk of incident atrial fibrillation. Circulation 2004; 110: 368-73.
15. Frost L, Vestergaard P. N-3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter the Danish Diet, Cancer, and Health Study. Am J Clin Nutr 2005; 81: 50-4.
16. Macchia A, Monte S, Pellegrini F, Romero M, Ferrante D, Doval H, et al. Omega-3 fatty acid supplementation reduces one-year risk of atrial fibrillation in patients hospitalized with myocardial infarction. Eur J Clin Pharmacol 2008; 64: 627-34.
17. Boriani G, Diemberger I, Biffi M, Domenichini G, Martignani C, Valzania C, et al. Electrical cardioversion for persistent atrial fibrillation or atrial flutter in clinical practice: predictors of long-term outcome. Int J Clin Pract 2007; 61: 748-56.
18. Kosior DA, Szulc M, Opolski G, Torbicki A, Rabczenko D. Long-term sinus rhythm maintenance after cardioversion of persistent atrial fibrillation: is the treatment's success predictable? Heart Vessels 2006; 21: 375-81.
19. Blich M, Edoute Y. Electrical cardioversion for persistent or chronic atrial fibrillation: outcome and clinical factors predicting short and long-term success rate. Int J Cardiol 2006; 107: 389-94.
20. Ninio DM, Murphy KJ, Howe PR, Saint DA. Dietary fish oil protects against stretch-induced vulnerability to atrial fibrillation in a rabbit model. J Cardiovasc Electrophysiol 2005; 16: 1189-94.
21. Aizer A, Gaziano JM, Manson JE, Buring JE, Albert CM. Relationship between fish consumption and the development of atrial fibrillation in men. Heart Rhythm 2006; 3: S5.
22. Brouwer IA, Heeringa J, Geleijnse JM. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. Am Heart J 2006; 151: 857-62.
23. Berry JD, Prineas RJ, van Horn L, Passman R, Larson J, Goldberger J, et al. Dietary fish intake and incident atrial fibrillation (from the Women's Health Initiative). Am J Cardiol 2010; 105: 844-8.
24. Erdoğan A, Bayer M, Kollath D, Greiss H, Voss R, Neumann T, et al. Omega AF study: polyunsaturated fatty acids (PUFA) for prevention of atrial fibrillation relapse after successful external cardioversion. Heart Rhythm 2007; 4: S185-6.
25. Savelieva I, Camm J. Statins and polyunsaturated fatty acids for treatment of atrial fibrillation. Nat Clin Pract Cardiovasc Med 2008; 5: 30-41.
26. Li GR, Sun HY, Zhang XH, Cheng LC, Chiu SW, Tse HF, et al. Omega-3 polyunsaturated fatty acids inhibit transient outward and ultra-rapid delayed rectifier K+ currents and Na+ current in human atrial myocytes. Cardiovasc Res 2009; 81: 286-93.
27. Pratt CM, Reiffel JA, Ellenbogen KA, Naccarelli GV, Kowey PR. Efficacy and safety of prescription omega-3-acid ethyl esters for the prevention of recurrent symptomatic atrial fibrillation: a prospective study. Am Heart J 2009; 158: 163-9.
28. Macchia A, Varini S, Grancelli H, Nul D, Laffaye N, Ferrante D et al. The rationale and design of the FORomegaARD Trial: a 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. Am Heart J 2009; 157: 423-7.