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Short Communication

Omega-3 fatty acid supplements and risk of atrial fibrillation and 'micro-atrial fibrillation': A secondary analysis from the OMEMI trial

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SUMMARY

Background & aims: Recent randomized clinical trials have raised concerns regarding potential off target adverse effects from supplementation of n-3 polyunsaturated fatty acids (PUFA) on atrial fibrillation (AF) risk. We aimed to assess risk and potential mediators of AF and 'micro-AF' from n-3 PUFA in post-myocardial infarction (MI) patients.

Methods: In the OMEMI trial, 70–82 y. o. patients with a recent MI were randomized to 1.8 g/day of eicosapentaenoic-/docosahexaenoic acid (EPA/DHA) or placebo (corn oil) for two years. New-onset AF and 'micro-AF' was recorded by clinical detection and by screening with Zenicor thumb-ECG (adjudicated by blinded investigators). Serum EPA and DHA were measured at baseline and study end.

Results: At baseline, 759 of 1014 (75%) patients had no AF history. These patients were aged 75 ± 4 years and 71% were male. During follow-up, 43 patients developed new-onset AF (39 clinically-detected and 4 by thumb-ECG screening). In addition, 27 patients had episodes of micro-AF, yielding a total of 70 patients with new-onset AF or 'micro-AF'. In the n-3 PUFA group 46 (11.9%) had AF/'micro-AF' (28 AF, 18 'micro-AF') and in the placebo group 24 (6.5%) had AF/micro-AF (15 AF, 9 micro-AF); HR 1.90 (95%CI 1.16–3.11), P = 0.011. Changes in serum EPA (but not DHA) mediated the effect from n-3 PUFA on AF risk, explaining 65% of the association.

Conclusion: Supplementation of n-3 PUFA post MI increases the risk of 'micro-AF' and AF, and increases in EPA seems to be an important mediator of the treatment effect from n-3 PUFA on the risk of AF.

Study registration: OMEMI Study; ClinicalTrails.gov identifier: NCT0184194.

1. Introduction

Long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA) have been proposed to have antiarrhythmic properties based on experimental studies, observational data and small clinical trials [1]. However, results from recent larger clinical trials have consistently demonstrated an increased risk of atrial fibrillation (AF) in patients randomized to n-3 PUFA and there seems to be a dose–response relationship with a 50% increased risk in high-dose trials and 12% increased risk in trials using ≤1 g daily [2,3]. Nonetheless, mechanisms underlying the increased AF risk from n-3 PUFA supplementation are unclear [4]. "Micro-AF" represents short AF-like activity and is associated with subsequent new-onset AF and increased risk of cardiovascular events [5,6]. In this study we aimed to assess the effect of n-3 PUFA on screen-detected "micro-AF" and AF, and the associations with changes in serum eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

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2. Material & methods

The OMega-3 fatty acids in Elderly patients with Myocardial Infarction (OMEMI) trial (NCT01841944) was a randomized, placebo-controlled trial testing the effect of 1.8 g/day of EPA/DHA on cardiovascular events in patients aged 70–82 years with a recent acute myocardial infarction (AMI) [7]. New-onset AF was the secondary endpoint. Serum EPA and DHA levels were analyzed by gas chromatography at randomization and after 24 months and presented as percent weight (%wt) of total fatty acids in serum phospholipids [8]. Electronic health records from hospitalizations and primary care visits were reviewed for incident AF (with date of occurrence) and a 12-lead ECG was obtained after 3, 12 and 24 months. A hand-held single-lead rhythm monitoring for 30 s twice daily for 14 consecutive days was performed at the 12-month visit (Zenicor Medical Systems AB, Stockholm, Sweden), and results were evaluated by two investigators blinded to treatment allocation and clinical data. "Micro-AF" represents short AF-like activity, defined as sudden onset episodes of ≥3 consecutive supraventricular beats, irregular RR-intervals, and absence of p-waves, lasting <30 s [6]. We used logistic regression to analyze for the association between treatment arm, changes in serum EPA/DHA and incident AF or "micro-AF". Changes in serum EPA and DHA, heart rate, blood pressure, body weight and triglycerides were analyzed in a mediation analysis of treatment allocation and incident "micro-AF"/AF by calculating the proportional reduction in magnitude of the β-coefficient. Changes in EPA were analyzed in association with "micro-AF"/AF in multivariable logistic regression models including age, sex, current smoking, body mass index, systolic blood pressure, heart rate, New York Heart Association functional class, hypertension, diabetes, heart failure, previous acute myocardial infarction, and previous coronary revascularization. OMEMI was approved by the Regional Medical Research Ethics Committee (#2012/1422). Requests for data sharing will be handled according to the regulation by the Data Protection Officer at Oslo University Hospital.

3. Results

After excluding 154 patients with established AF and 101 patients with new-onset AF during the index MI, 759 (75%) patients had no history of AF at randomization 2–8 weeks after discharge. These patients were aged 75 ± 4 years and 542 (71%) were male. The baseline concentrations of EPA and DHA were (mean ± SD) 2.8 ± 1.4%wt and 5.7 ± 1.4%wt, respectively. During 24 months follow-up, 43 cases of new-onset AF occurred, of which four were detected by the ECG-screening (available in n = 566). In addition, 27 cases of "micro-AF" were detected from ECG-screening, none of which had AF. Patients randomized to n-3 PUFA developed more AF (28 [7.2%] vs 15 [4.0%]) and micro-AF (18 [6.1%] vs 9 [3.3%]), with a total of 90% greater relative risk for the combined outcome of AF/"micro-AF": OR 1.96 (95%CI 1.17–3.28), P = 0.011 (Fig. 1), and this persisted in multivariable models (Suppl. Table 1). Patients with incident AF/"micro-AF" experienced greater increases in serum EPA from baseline to 24 months compared to those without AF (mean ± SD) 1.6 ± 2.4%wt vs 1.0 ± 2.1%wt, p = 0.035. In the total population, serum EPA increased 114% (1.8 ± 2.5%wt) in patients with incident AF, 81% (1.2 ± 2.2%wt) in patients with "micro-AF" and 56% (1.0 ± 2.1%wt) in patients without AF (Table 1). In patients randomized to n-3 PUFA, patients with incident AF, "micro-AF" and no-AF, serum EPA increased by 182% (3.4 ± 1.4%wt), 128% (2.1 ± 2.0% wt) and 117% (2.4 ± 1.9%wt), respectively. There were no associations between changes in serum DHA and risk of AF/"micro-AF": 0.5 ± 1.6%wt vs 0.3 ± 1.3%wt, p = 0.18. Greater changes in EPA were primarily driven by treatment with n-3 PUFA (Suppl. Table 2). In multivariable models with established risk factors, changes in EPA persisted as an independent predictor of "micro-AF"/AF (OR 1.38 (95%CI 1.12–1.69, P = 0.002) (Fig. 2). In a mediation analysis, increases in EPA explained 69% of the "micro-AF"/AF risk associated with n-3 PUFA treatment, and was the strongest mediator (Table 2).

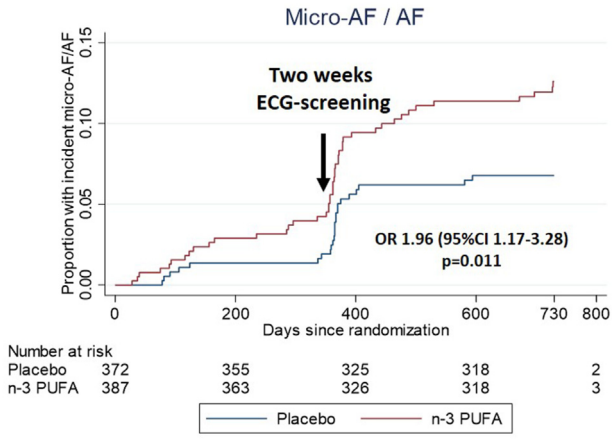

Fig. 1. Cumulative incidence of atrial fibrillation (AF) and "micro-AF" in patients randomized to n-3 polyunsaturated fatty acids (PUFA) or placebo. Screening with a hand-held single-lead rhythm monitoring for 30 s twice daily for 14 consecutive days was performed at the 12-month visit.

4. Discussion

We report the following novel findings from the OMEMI trial: 1) n-3 PUFA supplementation increased the risk of "micro-AF" similar to that of AF; 2) there was a graded relationship between increment in serum EPA (but not DHA) and AF severity, with the greatest increase in patients with incident AF and intermediate values in patients with "micro-AF"; 3) changes in serum EPA was the strongest mediator of AF risk from n-3 PUFA.

Data from large randomized control trials suggest an increased risk of AF from n-3 PUFA supplementation compared to placebo. The risk of AF appear greatest in the trials testing higher doses of n-3 PUFA [2]. In STRENGTH and REDUCE-IT, which used 4 g/day of n-3 PUFA, the increase in AF risk was 69% (2.2% vs 1.3%) and 35% (5.3% vs

Table 1
Relative changes in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from baseline to 24 months in patients without incident AF, patients with "micro-AF" and patients with incident AF. Presented are the results for the total study population and in patients randomized to n-3 PUFA only.

Both treatment arms

	No AF	Micro AF	AF
EPA absolute change, %wt	1.0 ± 2.1	1.2 ± 2.2	1.8 ± 2.5
EPA relative change	60 %	80 %	110 %
DHA absolute change, %wt	0.3 ± 1.3	0.6 ± 1.4	0.5 ± 1.7
DHA mean relative change	10 %	20 %	10 %

n-3 PUFA arm only

	No AF	Micro AF	AF
EPA absolute change, %wt	2.4 ± 1.9	2.1 ± 2.0	3.4 ± 1.4
EPA relative change	120 %	130 %	180 %
DHA absolute change, %wt	1.0 ± 1.2	1.2 ± 1.4	1.4 ± 1.2
DHA mean relative change	20 %	30 %	30 %

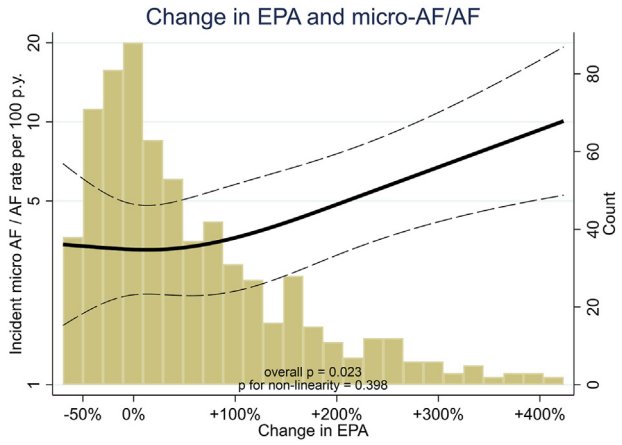

Fig. 2. Association between changes in serum eicosapentaenoic acid (EPA) from before randomization to the end of the study in association with incident "micro-AF" or AF. The model is adjusted for age, sex, current smoking, body mass index, systolic blood pressure, heart rate, New York Heart Association functional class, hypertension, diabetes, heart failure, previous acute myocardial infarction and previous coronary revascularization.

Table 2
Mediation analysis of treatment allocation (n-3 PUFA vs placebo) and incident "micro-AF"/AF by calculating the proportional reduction in magnitude of the β-coefficient from logistic regression models. Restricted to patients with all variables available (n = 653).

	β coefficient (95% CI)	Proportion of association mediated
Unadjusted treatment effect	*0.52 (-0.02 to 1.06)*	-
adjust: demographics/comorbidities	0.49 (−0.07 to 1.04)	6%
adjust: weight change	0.55 (0.01−1.10)	−6%
adjust: blood pressure change	0.52 (−0.02 to 1.07)	0%
adjust: heart rate change	0.69 (0.13−1.25)	−33%
adjust: triglycerides change	0.52 (−0.03 to 1.08)	−0%
adjust: EPA change	0.16 (−0.49 to 0.80)	69%
adjust: DHA change	0.32 (−0.31 to 0.95)	38%

Abbreviations: EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

3.9%) compared to placebo, respectively [9,10]. In trials testing 1 g/day there was only a non-significant trend towards an increased risk. In OMEMI, using 1.8 g/day, there was a close to significant (p = 0.056) 84% (7.2% vs 4.0%) increased risk of new-onset AF [7], and this was more pronounced in patients with greater increase in serum EPA [8]. We now add novel data on the effect of n-3 PUFA supplementation on screen-detected micro-AF in addition to the association between changes in serum EPA and DHA with the risk of micro-AF and AF.

"Micro-AF" is a risk factor for the development of AF and cardiovascular risk. In the STROKESTOP study, 50% of those with 'micro-AF' developed AF after two years of follow-up [6]. In the Copenhagen Holter Study, excessive supraventricular ectopic activity was associated with an increased risk of stroke and death [11]. In OMEMI, we have previously reported that "micro-AF" was associated with an almost 3-fold increased risk of MACE [5]. By screening older adults with a recent AMI, we detected 5% "micro-AF" and it was twice as common in patients randomized to n-3 PUFA vs placebo. This adds knowledge to findings from clinical trials suggesting a causal association between n-3 PUFA supplementation and AF [2]. The graded associations between changes in EPA and the risk of "micro-AF" and AF supports a dose−response-relationship. In contrast, we found no significant association between changes in DHA and "micro-AF"/AF. The mechanisms explaining the increased risk of AF from n-3 PUFA is unknown, although increased parasympathetic cardiac tone and heart rate variability may favor macro-reentry activity [12]. However, in our study, changes in heart rate and blood pressure was not a mediator of "micro-AF"/AF from n-3 PUFA supplementation, in contrast to changes in EPA which explained 69% of the association. Limitations include lack of continuous rhythm monitoring, which may have impacted the detection rate of both "micro-AF" and AF. "Micro-AF" is not an established medical concept and its clinical importance should be further investigated. Although our data are from a randomized placebo-controlled trial, the analysis is secondary with limited power, which reduces our ability to claim causation.

5. Conclusion

Our results suggest that supplementation with 1.8 g/day of n-3 PUFA not only increases the risk of AF, but also micro-AF after AMI. There seems to be a graded association between the increases in serum EPA and the risk of micro-AF and AF. These findings suggest caution in using n-3 PUFA supplementation for prevention of cardiovascular disease, especially formulas that have not been shown to reduce atherosclerotic events.

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Contribution of each author

P.L.M., **T.B.** and **A.T.** designed this OMEMI-substudy, performed data analysis and prepared the manuscript. **P.L.M.**, **A.A.K.**, **S.H.T.** and **K.L.** enrolled and monitored the participants in the OMEMI trial, and critically reviewed the manuscript. **E.B.S.** did the serum analysis of EPA and DHA and critically reviewed the manuscript. **S.S.**, **H.A.** and **I.S.** designed the OMEMI trial and critically reviewed the manuscript.

Conflicts of interest

P.L.M. has consulted for and/or received speaker fees from Amarin, AmGen, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Novartis, Novo Nordisk, Pharmacosmos, Vifor and Us2. ai. T.B. has received speaker fees from Boehringer-Ingelheim, Bayer and Pfizer/Bristol-Myers Squibb, outside the submitted work. S.S. has received consulting fees from Amarin. All other authors report no disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.07.002.

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