



UNIVERSITY
OF WOLLONGONG
AUSTRALIA

University of Wollongong
Research Online

Graduate School of Medicine - Papers (Archive)

Faculty of Science, Medicine and Health

2011

Sound assessment of a role for fish oil in therapeutics or prevention of cardiovascular disease jeopardised by confused study design

Peter L. McLennan

University of Wollongong, petermcl@uow.edu.au

Publication Details

McLennan, P. L. (2011). Sound assessment of a role for fish oil in therapeutics or prevention of cardiovascular disease jeopardised by confused study design *British Medical Journal United Kingdom* : BMJ Group. (Review)

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library:
research-pubs@uow.edu.au

Sound assessment of a role for fish oil in therapeutics or prevention of cardiovascular disease jeopardised by confused study design

Abstract

The study by Galan and colleagues in the SU.FOL.OM3 collaborative group has added further confusion to the omega-3 story, which in this case largely derives from confusion in the study design. Confusion about the likely mechanism of cardiovascular protection and hence expected outcomes; confusion in the subject selection; confusion about the timing of intervention; confusion about the active components of fish oil.

Keywords

sound, study, confused, jeopardised, disease, cardiovascular, prevention, therapeutics, oil, fish, role, assessment, design

Disciplines

Medicine and Health Sciences

Publication Details

McLennan, P. L. (2011). Sound assessment of a role for fish oil in therapeutics or prevention of cardiovascular disease jeopardised by confused study design British Medical Journal United Kingdom : BMJ Group. (Review)

Sound assessment of a role for fish oil in therapeutics or prevention of cardiovascular disease jeopardised by confused study design

8 January 2011

The study by Galan and colleagues in the SU.FOL.OM3 collaborative group has added further confusion to the omega-3 story, which in this case largely derives from confusion in the study design. Confusion about the likely mechanism of cardiovascular protection and hence expected outcomes; confusion in the subject selection; confusion about the timing of intervention; confusion about the active components of fish oil.

First: epidemiology emphasises reduced cardiovascular mortality with fatty fish consumption, especially from sudden cardiac (arrhythmic) death and heart failure. (1-4) Intervention trials that demonstrate reduced mortality often do so without preventing new ischaemic events. (5-6) This study population, by including acute coronary syndrome (ACS) and stroke in addition to post-MI patients demonstrates the primary expectation of ischaemia prevention and as a result includes less than 50% of subjects with a clear arrhythmic substrate or heart failure predisposition. This resulted in inclusion of mainly vascular primary endpoints including: non-fatal myocardial infarction; ischaemic stroke; death from fatal myocardial infarction or stroke; and aortic dissection (ACS was a secondary endpoint). What is the experimental evidence to suggest that fish oil can modify these events at low intakes? In contrast, experimental evidence suggests that the cardioprotective effects of fish oil are due primarily to their influence on cardiac function, which is dependent on omega-3 polyunsaturated fatty acid (PUFA) incorporation into myocardial cell membranes (7-8) producing intrinsic cardiac outcomes. (6,9) There can be little expectation that the unstable angina and especially stroke patients will have an arrhythmic episode or heart failure that might be prevented by low dose omega-3 PUFA. Similarly, although ACS may be prevented by regular fish intake, (10) and there is an experimental basis for altered myocardial response to ischaemia and reperfusion by nutritional preconditioning, (11-12) (not reduced incidence of ischaemia), the likelihood of identifying a change in ACS is diluted by the >70% stroke and post-MI patients in the study population.

Secondly: as noted by the authors, the mean interval between MI and entry into the study was 101 days. In the GISSI-P study subjects were recruited immediately post-MI (mean 16 days) and fatal arrhythmia prevention occurred early, with a significant difference in arrhythmic death evident by 120 days (close to the mean time of initial recruitment for subjects in this study). (6,13)

Thirdly: the fish oil preparation contained omega-3 PUFA predominantly as the fatty acid EPA. Considering the importance of omega-3 PUFA incorporation into membranes to modify heart function and ischaemic vulnerability, the principal omega-3 PUFA in the heart is undoubtedly DHA,(14,15) and animal studies show that, when provided in the diet in low doses, pure DHA is antiarrhythmic but pure EPA is not. (16) Similarly, preferential effects of DHA have been reported in several human conditions modified by fish oils. Although the omega-3 PUFA product used in the GISSI studies had EPA>DHA, it provided 380 mg DHA daily, almost double the dose used in this study. (6,9)

Fourthly: and not specific to this study, is the common consideration of EPA and DHA as equivalent and interchangeable. It is notable that the majority of food fish provide DHA in excess of EPA. (15) This may be an important contributor to the negative outcomes of this and other low-dose intervention studies which use high EPA oils (17) and which may not provide sufficient DHA to reproduce the effects associated with dietary habits in epidemiology.

Intervention trials such as this will likely continue to fail to reproduce the promise of the epidemiology and experimental studies and fail to translate them into clinical practice while they fail to reproduce the conditions revealed by those studies. By consistently looking for outcomes that are not supported by experimental evidence and biological plausibility or predicted by epidemiology, and in failing to reproduce the fatty acid intakes typical of dietary intake from fish, they are setting themselves up to fail. Before the concept of fish oil intervention for cardioprotection is rejected, it is important that some low-dose intervention trials are instigated that use a DHA intake more consistent with regular consumption of fish and address evidence-based biologically plausible mechanisms using appropriate subject groups in each case.

1. Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *J.A.M.A.* 1995;274(17):1363-67.
2. Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, et al. Fish consumption and risk of sudden cardiac death. *J.A.M.A.* 1998;279(1):23-28.
3. Mozaffarian D, Bryson CL, Lemaitre RN, Burke GL, Siscovick DS. Fish intake and risk of incident heart failure. *J. Am. Coll. Cardiol.* 2005;45(12):2015-21.
4. Streppel MT, Ocke MC, Boshuizen HC, Kok FJ, Kromhout D. Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen study. *European Heart Journal* 2008;29(16):2024-30.

5. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2(8666):757-61.
6. Valagussa F, Franzosi MG, Geraci E, Mininni N, Nicolosi GL, Santini M, et al. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354(9177):447-55.
7. McLennan PL, Abeywardena MY. Membrane basis for fish oil effects on the heart: Linking natural hibernators to prevention of human sudden cardiac death. *J. Memb. Biol.* 2005;206:85-102.
8. McLennan PL, Owen AJ, Slee EL, Theiss ML. Myocardial Function, Ischaemia and n-3 Polyunsaturated Fatty Acids: A membrane basis. *J. Cardiovasc. Med.* 2007 8 (suppl 1):S15-S18.
9. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372(9645):1223-30.
10. Bierregaard LJ, Joensen AM, Dethlefsen C, Jensen MK, Johnsen SP, Tjønneland A, et al. Fish intake and acute coronary syndrome. *European Heart Journal* 2010;31(1):29-34.
11. Abdukeyum GG, Owen AJ, McLennan PL. Dietary (n-3) Long-Chain Polyunsaturated Fatty Acids Inhibit Ischemia and Reperfusion Arrhythmias and Infarction in Rat Heart Not Enhanced by Ischemic Preconditioning. *J. Nutr.* 2008;138(10):1902-09.
12. Pepe S, McLennan PL. Cardiac Membrane Fatty Acid Composition Modulates Myocardial Oxygen Consumption and Post-Ischemic Recovery of Contractile Function. *Circulation* 2002;105(19):2303-08.
13. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the GISSI-Prevenzione. *Circulation.* 2002;105(16):1897-903.
14. Rocquelin G, Guenot L, Astorg PO, David M. Phospholipid content and fatty acid composition of human heart. *Lipids.* 1989;24(9):775-80.
15. Slee EL, McLennan PL, Owen AJ, Theiss ML. Low dietary fish oil threshold for myocardial membrane n-3 PUFA enrichment independent of n-6 PUFA intake in rats. *J. Lipid Res.* 2010;51:1841-48.
16. McLennan P, Howe P, Abeywardena M, Muggli R, Raederstorff D, Mano M, et al. The cardiovascular protective role of docosahexaenoic acid. *Europ. J. Pharmacol.* 1996;300(1-2):83-89.
17. Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial G. n-3 Fatty Acids and Cardiovascular Events after Myocardial Infarction. *N. Engl. J. Med.* 2010;363(21):2015-26.

Competing interests: Over the past 20 years, PMcL has received: payment for speaking at symposia by Abbott Pharmaceuticals, manufacturers of Omacor; reimbursement for travel costs and conference fees from Clover Corporation, manufacturers of high DHA tuna fish oil, and from Solvay Pharmaceuticals (Omacor); research funding from Roche Vitamins, manufacturers of RoPUFA-30 (fish oil) and purified EPA and DHA ethyl esters and from Clover Corporation, manufacturers of high DHA tuna fish oil; and gifts of RO-PUFA 30 and EPA & DHA ethyl esters from Roche Vitamins, Shaklee EPA from Shaklee Corporation, and High DHA tuna fish oil from Clover Corporation for use in research.

Peter L. McLennan, Professor of Physiology

Graduate School of Medicine, University of Wollongong, Australia

BMJ Group

© 2012 BMJ Publishing Group Ltd