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| ***Should you still recommend omega-3 supplements? J Fam Pract*. 2013;62:422-424.** |
| **Potential PURL Review Form: Meta-analysis** |
| **SECTION 1: IDENTIFYING INFORMATION** |
| **1.** Citation  | Rizos EC, Ntzani EE, Bika E, et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012;308:1024-1033. |
| **2.** Hypertext link to PDF of full article  | http://jama.jamanetwork.com/article.aspx?articleid=1357266 |
| **3.** First date published study available to readers  | September 12, 2012 |
| **4.** PubMed ID  | 22968891 |
| **5.** Nominated By  | Kate Rowland  |
| **6.** Institutional Affiliation of Nominator  | University of Chicago  |
| **7.** Date Nominated  | August 25, 2012 |
| **8.** Identified Through  | TOC |
| **9.** PURLS Editor Reviewing Nominated Potential PURL | Kate Rowland |
| **10.** Nomination Decision Date  | September 20, 2012 |
| **11.** Potential PURL Review Form (PPRF) Type  | Meta-analysis |
| **12.** Other comments, materials or discussion  |   |
| **13.** Assigned Potential PURL Reviewer  | Jen Bello |
| **14.** Reviewer Affiliation  | University of Chicago |
| **15.** Date Review Due  | October 18, 2012 |
| **16.** Abstract  | **CONTEXT:**Considerable controversy exists regarding the association of omega-3 polyunsaturated fatty acids (PUFAs) and major cardiovascular end points.**OBJECTIVE:**To assess the role of omega-3 supplementation on major cardiovascular outcomes.**DATA SOURCES:**MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through August 2012.**STUDY SELECTION:**Randomized clinical trials evaluating the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke.**DATA EXTRACTION:**Descriptive and quantitative information was extracted; absolute and relative risk (RR) estimates were synthesized under a random-effects model. Heterogeneity was assessed using the Q statistic and I2. Subgroup analyses were performed for the presence of blinding, the prevention settings, and patients with implantable cardioverter-defibrillators, and meta-regression analyses were performed for the omega-3 dose. A statistical significance threshold of .0063 was assumed after adjustment for multiple comparisons.**DATA SYNTHESIS:**Of the 3635 citations retrieved, 20 studies of 68,680 patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 myocardial infarctions, and 1490 strokes. No statistically significant association was observed with all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; risk reduction [RD] -0.004, 95% CI, -0.01 to 0.02), cardiac death (RR, 0.91; 95% CI, 0.85 to 0.98; RD, -0.01; 95% CI, -0.02 to 0.00), sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; RD, -0.003; 95% CI, -0.012 to 0.006), myocardial infarction (RR, 0.89; 95% CI, 0.76 to 1.04; RD, -0.002; 95% CI, -0.007 to 0.002), and stroke (RR, 1.05; 95% CI, 0.93 to 1.18; RD, 0.001; 95% CI, -0.002 to 0.004) when all supplement studies were considered.**CONCLUSION:**Overall, omega-3 PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association. |
| **sECTION 2: CRITICAL APPRAISAL OF VALIDITY** |
| **1.** What types of studies are included in this review? | Randomized controlled trials (RCTs) |
| **2.** What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses. | What is the association between omega-3 polyunsaturated fatty acids (PUFAs) and major patient-important cardiovascular outcomes? Outcomes: all-cause mortality, cardiac death, sudden death, myocardial infarction (MI), and all types of stroke. Treatment: omega-3 in diet or supplements. Trials: 20 RCTs (compared with placebo or another diet), n=68,680 treatment in primary or secondary cardiovascular disease (CVD) prevention, treatment for longer than one year. Presented meta-analysis of all studies with summary of risk of bias. Searched PubMed, EMBASE, and Cochrane Central Register of Controlled Trials for studies from 1989 through 2012. Main analyses: 1. omega-3 administration through diet, 2. omega-3 administration through supplement, 3. each individual outcome. Subgroup analyses: 1. patient history of CVD (primary vs secondary prevention), 2. presence of ICD. Meta-regression: using administered omega-3 dose as a continuous variable. Random-effects methods. Publication bias: looked at funnel plots, Begg-Mazumbar test (rank correlation method), trim-and-fill approach to get adjusted effect size taking publication bias into account. Statistical signicance at *P*=.0063 adjusting for multiple comparisons.Results: Administration through diet - 2 studies, open-label, 5147 participants of European descent, doses >1 g for secondary prevention (2-5 years of follow-up). All-cause mortality and cardiac death were assessed in both studies and found statiscially significant associations of opposite direction, did not pool results.Administration through supplements, findings by outcome:**1. All-cause mortality:** In 17 studies, including 63,279 participants with 6295 events, omega-3 PUFA supplementation was not statistically significantly associated with reduced all-cause mortality (RR 0.96; 95% confidence interval [CI], 0.91-1.02; *P*=.17; *I*2=12%; and RD -0.0004; 95% CI, -0.01 to 0.02; *P*=.19; *I*2=38%). There was no publication bias, and no association between treatment effect and the presence of blinding, dose, the prevention setting, or the presence of an implantable cardioverter-defibrillator (ICD).**2. Cardiac death:** In 13 studies, including 56,407 participants with 3480 events, omega-3 PUFA supplementation was not statistically significantly associated with cardiac death after correction for multiple comparisons (RR 0.91; 95% CI, 0.85-0.98; *P*=.01; *I*2=6%; and RD -0.01; 95% CI, -0.02 to 0.00, *P*=.09; *I*2=78%). There was no publication bias, and no association between treatment effect and presence of blinding, dose, the prevention setting, or the presence of an ICD.**3. Sudden death:** In 7 studies, including 41,751 participants with 1030 events, omega-3 PUFA supplementation was not statistically significantly associated with reduced rates of sudden death (RR 0.87; 95% CI, 0.75-1.01; *P*=.06; *I*2=8%; and RD -0.003; 95% CI, -0.012 to 0.006; *P*=.49), *I*2=91%). There was no publication bias, and no association between treatment effect and the presence of blinding, dose, the prevention setting, or the presence of an ICD.**4. MI:** In 13 studies, including 53,875 participants with 1755 events, omega-3 PUFA supplementation was not statisically significantly associated with a reduced risk of MI (RR 0.89; 95% CI, 0.76-1.04; *P*=.14; *I*2=35%; and RD -0.002; 95% CI, -0.007 to 0.002; *P*=.23; *I*2=35%). There was no association between treatment effect and the presence of blinding, dose, the prevention setting, or the presence of an ICD. There was possible publication bias – a funnel plot showed asymmetry and the Begg-Mazumbar test was significant (*P*=.010) – but the trim-and-fill approach yielded an identical imputed estimate.**5. Stroke:** In 9 studies (all non-ICD patients) including 52,589 patients with 1490 events, there was an opposite but not statistically significant effect on risk of stroke (RR 1.05; 95% CI, 0.93-1.18; *P*=.47; *I*2=14%; and RD 0.001; 95% CI, -0.002 to 0.004; *P*=.46; *I*2=15%). There was no publication bias, and no association between treatment effect and the presence of blinding, the prevention setting, or the the dose. |
| **3.** Study addresses an appropriate and clearly focused question - ***select one*** | Well covered |
| **4.** A description of the methodology used is included. | Well covered |
| **5.** The literature search is sufficiently rigorous to identify all the relevant studies. | Well covered  |
| **6.** Study quality is assessed and taken into account. | Well covered  |
| **7.** There are enough similarities between selected studies to make combining them reasonable. | Well covered Comments: The meta-analysis included 20 trials total, while studies with the same outcome were combined and studies with the same mode of omega-3 PUFA administration (diet vs supplement) were combined. Using a random-effects analysis, the individual-study RR estimates did not show between-study heterogeneity, while the individual-study RD estimates showed considerable between-study heterogeneity due to variation in the observed baseline risk estimates. |
| **8.** Are patient-oriented outcomes included? If yes, what are they? | Yes: All-cause mortality, cardiac death, sudden death, MI, and stroke. |
| **9.** Are adverse effects addressed? If so, how would they affect recommendations? | Adverse effects of omega-3 PUFA administration are not addressed. |
| **10.** Is funding a potential source of bias? If yes, what measures (if any) were taken to ensure scientific integrity? | No |
| **11.** To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized. | The study findings might apply to patients who are 49 to 70 years old, with or without a history of CVD, with or without an ICD, using dietary or supplemental omega-3 PUFAs for one to 6 years. |
| **12.** In what care settings might the findings apply, or not apply? | The findings would apply to outpatient family practice during care for patients with or without a history of CVD and in-hospital care post-MI. |
| **13.** To which clinicians or policy makers might the findings be relevant? | The findings might be relevant to primary care physicians caring for adults and to cardiologists. |
| **SECTION 3: REVIEW OF SECONDARY LITERATURE** |
| **1.** DynaMed excerpts |   |
| **2.** DynaMed citation/access date | Dietary recommendations for cardiovascular disease prevention. In: DynaMed [database online]. Available at: www.DynamicMedical.com. Last updated September 2012. Accessed October 14, 2012. |
| **3.** Bottom line recommendation or summary of evidence from DynaMed(1-2 sentences) | Comprehensive reviews including RCTs and cohort studies examining primary and secondary CVD prevention do not find clear conclusions about the efficacy of omega-3 fatty acids for cardiovascular disease prevention. |
| **4.** UpToDate excerpts |   |
| **5.** UpToDate citation/access date | Mozaffarian D. Fish oil and marine omega-3 fatty acids. I In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2012. Available at: http://www.uptodate.com. Last updated September 14, 2012. Accessed October 14, 2012. |
| **6.** Bottom line recommendation or summary of evidence from UpToDate(1-2 sentences) | Given the potential benefit and no evidence of suggested harm of fish oil supplementation on reduced coronary heart disease (CHD) death and sudden cardiac death, 1 g/d of omega-3 PUFA (including EPA+DHA) or one to 2 servings of oily fish per week are recommended for primary and secondary prevention of CHD outcomes.  |
| **7.** PEPID PCP excerpts[www.pepidonline.com](http://www.pepidonline.com)username: fpinauthorpw: pepidpcp | Anti-Inflammatory Diet1. Omega-3 and Omega-6 fats are precursors of prostaglandins (PGE1,2,3); prostaglandins (eicosanoids) are key modulators or the inflammatory response2. Recent research strongly linked CAD & other diseases to diffuse inflammatory processes3. Inflammation leads to free radical formation; cyclic process4. Dietary components linked to inflammatory processes within the body5. Modifying diet to decrease pro-inflammatory precursors consumed may significantly decrease incidence of CAD6. Markers of inflammation become important part of identification & management of CAD risk factors◦ Inflammatory markers (desirable lab values):▪ Homocysteine: <10 mmol/L▪ Lipoprotein (a) < 30▪ CRP, NS <0.7▪ Fibrinogen 200-400 mg/dL [2-4 g/L]7. Effects◦ Decr PGE2 (pro-inflammatory, promotes plt aggregation)◦ Incr PGE1 & PGE3 (decr inflammation, inhibit plt aggregation)8. To reduce inflammatory processes by diet:◦ Reduce saturated fats (arachidonic acid)▪ Animal products▪ Full fat (whole) dairy products◦ Reduce omega 6 fatty acids▪ Margarine, corn oil, cottonseed oil, peanut oil, sesame oil, soybean oil▪ Hydrogenated/partially hydrogenated oils▪ Avoid products that contain trans-fatty acids◦ Increase omega-3 fatty acids▪ Cold water fish (eg, salmon, mackerel, herring)▪ Flax meals or oil, walnuts, green leafy vegetables, soy, wild game, sunflower and pumpkin seeds◦ Avoid low-carbohydrate diets (eg, Atkins), which are typically high in animal meats◦ Avoid high glycemic foods9. Other reduction interventions:◦ Consider aspirin Rx◦ Supplement with fish oil capsules (1-3 g omega-3/d) |
| **8.** PEPID citation/access data | Anti-inflammatory diet In: PEPID [database online]. Available at: http://www.pepidonline.com. Accessed October 15, 2012. |
| **9.** PEPID content updating | 1. Do you recommend that PEPID get updated on this topic?Yes, there is important evidence or recommendations that are missingIf yes, which PEPID Topic, Title(s):Anti-inflammatory diet (the current symmary doesn't address the disparate results of RCTs and cohort studies on fish oil supplementation on CVD outcomes. |
| **10.** Other excerpts (USPSTF; other guidelines; etc.) | **FDA Announces Qualified Health Claims for Omega-3 Fatty Acids**The Food and Drug Administration (FDA) today announced the availability of a qualified health claim for reduced risk of CHD on conventional foods that contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids.Typically, EPA and DHA omega-3 fatty acids are contained in oily fish, such as salmon, lake trout, tuna and herring. These fatty acids are not essential to the diet; however, scientific evidence indicates that these fatty acids may be beneficial in reducing CHD."Coronary heart disease is a significant health problem that causes 500,000 deaths annually in the United States," said Dr. Lester M. Crawford, Acting FDA Commissioner. "This new qualified health claim for omega-3 fatty acids should help consumers as they work to improve their health by identifying foods that contain these important compounds."A qualified health claim on a conventional food must be supported by credible scientific evidence. Based on a systematic evaluation of the available scientific data, as outlined in FDA's "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements", FDA is announcing a qualified health claim for EPA and DHA omega-3 fatty acids. While this research is not conclusive, the FDA intends to exercise its enforcement discretion with respect to the following qualified health claim:"Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [name of food] provides [x] grams of EPA and DHA omega-3 fatty acids. [See nutrition information for total fat, saturated fat and cholesterol content.]In 2000, FDA announced a similar qualified health claim for dietary supplements containing EPA and DHA omega-3 fatty acids and the reduced risk of CHD. FDA recommends that consumers not exceed more than a total of 3 grams per day of EPA and DHA omega-3 fatty acids, with no more than 2 grams per day from a dietary supplement.The EPA and DHA omega-3 fatty acid qualified health claim is the second qualified health claim that FDA has announced for conventional food. For additional information about QHC visit: http://www.cfsan.fda.gov/~dms/lab-qhc.html. |
| **11.** Citations for other excerpts | FDA announces qualified health claims for omega-3 fatty acids. September 8, 2004. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108351.htm. Accessed October 15, 2012.  |
| **12.** Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences) | The FDA recommends increased omega-3 fatty acid dietary or supplemental intake to reduce the risk of coronary heart disease. |
| **SECTION 4: CONCLUSIONS** |
| **1.** **Validity:** How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) | 1  |
| **2.** If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results? | Good methodological quality - assessed publication bias and heterogeneity for each outcome analysis, used subanalysis and meta-regression to help explain their findings given the presence of heterogeneity, if any. The varying event rates and baseline risk estimates in the trials could explain some of the effect variation.  |
| **3. Relevance:** Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full-scope” family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) | 1  |
| **4.** If 4.3 was coded as 4, 5, 6, or 7,please provide an explanation. |   |
| **5. Practice-changing potential:** If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice) | 2  |
| **6.** If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit. | Current recommendations include omega-3 supplementation for primary and secondary prevention of CHD and for treatment of hypertriglyceridemia - this meta-analysis indicates no reduction in cardiovascular outcomes after 1-6 years of supplementation.  |
| 1. **Applicability to a Family Medical Care Setting:**

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting) | 1 |
| **8.** If you coded 4.7 as a 4, 5, 6 or 7, please explain.  |   |
| **9. Immediacy of Implementation:** Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market?Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied) | 1  |
| **10.** If you coded 4.9 as 4, 5, 6, or 7, please explain why. |   |
| **11. Clinical meaningful outcomes or patient-oriented outcomes:** Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented) | 4  |
| **12.** If you coded 4.11 as a 4, 5, 6, or 7, please explain why. | The study outcomes are clinically meaningful. However, the study finds no statistical signficance in the outcomes using a highly conservative and valid analytic approach. It is unclear to me if the small reductions in cardiovascular events are actually clinically meaningful.  |
| **13.** In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)Criteria for a Pending PURL:* Valid: Strong internal scientific validity; the findings appears to be true.
* Relevant: Relevant to the practice of family medicine
* Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
* Applicability in medical setting:
* Immediacy of implementation
 | 4  |
| **14.** Comments on your response in 4.13 | While no statistically significant reduction in CVD events was found, there was a slight reduction in all-cause mortality, cardiac death, sudden death, and MI that may be clinically significant. |