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IRB Protocol Proposal

Polyunsaturated Fatty Acid Supplementation for Secondary Stroke Prevention

Study Purpose and Rationale:

The American Heart Association (AHA) recently committed itself to improving the cardiovascular health of Americans. It has a goal to reduce cardiovascular disease and stroke 20%, by the year 2020. This comes soon after AHA's 2010 Heart and Stroke Statistical Update. The statistics are sobering. Approximately 81,000,000 Americans (one in three) have some sort of cardiovascular disease (HTN, CHD, CHF or Stroke) accounting for 831,272 or 34.3% of all deaths in 2006 that year. Coronary heart disease (CHD) accounted for 425,425 deaths (on in six deaths) and stroke accounted for 137,019 deaths (one in 18 deaths). [i]

Diet modification has long been studied as a preventative measure in the fight against cardiovascular disease (CVD). Observational studies have linked the Mediterranean diet with increased longevity and decreased cardiovascular events.[ii] [iii] The Lyon heart study was a randomized secondary prevention trial from 14 years ago, that found the Mediterranean diet to be effective in substantially decreasing all-cause mortality, cardiovascular mortality and cardiac events by 50% (rr 0.53, p = .0002).[iv]

These are significant findings, but are unlikely reproducible in certain patient populations. Columbia University Medical Center is located in an inner city neighborhood where most patients and their families have economic hardship and have limited access to specialty stores. Dietary supplementation would likely increase level of adherence in such a community. The Diet and Reinfarction Trial (DART) studied 2,033 men soon after MI, showing that fish intake and fish oil supplements, containing eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3), two polyunsaturated fatty acids (PUFA) mainly found in fish. Both, the group with increased fish intake and the supplementation group had an approximate 30% decrease in all-cause mortality ($p<.05$) and CAD associated mortality ($p<.01$) as compared to controls.[v]

These findings have been confirmed by the GISSI-Prevenzione trial, a randomized trial that divided 11,323 individuals (after recent myocardial infarction) between two study groups and a placebo group. They studied the effect of polyunsaturated fatty acid (PUFA) supplementation + Vitamin E vs. PUFA alone, and showed a. Findings were significant for a statistically significant and substantial decrease in overall and CVD associated mortalities (rr = 0.72, p = 0.27 and rr = 0.7 p = 0.39 respectively). There were no significant differences in incidence of nonfatal MI and stroke suggesting but the mortality curves separated early in the study suggesting that PUFA decrease arrhythmias; an observation attributed to their ability to decreasing membrane potential and stabilize electric potentials.[vi]

To further analyze this association, the Diet and Angina Randomized Trial (DART -2) studied 3114 individuals with angina. The study arm was either assigned to fish supplementation, with EPA only, and the option to eat fish instead or, a fish diet with the option to take EPA supplementation. Results actually showed a trend toward increase in overall mortality in the

study group (rr = 1.15 CI 0.97-1.34) and a significant increase in cardiovascular events (rr 1.31, CI 1.07-1.59) Further analysis suggests that this effect was in the EPA supplemented group. The significance of this study is unknown, especially since patients were only supplemented with EPA instead of EPA and DHA, as in previous studies.[vii]

A trial just published (published on Nov. 18th, 2010) in the NEJM called the Alpha Omega Trial was a double-blind, placebo-controlled study with 4837 individuals who had a previous MI and were on optimal medical management, were randomized to one of four treatment arms: a combination of EPA and DHA, α-linolenic acid (α-LNA, 18:3 n-3) alone, a combination of EPA, DHA, and α-LNA; or placebo. Results showed no differences in outcome. Subgroup analysis showed possible cardiovascular benefit in diabetic patients, similar to the effects seen in the GISSI trial. Discrepancies between studies may be due to advancement of medical care. The previous trials were performed 5-15 years ago when drug therapies and interventions weren't as advanced. For example, just 5% of patients in the GISSI trial were receiving statins, at baseline, as compared with 86% of patients in the Alpha Omega Trial. [viii]

Although there are a number of large randomized trials of PUFA supplementation for cardiovascular events, studies looking at the effect of PUFA on the brain primarily, are lacking. Multiple cohort studies have shown that Fish consumption has an inverse relationship with risk of stroke. [ix] [x] A meta-analysis of 8 cohort studies (>200,000 individuals) concluded that intake of fish is inversely related to risk of stroke and particularly ischemic stroke. [xi] With large randomized trials lacking, there is not yet enough data to determine the role of fish oil supplementation in stroke.

Hypothesis:

Supplementation with eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3) along with standard therapy, will prevent recurrence of Stroke, as compared to standard therapy alone. I will also examine the effect of EPA and DHA supplementation on all cardiovascular events and death.

Methods:

Primary outcomes will include stroke of any type. Secondary outcomes will be: 1) myocardial infarction 2) composite of pulmonary embolism and deep vein thrombosis, 3) death from any cause.

Stroke will be defined as acute focal neurological deficit lasting >24 hrs with diagnostic evidence by CT or MRI. Ischemic strokes will be classified using the TOAST classification system.[xii] This includes five subtypes of ischemic stroke: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology. Hemorrhagic stroke will be classified as major, life-threatening, intracranial, and minor. The NIHSS (scores ranging from 0-30 with greater score indicating greater disability) and Rankin scale (scores ranging from 0 to 6 with higher scores indicating greater disability) will be used to asses stroke severity within 24hrs of initial diagnosis, 3 months after and every 6 months thereafter, until the conclusion of the study.

Myocardial infarction and unstable angina will be defined using the ACS criteria, as defined by the American Heart Association. Diagnosis of pulmonary embolism will be made by clinical, plus diagnostic evidence . DVT will be defined by Doppler studies consistent with DVT.

Patient will be seen 3 months after enrollment in the study and every 6 months thereafter, where they will have a general examination and standard labs taken, including serum levels of major fatty acids (DHA, EPA, α-LNA, Arachidonic and linoleic acid).

Study Design:

Randomized, double blind, secondary stroke prevention trial of a) PUFA supplementation (1g of Fish oil/day) along with standard therapy vs. b) standard therapy alone with placebo capsules. Both groups will receive lifestyle modification information and will be urged to follow an a Mediterraneana style diet, as defined by the AHA.

Statistical Analysis:

The study will seek to enroll a total of 6,000 individuals, divided between study arm and control group. The incidence of recurrent stroke, with standard treatment, was estimated to be .09. A clinically significant effect would be a 20% decrease in recurrence of stroke or an estimated incidence of 0.07 in the study arm. The data will be analyzed using a chi-square analysis. Using the above estimates, 3,000 individuals in each group will be needed to achieve enough power to detect a 20% decrease in recurrence of stroke with a p-value <0.05. This was based on a large non-inferiority trial of secondary prevention measures for stroke.[xiii]

Subject Selection:

Eligible patients will be aged 50-75 with recent stroke or clinical evidence of a transient ischemic event (TIA) (in the past 90 days) who are clinically stable and able to comply with study requirements. Exclusion criteria will be severe disability as defined by modified Rankin scores of 4-6. Severe dementia as defined by a failed mini-cognitive exam, will also be excluded. This study will include minorities and women. Patients will be recruited by the physicians managing them. Informed consent will be obtained by written consent with explanation of study, its potential benefits, potential risks, and alternatives, in a manner that is clear and non-threatening to the patient. Potential difficulties in recruitment would be lack of candidates.

Description of study procedures: NA

Study Drugs: NA

Medical Devices: NA

Study Questionnaire: NA

Confidentiality of study: HIPPA requirements

Location of study: Multi-center, CUMC is the primary center

Risks and benefits: Potential benefits include decreased incidence of stroke and cardiovascular events and better outcome of initial stroke. Potential risks are an increase in cardiovascular events and stroke. Alternative therapies include standard secondary stroke prevention therapies. Compensation: no compensation will be given but all costs of study will be paid for, including transportation

Minors and research subjects: NA

Radiations: NA

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[i] Heart disease and stroke statistics. American heart Association. 2010 update

ii *Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O,Menotti A, van Staveren WA: Mediterranean diet, lifestyle factors, and 10-yearmortality in elderly European men and women: the HALE project.JAMA 292:1433–1439, 2004.*

[iii] Sofi F, Cesari F, Abbate R, Gensini GF, Casini A (2008). "Adherence to Mediterranean diet and health status: meta-analysis". BMJ (Clinical research ed.) 337: a1344.

[iv] de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation.* 1999;99:779–785

[v] Burr ML, et al. Effects of changes in fat, fish and fibre intake on death and myocardial infarction: diet and reinfarction trial (DART). Lancet. 19889; 2:757-61

[vi] GISSI-Prevenzione Investigators (1999). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet, 354, 447–455.

[vii] Burr ML, Ashfield-Watt PAL, Dunstan FDJ, Fehily AM, Breay P, Ashton T, Zotos PC, Haboubi NAA & Elwood PC (2003) Lack of benefit of dietary advice to men with angina: results of a controlled trial. European Journal of Clinical Nutrition 57, 193–200.

[viii] Kromhout D, Gitay EJ, Geleijnse JM, et al. N-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 2010; DOI:10.1056.NEJM0a.1003603.

[ix] Mozaffarian D, Longstreth WT, Jr., Lemaitre RN*, et al.* Fish consumption and stroke risk in elderly individuals: the cardiovascular health study. Arch Intern Med 2005; 165:200-206.

[x] Yamagishi K, Iso H, Date C*, et al.* Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. J Am Coll Cardiol 2008; 52:988-996.

[xi] He K, Song Y, Daviglus ML*, et al.* Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke 2004; 35:1538-1542.

[xii] Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.

[xiii] Sacco RL, Diener HC, Yusuf S, et al.: Aspirin and extendedrelease dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 2008, 359:1238–1251.