

Updating the Cardiovascular Benefits of n-3 Fatty Acids



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Introduction

In 2002 the American Heart Association recommended increased intakes of n-3 fatty acids (FA) for both primary and secondary prevention of coronary heart disease (CHD) (1), and in 2004, we proposed that blood n-3 FA levels be considered as a new risk factor for sudden cardiac death(2). This paper will review the latest evidence that continues to point to an important role for n-3 FA in cardiovascular disease (CVD) prevention.

Omega-3 vs. Omega-6 Fatty Acids

Omega-3 (or n-3) FAs are one of two families of essential FA in the human diet; the other is the omega-6 family (Figure). All FA are named by number of carbons in the chain, the number of double bonds, and the position of the first double bond counting from the terminal (omega, or nth) methyl group. As an example, the essential omega-6 FA linoleic acid (C18:2n-6) is the major component of most vegetable oils (corn, safflower, sunflower, soybean) and gives rise to arachidonic acid (C20:4n-6) which is the precursor of prostaglandins, thromboxanes, leukotrienes, etc. The most important omega-3 FAs are eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3). EPA can also be converted into similar eicosanoids (20-carbon moieties) as arachidonic acid, but those derived from EPA tend to be less potent thrombotic and inflammatory mediators. The long-chain omega-3 FA are found in fish and fish oils. A shorter-chain omega-3 FA is called α -linolenic acid (ALA, C18:3) and is a major component of flaxseed oil but also found in canola and soybean oil. It is only very poorly converted to EPA and DHA. The American diet is far richer (10-20x) in omega-6 than omega-3 FA.

Omega-3 Mechanisms of CVD Reduction

The mechanisms by which omega-3 FA (i.e., EPA and DHA) reduce risk for CHD events are not entirely clear. At doses that have been reported to reduce risk for sudden cardiac death [i.e., around 850 mg/day in the GISSI Prevenzione study (3)], no effects on serum lipids have been observed. The dose of EPA+DHA required to elicit significant triglyceride lowering is 3-4 g/day (4). Kinetic studies have shown that omega-3 FA slow the release of VLDL particles into the plasma (5), and our work has suggested that enhanced TG lipolysis may also play a role (6;7). The effects of these agents on HDL-C are inconsistent, but, as with other triglyceride-lowering agents like fibrates, LDL-C can increase as the triglycerides fall. The molecular (or even cellular) bases for the effects of omega-3 FA on lipid metabolism in humans are not yet known with certainty.

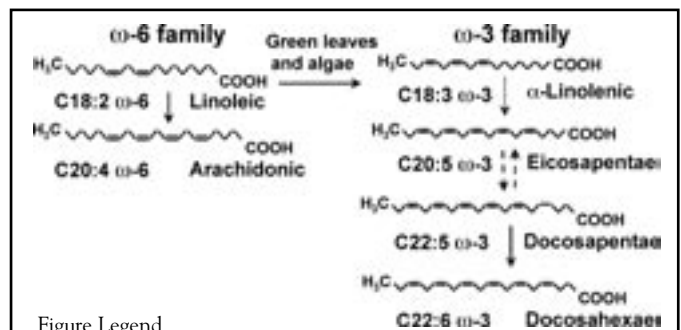


Figure Legend

Figure. The omega-6 and omega-3 families of polyunsaturated fatty acids. Of the omega-3 fatty acids, α -linolenic acid is found in plant oils whereas EPA and DHA are found in fish oils. Both arachidonic acid and EPA are substrates for cyclooxygenases and lipoxygenases, each producing a different family of compounds with differing physiological actions.

Similarly, although relatively large doses of omega-3 FA mildly inhibit platelet function (8), the effects of approximately 1g of EPA+DHA per day, especially in patients already taking aspirin, is not known but could theoretically play a role. Studies in animal models and in cultured cells have suggested that omega-3 FA have membrane-active effects that reduce the susceptibility of the myocardium to develop malignant arrhythmias in the setting of ischemia-reperfusion (9;10). They appear to inhibit both sodium and calcium channel function so as to maintain electrical stability during ischemic stress. In addition, omega-3 FA may also have direct effects on the autonomic nervous system, possibly by increasing vagal tone (11). Such an effect would be expected to reduce heart rate, and therefore, risk for sudden cardiac arrest.

Clinical Insights continued on page 3

in this issue...

- Clinical Insights 1
- President's Column 2
- Special Report. 6
- Therapeutic Lifestyle Changes 7

- Lipid Luminations 10
- Practical Pearls 11
- Meeting Highlights 14
- Continuing Education Programs 18
- News & Notes 21
- Meetings & Events Calendar 24

THERAPEUTIC LIFESTYLE CHANGES

Innovative Approaches to Comprehensive Cardiovascular Disease Risk Reduction: Focus on Therapeutic Lifestyle Changes

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Despite impressive technologic advances in the field of medicine during the 20th century, atherosclerotic cardiovascular disease (CVD) remains the leading cause of death in the United States and most developed countries.^{1,2} Modification of multiple risk factors through a combination of comprehensive lifestyle interventions and appropriate pharmacological therapy is now widely recognized as the cornerstone of initiatives aimed at the primary and secondary prevention of CVD.

Recent studies emphasize the need to intensify efforts aimed at the control of multiple CVD risk factors.^{3,4} To help facilitate this objective, national clinical guidelines advocate a multifactorial lifestyle approach to CVD risk reduction. This approach has been designated "therapeutic lifestyle changes" or "TLC" and includes exercise training together with correct nutrition and other appropriate lifestyle interventions such as cigarette smoking cessation.⁵⁻⁷

Primary care physicians and cardiologists generally work in an intensely busy environment. Typically, physicians do not have the time, infrastructure, or resources to focus adequate attention on certain prevention-related services, especially TLC. Moreover, physicians in the United States receive little or no compensation for the provision of TLC. In view of these and other barriers, it is not surprising that physicians in this country tend to limit most of their attention to acute medical problems presented during office visits, give low priority to preventive interventions in general, and when focusing on CVD risk reduction, prescribe pharmacologic therapy in preference to TLC. Indeed, because of the widespread availability of powerful cardioactive medications, the value of TLC per se in contemporary medical practice is often discounted by physicians, health insurers, and patients.

This article briefly summarizes the findings of the landmark lifestyle intervention trials that refute the commonly held notion among clinicians that TLC is not worth the effort and presents a "case study" of an innovative model for comprehensive lifestyle management and CVD risk reduction that we have successfully integrated into regular medical care.

Landmark Lifestyle Intervention Trials

Overwhelming evidence from a variety of sources, including epidemiological, prospective cohort, and intervention studies, links CVD and most other chronic diseases seen in the world today to physical inactivity, inappropriate diet consumption, and cigarette smoking.⁸ Recently, Iestra et al. performed a literature search on the effect of the generally agreed upon lifestyle recommendations (Table 1) on mortality in patients with coronary artery disease.⁹ Prospective cohort studies and randomized controlled trials of patients with established coronary artery disease were included if they reported all-cause mortality and had at least 6 months of follow-up. Increased physical activity, dietary changes, smoking cessation, and moderate alcohol use were all associated with a statistically significant risk

reduction, the magnitude of which was similar to that observed with low-dose aspirin, statins, beta-blockers, and ACE inhibitors after myocardial infarction (Table 2).

In a recent study of ours, 2,390 ethnically diverse men and women with hypertension, hyperlipidemia, and/or impaired fasting glucose or diabetes mellitus and who were not taking medication for these risk factors were evaluated before and after 12 weeks of participation in a community-based comprehensive lifestyle management program.¹⁰ TLC included exercise training, a low fat/cholesterol diet, weight management, smoking cessation, and stress management. Of the participants with an elevated baseline systolic blood pressure, diastolic blood pressure, LDL cholesterol, and/or fasting glucose, 64%, 67%, 11%, and 39%, respectively, achieved the goal value with TLC (without using pharmacotherapeutic agents, Figure 1). Of the patients

Table 1. Recommendations of Lifestyle and Dietary Factors to Improve Prognosis in Coronary Artery Disease Patients

1. Stop smoking
2. Engage in moderate intensity physical activity (for >30 minutes on at least 5, but preferably all, days of the week)
3. If you use alcohol: do so in moderation (maximum 2 alcoholic drinks per day for women and maximum 3 drinks per day for men)
4. Maintain or attain a healthy body weight (BMI <25 kg/m²); obese patients (BMI >30 kg/m²) should try to lose 10-15% of their current body weight
5. Limit your saturated fat intake (to a maximum of 10% of daily energy intake) and the intake of trans fatty acids (to a maximum of 1% of daily energy intake)
6. Consume fish regularly (at least 1 and preferably 2 portions of oily fish per week)
7. Consume sufficient amounts of fruits and vegetables (>400 g/d)
8. Use sufficient fiber containing grain products, legumes, and/or nuts (>3 U/d)
9. Reduce your salt intake (to maximal 2400 mg/day)

From reference 9.

with a baseline fasting glucose compatible with a diagnosis of diabetes, 37% decreased that value to <126 mg/dl. This study adds to the existing literature by reporting on the effectiveness (i.e., extent to which TLC works in actual practice) rather than on the efficacy (i.e., determining whether TLC can work when administered in a clinical trial) of TLC. Moreover, it should be noted that TLC can generally be implemented less expensively than most medications and, unlike single-drug therapy, favorably affects multiple risk factors. Therefore, these findings also have potentially important policy implications for health care payers, including the federal government, who often do not provide reimbursement for TLC but do provide prescription drug coverage.

Innovative Models for Comprehensive Lifestyle Management and CVD Risk Reduction: A Case Study

Through contact with millions of patients each year, physicians and other health care providers have an opportunity to favorably impact public health by promoting TLC. Clearly, however, innovative approaches are needed to assist physicians in the provision of long-term lifestyle management services to their patients. One example

THERAPEUTIC LIFESTYLE CHANGES

Therapeutic Lifestyle Changes continued from page 7

of such an approach is a program (called the INTERVENT Lifestyle Management and Cardiovascular Risk Reduction Program) that we have developed, tested and successfully implemented in a variety of clinical and community-based settings in the United States, Canada, and South Africa.¹¹ Outcome data, including results from randomized clinical trials, have documented the clinical- and cost-effectiveness of this approach.¹⁰⁻¹²

Briefly, the program content is organized into two core sets of services. One set is “mentor-assisted” (involving one-on-one counseling of participants by a non-physician health professional/case manager, called a “mentor”). The other set is an array of individualized “self-help” products, all of which are web-enabled. The programs can be administered in, or from, a variety of physical settings (including physician offices, hospitals, cardiac rehabilitation programs, work sites, and public locations) and via telephone and the Internet. In each of these settings, the program content has been adapted to enhance the applicability to the specific settings and clinical circumstances. Key program steps are as follows:

Step 1: Participant enrollment. Typically, patients are referred by their physicians or identified through health risk appraisals or various other referral channels (including, self-referral following marketing of the program to the community, health plan members, or employees). On enrollment, each participant in a mentor-assisted program is assigned to an appropriately trained health professional who serves as the participant’s case manager. Participants in a self-help program are provided instructions for accessing their individualized program via the Internet or mail. Participants often pay to participate in the program themselves (retail pricing currently ranges from approximately \$40 for 12 weeks of participation in a web-enabled self-help program to \$400 for 1 year of participation in a mentor-assisted program with telephone and Internet counseling). In certain instances, employers and/or health plans pay for program participation (discounted pricing, including capitation pricing, is used when working with employers, health plans, and other groups of program participants).

Step 2: Initial/intake assessment. Participants complete a comprehensive medical history and health habits questionnaire, with the option to include biometric measurements (such as, height, weight, waist circumference, blood pressure, fasting serum lipids and lipoproteins, fasting glucose, hemoglobin A1c, C-reactive protein, homocysteine, etc.) and exercise test and other test results, if available. Questionnaires may be completed online via a secure server, in hard copy (“pen and paper”), or via the telephone. The initial assessment evaluates current health status, risk factors for CVD, past medical history, medications, current lifestyle practices, readiness for change, barriers to change, resources for change, and other relevant information.

Step 3: Goal setting. Based on the initial assessment, computer-generated individualized short- and long-term goals are set for multiple CVD risk factors and health behaviors in accordance with national clinical guidelines.

Step 4: Action plan formulation. Based on the initial assessment, a computer generated individualized action plan is formulated to achieve the short- and long-term goals. The action plan focuses on important health habits (including physical activity/exercise training, nutrition, weight management, tobacco cessation and stress management). In addition to behavior modification, the action plan identifies the need for other self-care activities and physician referrals for prescription medications to optimize CVD risk reduction consistent with national guidelines. Physician letters notify the participants’ physicians of their participation in the program and the CVD risk reduction goals and action plans.

Step 5: Review/revision of goals and action plan. For

participants in mentor-assisted programs, referring physicians have an opportunity to review, revise, and authenticate the goals and action plan reports for their patients. Using an approach that has been favorably reviewed by the United States’ Department of Health and Human Services, physicians are sometimes compensated for providing this service for their patients. Participants access their goals and action plan reports via program visits, the Internet or mail. Reports are accompanied by an audio explanation, which can be accessed online or via CD. For participants

in mentor-assisted programs, mentors review goals and action plans with participants at face-to-face program visits or via the telephone and make revisions, if appropriate. When reviewing reports, mentors are guided by written instructions, referred to as mentor prompt sheets (or lesson plans). If the action plan includes physician referral for consideration of institution or adjustment of prescription medications, the mentor helps facilitate this and documents the outcome of the referral in the program database.

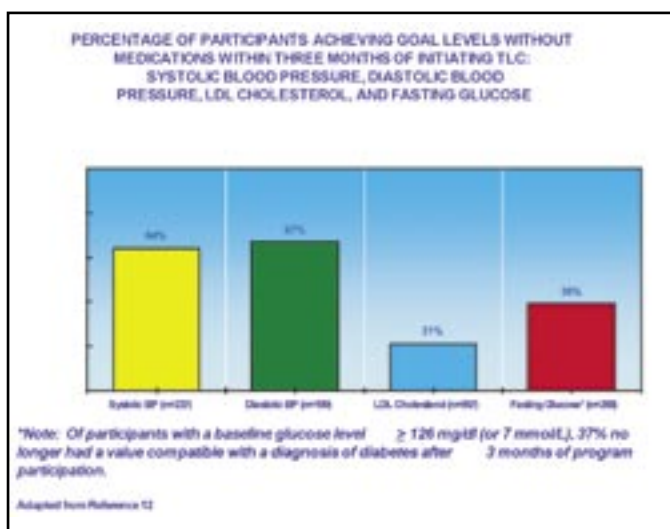
Step 6: Action plan implementation. Action plans are implemented using an individualized series of behavior change and education modules, each of which can be read and/or listened to by the participant during a 15-minute or so session. The modules are provided in printed form and via audio recordings, both of which can be accessed via the Internet and via “hard copy” form. The modules are effective in helping modify each participant’s behavior, using single concept learning theory, stages of readiness for change, and other behavior change strategies. Materials and messages are matched with each participant’s stage of readiness for change and personal circumstances, both clinical and otherwise.

Table 2. Approximate Mortality Reduction Potential of Lifestyle Changes Estimated From Studies in Coronary Artery Disease Patients: Comparison With Preventive Drug Interventions After Myocardial Infarction

Intervention	Mortality Risk Reduction
Low-dose aspirin	18%
Moderate alcohol	20%
Statins	21%
Beta-blockers	23%
Physical activity	25%
ACE inhibitors	26%
Smoking cessation	35%
Combined dietary changes	45%

Adapted from reference 9.

At each program interaction, the participant listens to a CD or web-enabled recording on the specific behavior modification topic, receives the accompanying written educational materials on the specific topic, and, if applicable, meets briefly with his/her program mentor (either physically or telephonically) for further counseling and to update the participant's individualized lifestyle modification and prevention program. Mentors assist participants in implementing individualized action plans through proactive, structured, one-on-one counseling sessions via face-to-face program visits or prescheduled telephone appointments. With assistance from a web-enabled participant management and tracking database, mentors typically guide participants through approximately 20 modules in the first year of program participation in an individualized, carefully sequenced, structured fashion.



Step 7: Follow-up assessment. After 12 weeks and 1 year of program participation, and at least annually thereafter, participants have an opportunity to complete a follow-up medical history and health habits questionnaire, with the option to include biometric measurements. Questionnaires may be completed online, in hard copy, or via telephone.

Step 8: Progress report and revision of goals/action plan. Based on program participation and the follow-up assessments, participants are provided computer generated reports documenting their progress and updating their goals/action plan. For participants in mentor-assisted programs, progress reports are reviewed at counseling sessions. As with the initial goals and action plan reports, physicians may be asked to review, revise, and sign progress reports for their patients, and in certain instances receive financial compensation for this service. Similarly, if the revised action plan includes physician referral for consideration of institution or adjustment of prescription medications, the mentor helps facilitate this and documents the outcome of the referral in the program database.

Step 9: Maintenance. Participants typically enroll in the program for either 12 weeks or 1 year at a time, but have access to continuing years of mentor-assisted program delivery or to self-help programs. Compliance with scheduled mentoring sessions, lifestyle interventions, and prescribed CVD risk reduction medications is tracked using the web-enabled participant management and tracking database.

Step 10: Outcomes assessment. Using a computerized outcomes analysis system, detailed outcomes reports are generated on a regular basis for specific program locations, individual physicians and groups of physicians, individual mentors, employers, and other groups of program participants. In certain instances, benchmarking is included. To date, the program database has also been used to generate data for approximately 70 published scientific abstracts and/or manuscripts.

It is our belief that the first decade of this new millennium will be remembered as the “decade of CVD prevention.” New and innovative approaches, such as the above “case study,” will be needed to fulfill the potential for improving quality of life and longevity through TLC and other CVD risk reduction interventions. ❤️

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See page 15 to view
 the 3 winning heart-
 healthy recipes from
 the 2005 SELA
 Annual Scientific
 Forum

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