Therapeutic Lifestyle Change and Adult Treatment Panel III: Evidence Then and Now

Neil J. Stone, MD, and Linda Van Horn, PhD, RD

Address
Departments of Medicine and Preventive Medicine, Feinberg School of Medicine of Northwestern University, 211 East Chicago Avenue, Suite 1050, Chicago, IL 60611, USA.
E-mail: n-stone@northwestern.edu

Current Atherosclerosis Reports 2002, **4:**433–443
Current Science Inc. ISSN 1523–3804

The Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) has an extensive section on nonpharmacologic therapy for those with abnormal blood lipids. ATP III focused on the high-saturated fat atherogenic diet, obesity, and sedentary lifestyle and recommended a program of therapeutic lifestyle change (TLC). This review discusses several issues, including 1) why ATP III changed from the Step I and Step II diets to TLC; 2) the benefits of keeping trans fatty acid intake low and the addition of viscous fiber and plant stanol/sterol esters to reduce low-density lipoprotein cholesterol beyond that seen with the Step II diet; 3) the de-emphasis on total fat and a sharper focus on the kinds of fat ingested in the new guidelines; 4) the endorsement of regular physical activity and weight loss as important first steps in reversing the unwanted metabolic effects of the metabolic syndrome; and 5) the emphasis of health-promoting aspects of the diet that include, among other things, fish and omega-3 fatty acids. At all stages of TLC, ATP III encourages the referral to registered dietitians or other qualified nutritionists for medical nutrition therapy. TLC and the ATP III guidelines should provide guidance to practitioners who wish to get low-density lipoprotein cholesterol to goal (whether or not drugs are used), prevent or treat the metabolic syndrome, and improve the overall health of the patient.

Introduction

The Third Report of the National Cholesterol Education Program's (NCEP) Adult Treatment Panel (ATP III) continued the process begun in 1988 of recommending to physicians and health professionals an updated approach to the diagnosis, evaluation, and treatment of patients with high cholesterol [1••]. An important component of the guidelines was a section on nonpharmacologic therapy that incorporated diet and exercise into the treatment plans of those who sought to lower their risk of coronary heart disease (CHD). New features in ATP III in this area included the following (Table 1).

1. A new approach to nonpharmacologic therapy linking diet, physical activity, weight loss, and behavioral change. Therapeutic lifestyle change was used to refer to this important nonpharmacologic component designed for both prevention and treatment of high cholesterol, risk factors for CHD, and CHD itself.
2. Changing from the Step I and Step II diets of ATP I and II to a new therapeutic program called Therapeutic Lifestyle Change (TLC).
3. Keeping intake of trans fatty acids low and increased use of plant stanol/sterol esters and more viscous fiber to augment low-density lipoprotein (LDL) cholesterol lowering beyond that seen with the Step II diet.
4. A de-emphasis on total fat and a sharper focus on the kinds of fat ingested. ATP III suggested limits for total fat of 25% to 35% of total energy while advising lowering saturated fat intake to less than 7% of total energy and keeping intake of trans fatty acids low. This also influenced total carbohydrate intake to stay under 60% of energy, an important issue for those with metabolic syndrome.
5. Recommendation of regular physical activity and weight loss as important first steps in reversing the adverse metabolic trends of the metabolic syndrome.
6. Emphasizing healthy aspects of diet consistent with the Dietary Guidelines for Americans 2000.
7. At all stages of TLC, physicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for medical nutrition therapy.

To assist physicians in accessing the large body of information available, a list of government-sponsored web sites

Table 1. Essential components of Therapeutic Lifestyle Change diet

Component	Recommendation
LDL-raising nutrients	
Saturated fats*	<7% of total calories
Dietary cholesterol	<200 mg/d
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 g/d
Increased viscous (soluble) fiber	10–25 g/d
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal/d

*Trans fatty acids are another LDL-raising fat that should be kept at low intake.
LDL—low-density lipoprotein.
Adapted from National Cholesterol Education Program [1••].

Table 2. Government-sponsored web sites listed in Adult Treatment Panel III

Diet	http://www.nhlbi.nih.gov/chd
	http://www.nhlbi.nih.gov (click on Aim for a Healthy Weight)
	http://www.nhlbi.nih.gov/hbp
	http://www.nutrition.gov
Physical activity	http://www.surgeongeneral.gov/ophs/pcpfs.htm
Body weight	http://www.nhlbi.nih.gov (click on Aim for a Healthy Weight)
Cholesterol	http://www.nhlbi.nih.gov/chd
Blood pressure	http://www.nhlbi.nih.gov/hbp
Smoking cessation	http://www.cdc.gov/tobacco/sgr_tobacco_use.htm

was also listed in the full report (Table 2). However, many physicians may not have time to access the full report. This article is designed to review the information base behind these recommendations, as well as present information that is new since the introduction of ATP III in May, 2001.

Changing from Step I and Step II to Therapeutic Lifestyle Change Diet

The Step I diet, with its goals of total fat less than 30%, saturated fats less than 10%, and dietary cholesterol less than 300 mg/d, was the healthy diet established for the population in ATP I. This diet, designed for primary prevention, was designed to lower LDL cholesterol. The Step I diet alone was demonstrated not to be a truly effective secondary prevention intervention by the numerous angiographic trials comparing statin and diet with placebo and diet in subjects with CHD. Angiographic progression was seen in those subjects randomized to placebo and the Step I diet as compared with the more aggressive treatments with statins [2]. The Step II diet with total fat less than 30%, saturated fat less than 7%, and dietary cholesterol less than 200 mg/dL was an effective therapeutic diet that clearly lowered LDL cholesterol in significant fashion. A meta-analysis showed that for every 1% decrease in energy consumed as a dietary saturated fatty acid, LDL cholesterol decreased by 0.05 mmol/L or 2 mg/dL [3]. Moreover, significant LDL cholesterol lowering was seen in both men and women and in those with either combined hyperlipidemia or with high LDL cholesterol only [4]. The beFIT study showed that the LDL cholesterol lowering obtained with the Step II diet was not trivial. They calculated that it would bring about a significant reduction in those patients who require lipid-lowering drugs to meet LDL cholesterol goals.

Intensive reduction of saturated fat can be an important adjunct to therapy. Indeed, looking at a wide range of demographics, Ginsberg *et al.* [5] investigated the effects of reducing dietary saturated fatty acids from 15% of total calories to 6.1% of total calories. On the diet low in saturated fatty acids, LDL cholesterol was reduced by 11%. These studies have demonstrated that dietary reduction of LDL cholesterol is small in comparison with the large amount of LDL cholesterol lowering achieved by statin therapy. Yet because further increments of statin therapy (*eg*, dose doubling) lower LDL cholesterol additionally only about 6%, dietary therapy could be used effectively to augment LDL cholesterol lowering in those on statin therapy, as it is as least as powerful as dose doubling. Safety issues are important as well. Large-scale, randomized, controlled trials have examined the effects of reduced intakes of saturated fatty acids and cholesterol in children and have found no evidence for compromised growth or development [6,7].

There are other metabolic advantages of the diet. Careful metabolic studies showed that the Step II diet significantly decreased triglyceride-rich lipoproteins and plasma apolipoprotein (apo) AI-V concentrations compared with the average diet in the United States [8]. Finally, lowering saturated fatty acid intake should reduce the risk for CHD.

The evidence base includes epidemiologic studies, including cross-country comparisons and migration studies [2], as well as a meta-analysis of the benefits of saturated fat reduction leading to lower serum cholesterol levels [9,10]. This analysis included six robust dietary trials, in aggregate enrolling 6356 individuals. There was a decreased incidence of CHD by 24%, and also a trend toward a decrease in coronary mortality (21%) and total mortality (6%). Importantly, no increase in non-CVD mortality was found. The data from dietary trials, in combination with the results of controlled, clinical trials with cholesterol-lowering medications [11,12•], document that reducing serum cholesterol and LDL cholesterol by diet alone or with pharmacologic means will reduce CHD endpoints. Evidence that a diet restricted in saturated fat could reduce angiographic progression and/or coronary events was seen in the St. Thomas Atherosclerosis Regression Study [13]. Despite a small sample size, the authors showed both clinical and angiographic benefit in the diet arm (27% dietary fat, 8% to 10% saturated fat, 100 mg/1000 kcal dietary cholesterol, increased viscous fiber) The authors found that after adjustment for plasma cholesterol and other risk factors, saturated fat intake and trans fatty acids explained 20% of variance in angiographically determined CAD progression in overweight British men.

The Step II diet was not a perfect diet, however. There were several concerns. First, when weight was held constant, the Step II diet lowered high-density lipoprotein (HDL) cholesterol, although not as much as LDL cholesterol [14], and it did not assess the potentially attenuating benefits of increased soluble fiber. Second, the beFIT study showed that HDL cholesterol was lowered in women and men, but only significantly so in women, irrespective of whether they had either a high blood cholesterol level or both high cholesterol and triglyceride levels. Third, the Dietary Alternatives study [15] demonstrated that intakes of fat below about 25% of energy and carbohydrate intake above approximately 60% of energy yielded no further LDL cholesterol lowering in hypercholesterolemic or combined hyperlipidemic male subjects and was counterproductive to triglyceride, HDL cholesterol, and apo B levels [16]. Knopp *et al*. [15,16] suggested that the lack of benefit appears to be explained by an enhanced endogenous synthesis of palmitic acid, which negates the benefit of additional saturated fat restriction. Again, the potentially modulating role of increased soluble fiber as part of increased complex carbohydrate intake was not addressed. The decrease in HDL cholesterol with fat restriction appeared to be due to decreased HDL apo A-1 secretion [17]. Fourth, in those subjects with low HDL cholesterol (<59 mg/dL in women, <44 mg/dL in men) exercise was required to lower LDL cholesterol by the Step II diet [18]. ATP III strongly advocates the need to lower saturated fatty acids in the diet. It recognizes, however, that the beneficial effects of this reduction can be enhanced by weight reduction in overweight persons [19,20].

Reducing Low-density Lipoprotein Further with Additional Dietary Measures

Trans fatty acids

Trans fatty acids (TFA) are fatty acids in which there is at least one double bond in the trans-configuration. They are produced commercially by hydrogenation of vegetable oils to form shortening and stick margarines. They are also found naturally in animal fats and dairy products as a by-product of rumination. There is good evidence from randomized feeding trials that TFAs raise LDL/HDL relative to oil in the natural state or cis fatty acids. Unlike saturated fatty acids, TFAs lower HDL cholesterol levels, although not strikingly until higher levels are consumed. TFAs also increase levels of lipoprotein(a) (Lp(a)), although the significance of this is not known. For example, Lichtenstein *et al*. [21] examined diets with a broad range of TFAs. They showed that levels of LDL cholesterol were reduced on average by 12%, 11%, 9%, 7%, and 5%, respectively, after subjects consumed the diets enriched with soybean oil, semi-liquid margarine, soft margarine, shortening, and stick margarine; HDL cholesterol was reduced by 3%, 4%, 4%, 4%, and 6%, respectively. Ratios of total cholesterol to HDL cholesterol were least favorable after the use of butter or stick margarine [21]. Cohort studies support a link between TFAs and increased risk for CHD [22–25]. Whether this association is due to adverse effects of TFAs on lipoproteins, to adverse nonlipid actions, or to confounding variables is uncertain. A possible cause for concern regarding TFAs is the recently demonstrated increase in production of inflammatory cytokines that appear to play an important role in atherosclerosis and unstable plaques [26]. ATP III thus recommends that intakes of TFA should be kept low. The use of liquid vegetable oil, soft margarine, and trans fatty acid-free margarine are encouraged instead of butter, stick margarine, and shortening.

Dietary cholesterol

The response in humans to the feeding of dietary cholesterol is more variable than that seen in laboratory animals. Whereas some people respond in striking fashion, others do not. Nonetheless, meta-analyses of studies done in controlled settings confirm that high intakes of dietary cholesterol raise LDL cholesterol in humans [27,28]. In the past four decades, there has been a progressive decline in intakes of dietary cholesterol and saturated fats. This appears to be the result of decreased intakes of eggs, high-fat meat, and high-fat dairy products. This reduction in dietary cholesterol intake, along with a substantial reduction in the proportion of calories from saturated fatty acids, corresponds with the decline in blood cholesterol levels that have occurred [29]. It is estimated that the average daily consumption of cholesterol in the United States is 256 mg, with intakes higher for men (331 mg/d) than for women (213 mg/d) [30]. Polymorphisms may affect blood lipid

response to dietary cholesterol intake, but at present, knowledge of these provides little advantage in deciding who would or would not benefit from dietary treatment [31].

Large-scale epidemiologic studies performed when dietary intakes of cholesterol were much higher than now demonstrated that dietary cholesterol was associated with CHD risk independently of its effect on serum cholesterol [20]. In contrast, data from two more recent, prospective cohort studies, the Nurses Health Study and the Health Professionals Study, found no significant association between frequency of reported egg consumption (about 213 mg of dietary cholesterol per egg) and CHD, except among diabetic women [32]. A meta-analysis of studies with a crossover design or control group and where HDL cholesterol was measured showed that cholesterol feeding does increase total cholesterol to HDL cholesterol ratios, so advice to limit cholesterol consumption for those at risk appears to be valid [33]. ATP III recommends that less than 200 mg/d of cholesterol should be consumed in the therapeutic diet to maximize the amount of LDL cholesterol lowering that can be achieved through reduction in dietary cholesterol.

Viscous fiber

Viscous (also known as soluble) forms of dietary fiber can help reduce LDL cholesterol beyond what can be achieved by reducing saturated fat alone. In contrast, nonviscous or insoluble fiber does not significantly reduce LDL cholesterol [34], but may be inversely related to risk of diabetes [35]. There are two primary benefits of increasing dietary fiber intake. First, clinical trial data demonstrate that an increase in viscous fiber from oats, psyllium, or pectin resulted in small but significant reductions in LDL cholesterol [36]. Moreover, long-term treatment with a mixture of dietary fibers of 20 g given twice daily to hypercholesterolemic subjects lowered LDL cholesterol approximately 9% without significant change in HDL cholesterol or triglycerides [37]. Second, high-fiber diets may protect against obesity and CVD by lowering insulin levels and improving satiety compared with diets high in refined carbohydrates. The Cardiovascular Risk Development in Young Adults (CARDIA) study reported long-term observational results among 2909 healthy black and white adults, 18 to 30 years of age at enrollment, and followed for 10 years. Significant inverse associations with increased fiber intake were reported for body weight, waist-to-hip ratio, fasting insulin adjusted for body mass index (BMI), and 2-hour post-glucose insulin adjusted for BMI [38].

The ATP III panel recommends that the therapeutic diet be enriched by foods that provide a total of at least 5 to 10 g/d of viscous fiber and noted that even higher intakes of 10 to 25 g/d can be beneficial.

Plant stanols/sterols

Another therapeutic option is the use of plant stanols/sterols to lower cholesterol absorption by interfering with micelles. Plant sterols are ubiquitous in nature and eaten in considerable quantity by vegetarians. Hydrogenating sterols leads to stanols. Both are poorly absorbed, with plant stanols being the least well absorbed. Plant stanols and sterols from tall pine tree oils and soybeans are esterified to unsaturated fatty acids (creating stanol/sterol esters) to increase lipid solubility and allow use in margarines. The LDL cholesterol-lowering ability of plant sterols and plant stanols is comparable [39,40].

Plant stanols/sterols eaten consistently at optimal dosage are effective in those with hypercholesterolemia or diabetes and result in additional LDL cholesterol lowering in those patients on statins [41]. Interestingly, there is a greater percent lowering of LDL cholesterol in older people than in younger people [42•]. Plant stanol/sterol esters at dosages of 2 to 3 g/d lower LDL cholesterol levels by 6% to 15% with little or no change in HDL cholesterol or triglyceride levels. No studies have been conducted to determine the effect of plant stanols/sterols on CHD risk, although Law [42•] has projected that their use should double the beneficial effect on CHD risk achieved by reducing dietary saturated fatty acids and cholesterol. These margarines appear to be safe. There has been concern that they could reduce absorption of dietary carotenoids and decrease plasma levels of beta-carotene [40]. Plant sterols/stanols reduce absorption of dietary carotenoids, which can result in decreased beta-carotene concentrations. This can be overcome by an increase of one daily serving of high-carotenoid vegetables or fruit [43].

The ATP III diet recommends plant stanol/sterol esters (2 g/d) as a therapeutic option to enhance LDL cholesterol lowering in those at risk.

A De-emphasis on Total Fat and a Sharper Focus on the Kinds of Fat Ingested

A major focus of the dietary approach in ATP III is reducing CHD risk by limiting dietary fatty acids that raise LDL cholesterol concentrations. The focus is not on total fat; rather, TLC emphasizes a reduction in saturated fatty acids and calorie control to prevent obesity. Furthermore, ATP III recognizes that carbohydrate intakes above 60% may not be advantageous. ATP III underscores the importance of individualizing dietary prescriptions of types and amounts of fat, carbohydrate, and calories to optimize prevention and treatment of metabolic syndrome, diabetes, and their associated lipid abnormalities.

Unsaturated fatty acids do not raise LDL cholesterol when substituted for carbohydrate in the diet. The benefits of this approach are seen most clearly in those with metabolic syndrome or diabetes in whom high levels of carbohydrates accompanying a very low-fat diet may produce unwanted effects on the lipid/lipoprotein profile [44]. Those who question the recommendations of intakes of fat in the 25% to 35% range have raised concerns regarding both cancer and obesity. Importantly, there are no convincing data to confirm a causal association

between ATP III's proposed fat intake of 25% to 35% and cancer [45–47]. Also, there is no convincing evidence linking level of fat intake with obesity [48,49] as long as total calories are controlled. Indeed, isocaloric exchange of fat for carbohydrate does not produce weight gain over a period of many months [50,51]. Some patients may prefer a higher total (unsaturated) fat intake for purposes of satiety and perceived ease of adherence to lower calorie intake over the long term. This approach can be explored through skillful dietary intervention.

The concern of the ATP III panel was that high intakes of carbohydrates (>60% of calories) in overweight/obese persons can aggravate the risk factor status of those with metabolic syndrome or diabetes due to higher blood sugars, fasting and postprandial lipids, and lower HDL cholesterol [44,52–55]. ATP III recommends that for persons with lipid disorders or the metabolic syndrome, extremes of total fat intake or carbohydrate intake—either high or low—should be avoided. In such persons, total fat intakes should range from 25% to 35% of calories, and carbohydrates should be derived from complex rather than refined sources. For some persons with the metabolic syndrome, a total fat intake of 30% to 35% may reduce lipid and nonlipid risk factors. Individualized dietary prescriptions are needed in these cases.

Clinical studies show that monounsaturated fatty acid (MUFA) lowers LDL cholesterol relative to saturated fatty acids [56]. Moreover, substitution of MUFAs for saturated fatty acids results in a more favorable balance of HDL cholesterol and triglyceride compared with very high intakes of carbohydrates (>60% of calories). Little or no decrease in HDL cholesterol and often a decrease in triglycerides occurs with increased dietary MUFA intake [57,58]. Epidemiologic studies point to low rates of CHD in Mediterranean populations that have higher intakes of MUFA [59]. Increased MUFA from adding nuts to the diet may explain, in part, the reduced risk of CHD observed in Seventh Day Adventists [60], as well as the 86,016 nurses followed in the Nurses Health Study [61]. Despite increased interest in olive oil and other MUFAs, there are inadequate data from controlled clinical trials to show the benefit of MUFA on CHD endpoints. This lack of MUFA data contrasts with several trials that replaced saturated fat with polyunsaturated fat (discussed in the following text). ATP III suggests that intake of MUFA can range up to 20% of calories, and that MUFA should be derived from vegetable sources, including plant oils and nuts.

The other unsaturated fatty acids that may be increased when saturated fatty acids are reduced (or if it is deemed desirable to decrease carbohydrate intake) are polyunsaturated fatty acids (PUFAs). These include either omega-6 (n-6) fatty acids (seed oils) such as linoleic acid, an essential fatty acid, or omega-3 (n-3) fatty acids such as eicosapentanoic acid (EPA) or docosahexanoic acid. (DHA) Compared with cis-MUFA, n-6 PUFA may cause a slightly greater reduction in LDL cholesterol levels [56]. A careful meta-analysis comparing effects of cis-MUFA and PUFA concluded that there was no significant difference in LDL or HDL cholesterol levels when oils high in either fatty acid were substituted in the diet. The meta-analysis suggested that the effects of MUFA and PUFA on blood lipids were not substantial enough to choose one over the other on these criteria alone [62].

Several controlled, clinical trials have compared the effects of cholesterol-lowering diets with an increase in n-6 PUFA as a replacement for saturated fatty acids on coronary endpoints [12]. Meta-analysis of trial results indicates that substitution of n-6 PUFA for saturated fatty acids reduces risk for CHD [10,11,56]. Perhaps even more impressive, however, is a growing body of evidence that relates improvement in CHD mortality with n-3 (fish oil) intake [63]. This topic is discussed later in this article. ATP III suggests that n-6 PUFA are one form of unsaturated fatty acids that can replace saturated fat. Most n-6 PUFAs should be derived from liquid vegetable oils, semi-liquid margarines, and other margarines low in trans fatty acids. Intakes of n-6 PUFA can range up to 10% of total calories.

As noted previously, when carbohydrate is substituted for MUFA, especially from refined sources, there is frequently a fall in HDL cholesterol and a rise in triglycerides [56]. There are conflicting data regarding whether the triglyceride rise is chronic. Nonetheless, when complex carbohydrates with higher fiber contents are consumed, the potential rise in triglycerides or fall in HDL cholesterol are reportedly reduced [64–66]. This may be further explained by the concept of the "glycemic" potential of different foods. Simply put, some carbohydrates elevate blood sugar more than others do. The glycemic index (GI) is a measure used to categorize foods by their ability to elevate blood glucose levels compared with a known standard. Observational studies using food frequency questionnaires have reported that GI varied positively with triglycerides and inversely with HDL cholesterol [67,68]. Due to the absence of controlled, clinical trial data at the time of publication, ATP III did not advocate inclusion of the GI in recommending TLC diets because current research findings remain inconclusive. GI can vary widely for each group of foods, attributed to factors such as its form when eaten, the way it is processed, how it is chewed, how it is emptied from the stomach, and an individual's physiologic and metabolic responses [69]. The recently published international table of GI and glycemic load values will permit more standardized research on this important topic [70•]. Clearly, continued investigation into ways to categorize carbohydrate intake is warranted. In summary, ATP III recommended that carbohydrate intakes should be limited to 60% of total calories in persons with the metabolic syndrome. Lower intakes (*eg*, 50% of calories) should be considered for persons with elevated triglycerides or low HDL cholesterol. Regardless of intakes, most of the carbohydrate intake should come from grain products, especially whole grains, vegetables, fruits, and fat-free and low-fat dairy products.

Recommendation of Regular Physical Activity and Weight Loss As Important First Steps in Reversing the Adverse Metabolic Trends of the Metabolic Syndrome

In ATP III, emphasis on weight reduction is delayed until after dietary measures for LDL cholesterol lowering are introduced. After an adequate trial of LDL cholesterol-lowering measures, the focus is on the metabolic syndrome and its associated abnormalities in HDL cholesterol, triglyceride, and glucose. Weight reduction and daily exercise are recommended. Physicians need to remind patients that small, achievable amounts of weight loss can improve blood pressure, lipids, and glucose metabolism [71].

The potential for benefit is great. Utilizing a lower saturated fat intake, more fiber, and more exercise, two large, clinical trials of those with impaired glucose tolerance have shown that diabetes can be prevented in 58% of subjects [72•,73•]. These trials were published after ATP III guidelines were released, but corroborate the emphasis of ATP III on treating the metabolic syndrome.

Emphasizing Healthy Aspects of Diet

Epidemiologic studies strongly suggest that other nutrient factors affect baseline risk for CHD. Kris-Etherton *et al*. [74•] noted that although hard to define precisely, a "Mediterranean style-diet emphasizes a diet that is high in fruits, vegetables, bread, other forms of cereals, potatoes, beans, nuts, and seeds. It includes olive oil as an important fat source and dairy products, fish, and poultry consumed in low to moderate amounts; eggs consumed zero to 4 times weekly; and little red meat. In addition, wine is consumed in low to moderate amounts. This dietary pattern is based on food patterns typical of many regions in Greece and southern Italy in the early 1960s. The Mediterranean-style Step I diet used in the Lyon Diet Heart study was comparable to this pattern, but uniquely different in that it was high in alpha-linolenic acid." The Lyon Study [75•] was a randomized, dietary clinical trial of myocardial infarction (MI) survivors that fed subjects a Mediterranean-style diet high in alpha-linolenic acid (ALA) due to a canola oil-enriched margarine, but had more fiber, monounsaturates, and less dietary cholesterol and saturated fat than the control group. There was no significant difference in alcohol intake between the groups. The benefit was striking, with a significant reduction in CHD deaths that was independent of any effects on lipids and is consistent with an emerging data base suggesting a reduction in sudden death in those who have diets enriched in n-3 PUFA. Kris-Etherton *et al*. [74•] noted that n-3 PUFAs could have exerted their cardioprotective effects via multiple mechanisms, including effects on arrhythmias in post-MI subjects, inflammation with decrease in the synthesis of cytokines and mitogens, the stimulation of endothelial-derived nitric oxide, the thrombotic process as fish oils prolonged the bleeding time, and prostaglandin and leukotriene precursors.

Omega-3 polyunsaturated fatty acids

Omega-3 PUFAs or omega-3 fatty acids occur in certain vegetable sources such as soybean, canola oil, English walnuts, or flaxseed oil as ALA (18:3). Marine lipids include EPA (20:5) and DHA (22:6). High intakes of marine n-3 fatty acids reduce triglyceride levels [76]; this effect appears to be secondary to decreased very low-density lipoprotein (VLDL) production [77]. Generally, marine n-3 fatty acids have no effect on LDL cholesterol levels, but large doses have been shown to reciprocally increase LDL cholesterol levels in persons with hypertriglyceridemia [78].

The data for primary prevention of CHD was not as strong as that for secondary prevention when the ATP guidelines were written. The effect in most, but not all, studies appeared to be that moderate fish consumption reduced sudden cardiac death or fatal occurrences of CHD [79–81]. Some prospective cohort studies did not show a protective effect of fish oil at all [82,83]. This is an important finding because more than half of coronary mortality is in the form of sudden death. In the Framingham study, 50% of the sudden deaths in men and 64% in women occur in persons without prior CHD, whereas 18% of coronary attacks in men and 24% in women present as sudden death [84]. Albert *et al*. [85••] extended earlier observations that fish consumption reduced sudden death in the Physician's Health Study. They noted in a prospective case-control analysis of healthy subjects who had levels of n-3 fatty acid in blood drawn at the beginning of the trial that those in the upper quartile had an 81% less risk of sudden death than those in the bottom quartile of the distribution [85••]. Earlier data from the Physician's Health Study had shown that n-3 fatty acids did not predict MI [86]. Albert *et al*.'s data is consistent with the nested, case-control study by Siscovick *et al*. [87] that found an inverse relationship between risk for sudden cardiac death and both reported intake of marine n-3 fatty acids and erythrocyte n-3 fatty acid level.

The data for increased n-3 fatty acids reducing sudden death in those with CHD is striking. Four clinical trials suggest that n-3 fatty acids from marine or plant sources reduce sudden death and overall death in populations with pre-existing cardiovascular disease. The DART trial [88] was a relatively large, secondary prevention trial in which subjects advised to eat fatty fish had a 29% reduction in 2-year all-cause mortality compared with those not so advised, although MI and coronary death were not specifically reduced. The Lyon Heart trial [75] included increased intakes of ALA as part of a Mediterranean diet. Compared with the control group, subjects consuming the Mediterranean diet had fewer coronary events. The authors attributed some of the benefit to higher intakes of n-3 fatty acids. In a small supplement trial, Singh *et al*. [89] treated patients with suspected acute MI with fish oil capsules (EPA, 1.08 g/d), mustard oil (ALA, 2.9 g/d), or placebo. After 1 year, total cardiac events were significantly less in the groups on fish oil and mustard oil supplements. Furthermore, the large, placebo-controlled (although unblinded) Gruppo Italiano per lo Studio della

Table 3. Macronutrient recommendations for the Therapeutic Lifestyle Change diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%–35% of total calories*
Carbohydrate†	50%–60% of total calories*
Dietary fiber	20–30 g/d
Protein	Approximately 15% of total calories

*Diet allows for an increase in total fat to 35% of total calories and a reduction in carbohydrate to 50% for patients with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.
†Carbohydrates should derive predominantly from foods rich in complex carbohydrates and fiber, including grains (especially whole grains), fruits, and vegetables.
Adapted from National Cholesterol Education Program [1••].

Sopravvivenza nell'Infarto Miocardio (GISSI) Prevenzione trial [63] administered fish oil supplements containing n-3 fatty acids (1 g/d of fish oil, n=2836 subjects) and compared coronary outcomes with control subjects (n=2828). The group receiving fish oil supplements had a reduction of sudden death of 45% [63]. A reanalysis of this study showed the early influence of giving the n-3 fatty acids, supporting the contention that an antiarrhythmic effect was at the basis of the benefit [90]. Leaf [91] argued that an excess of n-6 PUFAs and their metabolites when unbalanced by n-3 fatty acids might increase coronary atherosclerosis and sudden cardiac arrhythmic deaths.

A note of caution regarding general recommendations about fish was provided by data that show some fish have a high mercury content and the toxic effects of mercury could attenuate the protective effects of fish. Also, the cardiac benefit of fish does not extend to preventing consistently significant angiographic progression or restenosis after angioplasty.

The ATP III panel recognized that the mechanisms whereby n-3 fatty acids would reduce coronary events were unknown and might be multiple. Data from Leaf's laboratory [91] suggest an important effect on raising the threshold for ischemic ventricular arrhythmias. ATP III suggested that higher dietary intakes of n-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of the evidence was only moderate at its writing and there was concern over safety issues. ATP III supports the American Heart Association's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective n-3 fatty acids. A dietary recommendation for a specific amount of n-3 fatty acids was not made.

Although the data suggesting benefit of fish oil for those at risk for arrhythmic death (post-MI survivors) are compelling, many physicians are unaware that some fish oil capsules that are labeled as 1-g doses may only contain 300 mg of DHA plus EPA. This is not what was given in GISSI Prevenzione. (they gave fish oil capsules containing 850 to 882 mg of EPA and DHA as ethyl esters.) If safety issues are not of concern and proper dosages can be given, it may be reasonable to recommend for those at high risk two to three meals of fish per week, or if patients are unable to tolerate fish intake to that extent or are at high risk, fish oil capsules to duplicate what was given in DART and GISSI Prevenzione can be prescribed.

Application of Therapeutic Lifestyle Change

The ATP III panel suggested an orderly sequence of interactions between physician and patient to ensure optimal TLC. After the initial visit, when therapeutic diet and advice about regular exercise are introduced, the patient should be followed-up in approximately 6 weeks. If the LDL cholesterol goal has been achieved, or if progress in LDL lowering has occurred, dietary therapy should be continued and the patient encouraged in their adherence (Table 3). If the LDL goal is not achieved, the physician has several options, beginning with assessment of adherence to the recommended diet. The assistance of a nutrition professional for formal nutritional instruction and counseling (medical nutrition therapy) is especially valuable at this time. Second, additional therapeutic dietary adjuncts for LDL cholesterol lowering (plant stanols/sterols and increased viscous fiber) can be emphasized to enhance LDL lowering. At the third visit, if LDL cholesterol goals are still not met, the focus should shift to treating the metabolic syndrome as noted previously. Attention to weight reduction is key, and emphasis is on regular physical activity to sustain any weight loss.

How well this program works depends upon many factors. Knowledge, attitude, and readiness to change in the patient are important considerations. Time, training, and counseling skills of the interventionist will also influence results. Addition of physical activity can have tremendous benefits in both weight control and lipid management, but again the level of adherence and motivation of the patient are essential features. Benefits of physical activity increase with increasing levels of activity, but benefits are likely even if modest levels for approximately 30 minutes are carried out on most days of the week [96]. Despite a lack of compelling evidence that counseling results in long-term changes in physical activity behaviors [97], adherence to the

Surgeon General's recommendations of regular physical activity remains a laudable goal. Finding more effective ways of counseling patients to help stimulate adherence to regular physical activity should continue to command research attention. The Patient-centered Assessment & Counseling for Exercise & Nutrition (PACE) program is one example of a cost- and time-effective way of working with patients to achieve more physical activity that might prove useful in some settings [98].

A recent review of the literature on behavioral counseling on physical activity by the US Preventive Services Task Force stated that the evidence was insufficient to recommend for or against behavioral counseling in primary care settings to promote physical activity [99•]. Large, prospective studies are needed to evaluate the benefits and risks associated with this approach over the long term (>2 years) and with objective data regarding why subjects drop out of such trials. The potential benefits of diet and exercise have already been shown (as mentioned previously) in high-risk subjects with impaired glucose tolerance in two large, long-term, clinical trials [72•,73•].

Conclusions

The ATP III panel presents an evidence-based approach to nonpharmacologic therapy linking diet, physical activity, weight loss, and behavioral change. This therapeutic lifestyle change has the potential to improve lipids and overall cardiovascular health in various ways. In a society where there is growing concern over expanding waistlines, obesity, and increased incidence of diabetes, the focus on TLC by the ATP III guidelines should provide needed guidance to practitioners who wish to not only improve lipids profiles and CHD risk, but prevent metabolic syndrome and type II diabetes as well.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• **Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).** *JAMA* 2001, **285:**2486.

A concise summary of the larger document that is found at http://www.nhlbi.nih.gov/guidelines.

2. Stone NJ, Blum C: *Management of Lipids in Clinical Practice,* edn 4. Cado, Oklahoma: Professional Communications; 2002.
3. Yu-Poth S, Zhao G, Etherton T, *et al.*: **Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis.** *Am J Clin Nutr* 1999, **69:**632–646.
4. Walden CE, Retzlaff BM, Buck BL, McCann BS, Knopp RH: **Lipoprotein lipid response to the National Cholesterol Education Program step II diet by hypercholesterolemic and combined hyperlipidemic women and men.** *Arterioscler Thromb Vasc Biol* 1997, **17:**375–382.
5. Ginsberg HN, Kris-Etherton P, Dennis B, Elmer PJ, *et al.*, for the Delta Research Group: **Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects. The Delta Study, Protocol 1.** *Arterioscler Thromb Vasc Biol* 1998, **18:**441–449.
6. Niinikoski H, Lapinleimu H, Viikari J, *et al.*: **Growth until three years of age in a prospective randomized trial of a diet with reduced saturated fat and cholesterol.** *Pediatrics* 1997, **99:**687–694.
7. Obarzanek E, Hunsberger SA, Van Horn L, *et al.*: **Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC).** *Pediatrics* 1997, **100:**51–59.
8. Sun Z, Welty FK, Dolnikowski GG, Lichtenstein AH, Schaefer EJ: **Effects of a National Cholesterol Education Program Step II Diet on apolipoprotein A-IV metabolism within triacylglycerol-rich lipoproteins and plasma.** *Am J Clin Nutr* 2001, **74:**308–314.
9. Gordon DJ: **Cholesterol and mortality: what can meta-analysis tell us.** In *Cardiovascular Disease 2: Cellular and Molecular Mechanisms, Prevention, and Treatment.* Edited by Gallo LL. New York: Plenum Press; 1995:333–340.
10. Gordon DJ: **Cholesterol lowering and total mortality.** In *Lowering Cholesterol in High-risk Individuals and Populations.* Edited by Rifkind BM. New York: Marcel Dekker; 1995:33–47.
11. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD: **Cholesterol reduction yields clinical benefit: impact of statin trials.** *Circulation* 1998, **97:**946–952.
12.• Brousseau ME, Schaefer EJ: **Diet and coronary heart disease: clinical trials.** *Curr Atheroscler Rep* 2000, **2:**487–493.

Careful analysis of the major dietary trials.

13. Watts GF, Lewis B, Brunt JN, *et al.*: **Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St. Thomas' Atherosclerosis Regression Study (STARS).** *Lancet* 1992, **339:**563–569.
14. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, *et al.*: **Efficacy of a National Cholesterol Education Program Step 2 diet in normolipidemic and hypercholesterolemic middle-aged and elderly men and women.** *Arterioscler Thromb Vasc Biol* 1995, **15:**1079–1085.
15. Knopp RH, Walden CE, Retzlaff BM, *et al.*: **Long-term cholesterol-lowering effects of 4 fat-restricted diets in hypercholesterolemic and combined hyperlipidemic men. The Dietary Alternatives Study.** *JAMA* 1997, **278:**1509–1515.
16. Knopp RH, Retzlaff B, Walden C, *et al.*: **One-year effects of increasingly fat-restricted, carbohydrate-enriched diets on lipoprotein levels in free-living subjects.** *Proc Soc Exp Biol Med* 2000, **225:**191–199.
17. Velez-Carrasco W, Lichtenstein AH, Welty FK, *et al.*: **Dietary restriction of saturated fat and cholesterol decreases HDL apoA-I secretion.** *Arterioscler Thromb Vasc Biol* 1999, **19:**918–924.
18. Stefanick ML, Mackey S, Sheehan M, *et al.*: **Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol.** *N Engl J Med* 1998, **339:**12–20.
19. Caggiula AW, Christakis G, Farrand M, *et al.*: **The Multiple Risk Intervention Trial (MRFIT). IV. Intervention on blood lipids.** *Prev Med* 1981, **10:**443.
20. Stamler J, Shekelle R: **Dietary cholesterol and human coronary heart disease. The epidemiologic evidence.** *Arch Pathol Lab Med* 1988, **112:**1032–1040.
21. Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ: **Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels.** *N Engl J Med* 1999, **340:**1933–1940.
22. Hu FB, Stampfer MJ, Manson JE, *et al.*: **Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women.** *Am J Clin Nutr* 1999, **70:**1001–1008.
23. Kromhout D, Menotti A, Bloemberg BP, *et al.*: **Dietary saturated and trans fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study.** *Prev Med* 1995, **24:**308–315.

24. Pietinen P, Ascherio A, Korhonen P, *et al.*: **Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.** *Am J Epidemiol* 1997, **145:**876–887.
25. Willett WC, Stampfer MJ, Manson JE, *et al.*: **Intake of trans-fatty acids and risk of coronary heart disease among women.** *Lancet* 1993, **341:**581–585.
26. Han SN, Leka LS, Lichtenstein AH, *et al.*: **Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia.** *J Lipid Res* 2002, **43:**445–452.
27. Hopkins PN: **Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review.** *Am J Clin Nutr* 1992, **55:**1060–1070.
28. Clarke R, Frost C, Collins R, Appleby P, Peto R: **Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies.** *BMJ* 1997, **314:**112–117.
29. Ernst ND, Sempos CT, Briefel RR, Clark MB: **Consistency between U.S. dietary fat intake and serum total cholesterol concentrations: the National Health and Nutrition Examination Surveys.** *Am J Clin Nutr* 1997, **66(suppl 4):**965S–972S.
30. Tippett KS, Cleveland LE: **How current diets stack up: comparison with dietary guidelines.** In *America's Eating Habits: Changes and Consequences.* Washington, DC: United States Department of Agriculture, Economic Research Service; 2000:51–70.
31. Weggemans RM, Zock PL, Ordovas JM, Ramos-Galluzzi J, Katan MB: **Genetic polymorphisms and lipid response to dietary changes in humans.** *Eur J Clin Invest* 2001, **31:**950–957.
32. Hu FB, Stampfer MJ, Rimm EB, *et al.*: **A prospective study of egg consumption and risk of cardiovascular disease in men and women.** *JAMA* 1999, **281:**1387–1394.
33. Weggemans RM, Zock PL, Katan MB: **Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis.** *Am J Clin Nutr* 2001, **73:**885–891.
34. Anderson JW, Hanna TJ: **Impact of nondigestible carbohydrates on serum lipoproteins and risk for cardiovascular disease.** *J Nutr* 1999, **129:**1457S–1466S.
35. Meyer KA, Kushi LH, Jacobs DR Jr, *et al.*: **Carbohydrates, dietary fiber, and incident type 2 diabetes in older women.** *Am J Clin Nutr* 2000, **71:**921–930.
36. Brown L, Rosner B, Willett WW, Sacks FM: **Cholesterol-lowering effects of dietary fiber: a meta-analysis.** *Am J Clin Nutr* 1999, **69:**30–42.
37. Hunninghake DB, Miller VT, LaRosa JC, *et al.*: **Hypocholesterolemic effects of a dietary fiber supplement.** *Am J Clin Nutr* 1994, **59:**1050–1054.
38. Ludwig DS, Pereira MA, Kroenke CH, *et al.*: **Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults.** *JAMA* 1999, **282:**1539–1546.
39. Hallikainen MA, Sarkkinen ES, Gylling H, Erkkila AT, Uusitupa MI: **Comparison of the effects of plant sterol ester and plant stanol ester-enriched margarines in lowering serum cholesterol concentrations in hypercholesterolaemic subjects on a low-fat diet.** *Eur J Clin Nutr* 2000, **54:**715–725.
40. Westrate JA, Meijer GW: **Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects.** *Eur J Clin Nutr* 1998, **52:**334–343.
41. Blair SN, Capuzzi DM, Gottlieb SO, *et al.*: **Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy.** *Am J Cardiol* 2000, **86:**46–52.
42. • Law M: **Plant sterol and stanol margarines and health.** *BMJ* 2000, **320:**861–864.

Thoughtful discussion of plant stanol and sterol supplementation of the diet and its potential role in reducing coronary heart disease through improvement of low-density lipoprotein cholesterol.

43. Noakes M, Clifton P, Ntanios F, *et al.*: **An increase in dietary carotenoids when consuming plant sterols or stanols is effective in maintaining plasma carotenoid concentrations.** *Am J Clin Nutr* 2002, **75:**79–86.
44. Reaven G: **Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease.** *Circulation* 2002, **106:**286–288.
45. Zock PL: **Dietary fats and cancer.** *Curr Opin Lipidol* 2001, **12:**5–10.
46. Holmes MD, Hunter DJ, Colditz GA, *et al.*: **Association of dietary intake of fat and fatty acids with risk of breast cancer.** *JAMA* 1999, **281:**914–920.
47. Rose DP: **Dietary fatty acids and cancer.** *Am J Clin Nutr* 1997, **66(suppl 4):**998S–1003S.
48. Heitmann BL, Lissner L, Sorensen TI, Bengtsson C: **Dietary fat intake and weight gain in women genetically predisposed for obesity.** *Am J Clin Nutr* 1995, **61:**1213–1217.
49. Lissner L, Heitmann BL: **The dietary fat: carbohydrate ratio in relation to body weight.** *Curr Opin Lipidol* 1995, **6:**8–13.
50. Hirsch J, Hudgins LC, Leibel RL, Rosenbaum M: **Diet composition and energy balance in humans.** *Am J Clin Nutr* 1998, **67(suppl 3):**551S–555S.
51. Leibel RL, Hirsch J, Appel BE, Checani GC: **Energy intake required to maintain body weight is not affected by wide variation in diet composition.** *Am J Clin Nutr* 1992, **55:**350–355.
52. Garg A: **High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis.** *Am J Clin Nutr* 1998, **67(suppl 3):**577S–582S.
53. Chen YD, Coulston AM, Zhou MY, Hollenbeck CB, Reaven GM: **Why do low-fat high-carbohydrate diets accentuate postprandial lipemia in patients with NIDDM?** *Diabetes Care* 1995, **18:**10–16.
54. Grundy SM: **Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol.** *N Engl J Med* 1986, **314:**745–748.
55. Mensink RP, Katan MB: **Effect of monounsaturated fatty acids versus complex carbohydrates on high-density lipoproteins in healthy men and women.** *Lancet* 1987, **1:**122–125.
56. Mensink RP, Katan MB: **Effects of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials.** *Arterioscler Thromb* 1992, **12:**911–9.
57. Garg A: **High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis.** *Am J Clin Nutr* 1998, **67(suppl 3):**577S–582S.
58. Kris-Etherton PM, Kris-Etherton PM, Binkoski AE, *et al.*: **Dietary fat: assessing the evidence in support of a moderate-fat diet; the benchmark based on lipoprotein metabolism.** *Proc Nutr Soc* 2002, **61:**287–298.
59. Verschuren WM, Jacobs DR, Bloemberg BP, *et al.*: **Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study.** *JAMA* 1995, **274:**131–136.
60. Fraser GE, Sabate J, Beeson WL, Strahan TM: **A possible protective effect of nut consumption on risk of coronary heart disease: the Adventist Health Study.** *Arch Intern Med* 1992, **152:**1416–1424.
61. Hu FB, Stampfer MJ, Manson JE, *et al.*: **Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study.** *BMJ* 1998, **317:**1341–1345.
62. Gardner CD, Kraemer HC: **Monounsaturated versus polyunsaturated dietary fat and serum lipids A meta-analysis.** *Arterioscler Thromb Vasc Biol* 1995, **15:**1917–1927.

63. **Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.** *Lancet* 1999, **354:**447–455.
64. Jenkins DJ, Wolever TM, Rao AV, *et al.*: **Effect on blood lipids of very high intakes of fiber in diets low in saturated fat and cholesterol.** *N Engl J Med* 1993, **329:**21–26.
65. Turley ML, Skeaff CM, Mann JI, Cox B: **The effect of a low-fat, high-carbohydrate diet on serum high density lipoprotein cholesterol and triglyceride.** *Eur J Clin Nutr* 1998, **52:**728–732.
66. Vuksan V, Sievenpiper JL, Owen R, *et al.*: **Beneficial effects of viscous dietary fiber from Konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial.** *Diabetes Care* 2000, **23:**9–14.
67. Liu S, Willett WC, Stampfer MJ, *et al.*: **A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women.** *Am J Clin Nutr* 2000, **71:**1455–1461.
68. Liu S, Manson JE, Stampfer MJ, *et al.*: **Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women.** *Am J Clin Nutr* 2001, **73:**560–566.
69. Levin RJ: **Carbohydrates.** *In Modern Nutrition in Health and Disease,* edn 9. Edited by Shils ME, Olson JA, Shine M, Ross AC. Baltimore: Williams and Wilkins; 1999:63–64.
70.• Foster-Powell K, Holt SH, Brand-Miller JC: **International table of glycemic index and glycemic load values: 2002.** *Am J Clin Nutr* 2002, **76:**5–56.

Useful resource for determining the effect of glycemic index and glycemic load values on metabolic status.

71. Su HY, Sheu WH, Chin HM, *et al.*: **Effect of weight loss on blood pressure and insulin resistance in normotensive and hypertensive obese individuals.** *Am J Hypertens* 1995, **8:**1067–1071.
72.• Knowler WC, Barrett-Connor E, Fowler SE, *et al.*: **Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin.** *N Engl J Med* 2002, **346:**393–403.

Important trial confirmed the value of lifestyle intervention in preventing diabetes and found that lifestyle change was even more potent than drug therapy.

73.• Tuomilehto J, Lindstrom J, Eriksson JG, *et al.*: **Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.** *N Engl J Med* 2001, **344:**1343–1350.

Published at approximately the same time as ATP III, the findings support the concept of Therapeutic Lifestyle Change as espoused by ATP III.

74.• Kris-Etherton P, Eckel RH, Howard BV, St. Jeor S, Bazzarre TL: **AHA Science Advisory: Lyon Diet Heart Study. Benefits of a Mediterranean-style, National Cholesterol Education Program/American Heart Association Step I Dietary Pattern on Cardiovascular Disease.** *Circulation* 2001, **103:**1823–1825.

Careful analysis of what we have learned from this trial and what we need to learn to understand how to use this information successfully.

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

An important clinical trial of a Mediterranean diet supplemented with a canola oil-enriched margarine. Increased levels of omega-3 fatty acids were noted in the treatment group. The striking benefit was not due to lipid alterations.

76. Roche HM, Gibney MJ: **Effects of long-chain n-3 polyunsaturated fatty acids on fasting and postprandial triacylglycerol metabolism.** *Am J Clin Nutr* 2000, **71:**232S–237S.
77. Harris WS: **Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review.** *J Lipid Res* 1989, **30:**785–807.
78. Harris WS: **n-3 fatty acids and serum lipoproteins: human studies.** *Am J Clin Nutr* 1997, **65(suppl 5):**1645–1654.
79. Albert CM, Hennekens CH, O'Donnell CJ, *et al.*: **Fish consumption and risk of sudden cardiac death.** *JAMA* 1998, **279:**23–28.
80. Daviglus ML, Stamler J, Orencia AJ, *et al.*: **Fish consumption and the 30-year risk of fatal myocardial infarction.** *N Engl J Med* 1997, **336:**1046–1053.
81. Dolecek TA, Granditis G: **Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT).** *World Rev Nutr Diet* 1991, **66:**205–216.
82. Morris MC, Manson JE, Rosner B, *et al.*: **Fish consumption and cardiovascular disease in the Physicians' Health Study: a prospective study.** *Am J Epidemiol* 1995, **142:**166–175.
83. Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC: **Trans fatty acids and coronary heart disease.** *N Engl J Med* 1999, **340:**1994–1998.
84. Kannel WB, Schatzkin A: **Sudden death: lessons from subsets in population studies.** *J Am Coll Cardiol* 1985, **5(suppl 6):**141B–149B.
85.•• Albert CM, Campos H, Stampfer MJ, *et al.*: **Blood levels of long-chain n-3 fatty acids and the risk of sudden death.** *N Engl J Med* 2002, **346:**1113–1118.

The authors conducted a prospective, nested, case-control analysis among apparently healthy men who were followed for up to 17 years in the Physicians' Health Study. The strength of the study was the measurement of fatty acid composition of previously collected blood samples by gas-liquid chromatography in those whose first manifestion of cardiovascular disease was sudden death. Baseline levels of omega-3 fatty acids were inversely related with sudden death even after adjustment.

86. Guallar E, Hennekens CH, Sacks FM, Willett WC, Stampfer MJ: **A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians.** *J Am Coll Cardiol* 1995, **25:**387–394.
87. Siscovick DS, Raghunathan TE, King I, *et al.*: **Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest.** *JAMA* 1995, **274:**1363–1367.
88. Burr ML, Fehily AM, Gilbert JF, *et al.*: **Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART).** *Lancet* 1989, **2:**757–761.
89. Singh RB, Niaz MA, Sharma JP, *et al.*: **Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival—4.** *Cardiovasc Drugs Ther* 1997, **11:**485–491.
90. Marchioli R, Barzi F, Bomba E, *et al.*: **Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione.** *Circulation* 2002, **105:**1897–1903.
91. Leaf A: **On the reanalysis of the GISSI-Prevenzione.** *Circulation* 2002, **105:**1874–1875.
92. Rissanen T, Voutilainen S, Nyyssonen K, Lakka TA, Salonen JR: **Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study.** *Circulation* 2000, **102:**2677–2679.
93. Sacks FM, Stone PH, Gibson CM, *et al.*: **Controlled trial of fish oil for regression of human coronary atherosclerosis.** *J Am Coll Cardiol* 1995, **25:**1492–1498.
94. von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H: **The Effect of dietary n-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial.** *Ann Intern Med* 1999, **130:**554–562.
95. Leaf A, Jorgensen MB, Jacobs AK, *et al.*: **Do fish oils prevent restenosis after coronary angioplasty?** *Circulation* 1994, **90:**2248–2257.

96. *Physical Activity and Health: a Report of the Surgeon General*. U.S. Department of Health and Human Services. McLean, VA: International Medical Publishing; 1996.
97. Blackburn DG: **Establishing an effective framework for physical activity counseling in primary care settings.** *Nutr Clin Care* 2002, **5:**95–102.
98. Schwenk TL, Chenoweth J, Carter R, *et al.*: **A multisite field test of the acceptability of physical activity counseling in primary care: project PACE.** *Am J Prev Med* 1996, **12:**73–81.
99.• US Preventive Services Task Force: **Behavioral counseling in primary care to promote physical activity: recommendations and rationale.** *Ann Intern Med* 2002, **137:**205–207.
A statement summarizing the Task Force recommendations on counseling by primary care physicians to promote physical activity. They pointed out the many significant benefits to reduce chronic disease morbidity. Nonetheless, they concluded that the evidence is insufficient to recommend for or against behavioral counseling in primary care settings to promote physical activity. They noted that trials in adult primary care patients were of variable quality and had mixed results.