UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

ORIGINAL

In the Matter of	)	
	)	
POM WONDERFUL LLC and ROLL GLOBAL, as successor in interest to Roll International companies and	)	Docket No. 9344 PUBLIC
	)	
STEWART A. RESNICK, LYNDA RAE RESNICK, and MATTHEW TUPPER, individually and as officers of the companies.	)	

RESPONDENTS' MOTION FOR ADMISSION OF DOCUMENTS

Respondents hereby request that the Court include documents labeled RX1692, RX5000, RX5001, RX5003, RX5007, RX5010, RX5017, RX5019, RX5020, RX5021, RX5022, and RX5025 in the evidentiary record. An index of these documents, along with the documents themselves, are attached for the Court's convenience. See Exhibit A.

These documents were used by Respondents' counsel during witness examinations and should properly be admitted into the record. One document, RX5007, was admitted into the record at the time of hearing. Respondents' counsel understood from the Court that they should address the admission of the remaining documents, RX1692, RX5000, RX5001, RX5003, RX5010, RX5017, RX5019, RX5020, RX5021, RX5022, and RX5025, at a later stage of the proceedings. This is the appropriate time to admit these documents into the record, before the record closes. To Respondents' surprise, Complaint Counsel has now refused to consent to the introduction of these documents. During our meet and confer with Complaint Counsel on this issue, Counsel failed to identify any valid grounds for objection to the documents. As the face of the documents make clear, there are no issues with admissibility or reliability. Because these documents were used with witnesses at the hearing, Respondents contend that it will be useful

for the Court to have the documents available in the record for reference. As this Court has acknowledged throughout the proceedings, the standard for admission of evidence in adjudicatory proceedings under the Commission's Rules of Practice is permissive and, absent a serious showing of unreliability, inauthenticity, or irrelevance, the Court should admit the documents. *See* Rule 3.43(b).

For the foregoing reasons, RX1692, RX5000, RX5001, RX5003, RX5010, RX5017, RX5019, RX5020, RX5021, RX5022, and RX5025 should be admitted.

Dated: November 16, 2011

Respectfully submitted,

/s/ Skye Perryman

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Counsel for Respondents

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BEFORE THE FEDERAL TRADE COMMISSION

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	)	
	)	
	)	
	)	

MEET AND CONFER STATEMENT

On November 14, 2011, Respondents met and conferred with Complaint Counsel regarding the enumerated exhibits and Complaint Counsel refused to consent to their inclusion in the record. On November 16, 2011, Respondents contacted Complaint Counsel about a remaining exhibit, RX1692, and Complaint Counsel declined to consent to the admission of this exhibit.

Dated: November 16, 2011

Respectfully submitted,

/s/ Skye Perryman

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Counsel for Respondents

UNITED STATES OF AMERICA
FEDERAL TRADE COMMISSION

In the Matter of	)	
	)	
POM WONDERFUL LLC and	)	
ROLL GLOBAL LLC,	)	
as successor in interest to Roll	)	
International Corporation,	)	
	)	
companies, and	)	Docket No. 9344
	)	PUBLIC
STEWART A. RESNICK,	)	
LYNDA RAE RESNICK, and	)	
MATTHEW TUPPER, individually and	)	
as officers of the companies.	)	

CERTIFICATE OF SERVICE

I hereby certify that this is a true and correct copy of Respondents' **MOTION FOR ADMISSION OF DOCUMENTS**, and that on this 16th day of November, 2011, I caused the foregoing to be served by FTC E-File, hand delivery and e-mail on the following:

Donald S. Clark
The Office of the Secretary
Federal Trade Commission
600 Pennsylvania Avenue, NW
H-159
Washington, DC 20580

The Honorable D. Michael Chappell
Administrative Law Judge
Federal Trade Commission
600 Pennsylvania Avenue, NW
Rm. H-110
Washington, DC 20580

I hereby certify that this is a true and correct copy of Respondents' **MOTION FOR ADMISSION OF DOCUMENTS**, and that on this 16th day of November, 2011, I caused the foregoing to be served by e-mail on the following:

Mary Engle
Associate Director for Advertising Practices
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Mary Johnson, Senior Counsel
Heather Hippsley
Tawana Davis
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Counsel for Respondents

Dated: November 16, 2011

RX	Document
RX1692	*The Pomegranate is a Superfruit*, NiKOO 100% Pomegranate Juice Advertisement
RX5000	Interview by Norman Swan (Australian Broadcasting Corporation, Radio National's Health Report) with Meir Stampfer, Prof. of Epidemiology and Nutrition at Harvard School of Public Health (Jan. 24, 2005)
RX5001	*Professor Stampfer Takes Flak for A-B Gig*, 56 Modern Brewery Age (Dec. 19, 2005)
RX5003	Stampfer, M. and Willett, W., *Rebuilding the Food Pyramid*, Scientific American (Jan. 2002)
RX5010	Lizzy Ratner, *We're Erection Central! Genetic Big Shots Find DNA Chain for Stiff Stuff*, The New York Observer, July 30, 2006
RX5017	Melman, A., et al., *Can self-administered questionnaires supplant objective testing of erectile function? A comparison between the international index of erectile function and objective studies*, 18 Int'l J. Impotence Res. 126-129 (2006
RX5019	Karanja, N., et al., *The DASH diet for high blood pressure: From clinical trial to dinner table*, 71 Cleveland Clinic J. Medicine 745 - 753 (Sept. 2004)
RX5020	Bonnie Liebman, *DASH A Diet for All Diseases*, Nutrition Action Health Letter (Oct. 1997)
RX5021	Sacks, F., et al., *The Importance of Population-Wide Sodium Reduction as a Means to Prevent Cardiovascular Disease and Stroke: A Call to Action from the American Heart Association,* 123 Circulation, J. of the AMA 1138 - 1143 (2011)
RX5022	Sacks, F., et al, *Omega-6 Fatty Acids and Risk for Cardiovascular Disease: A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention*, 119 Circulation, J. of the AMA 902 - 907 (2009)
RX5025	Sacks, F., et al., *Striking the Right Balance: The Residual Risk of Coronary Artery Disease*, 48 Consultant 51 - 59, 517 (Supp. to Nov. 2008)

RX	Document
RX1692	*The Pomegranate is a Superfruit*, NiKOO 100% Pomegranate Juice Advertisement
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RX5025	Sacks, F., et al., *Striking the Right Balance: The Residual Risk of Coronary Artery Disease*, 48 Consultant 51 - 59, 517 (Supp. to Nov. 2008)

The Pomegranate is a Superfruit

The pomegranate is one of the healthiest foods on earth.

The name pomegranate derives from Latin *pomum* ("apple") and *granatus* ("seeded").

Pomegranate juice consumption is extremely beneficial because pomegranate juice:

- is rich in antioxidant phytonutrients
- contains the highest antioxidant capacity compared to green tea, red wine, white wine, apple juice, cranberry juice, grapefruit juice, and orange juice
- slows aging
- contains chemicals called polyphenolic flavanoids that have cancer fighting benefits
- is effective in reducing heart disease factors
- is an excellent inhibitor of LDL oxidation
- reduces ACE (angiotensin converting enzyme), thereby lessening the progression of atherosclerosis
- increases blood flow to the heart
- reduces blood pressure
- lowers cholesterol
- reduces the risk of developing Alzheimer's disease
- reduces the occurrence of erectile dysfunction
- helps to decrease the inflammation associated with arthritis
- inhibits the actions of enzymes that cause cartilage to deteriorate
- has antibacterial effects against dental plaque
- can help to prevent macular degeneration, one of the most common causes of blindness in the elderly
- may inhibit viral infections

ABC Australian Broadcasting Corporation Radio National The Health Report

The Health Report: 24 January 2005 - Effects of Moderate Alcohol Consumption on Cognitive Function in Women

[This is the print version of story http://www.abc.net.au/rn/talks/8.30/helthrpt/stories/s1288465.htm]

Norman Swan: Welcome to the program.

This morning on The Health Report, do we have the ability to postpone the day that we die, holding out for a special occasion? A new and large study sheds light on what's been quite a nice thought.

Science intervenes in families where there's been more than one unexplained and unexpected infant death. Is it as some paediatricians have argued, murder without question?

Some worrying news about some herbs, and alcohol and women's brains.

This week's edition of the *New England Journal of Medicine* reports on a study of over 12,000 healthy women aged between 70 and 81 looking at their thinking ability. They measured it on two occasions, two years apart, compared to their alcohol intake, which actually had been fairly stable over the last 10 or 20 years.

The results were good for the moderate tippler.

Meir Stampfer is Professor of Epidemiology and Nutrition at Harvard School of Public Health. He led the research.

Meir Stampfer: There had been a variety of previous studies pointing to both the benefit of moderate alcohol consumption, and of course, the adverse effect of excess consumption is very well known to us all.

Previous studies had been criticised on a number of grounds; many had been small, and many had relied upon an assessment of alcohol that was very short-term. So there was concern that people may be changing their alcohol because of their change in cognitive function, and the direction of causality was unclear.

Norman Swan: The chicken and egg.

Meir Stampfer: Right.

Norman Swan: And just briefly, we're talking here about memory, problem solving, this sort of

stuff?

Meir Stampfer: Yes, it's memory, short-term memory, being able to come up with words and names quickly, marshalling thoughts rapidly, remembering sequences, that sort of thing.

Norman Swan: And just what was the relationship that you found?

Meir Stampfer: What we found was that compared to the non-drinkers, women who drank moderately, low levels of alcohol like one drink a day, had a significant reduction in the decline in cognitive function. So they performed better. The mild drinkers performed better than the non-drinkers, and the risk of cognitive impairment was reduced by about 20% .

Norman Swan: Is this the sort of difference that somebody would notice? Either them themselves, or the people living with them?

Meir Stampfer: It's a bit of a subtle difference unless you really look for it. But it portends a big difference in the future. So a difference like this would be equivalent to being about two years older. At that age, a two-year difference in cognitive function is noticeable in a subtle way.

Norman Swan: So your point is that if you extend it over a longer period of time, you might actually see an impact in a public health sense, in terms of more severe cognitive decline?

Meir Stampfer: Yes, changes of this magnitude in other studies for other factors, have been strong predictors for frank dementia.

Norman Swan: At what point did you see a decline in cognitive function in terms of excessive drinking? Or did you see it at all?

Meir Stampfer: Well we didn't see it because in this cohort we have so few heavy drinkers. Heavy drinkers just tend not to volunteer for health surveys. And so we couldn't study that.

Norman Swan: Your study also, the nurses' health study was one of the first to show a link between alcohol consumption and breast cancer, but in this case it was alcohol consumption increased risk of breast cancer. Just give us a sense of the balance here, in terms of risks versus benefits.

Meir Stampfer: For women there is a trade-off. Our study, and many others, find that moderate alcohol consumption does appear to raise the risk of breast cancer a little bit, but it is statistically significant. It also lowers risk not only of cognitive impairment but also heart disease. On balance, if you look at total mortality, it's clear that the best mortality experiences among the moderate drinkers compare either to non-drinkers or to heavy drinkers. Women naturally are concerned about the breast cancer risk, and a variety of studies suggest that if you get enough folate, folic acid in the diet, or through supplements, you can mitigate against the alcohol-induced excess risk for breast cancer. So I recommend anyone, even who drinks moderately, that they make sure they get enough folate.

Norman Swan: Munch the green vegetables at the same time. And that comes from observational studies, or randomised trials? My understanding is there haven't been any randomised trials yet on that.

Meir Stampfer: That's correct. For folate there have been some, but not for breast cancer.

Norman Swan: Your accompanying editorial questions just how reliable the results are. For example, and it's the again, chicken and egg, which you said you were confident you'd eliminated, but the point is, somebody who's drinking moderately may actually be in better health in the first place, and it's very hard to control for that statistically, and you still just might have a bias towards, in the same way as the HRT studies in California had a bias towards people who were middle-class and slightly better off, there's a bias here towards people who are just basically healthier anyway, and the alcohol is incidental.

Meir Stampfer: Right. What we've ruled out I think pretty well, is the possibility that cognitive decline influenced their alcohol. So in that sense the chicken and egg issue is settled. But is alcohol causing the benefit, or is it just a marker for a healthy lifestyle? And that's a legitimate question. The way we've addressed that is to try to identify all the other markers of a healthy lifestyle. For example, degree of education, physical activity, dietary factors, mental factors, a whole range of things that we could identify and when we adjust for those, it didn't seem to have any impact. That doesn't completely settle the issue but it suggests that a causal link is the most likely.

Norman Swan: The other criticism they made was that because you were sort of looking, if you like, cross-sectionally, just snapshots in time, the true change might not be a real change. In other words it's a question of whether or not you really are assessing change in thinking ability accurately and realistically.

Meir Stampfer: Actually our paper initially was submitted a few years ago, and was just a cross-sectional study and the New England Journal rejected it and said Come back when you have follow-up data with time course changes. And so we actually did do that. So we have both a cross-sectional assessment as well as a second assessment two years later, and they both show the same thing. The editorial is correct, that it would be nice to have yet another assessment two years down the road, and we plan to do that. And ultimately it will be good to see long-term what the impact is on Alzheimer's disease and the shape of the curve over time.

Norman Swan: And just finally, then, what is the public health message then if you just boil up all the stuff that's going around with moderate alcohol intake and women, what's the public health message as it stands at the moment, do you think?

Meir Stampfer: I think the public health message is that for older people who are drinking moderately, they can continue to do that, knowing that they're not doing their brains any harm, and in fact they're probably doing their brains some good. For people who avoid alcohol solely out of health concerns, in other words, they don't have some religious objection, they ought to re-think that.

Norman Swan: Dr Meir Stampfer is Professor of Epidemiology and Nutrition at Harvard School of Public Health in Boston.

References:
Stampfer J.M. et al. Effects of Moderate Alcohol Consumption on Cognitive Function in Women. *New England Journal of Medicine*, January 20, 2005;3;352:245-253

Evans A. D. and Bienias J.L. Alcohol Consumption and Cognition. Editorial. *New England Journal of Medicine*, January 20, 2005;3;352:289-290

Guests on this program:

Dr Meir Stampfer
Professor of Nutrition and Epidemiology
Chair,
Department of Epidemiology and Nutrition
Harvard School of Public Health
Boston, MA
U.S.A.

Further information:

Alcohol - Health Matters fact file
http://abc.net.au/health/library/alcohol_ff.htm

Presenter: Norman Swan
Producer: Brigitte Seega

12/19/05 Mod. Brewery Age 1
2005 WLNR 22557655

Modern Brewery Age

December 19, 2005

Volume 56; Issue 51

Professor Stampfer takes flak for A-B gig.

Harvard University. School of Public Health's Meir Stampfer's research on alcohol consumption at Anheuser-Busch Companies Inc.' conference

Prof. Meir Stampfer, the Harvard Public Health (HSPH) professor who has been making presentations for Anheuser-Busch on the benefits of moderate alcohol consumption, is under fire in the press for his association with the brewer.

Prof. Stampfer, the chair of HSPH's department of epidemiology, attended Anheuser-Busch sponsored luncheons in New York and Chicago to discuss his studies, and A-B paid for his travel expenses.

During the luncheons, Prof. Stampfer presented the results of some of his research, pointing to potential cardiovascular and neurological benefits from consuming moderate quantities of alcohol.

Prof. Stampfer was not paid for the presentations, but Anheuser-Busch has made a $150,000 donation to the Harvard School of Public Health for student scholarships.

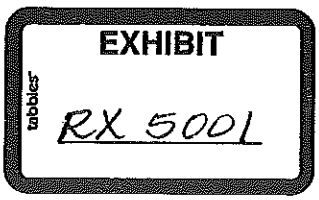
Doctor Stampfer's work with A-B was first reported in the mainstream press by the Boston Herald on December 13th, in an article titled "Harvard Doc is good Buds with beer king."

In the article, it was reported that, "The renowned chairman of Harvard's epidemiology department has been moonlighting for Anheuser-Busch--traveling to events across the country touting the "health" benefits of swigging beer. Stampfer's next stop on the party train was a beer tasting luncheon scheduled for tomorrow at Boston's upscale Radius restaurant--but he abruptly canceled late yesterday. "

Dr. Stampfer has criticized the press coverage, saying that the presentations are no different from countless lectures he's given over the years.

"I have never discussed beer's health benefits specifically, and do not propose to do so," Stampfer told the Harvard Crimson. "I have given lectures at scientific meetings all over the world on the health effects of moderate alcohol consumption and have studied this for over 20 years."

Stampfer said his research has shown that moderate alcohol consumption can lead to a reduction in incidence of coronary heart disease.



"There are dozens and dozens of studies showing that individuals with moderate levels of alcohol consumption have lower rates of heart disease and overall mortality compared with non-drinkers or with heavy drinkers," Stampfer told the Crimson.

Dr. Stampfer has said that the idea for the talks came after he met the CEO of Anheuser-Busch at a football game some years ago.

Dr. Stampfer told the Crimson that he would continue his work on alcohol consumption research, but was not sure he would continue to speak at the Anheuser-Busch-sponsored luncheons.

---- INDEX REFERENCES ---

COMPANY: ANHEUSER BUSCH COMPANIES INC

NEWS SUBJECT: (Drug Addiction (1DR84); Alcohol Abuse (1AL63); Health & Family (1HE30))

REGION: (Massachusetts (1MA15); USA (1US73); Americas (1AM92); New England (1NE37); North America (1NO39))

Language: EN

OTHER INDEXING: (Stampfer, Meir) (ANHEUSER BUSCH; ANHEUSER BUSCH COMPANIES INC; BOSTON HERALD; CRIMSON; HARVARD; HARVARD CRIMSON; HARVARD DOC; HARVARD PUBLIC HEALTH; HARVARD SCHOOL; HARVARD UNIVERSITY; HSPH; PUBLIC HEALTH; SCHOOL OF PUBLIC HEALTH) (Doctor Stampfer; Meir Stampfer; Prof; Stampfer) (All product and service information; R&D expenditures) (North America (NOAX); United States (USA))

COMPANY TERMS: ANHEUSER BUSCH COMPANIES INC; HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH

PRODUCT: Malt beverages208200

Word Count: 494
12/19/05 MODBREWAGE 1
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Rebuilding the Food Pyramid

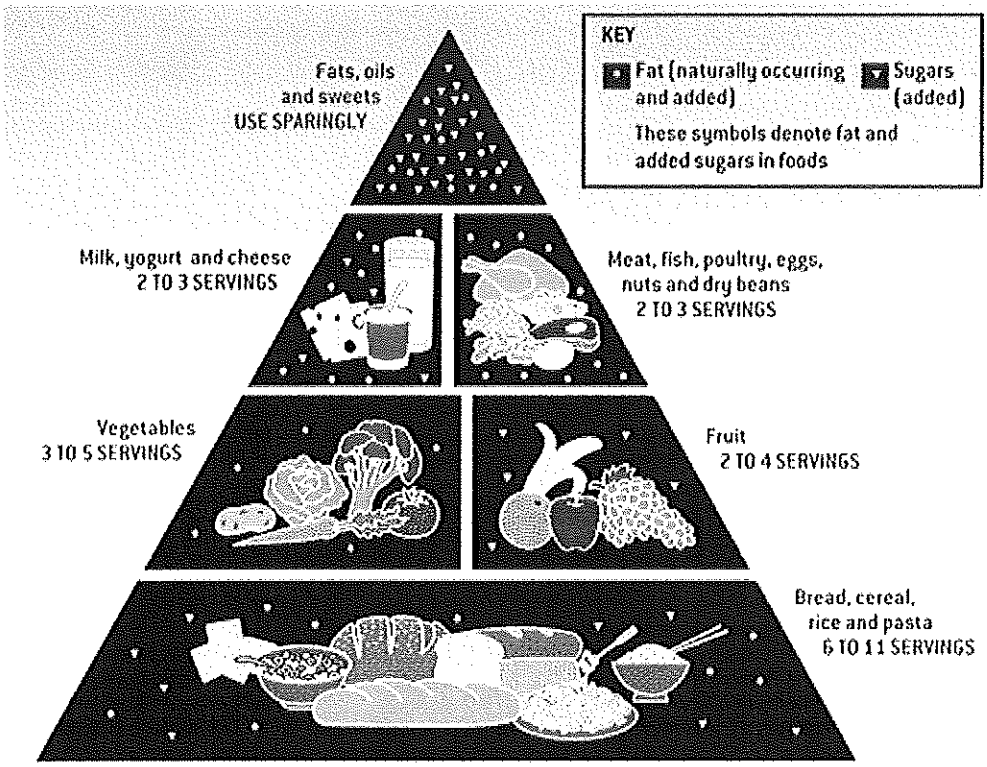
The dietary guide introduced a decade ago has led people astray. Some fats are healthy for the heart, and many carbohydrates clearly are not

By Walter C. Willett and Meir J. Stampfer

In 1992 the U.S. Department of Agriculture officially released the Food Guide Pyramid, which was intended to help the American public make dietary choices that would maintain good health and reduce the risk of chronic disease. The recommendations embodied in the pyramid soon became well known: people should minimize their consumption of fats and oils but should eat six to 11 servings a day of foods rich in complex carbohydrates--bread, cereal, rice, pasta and so on. The food pyramid also recommended generous amounts of vegetables (including potatoes, another plentiful source of complex carbohydrates), fruit and dairy products, and at least two servings a day from the meat and beans group, which lumped together red meat with poultry, fish, nuts, legumes and eggs.

Even when the pyramid was being developed, though, nutritionists had long known that some types of fat are essential to health and can reduce the risk of cardiovascular disease. Furthermore, scientists had found little evidence that a high intake of carbohydrates is beneficial. Since 1992 more and more research has shown that the USDA pyramid is grossly flawed. By promoting the consumption of all complex carbohydrates and eschewing all fats and oils, the pyramid provides misleading guidance. In short, not all fats are bad for you, and by no means are all complex carbohydrates good for you. The USDA's Center for Nutrition Policy and Promotion is now reassessing the pyramid, but this effort is not expected to be completed until 2004. In the meantime, we have drawn up a new pyramid that better reflects the current understanding of the relation between diet and health. Studies indicate that adherence to the recommendations in the revised pyramid can signif- icantly reduce the risk of cardiovascular disease for both men and women.

How did the original USDA pyramid go so wrong? In part, nutritionists fell victim to a desire to simplify their dietary recommendations. Researchers had known for decades that saturated fat--found in abundance in red meat and dairy products--raises cholesterol levels in the blood. High cholesterol levels, in turn, are associated with a high risk of coronary heart disease (heart attacks and other ailments caused by the blockage of the arteries to the heart). In the 1960s controlled feeding studies, in which the participants eat carefully prescribed diets for several weeks, substantiated that saturated fat increases cholesterol levels. But the studies also showed that polyunsaturated fat--found in vegetable oils and fish--reduces cholesterol. Thus, dietary advice during the 1960s and 1970s emphasized the replacement of saturated fat with polyunsaturated fat, not total fat reduction. (The subsequent doubling of polyunsaturated fat consumption among Americans probably contributed greatly to the halving of coronary heart disease rates in the U.S. during the 1970s and 1980s.)



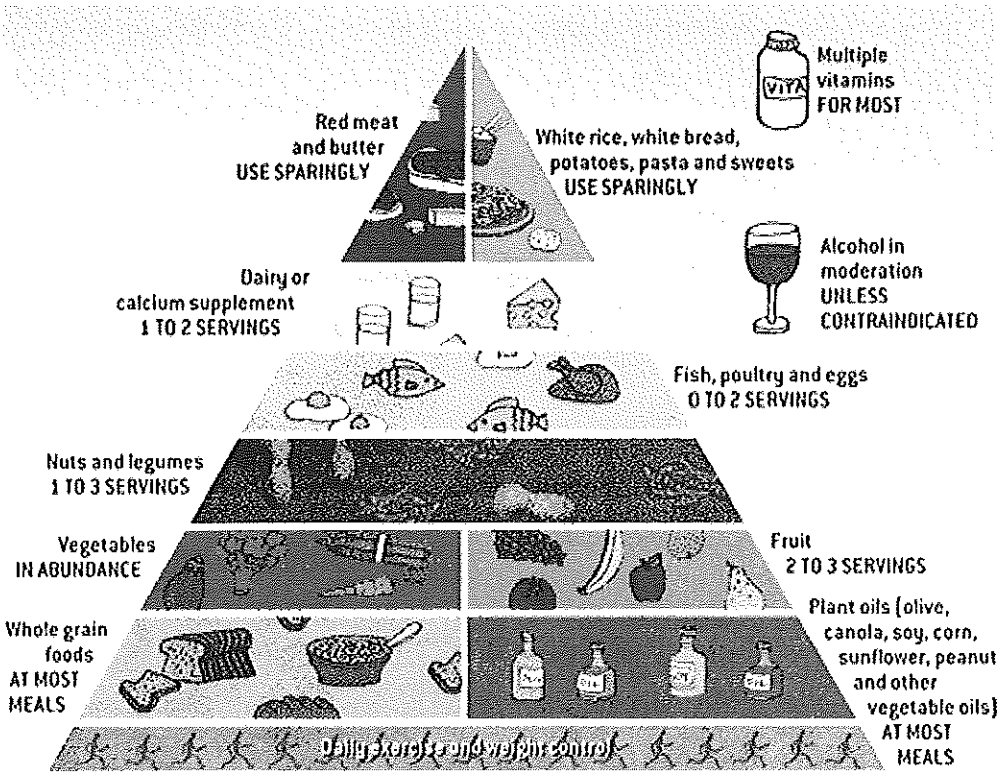
OLD FOOD PYRAMID

conceived by the U.S. Department of Agriculture was intended to convey the message "Fat is bad" and its corollary "Carbs are good." These sweeping statements are now being questioned.

For information on the amount of food that counts as one serving, visit www.nal.usda.gov:8001/py/pmap.htm

The notion that fat in general is to be avoided stems mainly from observations that affluent Western countries have both high intakes of fat and high rates of coronary heart disease. This correlation, however, is limited to saturated fat. Societies in which people eat relatively large portions of monounsaturated and polyunsaturated fat tend to have lower rates of heart disease. On the Greek island of Crete, for example, the traditional diet contained much olive oil (a rich source of monounsaturated fat) and fish (a source of polyunsaturated fat). Although fat constituted 40 percent of the calories in this diet, the rate of heart disease for those who followed it was lower than the rate for those who followed the traditional diets of Japan, in which fat made up only 8 to 10 percent of the calories. Furthermore, international comparisons can be misleading: many negative influences on health, such as smoking, physical inactivity and high amounts of body fat, are also correlated with Western affluence.

Unfortunately, many nutritionists decided it would be too difficult to educate the public about these subtleties. Instead they put out a clear, simple message: "Fat is bad." Because saturated fat represents about 40 percent of all fat consumed in the U.S., the rationale of the USDA was that advocating a low-fat diet would naturally reduce the intake of saturated fat. This recommendation was soon reinforced by the food industry, which began selling cookies, chips and other products that were low in fat but often high in sweeteners such as high-fructose corn syrup.



NEW FOOD PYRAMID

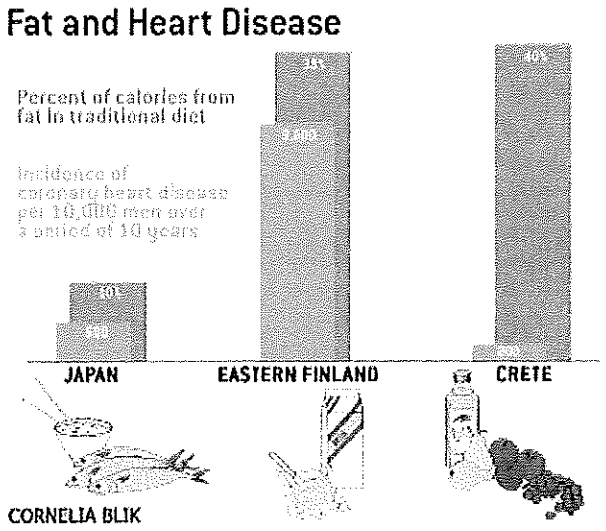
outlined by the authors distinguishes between healthy and unhealthy types of fat and carbohydrates. Fruits and vegetables are still recommended, but the consumption of dairy products should be limited.

When the food pyramid was being developed, the typical American got about 40 percent of his or her calories from fat, about 15 percent from protein and about 45 percent from carbohydrates. Nutritionists did not want to suggest eating more protein, because many sources of protein (red meat, for example) are also heavy in saturated fat. So the "Fat is bad" mantra led to the corollary "Carbs are good." Dietary guidelines from the American Heart Association and other groups recommended that people get at least half their calories from carbohydrates and no more than 30 percent from fat. This 30 percent limit has become so entrenched among nutritionists that even the sophisticated observer could be forgiven for thinking that many studies must show that individuals with that level of fat intake enjoyed better health than those with higher levels. But no study has demonstrated long-term health benefits that can be directly attributed to a low-fat diet. The 30 percent limit on fat was essentially drawn from thin air.

The wisdom of this direction became even more questionable after researchers found that the two main cholesterol-carrying chemicals--low-density lipoprotein (LDL), popularly known as "bad cholesterol," and high-density lipoprotein (HDL), known as "good cholesterol"--have very different effects on the risk of coronary heart disease. Increasing the ratio of LDL to HDL in the blood raises the risk, whereas decreasing the ratio lowers it. By the early 1990s controlled feeding studies had shown that when a person replaces calories from saturated fat with an equal amount of calories from carbohydrates the levels of LDL and total cholesterol fall, but the level of HDL also falls. Because the ratio of LDL to HDL does not change, there is only a

small reduction in the person's risk of heart disease. Moreover, the switch to carbohydrates boosts the blood levels of triglycerides, the component molecules of fat, probably because of effects on the body's endocrine system. High triglyceride levels are also associated with a high risk of heart disease.

The effects are more grievous when a person switches from either monounsaturated or polyunsaturated fat to carbohydrates. LDL levels rise and HDL levels drop, making the cholesterol ratio worse. In contrast, replacing saturated fat with either monounsaturated or polyunsaturated fat improves this ratio and would be expected to reduce heart disease. The only fats that are significantly more deleterious than carbohydrates are the trans-unsaturated fatty acids; these are produced by the partial hydrogenation of liquid vegetable oil, which causes it to solidify. Found in many margarines, baked goods and fried foods, trans fats are uniquely bad for you because they raise LDL and triglycerides while reducing HDL.



INTERNATIONAL COMPARISONS reveal that total fat intake is a poor indicator of heart disease risk. What is important is the type of fat consumed. In regions where saturated fats traditionally made up much of the diet (for example, eastern Finland), rates of heart disease were much higher than in areas where monounsaturated fats were prevalent (such as the Greek island of Crete). Crete's Mediterranean diet, based on olive oil, was even better for the heart than the low-fat traditional diet of Japan.

The Big Picture

To evaluate fully the health effects of diet, though, one must look beyond cholesterol ratios and triglyceride levels. The foods we eat can cause heart disease through many other pathways, including raising blood pressure or boosting the tendency of blood to clot. And other foods can prevent heart disease in surprising ways; for instance, omega-3 fatty acids (found in fish and some plant oils) can reduce the likelihood of ventricular fibrillation, a heart rhythm disturbance that causes sudden death.

The ideal method for assessing all these adverse and beneficial effects would be to conduct large-scale trials in which individuals are randomly assigned to one diet or another and followed for many years. Because of practical constraints and cost, few such studies have been conducted, and most of these have focused on patients who already suffer from heart disease. Though limited, these studies have supported the benefits of replacing saturated fat with polyunsaturated fat, but not with carbohydrates.

The best alternative is to conduct large epidemiological studies in which the diets of many people are periodically assessed and the participants are monitored for the development of heart disease and other conditions. One of the best-known examples of this research is the Nurses' Health Study, which was begun in 1976 to evaluate the effects of oral contraceptives but was soon extended to nutrition as well. Our group at Harvard University has followed nearly 90,000 women in this study who first completed detailed questionnaires on diet in 1980, as well as more than 50,000 men who were enrolled in the Health Professionals Follow-Up Study in 1986.

After adjusting the analysis to account for smoking, physical activity and other recognized risk factors, we found that a participant's risk of heart disease was strongly influenced by the type of dietary fat consumed. Eating trans fat increased the risk substantially, and eating saturated fat increased it slightly. In contrast, eating monounsaturated and polyunsaturated fats decreased the risk--just as the controlled feeding studies predicted. Because these two effects counterbalanced each other, higher overall consumption of fat did not lead to higher rates of coronary heart disease. This finding reinforced a 1989 report by the National Academy of Sciences that concluded that total fat intake alone was not associated with heart disease risk.

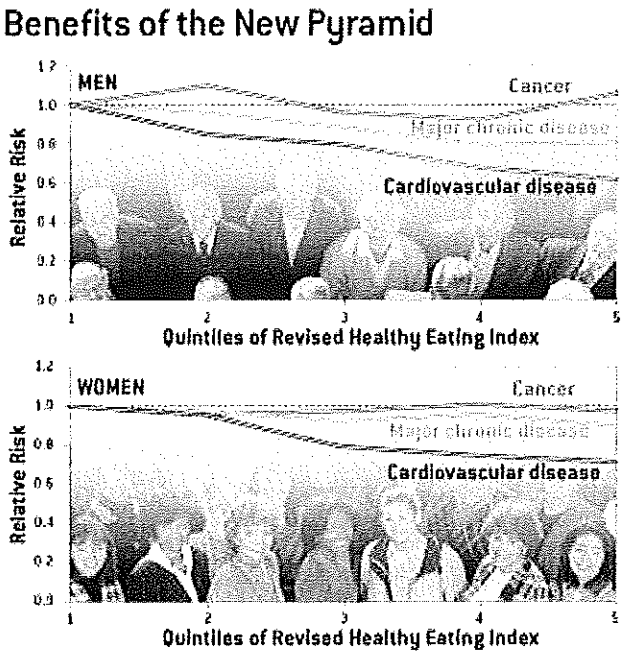
But what about illnesses besides coronary heart disease? High rates of breast, colon and prostate cancers in affluent Western countries have led to the belief that the consumption of fat, particularly animal fat, may be a risk factor. But large epidemiological studies have shown little evidence that total fat consumption or intakes of specific types of fat during midlife affect the risks of breast or colon cancer. Some studies have indicated that prostate cancer and the consumption of animal fat may be associated, but reassuringly there is no suggestion that vegetable oils increase any cancer risk. Indeed, some studies have suggested that vegetable oils may slightly reduce such risks. Thus, it is reasonable to make decisions about dietary fat on the basis of its effects on cardiovascular disease, not cancer.

Finally, one must consider the impact of fat consumption on obesity, the most serious nutritional problem in the U.S. Obesity is a major risk factor for several diseases, including type 2 diabetes (also called adult-onset diabetes), coronary heart disease, and cancers of the breast, colon, kidney and esophagus. Many nutritionists believe that eating fat can contribute to weight gain because fat contains more calories per gram than protein or carbohydrates. Also, the process of storing dietary fat in the body may be more efficient than the conversion of carbohydrates to body fat. But recent controlled feeding studies have shown that these considerations are not practically important. The best way to avoid obesity is to limit your total calories, not just the fat calories. So the critical issue is whether the fat composition of a diet can influence one's ability to control caloric intake. In other words, does eating fat leave you more or less hungry than eating protein or carbohydrates? There are various theories about why one diet should be better than another, but few long-term studies have been done. In randomized trials, individuals assigned to low-fat diets tend to lose a few pounds during the first months but then regain the weight. In studies lasting a year or longer, low-fat diets have consistently not led to greater weight loss.

Carbo-Loading

Now let's look at the health effects of carbohydrates. Complex carbohydrates consist of long chains of sugar units such as glucose and fructose; sugars contain only one or two units. Because of concerns that sugars offer nothing but "empty calories"--that is, no vitamins, minerals or other nutrients--complex carbohydrates form the base of the USDA food pyramid. But refined carbohydrates, such as white bread and white rice, can be very quickly broken down to glucose, the primary fuel for the body. The refining process produces an easily

absorbed form of starch--which is defined as glucose molecules bound together--and also removes many vitamins and minerals and fiber. Thus, these carbohydrates increase glucose levels in the blood more than whole grains do. (Whole grains have not been milled into fine flour.)



KEN FISHER (*men*) and ED HONOWITZ (*women*) *Getty Images;* CORNELIA BLIK (*graph*)

HEALTH EFFECTS of the recommendations in the revised food pyramid were gauged by studying disease rates among 67,271 women in the Nurses' Health Study and 38,615 men in the Health Professionals Follow-up Study. Women and men in the fifth quintile (the 20 percent whose diets were closest to the pyramid's recommendations) had significantly lower rates of cardiovascular disease than those in the first quintile (the 20 percent who strayed the most from the pyramid). The dietary recommendations had no significant effect on cancer risk, however.

Or consider potatoes. Eating a boiled potato raises blood sugar levels higher than eating the same amount of calories from table sugar. Because potatoes are mostly starch, they can be rapidly metabolized to glucose. In contrast, table sugar (sucrose) is a disaccharide consisting of one molecule of glucose and one molecule of fructose. Fructose takes longer to convert to glucose, hence the slower rise in blood glucose levels

A rapid increase in blood sugar stimulates a large release of insulin, the hormone that directs glucose to the muscles and liver. As a result, blood sugar plummets, sometimes even going below the baseline. High levels of glucose and insulin can have negative effects on cardiovascular health, raising triglycerides and lowering HDL (the good cholesterol). The precipitous decline in glucose can also lead to more hunger after a carbohydrate-rich meal and thus contribute to overeating and obesity.

In our epidemiological studies, we have found that a high intake of starch from refined grains and potatoes is associated with a high risk of type 2 diabetes and coronary heart disease. Conversely, a greater intake of fiber is related to a lower risk of these illnesses. Interestingly,

though, the consumption of fiber did not lower the risk of colon cancer, as had been hypothesized earlier.

Overweight, inactive people can become resistant to insulin's effects and therefore require more of the hormone to regulate their blood sugar. Recent evidence indicates that the adverse metabolic response to carbohydrates is substantially worse among people who already have insulin resistance. This finding may account for the ability of peasant farmers in Asia and elsewhere, who are extremely lean and active, to consume large amounts of refined carbohydrates without experiencing diabetes or heart disease, whereas the same diet in a more sedentary population can have devastating effects.

Eat Your Veggies

High intake of fruits and vegetables is perhaps the least controversial aspect of the food pyramid. A reduction in cancer risk has been a widely promoted benefit. But most of the evidence for this benefit has come from case-control studies, in which patients with cancer and selected control subjects are asked about their earlier diets. These retrospective studies are susceptible to numerous biases, and recent findings from large prospective studies (including our own) have tended to show little relation between overall fruit and vegetable consumption and cancer incidence. (Specific nutrients in fruits and vegetables may offer benefits, though; for instance, the folic acid in green leafy vegetables may reduce the risk of colon cancer, and the lycopene found in tomatoes may lower the risk of prostate cancer.)

The best way to avoid obesity is to LIMIT YOUR TOTAL CALORIES, not just the fat calories.

The real value of eating fruits and vegetables may be in reducing the risk of cardiovascular disease. Folic acid and potassium appear to contribute to this effect, which has been seen in several epidemiological studies. Inadequate consumption of folic acid is responsible for higher risks of serious birth defects as well, and low intake of lutein, a pigment in green leafy vegetables, has been associated with greater risks of cataracts and degeneration of the retina. Fruits and vegetables are also the primary source of many vitamins needed for good health. Thus, there are good reasons to consume the recommended five servings a day, even if doing so has little impact on cancer risk. The inclusion of potatoes as a vegetable in the USDA pyramid has little justification, however; being mainly starch, potatoes do not confer the benefits seen for other vegetables.

Another flaw in the USDA pyramid is its failure to recognize the important health differences between red meat (beef, pork and lamb) and the other foods in the meat and beans group (poultry, fish, legumes, nuts and eggs). High consumption of red meat has been associated with an increased risk of coronary heart disease, probably because of its high content of saturated fat and cholesterol. Red meat also raises the risk of type 2 diabetes and colon cancer. The elevated risk of colon cancer may be related in part to the carcinogens produced during cooking and the chemicals found in processed meats such as salami and bologna.

Poultry and fish, in contrast, contain less saturated fat and more unsaturated fat than red meat does. Fish is a rich source of the essential omega-3 fatty acids as well. Not surprisingly, studies have shown that people who replace red meat with chicken and fish have a lower risk of coronary heart disease and colon cancer. Eggs are high in cholesterol, but consumption of up to one a day does not appear to have adverse effects on heart disease risk (except among diabetics), probably because the effects of a slightly higher cholesterol level are

counterbalanced by other nutritional benefits. Many people have avoided nuts because of their high fat content, but the fat in nuts, including peanuts, is mainly unsaturated, and walnuts in particular are a good source of omega-3 fatty acids. Controlled feeding studies show that nuts improve blood cholesterol ratios, and epidemiological studies indicate that they lower the risk of heart disease and diabetes. Also, people who eat nuts are actually less likely to be obese; perhaps because nuts are more satisfying to the appetite, eating them seems to have the effect of significantly reducing the intake of other foods.

Yet another concern regarding the USDA pyramid is that it promotes overconsumption of dairy products, recommending the equivalent of two or three glasses of milk a day. This advice is usually justified by dairy's calcium content, which is believed to prevent osteoporosis and bone fractures. But the highest rates of fractures are found in countries with high dairy consumption, and large prospective studies have not shown a lower risk of fractures among those who eat plenty of dairy products. Calcium is an essential nutrient, but the requirements for bone health have probably been overstated. What is more, we cannot assume that high dairy consumption is safe: in several studies, men who consumed large amounts of dairy products experienced an increased risk of prostate cancer, and in some studies, women with high intakes had elevated rates of ovarian cancer. Although fat was initially assumed to be the responsible factor, this has not been supported in more detailed analyses. High calcium intake itself seemed most clearly related to the risk of prostate cancer.

Men and women eating in accordance with THE NEW PYRAMID had a lower risk of major chronic disease.

More research is needed to determine the health effects of dairy products, but at the moment it seems imprudent to recommend high consumption. Most adults who are following a good overall diet can get the necessary amount of calcium by consuming the equivalent of one glass of milk a day. Under certain circumstances, such as after menopause, people may need more calcium than usual, but it can be obtained at lower cost and without saturated fat or calories by taking a supplement.

A Healthier Pyramid

Although the usda's food pyramid has become an icon of nutrition over the past decade, until recently no studies had evaluated the health of individuals who followed its guidelines. It very likely has some benefits, especially from a high intake of fruits and vegetables. And a decrease in total fat intake would tend to reduce the consumption of harmful saturated and trans fats. But the pyramid could also lead people to eat fewer of the healthy unsaturated fats and more refined starches, so the benefits might be negated by the harm.

To evaluate the overall impact, we used the Healthy Eating Index (HEI), a score developed by the USDA to measure adherence to the pyramid and its accompanying dietary guidelines in federal nutrition programs. From the data collected in our large epidemiological studies, we calculated each participant's HEI score and then examined the relation of these scores to subsequent risk of major chronic disease (defined as heart attack, stroke, cancer or nontraumatic death from any cause). When we compared people in the same age groups, women and men with the highest HEI scores did have a lower risk of major chronic disease. But these individuals also smoked less, exercised more and had generally healthier lifestyles than the other participants. After adjusting for these variables, we found that participants with

the highest HEI scores did not experience significantly better overall health outcomes. As predicted, the pyramid's harms counterbalanced its benefits.

Because the goal of the pyramid was a worthy one--to encourage healthy dietary choices--we have tried to develop an alternative derived from the best available knowledge. Our revised pyramid emphasizes weight control through exercising daily and avoiding an excessive total intake of calories. This pyramid recommends that the bulk of one's diet should consist of healthy fats (liquid vegetable oils such as olive, canola, soy, corn, sunflower and peanut) and healthy carbohydrates (whole grain foods such as whole wheat bread, oatmeal and brown rice). If both the fats and carbohydrates in your diet are healthy, you probably do not have to worry too much about the percentages of total calories coming from each. Vegetables and fruits should also be eaten in abundance. Moderate amounts of healthy sources of protein (nuts, legumes, fish, poultry and eggs) are encouraged, but dairy consumption should be limited to one to two servings a day. The revised pyramid recommends minimizing the consumption of red meat, butter, refined grains (including white bread, white rice and white pasta), potatoes and sugar.

Trans fat does not appear at all in the pyramid, because it has no place in a healthy diet. A multiple vitamin is suggested for most people, and moderate alcohol consumption can be a worthwhile option (if not contraindicated by specific health conditions or medications). This last recommendation comes with a caveat: drinking no alcohol is clearly better than drinking too much. But more and more studies are showing the benefits of moderate alcohol consumption (in any form: wine, beer or spirits) to the cardiovascular system.

Can we show that our pyramid is healthier than the USDA's? We created a new Healthy Eating Index that measured how closely a person's diet followed our recommendations. Applying this revised index to our epidemiological studies, we found that men and women who were eating in accordance with the new pyramid had a lower risk of major chronic disease. This benefit resulted almost entirely from significant reductions in the risk of cardiovascular disease--up to 30 percent for women and 40 percent for men. Following the new pyramid's guidelines did not, however, lower the risk of cancer. Weight control and physical activity, rather than specific food choices, are associated with a reduced risk of many cancers.
Of course, uncertainties still cloud our understanding of the relation between diet and health. More research is needed to examine the role of dairy products, the health effects of specific fruits and vegetables, the risks and benefits of vitamin supplements, and the long-term effects of diet during childhood and early adult life. The interaction of dietary factors with genetic predisposition should also be investigated, although its importance remains to be determined. Another challenge will be to ensure that the information about nutrition given to the public is based strictly on scientific evidence. The USDA may not be the best government agency to develop objective nutritional guidelines, because it may be too closely linked to the agricultural industry. The food pyramid should be rebuilt in a setting that is well insulated from political and economic interests.

- Scientific American, www.sciam.com, January 2002.

THE NEW YORK OBSERVER

We're Erection Central! Genetic Big Shots Find DNA Chain for Stiff Stuff

By Lizzy Ratner
July 30, 2006 | 8:00 p.m

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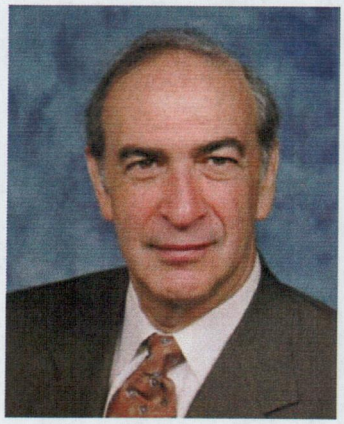

Dr. Arnold Melman.

+Enlarge

The Laboratory of Molecular and Integrative Urology at the Albert Einstein College of Medicine is a startling, almost radical study in the aesthetics of the unsexy. Its six dim-lit labs are drab and boxy, and filled with the kind of whirring, buzzing equipment that might make a man fear for his gonads. There are scalpels for slicing and incubators for heating and large Cryostar freezers for extreme, minus-70-degree freezing. In one lab, rats get snipped down the middle so teeny-tiny catheters can be inserted into their bladders—not the most arousing sight.

And yet, the small Bronx laboratory is on track to make erectile history, to go down in the urology books—if not girlie mags and geezer journals—as one of the sacred shrines of male potency. Thanks to the promise of an experimental new gene therapy, it could become birthplace of the world's first genetically engineered erection.

"We think that we've hit on something," said Dr. Arnold Melman, the eminent urologist whose serves as director of the lab and chair of the Albert Einstein department of urology, as he sat in his office on a recent Wednesday morning. "[Gene therapy] has been a disappointment ... so if this works, it has a chance of being one of the success stories. It would be a gigantic step forward."

Leave it to the hard-on to revolutionize medicine.

Erectile dysfunction is an unlikely candidate for gene therapy, the brave, super-hyped practice of inserting genes into a patient's cells to treat a disease. To begin, it has proved largely disappointing —impotent, one might say—as a near-term solution to the body's most devastating diseases. And because of its potential risks, scientists have embraced it almost exclusively as a treatment for serious, pulse-stopping ailments like cancer—not as a treatment for lifestyle conditions.

But for some six years now, Dr. Melman and his small hive of scientists have been plugging away to bring the promise of gene therapy to the war on impotence. With the help of funding from a few wealthy patients, they tried and erred. And eventually stumbled on hMaxi-K, a treatment that uses what is known as the Slo gene to restore vim and vitality to the vertically challenged penis. Each injectable treatment is expected to last as much as six months.

The gene therapy is still in its early, test-and-tweak phase. But just last month, the scientists celebrated the completion of the first hMaxi-K clinical trial, a two-and-a-half-year process that demonstrated that the treatment did not turn its 11 human guinea pigs into two-headed, hyper-virile monsters—or, at least, that it didn't seep into sperm, spark an allergic reaction or inspire any other "adverse events." And within the next few months they plan to embark on a 100-patient, phase-two trial to show that the drug actually works. If all goes according to plan, they hope to begin marketing the world's first genetically modified erection treatment within five to six years.

"The concept is fascinating. And if it works, it's great," said Dr. Andrew McCullough, director of male sexual health at New York University Medical Center and one of the two principle investiga the hMaxi-K clinical trial. "It would be huge; it would be as big as Viagra was when it hit."

Eight years after Pfizer's little blue pill galvanized the impotence industry, the quest for a n

perfect erection continues—in part out of scientific fervor, in part out of the promise of profit, and in part because the extant drugs (including Levitra and Cialis) are not quite the wonder pills they were hailed to be.

For all the hype, today's holy trinity of erection drugs work in only 60 percent of patients, and even then the side effects—like headaches, indigestion and blue-tinted vision—can dull the enthusiasm of the most eager user. More recently, reports of blindness in as many as 50 Viagra-takers have sparked an F.D.A. investigation into the billion-dollar love drug. And then there's the minor problem of timing: The awkward, unromantic fact that after the naughty urge arises, it can take as long as 35 thumb-twiddling minutes for old pokey to rise and shine.

Such design flaws have created an opening for scientists like Dr. Melman and a handful of his fellow erectile-dysfunction pioneers. At present, at least two other labs are working on their own gene-therapy elixirs—the labs of Drs. Jacob Rajfer and Nestor Gonzalez-Cadavid at U.C.L.A., and of Dr. Wayne Hellstrom at Tulane University (though Dr. Hellstrom's work has been largely stalled since Hurricane Katrina). Only Dr. Melman, however, has succeeded in taking the next experimental step: reproducing the gene-therapy tests in the human male.

(In the wake of his early success with E.D., Dr. Melman is also preparing to launch an hMaxi-K trial for overactive bladder, one of several so-called smooth-muscle-cell conditions that include asthma, hypertension and diabetes as well as impotence. Dr. Melman believes they could all conceivably benefit from hMaxi-K someday.)

"As in everything in science, every group is competing with the other," said Dr. Gonzalez-Cadavid when asked whether the news of Dr. Melman's early research success concerned him. But, he added, he was also glad for his competitor's progress, since it demonstrated that other erectile-dysfunction warriors were on the right path.

"This," he said, "will be [an] incentive for our groups and other groups to go to the clinical area."

THE SCIENCE OF THE GENETICALLY ENGINEERED erection—a science that is at once rigorous, elegant and mind-scramblingly involved—begins with a paradox: In order to make a penis hard, the smooth muscle cells of the shaft need to be soft, or relaxed.

In the case of many impotence sufferers, however, these smooth muscle cells have a hard time relaxing. They remain tense, rigid, unable to respond to the stimuli that set their sex machinery in motion. And that is where gene therapy comes in. With the injection of the Slo gene, the smooth muscle cells produce a protein that, in turn, sets off a chain of reactions that cause the cells to relax.

Or, as Dr. McCullough explained, "Basically, the guy comes in, he has a tourniquet put around his penis, you give him the injection, you leave it on for 30 minutes, you take it off, end of story." For the next three to six months, his penis should be able rise and fall on command.

This, at least, is the operating theory.

Thus far, only 11 brave men with moderate to severe erectile dysfunction have dared clamp on the tourniquet and try out the treatment. These men were volunteers in the phase-one clinical trial that began in January 2004 and ran, in six-month increments, until this past June 6. Because the trial was meant to test safety rather than efficacy, the drug was administered at cautious, lower-than-treatment-level doses, which didn't generally produce Johnny Wadd erections—or, in some cases, any erections at all. But in the two men who received the higher doses, the medicine seems to have waved its magic, cell-relaxing wand, because, well, they got their hard-ons.

"They said it was like they were young men again. They were having spontaneous, normal erections," said Dr. Melman in his precise, Bronx-inflected accent—though he also warned these results could not be read as proof of success. "It's only a phase-one trial with a limite of people, so you have to have very limited claims," he said.

But even if later trials should prove wildly successful, will men really submit to having their penises pricked and injected every six months? Will the injections actually work in the diverse, flaccid masses? And is it really safe?

Ever since an 18-year-old boy with a rare metabolic disorder died in a gene-therapy trial in 1999, the bold new biotechnology has been tainted with the risk of deadly, unintended consequences. These tend to be rare, but in several trials, patients have come down with everything from serious immune-system reactions to cancer—hardly the kind of risks one wants to take for a hard-on.

Dr. Melman and his peers brushed off these concerns, insisting that hMaxi-K was safe, in large part because it is designed somewhat differently than most gene therapies. While many treatments rely on weakened viruses to guide genes into cells, hMaxi-K uses something called, appropriately, naked DNA to do its maneuvering. And this slinky, simple, naked DNA hasn't (thus far) been linked to dire diseases.

"I would say [there are] no issues about safety," said Dr. McCullough, the phase-one investigator.

Even so, at least one doctor wondered whether the public would be willing to overlook all the ghoulish what-if scenarios, to stake their health on the promise of an erection.

"I think the issue of an injection that works for six months—that's going to require some fairly heavy-duty safety data, long-term safety data," said Leonore Tiefer, a veteran sexologist and clinical-psychiatry professor at N.Y.U., launching into a monologue about potential side effects and the unpleasantness of injections—particularly the unpleasantness of injections.

"It's not a trivial thing," she said. "The penis looks a little delicate, so to be shooting things into it just raises worries."

And yet, for all the sexologist's skepticism, men might prove all too willing to brave a few pricks and prodding.

"I put in a manuscript once that it [was] the fountain of youth," said Dr. Melman of his hMaxi-K therapy. "We're talking about modifying the aging process."

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ORIGINAL ARTICLE

Can self-administered questionnaires supplant objective testing of erectile function? A comparison between the international index of erectile function and objective studies

A Melman, J Fogarty and J Hafron

Department of Urology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

To determine whether the results of the self-reported International Index of Erectile Function (IIEF) to assess erectile function can overestimate the degree of erectile impairment. A total of 32 consecutive patients seeking treatment for erectile dysfunction (ED) at a urologist's office were evaluated by completion of the erectile function domain of the IIEF. Nocturnal penile tumescence testing using the Rigiscan (Timm Medical Technologies Inc., USA) was performed in these patients after completion of the IIEF. The median IIEF-6 score was 9 of 30 (range, 1–25; mean, 11/30). Rigiscan results were abnormal in six patients (19%), normal in 25 patients (78%), and unable to interpret in one patient (3%). IIEF-6 scores were subdivided by severity along with Rigiscan results. There was no correlation between age, IIEF score, or Rigiscan results. In conclusion, the IIEF is a useful tool and is helpful for follow-up of a patient to evaluate efficacy of treatments for ED, but should not replace objective testing to diagnose the quality of ED.
International Journal of Impotence Research (2006) **18**, 126–129. doi:10.1038/sj.ijir.3901361; published online 4 August 2005

Keywords: erectile dysfunction; IIEF; NPT; ED evaluation; Rigiscan

Introduction

Numerous self-report measures used to assess erectile dysfunction (ED) have been developed. Initial interest for these questionnaires stemmed from differentiating psychogenic from nonpsychogenic ED.[1–3] The most widely used self-administered questionnaire, the International Index of Erectile Function (IIEF) or one of its derivatives, has been used widely in more than 50 clinical trials as the primary end point in evaluating the efficacy of sildenafil in various patient populations, as well as the most recently released oral phoshodiesterase-5 (PDE-5) inhibitors vardenafil and tadalafil.[4–6] The IIEF was developed in conjunction with, and as an adjunct to, the evaluation of clinical efficacy of the first oral PDE-5 inhibitor, sildenafil.[7]

One reason for such widespread implementation of the IIEF in clinical trials lies in its cost effectiveness and its ability to allow drug companies a method to quantify treatment responses in a way that is presentable for Food and Drug Administration reviews. The IIEF was not developed as a diagnostic tool, but rather as a means to evaluate a treatment effecting in a longitudinal fashion. An important limitation of the IIEF is its inability to differentiate between specific causes of ED.[8,9]

Nocturnal penile tumescence (NPT) testing is able to quantify the normal physiologic erections that occur during sleep, primarily during rapid eye movement sleep. Nocturnal erections rely on intact corticospinal efferents as well as the vascular responsiveness of penile tissue to those signals. A nocturnal monitoring device measures the number of erectile episodes, tumescence, maximal penile rigidity, and duration. NPT is the only objective measure available to differentiate between the ability and inability to attain sustained penile rigidity, that is, psychogenic and organic ED. It is considered as one of the fundamental tools for evaluation and selection of appropriate management for patients. NPT is considered an essential research tool for objective assessment of pharmacologic therapies. However, its use and the use of other objective measures to evaluate erectile function largely have been supplanted by self-assessment questionnaires such as the IIEF.[10] The aim of the

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present study was to question the diagnostic accuracy of the current popular trend that uses the results of the IIEF for either prescribing one of the PDE-5 inhibiting drugs as first-line therapy or accepting the diagnostic score as an estimate of the true prevalence of ED.

Methods

All procedures and methods of data collection were approved by the Institutional Review Board before commencement of the study. Between February and November, 2003, 32 consecutive patients with a chief symptom of ED seeking treatment at the urologist's office were evaluated by history, physical examination, and completion of the erectile function domain of the IIEF, also known as the IIEF-6.[11] An IIEF-6 score of less than 26 was considered abnormal. NPT testing using the Rigiscan with Rigiscan Plus software (Timm Medical Technologies Inc., USA) was performed in these patients after completion of the IIEF-6. The patients were instructed on proper use of the instrument. Baseline parameters were obtained and calibration was performed before the patients left the office. Data from two consecutive nights were obtained. Data collected from Rigiscan evaluation included tumescence activity units (TAU) and rigidity activity units (RAU) at the tip and the base, total number of events, best event time, and total time. The criterion used for a normal Rigiscan result was the finding of a single best event of more than 70% rigidity at the tip for more than 10 min. A Pearson's correlation was performed using GraphPad Prism software (GraphPad Software, San Diego, CA, USA) with regard to age, IIEF score, and Rigiscan results. A P-value of $\leqslant 0.05$ was considered statistically significant.

Results

The median age of the study group was 40 years (range, 24–61 years; mean, 41 years). The median IIEF-6 score was 9 of 30 (range, 1–25; mean, 11 of 30). Comorbidities included diabetes mellitus in eight patients (25%), hypertension in nine patients (28%), and both diabetes and hypertension in five patients (16%). Rigiscan results using single best event were abnormal in six patients (19%), normal in 25 patients (78%), and unable to be interpreted in one patient (3%). IIEF-6 scores were subdivided by severity along with Rigiscan results, including average RAUs and TAUs at the tip of the penis, as shown in Table 1.

Pearson's correlation for age, $r=-0.181$ (95% confidence interval (CI), −0.5082 to 0.1919; $P=$ n.s.). For IIEF score versus Rigiscan results, the average tip TAU was $r=0.2856$ (95% CI, −0.08337 to 0.5856; $P=$ n.s.), and the average tip RAU was $r=0.229$ (95% CI, −0.1432 to 0.5444; $P=$ n.s.). The average base TAU was $r=0.2951$ (95% CI, −0.07303 to 0.5924; $P=$ n.s.), and the average base RAU was $r=0.2897$ (95% CI, −0.07889 to 0.5886; $P=$ n.s.). There was no correlation between age, IIEF score, or Rigiscan results.

Comment

In the current accepted approach to the treatment of patients seeking treatment for ED is that the expected incidence of normal erectile function in is expected to be less than the 78% shown in this study. Thus, in a recent report using duplex ultrasound to assess penile blood flow after intracavernosal injection of alprostadil showed a normal vascular response in only 30 of 80 (38%) participants, all of whom had abnormal IIEF results. There was no correlation with severity of ED by IIEF score and results of duplex ultrasound in that study.[12]

A limitation of this current report is that it is not population based. However, patients seeking treatment at a urologist's office were not chosen based on the suspicion of psychogenic impotence. Rather, they were consecutive patients who reported ED and underwent Rigiscan testing with the goal of eliminating selection bias on the part of the clinician. In the era of massive advertising for easily available

Table 1 IIEF score compared with Rigiscan result

IIEF score	*IIEF diagnostic categories*	*Rigiscan result*			
		Normal	*Abnormal*	*Average tip RAU (mean) normal >9.5*	*Average tip TAU (mean) normal >6.5*
1–10	Severe	12	5	24.3	24.3
11–21	Moderate	9	0	55.7	27.2
22–25	Mild	3	1	19.75	19.25
26–30	Normal	0	0		

$P=$ n.s.

oral remedies, the younger median age in our study than that of the typical patient population seeking treatment for ED can represent a selection bias on the part of today's patients requesting diagnosis and treatment. In the era before sildenafil, we reported on a population of patients of whom more than 60% were between 50 and 70 years of age,[13] which is a higher age than the patients in the present report. The difference may represent a consequence of the pressures of advertising on younger men to 'perform better' in their relationships.

Objective tools providing anatomic and physiologic data used to evaluate ED as part of the urologists' armamentarium both to diagnose a specific cause and to evaluate response to treatment include physical examination, NPT testing, plethysmography, neurophysiologic testing including warm thermal thresholds, Doppler ultrasound, pelvic angiography, and cavernosometry.[14–18] Each of these tools provide unique information with distinct indications and limitations, depending on the cause of ED suspected for an individual patient. Through the use of these tools, a more accurate assessment of the incidence and prevalence of specific causes can become apparent with properly designed trials. Adequate studies using appropriate subgroups then can be performed. With the advent of novel pharmacotherapy for ED, enrollment of a proper patient cohort will be necessary to explain why certain medications and treatment methods work in some patients and not in others.

NPT has been validated, and with development of the Rigiscan Plus software, which includes area-under-the-curve analysis with radial RAU measurements and TAU measurements and their corresponding nomograms, has produced a standardization that improves its sensitivity and specificity for accurate recognition of an erection that is of sufficient rigidity and duration for intercourse. Sensitivities and specificities of 42–85% and of 93–100%, respectively, have been reported.[17,19,20] The use of NPT is based on the concept that to produce a nocturnal erection, the corticospinal efferents to the penis and the vascular responsiveness of the penile tissue to those nerve signals must be intact. However, production of an erection in the context of sexual activity also requires normal responsiveness to sensory stimuli. The inability of NPT to evaluate impairment of afferent signals from the penis is an important limitation. Considering patients with normal results by Rigiscan data alone as having normal erectile function includes men with a sensory neurogenic cause and would contribute to specificities of less than 100%.

The introduction of sildenafil has increased public awareness and has enlightened public perceptions of ED as a medical condition. With increased media exposure and the subsequent increasing public awareness, there has been a shift in popular perceptions of ED. These new oral medications, with associated promotion, are changing ED from something embarrassing and rarely admitted to something quite common that is almost perceived as a normal part of aging.

The IIEF and other self-assessment questionnaires have been shown in previous studies to be unable to differentiate between various causes of ED.[21,22] However, few clinical trials have been performed since the introduction of sildenafil in which the IIEF was not used as a primary end point. The target of the IIEF is the primary care provider. The Process of Care Model for the Evaluation and Treatment of ED segregates therapies as first line, second line, and third line.[23] First-line therapies include oral agents, vacuum erection devices, and couples or individual sex therapy. These are considered to be the realm of the primary care provider. Second- and third-line therapies include intraurethral and intracavernosal medications and the surgical placement of penile prostheses. Referral to a urologist is based on the need for these second- and third-line therapies, on the need or request for diagnostic testing or management, or both. In this paradigm, with increased use of the IIEF, management by the primary care provider, and the treatment of patients with psychogenic impotence as well as of ED resulting from other causes, treatment with PDE-5 inhibitors is likely to be maintained or increased.

This goal-directed approach, with the end being improved erectile function by administering oral treatments to patients who report ED, as substantiated by self-administered questionnaires such as the IIEF, imposes the inclusion of patients with various causes of ED. This model leads to prescription of medications incorrectly to a significant population of patients, when the medication does not match the cause of ED. In the case of psychogenic impotence, the drug may help alleviate the problem (lack of a sustained erection) for the wrong-stated reasons (physical cause of the problem).

We are now in an era of development of cause-specific oral pharmacotherapy for ED. For example, research in the realm of gene therapy includes gene therapy and transfer of nitric oxide synthases, growth factors, cytokines, brain-derived neurotrophic factors, neurotransmitters, or enzymes as well as gene therapy and transfer to effect myocyte excitability and sensitization.[24] Ion channel gene therapy uses potassium channels to effect voltage-gated calcium channels through hyperpolarization, increasing the responsiveness of corporal smooth muscle to endogenous smooth muscle relaxants. The maxi-K channel, currently in phase I testing, has shown effectiveness up to 6 months after intracavernosal injection in the rat model.[24–26] By targeting enzymes that effect smooth muscle dilatation and increase penile blood flow, the oral PDE-5 inhibitors are cause-specific treatments of vasculogenic ED. Dopamine receptor agonists such as the

melanocortins act as central initiators of erections in the paraventricular nucleus of the hypothalamus. They function as proerectile conditioners at this level to increase the responses of the erectile pathway after appropriate sexual stimulation and have shown some effect in the treatment of psychogenic impotence.[9,17,21]

With the development of mechanism-specific medications for ED, entry studies need to assure that the target population studied has the type of ED that the medication is proposed to treat. Objective measures are needed to select these patients properly for clinical trials to determine efficacy accurately. The current data suggest that pen-and-pencil, self-administered tests are not sufficiently accurate to assess the problem.

Conclusions

Although the IIEF is a useful tool and is helpful for follow-up of a patient to evaluate efficacy of treatments for ED, it should not replace objective testing. Careful history and physical examination of both the patient and his sexual partner are necessary.[22,23] The results of this paper are a caution of overdependency on the results from subjective data. Rigorous statistical methods using subjective data do not equate with the results obtained from objective testing.

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The DASH diet for high blood pressure: From clinical trial to dinner table

ABSTRACT

Three recent studies show that a diet rich in fruits, vegetables, whole grains, and lowfat dairy products and low in fat, refined carbohydrates, and sodium can lower blood pressure either alone or in combination with other lifestyle changes. These studies have greatly expanded our knowledge of nonpharmacologic interventions to prevent and manage hypertension. They also underscore the need for diet and lifestyle counseling in the primary care setting.

KEY POINTS

The DASH study demonstrated that blood pressure can be significantly reduced with a diet abundant in fruits, vegetables, complex carbohydrates, and lowfat dairy products.

The DASH and DASH-Sodium studies provide a scientific basis for a dietary sodium goal lower than currently recommended, and highlight the benefit of reducing sodium intake even for nonhypertensive persons.

The behavioral interventions used in the PREMIER study led to substantial weight loss, reduced sodium intake, and increased physical fitness.

Subjects who were hypertensive, African American, or older tended to experience the greatest reduction in blood pressure from the DASH diet and lifestyle changes.

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PATIENT INFORMATION
Ten tips to help you control your blood pressure page 754

EATING RIGHT lowers blood pressure by about as much as any single antihypertensive drug—but will patients do it?

See related editorial, page 755

Three recent randomized studies proved that a diet high in complex carbohydrates, fruits, vegetables, and lowfat dairy products and low in fat and sodium (not necessarily vegetarian and, on the other extreme, certainly not low-carbohydrate) lowers blood pressure effectively and quickly.

But studies are not like the real world. In two of the studies the patients had all of their food prepared for them, and in the third they underwent intensive counseling. How can physicians hope to convince and teach their patients to change their eating habits, given the time constraints of primary care?

Here, we summarize what we have learned about the impact of diet on blood pressure from three studies:

- Dietary Approaches to Stop Hypertension (DASH)[1]
- DASH-Sodium[2]
- PREMIER.[3]

We also provide practical advice to translate the results of these studies into clinical practice.

WHAT WE KNEW BEFORE DASH

Before DASH, the only nondrug options for managing high blood pressure were salt reduction, weight control, and moderation in alcohol consumption.[4]

These have limitations. Most people have trouble keeping weight off; as many as 95% of

people who lose weight gain it back within 5 years.[5] Similarly, efforts to reduce salt consumption are hampered by the wide availability of processed foods, the source of 70% to 80% of all salt consumed in the United States.[6] Furthermore, the role of sodium restriction in preventing and managing hypertension remained controversial.[7,8]

There was therefore a clear need to increase the number of nondrug options for people who are at risk for hypertension, but who do not meet the clinical definition of hypertension, and to provide alternative or adjunct therapy to those with hypertension.

Individual nutrients or whole diet?

Vegetarians and populations that routinely consume plant-based foods have lower blood pressure and do not experience the age-related rise in blood pressure seen in populations that consume meat-based diets.[9,10] Diets high in calcium and protein are also associated with lower blood pressure.[11,12]

The prevailing wisdom at the time the DASH study was designed was that individual nutrients were responsible for lowering blood pressure. Candidate nutrients included the minerals calcium, potassium, and magnesium and the macronutrients fat, fiber, and carbohydrates. But when these nutrients were tested individually—primarily through supplement use—blood pressure went down only modestly (< 3 mm Hg systolic and < 1 mm Hg diastolic) or not at all.[13–15] In contrast, lowfat, vegetarian diets lowered systolic blood pressure by 5 to 6 mm Hg.[10,11] These results strongly suggested that the beneficial effects seen in the observational studies were due to overall dietary patterns that included a variety of food components.

The DASH diet lowered blood pressure by 11/6 mm Hg in hypertensive subjects

THE DASH STUDY

The DASH study was organized and funded by the National Heart, Lung, and Blood Institute (NHLBI) to assess the impact of two diets on blood pressure.

How the DASH study was conducted

The DASH study included 459 adults (age 22 years or older) with systolic blood pressure lower than 160 mm Hg and diastolic pressure 80 to 95 mm Hg—prehypertension or stage 1 hypertension by the current classification system. None were taking antihypertensive medications.

About half of the participants were women, and 60% were African Americans, who bear a disproportionate burden of hypertension in the United States.

At baseline, 29% of participants had hypertension, and 27% were smokers.

Over 8 weeks, the participants were randomly assigned to one of three diet groups:

- **Control:** A diet similar to what many Americans consume, although somewhat lower in potassium, magnesium, and calcium.
- **Fruits and vegetables:** Similar to the control diet, but with more fruits and vegetables.
- **DASH:** A diet high in fruits, vegetables, lowfat dairy products, whole grains, poultry, fish, and nuts and low in fats, red meat, sweets, and sugar-containing beverages (TABLE 1). As a result, the diet is high in calcium, magnesium, potassium, and fiber. It is low in total fat, particularly saturated fat and cholesterol. Its 18% protein content is somewhat higher than the typical American diet, which is 15% protein.[16,17]

Participants received all their food and beverages in prepared meals and snacks for the 11 weeks of the study. They were asked to eat only the food provided and nothing else. Uneaten or nonstudy foods were recorded.

All three diets contained the same amount of sodium (3,000 mg/day), and participants were allowed 500 mg of discretionary sodium. Alcohol intake was limited to two drinks or fewer per day, and weight was intentionally held constant.

What we learned from the DASH study

The DASH diet lowered systolic blood pressure by an average of about 6 mm Hg and diastolic pressure by about 3 mm Hg. The diet that was merely higher than the typical American diet in fruits and vegetables also lowered blood pressure, but by a lesser amount: about 3 mm Hg systolic and 2 mm Hg diastolic.

For participants with stage 1 hypertension (blood pressure 140/90–159/99 mm Hg), the DASH plan was even more effective, reducing

TABLE 1

The DASH diet

FOOD GROUP	DAILY SERVINGS*	SERVING SIZES, EXAMPLES, AND SIGNIFICANCE
Grains, grain products	7–8	**Serving sizes:** 1 slice bread, 1 oz dry cereal,† 1/2 cup cooked rice, pasta, or cereal **Examples:** Whole wheat bread, English muffin, pita bread, bagel, cereals, grits, oatmeal, crackers, unsalted pretzels, popcorn **Significance:** Major sources of energy and fiber
Vegetables	4–5	**Serving sizes:** 1 cup raw leafy vegetable, 1/2 cup cooked vegetable, 6 oz vegetable juice **Examples:** Tomatoes, potatoes, carrots, green peas, squash, broccoli, turnip greens, collards, kale, spinach, artichokes, green beans, lima beans, sweet potatoes **Significance:** Rich sources of potassium, magnesium, and fiber
Fruits	4-5	**Serving sizes:** 6 oz fruit juice, 1 medium fruit, 1/4 cup dried fruit, 1/2 cup fresh, frozen, or canned fruit **Examples:** Apricots, bananas, dates, grapes, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines **Significance:** Important sources of potassium, magnesium, and fiber
Lowfat or fat-free dairy	2–3	**Serving sizes:** 8 oz milk, 1 cup yogurt, 1 1/2 oz cheese **Examples:** Fat-free (skim) or lowfat (1%) milk, fat-free or lowfat buttermilk, fat-free or lowfat regular or frozen yogurt, lowfat and fat-free cheese **Significance:** Major sources of calcium and protein
Meats, poultry, and fish	2 or less	**Serving sizes:** 3 oz cooked meats, poultry, or fish **Note:** Select only lean meats; trim away visible fat; broil, roast, or boil, instead of frying; remove skin from poultry **Significance:** Rich sources of protein and magnesium
Nuts, seeds, and dry beans	4–5 per week	**Serving sizes:** 1/3 cup or 1 1/2 oz nuts, 2 Tbsp or 1/2 oz seeds, 1/2 cup cooked dry beans **Examples:** Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils, peas **Significance:** Rich sources of energy, magnesium, potassium, protein, and fiber
Fats and oils‡	2–3	**Serving sizes:** 1 tsp soft margarine, 1 Tbsp lowfat mayonnaise, 2 Tbsp light salad dressing, 1 tsp vegetable oil **Examples:** Soft margarine, lowfat mayonnaise, light salad dressing, vegetable oil (eg, olive, corn, canola, safflower) **Note:** DASH has 27% of calories as fat, including that in or added to foods
Sweets	5 per week	**Serving sizes:** 1 Tbsp sugar, 1 Tbsp jelly or jam, 1/2 oz jelly beans, 8 oz lemonade **Examples:** Maple syrup, sugar, jelly, jam, fruit-flavored gelatin, jelly beans, hard candy, fruit punch, sorbet, ices **Note:** Sweets should be low in fat

*The DASH eating plan is based on 2,000 calories a day. The number of daily servings in a food group may vary from those listed, depending on the patient's caloric needs. Patients should use this chart to help plan their menus or take it with them when they go to the store.
†Equals 1/2 to 1 1/4 cup, depending on cereal type. Check the product's nutrition label.
‡Fat content changes serving counts for fats and oils. For example, 1 Tbsp of regular salad dressing equals 1 serving, 1 Tbsp of lowfat dressing equals 1/2 serving, 1 Tbsp of a fat-free dressing equals 0 servings.

SOURCE: HTTP://WWW.NHLBI.NIH.GOV/HEALTH/PUBLIC/HEART/HBP/DASH/INDEX.HTM

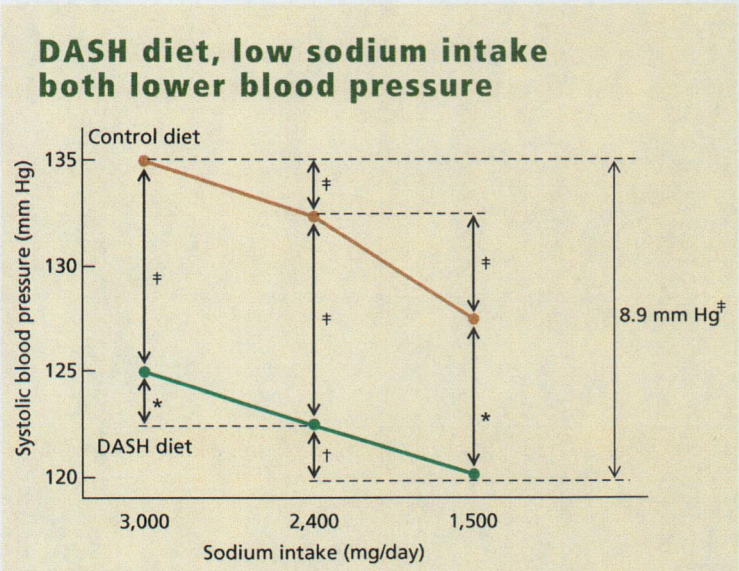

FIGURE 1. Reduction in systolic blood pressure in the DASH-Sodium study. Participants were randomized to a control diet or the DASH diet (see text and TABLE 1); within each group, each participant rotated through three sodium intake levels (3,000, 2,400, and 1,500 mg/day).

FROM SACKS FM, SVETKEY LP, VOLLMER WM, ET AL. EFFECTS ON BLOOD PRESSURE OF REDUCED DIETARY SODIUM AND THE DIETARY APPROACHES TO STOP HYPERTENSION (DASH) DIET. DASH-SODIUM COLLABORATIVE RESEARCH GROUP. N ENGL J MED 2001; 344:3–10.

systolic blood pressure by an average of 11 mm Hg and diastolic blood pressure by 6 mm Hg.[1,17] Moreover, the reductions in blood pressure happened quickly, within 2 weeks of starting the diet.

These dramatic results demonstrated that the DASH diet can lower blood pressure significantly, and prompted the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to recommend the DASH diet to aid in blood pressure control.[18]

THE DASH-SODIUM STUDY

All three of the diets in the DASH study contained about 3,000 mg of sodium daily—roughly 20% below the US average for adults but still above the recommended intake of 2,400 mg per day.

Building on the DASH findings, investigators designed the DASH-Sodium study to answer key questions about the relationship between sodium intake, diet, and hypertension:

- What is the effect of reducing sodium in the context of a typical American diet and the DASH diet?
- What is the combined effect of the DASH diet and reducing sodium?
- To what extent does reducing sodium or following the DASH diet or both lower blood pressure in people without hypertension (a critical question for the primary prevention of hypertension)?

How the DASH-Sodium study was conducted

Like its predecessor, the DASH-Sodium study was a multicenter, randomized, outpatient feeding study. Participants were adults with prehypertension or stage 1 hypertension—120 to 159 mm Hg systolic and 80 to 95 mm Hg diastolic. They were randomized to two diet groups: the DASH diet and a control diet that approximated the average American fat intake (although, as in the original study, slightly lower in potassium, magnesium, and calcium).

Within each diet, participants received three different levels of sodium intake (3,000, 2,400, and 1,500 mg/day) in random order for 30 days, each in a crossover fashion. Thus, each person consumed all three sodium levels on his or her assigned diet, either DASH or control.

What we learned from the DASH-Sodium study

Reducing sodium intake lowered systolic and diastolic blood pressure significantly in both the control and DASH diet groups (**FIGURE 1**).[2,19] Key findings:

- The DASH diet lowered blood pressure at all levels of sodium intake.
- Lowering sodium intake to the currently recommended level (2,400 mg) effectively reduced blood pressure for all participants.
- Lowering sodium intake even further to 1,500 mg lowered blood pressure by twice as much.
- Lowering sodium intake to 1,500 mg/day in nonhypertensive subjects lowered blood

TABLE 2

The PREMIER study: Effects of dietary interventions at 6 months

OUTCOME	BASELINE	AT 6 MONTHS		
		ADVICE-ONLY GROUP	ESTABLISHED RECOMMENDATIONS GROUP	ESTABLISHED-PLUS-DASH GROUP
Percent with hypertension	37	26	17*	12†
Percent with optimal blood pressure	0	19	30†	35†

*$P < .01$ vs advice-only group; †$P < .001$ vs advice-only group

DATA FROM THE WRITING GROUP OF THE PREMIER COLLABORATIVE RESEARCH GROUP. EFFECTS OF COMPREHENSIVE LIFESTYLE MODIFICATION ON BLOOD PRESSURE CONTROL: MAIN RESULTS OF THE PREMIER CLINICAL TRIAL. JAMA 2003; 289:2083–2093.

pressure by 5.6/2.8 mm Hg on the control diet and by 1.7/1.1 mm Hg on the DASH diet.

- The effect of lower sodium intake and the DASH diet on blood pressure was substantially greater when combined. The combined effect of the DASH diet and lowering sodium intake to 1,500 mg was a reduction of 8.9/4.5 mm Hg (7.1/3.7 mm Hg in nonhypertensive subjects and 11.5/5.7 mm Hg in hypertensive subjects).

These findings have far-reaching implications. First, they provide a scientific basis for a dietary sodium goal lower than currently recommended. Second, they highlight the benefit of reducing sodium intake even in people without hypertension.

FURTHER QUESTIONS ABOUT THE DASH DIET IN DAILY LIFE

The two DASH studies conclusively demonstrated that diet can lower blood pressure. Both studies, however, were conducted in a highly controlled fashion. Participants were given all their food and beverages for the entire time they were in the study. The meals were prepared and tailored to optimize nutrient and calorie content for each participant. Thus, minimal effort was required of participants. Several key questions remained:

- What would happen if people attempted to follow the DASH eating plan on their own?
- Would the daily challenges of acquiring and preparing food result in a less-than-optimal compliance with the diet?
- Would this attenuate the effects of the diet on blood pressure?
- What would happen if the DASH diet was combined with established lifestyle changes known to lower blood pressure (ie, reduced sodium intake, increased physical activity, limited alcohol intake, and weight reduction in overweight persons)?

These questions were addressed in a third study called PREMIER.[3]

Blood pressure was lowered within 2 weeks of starting the DASH diet

THE PREMIER STUDY

PREMIER was also a multicenter, randomized study, but unlike in the DASH and DASH-Sodium studies, food was not provided. Instead, the participants, who had prehypertension or stage 1 hypertension, were randomly assigned to undergo one of three different interventions:

- **Advice-only** (the control intervention): a single education session, with printed handouts provided.
- **Established recommendations:** behavioral counseling based on established recommendations for the nonpharmacologic management of hypertension (ie, reduced sodium intake, increased physical activity, limited alcohol intake, and weight loss). Participants attended a total of 18 sessions with trained interventionists (typically registered dietitians) over 6 months.[3]
- **Established-plus-DASH:** 18 sessions

TABLE 3

Diet lowers blood pressure as much as drugs do

TREATMENT	REDUCTION (MM HG)
Hydrochlorothiazide (thiazide diuretic)*	11/5
Atenolol (beta-blocker)*	8/7
Captopril (angiotensin-converting enzyme inhibitor)*	6/5
Diltiazem (calcium channel blocker)*	10/9
Prazosin (alpha-1 blocker)*	9/6
DASH plus 1,500 mg sodium diet†	11/6

*When given as monotherapy to men with stage 1 hypertension in the Veterans Affairs Cooperative study[21]
†When applied to men and women with stage 1 hypertension in the Dietary Approaches to Stop Hypertension (DASH)-Sodium study[2,19]; see text and TABLE 1 for a description of the DASH diet

Diet lowered blood pressure the most in hypertensive, African-American, and older subjects

based on the established recommendations plus the DASH diet.

Goals for weight loss, physical activity, and sodium and alcohol reduction were the same in both the established-recommendation group and the established-plus-DASH group. Those in the established-plus-DASH group set additional goals related to fruits, vegetables, dairy, and fat consumption.

The main outcomes in PREMIER were blood pressure and hypertension status at 6 months.

What we learned from the PREMIER study

Both the established-recommendation group and the established-plus-DASH group lost substantial weight, reduced their sodium intake, and increased their physical fitness. Blood pressure and hypertensive status improved for all three groups (TABLE 2).

Hypertension was best controlled in the established-plus-DASH group, in which 77% of participants who started with stage 1 hypertension ended the study with blood pressure lower than 140/90 mm Hg.

The effects attributed to the DASH diet were less than in previous studies, however. In particular, the difference in blood pressure was not statistically significant between the established-plus-DASH group and the established-recommendation group. Furthermore, the advice-only group achieved changes that were better than any observed in control groups of similar studies.[3]

While participants made changes consistent with the DASH diet and other recommendations, they did not do so to the same extent as in the controlled-feeding studies. For example, those in the established-plus-DASH group increased their intake of fruits and vegetables to only 7.8 servings instead of the 9.6 servings in the DASH and DASH-Sodium studies. Therefore, they did not receive the same magnitude of benefit as in those studies. It is also plausible that participants found it more challenging to pay equal attention to each component of the intervention, resulting in the subadditive effects on blood pressure that we observed.

The larger-than-expected effect in the advice-only group is intriguing and unexplained. It is possible that even though their one-time counseling session was brief, the participants in this group were more motivated to make changes using the advice materials they were given. Furthermore, even though they did not attend weekly sessions, they still came to the clinics for measurements, and this contact with health care professionals may have had an effect on their lifestyle choices in the absence of active counseling.

Effects in subgroups

The DASH, DASH-Sodium, and PREMIER studies explored whether certain subgroups defined by lifestyle factors (eg, physical activity, alcohol use) and sociodemographic factors (eg, age, gender, race, income, education) responded differently to dietary patterns.

While all participants benefitted from the interventions in the PREMIER study, the greatest reductions in blood pressure were in hypertensive patients, African Americans, and older participants.[1,19,20]

IMPLICATIONS FOR PRACTICE

The DASH, DASH-Sodium, and PREMIER studies have far-reaching implications for clinical practice and public health. If we compare

the blood pressure-lowering effects of the five antihypertensive medications used in the Veterans Affairs Cooperative study,[21] and of the DASH and DASH-Sodium diets (TABLE 3), it would appear that the diets lower blood pressure as much as the drugs do, at least when the drugs are used as monotherapy. For patients with hypertension, then, the DASH diet and other lifestyle changes can be recommended as an adjunct to pharmacologic treatment of hypertension.

The greatest benefits of the DASH diet and other nonpharmacologic therapies may accrue to people with prehypertension—blood pressure 120–139/80–89 mm Hg. Although drug treatment for this group is rarely indicated, adults with prehypertension have a 2.5-fold (men) and 1.6-fold (women) higher risk of a cardiovascular event than adults with optimal blood pressure.[22] Efforts to reduce the risk of cardiovascular disease in this group are worthwhile.

LIFESTYLE COUNSELING IN THE OFFICE

Given the well-known difficulty of changing one's lifestyle, patients wishing to adopt the DASH diet and make other lifestyle changes are likely to need support, which physicians are in a unique position to provide. The average American visits his or her health care provider 3.1 times a year,[23] the highest level of contact between any professional and the general public.

When patients visit their physicians, they are receptive to suggestions to make lifestyle changes,[24,25] and brief patient-provider conversations increase the chances that patients will comply with recommendations to reduce disease risk.[26]

But how does one implement a counseling program in a busy primary care clinic, where there are competing demands and severe time constraints?

Three levels of counseling

The United States Preventive Services Task Force[27] defines three levels of counseling to change diet and lifestyle behavior:

- **Brief** sessions last about 5 minutes and are typically delivered during a medical visit. Patients have reported that they have changed their habits as a result, but the long-term effects are unknown.[28]
- **Medium-intensity face-to-face** sessions consist of two or three group or individual sessions lasting for 30 minutes or more and are delivered by dietitians or specially trained primary care physicians or nurses.
- **High-intensity** counseling, similar to that in the PREMIER, study includes multiple sessions over periods of up to 6 years. Such intense counseling has the greatest impact on reducing disease risk.[29]

Brief counseling

The key role of the physician in a brief counseling session is to suggest lifestyle change as a means of managing elevated blood pressure and to guide the patient to self-help materials to accomplish this task.

Linkage to resources can be as simple as providing the Internet address of the NHLBI from which to download the brochure "Following the DASH Diet," ie, **www.nhlbi.nih.gov/health/public/heart/hbp/dash/index.htm**. This brochure provides guidelines on how to follow the DASH diet, including the servings and food groups for the eating plan and the number of servings appropriate to the patient's caloric needs. Multiple printed copies can be obtained at nominal cost from the NHLBI. Also available is the book *The DASH Diet for Hypertension*, which includes menus and recipes.

See patient information, page 754

Additional support might include office charts that illustrate the DASH diet in terms of the kinds of foods one might actually eat (TABLE 1), and more details can be found on the NHLBI Web site. Other patient information about making lifestyle changes can be found in **Ten tips to help you control your high blood pressure** (page 754).

Medium-intensity counseling

Medium-intensity counseling still involves the physician in his or her other role as a motivator, but counseling might be delivered by a trained staff member who may be a physician, nurse, or dietitian.

Like the more intense counseling formats, medium-intensity counseling aims to change behavior by using the principles of motivation.

Staff members should be trained in motivation assessment and enhancement techniques, such as evaluating the client's stage of change (ie, not thinking about changing one's lifestyle, thinking about changing, or in the process of making changes—counseling is different in each stage).[30,31] They also should be trained in motivational interviewing, a directive, patient-centered technique intended to help patients explore and resolve their ambivalence to change—an important part of getting patients ready to change their behavior.

The five A's of counseling

Successful interventions use the "five A's" framework. These steps are:

- **Assess** the patient's eating behavior and readiness to change. Short dietary assessments and screening tests are available for this purpose. Also, assess other factors that might interfere with attempts to make lifestyle changes.
- **Advise:** Provide clear, specific advice tailored to the patient. Emphasize the value of making lifestyle changes in controlling blood pressure.
- **Agree:** Make sure that you and the patient agree on the most appropriate target behavior to focus on, and the best method to achieve this behavior. Typically, the patient chooses a dietary goal (eg, increase fruit and vegetables) and creates an action plan for achieving this goal (eg, have a piece of fruit for breakfast).
- **Assist** the patient as he or she attempts to make changes. This includes, but is not limited to, giving patients tools and skills to monitor themselves and overcome barriers to behavioral change. Nutrition education is also provided, including information about serving sizes and tips on how to shop for and prepare food.
- **Arrange:** Schedule follow-up contacts to provide ongoing support and advice, adjust lifestyle goals as needed, and refer for intensive counseling if needed.

This counseling algorithm, combined with efficient clinic flow, can facilitate counseling.[31] For example, the patient may complete the dietary and stage-of-change assessment in the waiting room. The goal that the patient may have set in previous visits can be flagged to provide a counseling cue for the provider, and materials (eg, food preparation tips) associated with that visit may be assembled ahead of time.

Intense counseling

Intense counseling of the kind delivered in the PREMIER study has the highest impact on disease risk, but is not feasible in the office setting. Nevertheless, the provider can again play a critical role in motivating patients and preparing them for intense counseling through referrals, as well as provide ongoing motivation and support during office visits.

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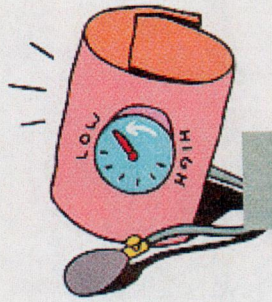

DASH A Diet for All Diseases

BY BONNIE LIEBMAN

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Don't have high blood pressure?

Don't assume you never will.

One out of four American adults does. Among people 60 or over, it's one out of two (see "Older and Higher").

But that doesn't mean everyone else is in the clear.

Say your doctor says that your blood pressure is "high normal," or even "normal." Sounds good, huh?

Not so good.

Even so-called normal blood pressure raises the risk of heart disease and stroke. What you want is "optimal" blood pressure (see "What's Your Risk?"). Less than half of all Americans have it ... and most of them are young.

How can you keep your blood pressure from creeping up from optimal to normal to high?

For years, experts have recommended four proven strategies. The Big Four: cut back on salt; lose excess weight; exercise; and, if you drink, limit alcoholic beverages to two drinks a day.

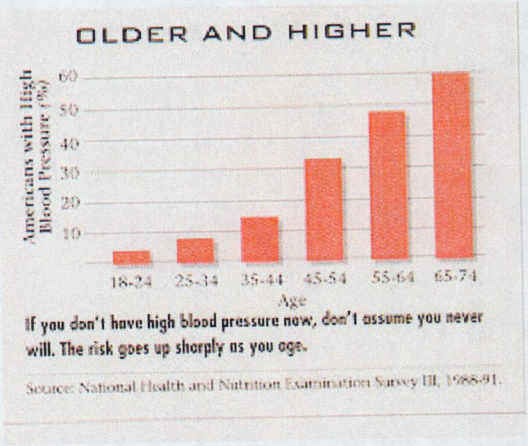
Now we can make it the Big Five. A landmark study called DASH -- Dietary Approaches to Stop Hypertension -- shows that eating the right foods also works. It can lower blood pressure as much as taking a drug.

Better yet: It's the same diet that may help cut your risk of cancer, heart disease, osteoporosis, and diabetes.

Designing DASH

For years, researchers were stumped.

"In the 1970s, we found that blood pressures were lower in vegetarians, who eat little or no fat and cholesterol and lots of fruits, vegetables, and grains rich in potassium, magnesium, and fiber," says Frank Sacks, a researcher at Harvard Medical School who helped create the DASH study.



Other studies showed that people who ate more protein also had lower blood pressure. And some scientists argued that calcium played a role as well.

But when researchers gave people calcium or magnesium supplements, blood pressures barely budged.

"In the Trials of Hypertension Prevention, the only thing that lowered blood pressure was cutting back on salt and reducing overweight," says Jeremiah Stamler, professor emeritus at Northwestern University Medical School in Chicago, who also helped design DASH.

"The scientific literature was confusing," says Lawrence J. Appel, a DASH researcher at Johns Hopkins University in Baltimore. So they constructed a diet to provide all of the promising nutrients.

"We decided to test the whole diet, not supplements," says Sacks.

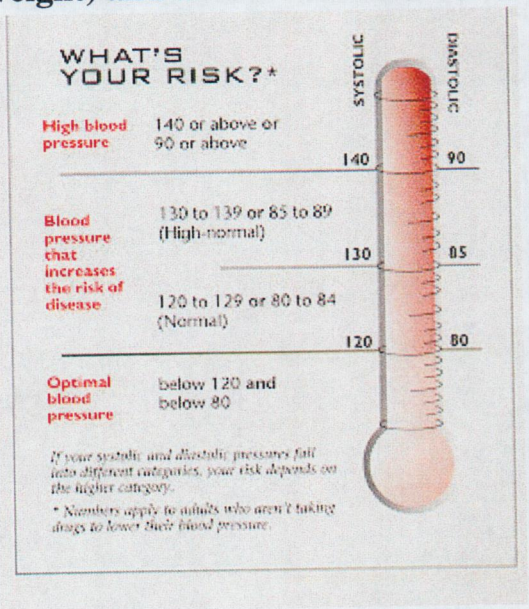
Researchers enrolled 459 adults at four centers around the country. Less than a third already had hypertension. The rest had normal or high-normal blood pressure -- that is, diastolic pressure between 80 and 89. ("Diastolic" is the lower of the two blood pressure numbers.)

For eight weeks, people were randomly assigned to one of three diets:

- **The "control" diet had levels of fat and cholesterol that matched the average American's diet, and lower-than-average levels of potassium, magnesium, and calcium.**
- **The "fruit and vegetable" diet matched the control diet in fat, saturated fat, cholesterol, and protein. The only difference: Potassium, magnesium, and fiber got a boost when fruits and vegetables replaced some snacks and sweets.**

- **The "combination" diet had less total fat, saturated fat, and cholesterol than the fruit and vegetable diet or the control diet (see "Count the Nutrients"). It was rich in fruits, vegetables, and low-fat dairy products (which upped the potassium, magnesium, calcium, fiber, and protein).**

"We kept the salt constant in all three diets at 3,000 mg a day," says Appel. (That's slightly less than the average American's 3,600 to 4,000 mg a day, but more than the 2,400 mg health experts recommend.) Ditto for other things known to influence blood pressure: Calories were the same for all three diets (so no one would gain or lose weight) and alcohol was limited to a drink or two a week.



The researchers didn't have to wait long.

The Winner

"Blood pressure fell within days," says Appel. The fruit and vegetable diet lowered pressure significantly. But the combination diet won hands down. It lowered average pressures by:

3.5 points (systolic) over 2.1 points (diastolic) in those with normal or high-normal blood pressure, and
11.4 points over 5.5 points in those with high blood pressure.

"That's about what you'd get in people given a drug," says Appel.

Why such success when supplements of calcium, magnesium, and other individual nutrients flopped in earlier studies?

"Maybe you need to eat the nutrients together because the effect of each one is small," says Eva Obarzanek, a DASH co-author at the National Heart, Lung and Blood Institute in Bethesda, Maryland. "Or maybe the foods improve the absorption of the nutrients."

It's also possible that something else in fruits, vegetables, and low-fat dairy products lowers blood pressure. The DASH can't say. Nor can it say which nutrients made the difference.

But it said enough.

"Now we have everything we need to know to

end the epidemic rise in blood pressure with age -- and high blood pressure -- in this country," says Jeremiah Stamler.

"We've known how to lower blood cholesterol since 1960. Now we know the same about blood pressure. So we can prevent both major diet-related risk factors for heart disease and stroke."

DASH-2 is already under way. It will test the combination diet at three levels of sodium intake: 3,450 mg, 2,300 mg, and 1,650 mg a day. "We want to see what bang you get for your buck when you combine the DASH diet with less salt," says Appel.

And who knows? Maybe someday, someone will compare the DASH diet to those recommended by Nathan Pritikin and Dean Ornish to see if their advice -- to cut fats and cholesterol even further, use only whole grains, and add little or no sugar -- yields even greater benefits.

But you needn't wait. Adding the DASH diet to the Big Four (see "The Bottom Line") is easy to follow, inexpensive, and not too strict.

"The beauty of DASH is that it doesn't take a genius to follow," says Norman Kaplan, a hypertension expert at the University of Texas Health Sciences Center in Dallas. "You just cut the fat, double your fruits and vegetables, and use low-fat dairy products."

What's more, the DASH has everything: fruits and vegetables to cut your risk of cancer, calcium to lower your risk of osteoporosis, and limits on saturated fat and cholesterol to cut your risk of heart disease.

"It's not a diet for one disease," says Appel. "It's a diet for all diseases."

A TYPICAL DASH MENU

Here's a typical day's menu for the DASH "Combination Diet." It supplies 2,000 calories a day. If you eat more or less, adjust accordingly.

FOOD	AMOUNT	SERVINGS
Breakfast		
orange juice	3/4 cup	1 fruit
1% low-fat milk	1 cup	1 dairy
corn flakes (with 1 tsp. sugar)	1 cup	2 grains
banana	1 medium	1 fruit
whole wheat bread (with 1 Tbs. jelly)	1 slice	1 grain
soft margarine	1 tsp.	1 fat
Lunch		
chicken salad	3/4 cup	1 poultry
pita bread	1/2 large	1 grain
raw vegetable medley:		
carrot & celery sticks	3-4 sticks each	1 vegetable
radishes	2	
loose-leaf lettuce	2 leaves	
part-skim mozzarella cheese	1 1/2 slices (1 1/2 oz.)	1 dairy
1% low-fat milk	1 cup	1 dairy
fruit cocktail in light syrup	1/2 cup	1 fruit
Dinner		
herbed baked cod	3 oz.	1 fish
scallion rice	1 cup	2 grains
steamed broccoli	1/2 cup	1 vegetable
stewed tomatoes	1/2 cup	1 vegetable
spinach salad:		
raw spinach	1/2 cup	1 vegetable
cherry tomatoes	2	
cucumber	2 slices	
light Italian salad dressing	1 Tbs.	1/2 fat
whole wheat dinner roll	1 small	1 grain
soft margarine	1 tsp.	1 fat
melon balls	1/2 cup	1 fruit
Snacks		
dried apricots	1/4 cup	1 fruit
mini-pretzels	3/4 cup (1 oz.)	1 grain
mixed nuts	1/3 cup	1 nuts
diet ginger ale	12 oz.	0

Source: DASH clinical study.

NUTRITION ACTION HEALTHLETTER October 1997 11

COUNT THE NUTRIENTS

The DASH "Combination Diet" is low in cholesterol, high in fiber, potassium, calcium, and magnesium, and moderately high in protein. Here's how it compares with the DASH "Control Diet," which is closer to what the typical American eats. (Both diets supply 2,000 calories a day.)

Nutrient	DASH Combination Diet	DASH Control Diet
Fat (% of cals.)	27	37
Saturated Fat (% of cals.)	6	16
Monounsaturated Fat (% of cals.)	13	13
Polyunsaturated Fat (% of cals.)	8	8
Carhohydrates (% of cals.)	55	48
Protein (% of cals.)	18	15
Cholesterol (mg per day)	150	300
Fiber (grams per day)	31	9
Potassium (mg per day)	4,700	1,700
Magnesium (mg per day)	500	165
Calcium (mg per day)	1,240	450
Sodium (mg per day)	3,000	3,000

SOURCE: DASH clinical study

THE BOTTOM LINE

If your blood pressure is optimal, following all of these Big Five proven strategies will help keep it from climbing as you get older. If your blood pressure is normal or high-normal, the Big Five may help lower it. If your pressure is high, the Big Five my enable you to use less -- or get off -- medication.

1. **Lose weight** if you're overweight. Dropping as few as ten pounds can make a difference.
2. **Cut sodium** to less than about 2,400 mg a day. Check labels for the lowest-sodium brands. Limit foods with 480 mg of sodium or more per serving. That's 20 percent of the Daily Value.
3. **Walk briskly, jog, swim, cycle**, or do other aerobic exercise for 30 to 45 minutes a day at least three times a week.
4. **If you drink**, keep it to no more than two servings of beer, wine, or liquor a day to keep blood pressure from rising. Women should limit themselves to one drink a day. Consuming more may increase the risk of breast cancer.
5. **Try a DASH-like diet.** It should help reduce your risk of heart disease, stroke, cancer, osteroporosis, and diabetes.

The DASH Diet

It's not tough to follow the DASH diet. "Almost 100 percent of the participants completed the study," says researcher Lawrence Appel. Granted, when it came to food, all they had to do was eat. The researchers did all the planing, shopping, and cooking. Still, the foods weren't unusual -- no specialty foods with fat substitutes, nothing you couldn't buy at a local supermarket. (For detailed information about the DASH study, the results, and the diet, see the DASH's web page.)

Here's *how many* servings of *which* kinds of foods were in the DASH study's 2,000-calorie-a-day "Combination Diet" -- the one that lowered blood pressure the most.

Food and Servings	Examples of 1 Serving	Our Comments
Grains and grain products 7 to 8 a day	1 slice bread, half a cup dry cereal, half a cup cooked rice, pasta, or cereal	Seven or eight servings a day seem like a lot, but they're small
Vegetables 4 to 5 a day	1 cup raw leafy vegetable, half a cup cooked vegetable, three quarter cup vegetable juice	Eight to ten servings a day of fruits and vegetables tops the five to nine servings recommended by the National Cancer Institute's "5 A Day" program. The averae American is stuck at just over three.
Fruits 4 to 5 a day	three quarter cup fruit juice, 1 medium fruit, one quarter cup dried fruit, one half cup fresh, frozen, or canned fruit	Ditto
Low-fat or non-fat dairy food 2 to 3 a day	1 cup skim or 1% milk, 1 cup low-fat yogurt, 1 and a half oz. part-skim or non-fat cheese	Three servings a day is better to help reduce the risk of osteoporosis
Meats, poultry, & fish 2 or less a day	3 oz. broiled or roasted lean meats, skinless poultry, or fish	We now average more than two servings a day, and they're often fatty: hamburgers, fried chicken or fish, or chicken with the skin.
Nuts, seeds, & bean 4 to 5 a week	one third cup nuts, 2 Tbs. sunflower seeds, half cup cooked beans	Most people eat only two servings of beans a week. They're missing out on delicious lentil soups, Cuban black-beans-and-rice, Middle Eastern hummus, Mexican bean burritos, etc.
Added fats, oils, & salad dressing 2 to 3 a day	1 tsp. oil or soft margarine, 1 tsp. regular mayonnaise, 1 Tbs. low-fat mayonnaise, 1 Tbs. regular salad dressing, 2 Tbs. light salad dressing	The "control" diet had six servings a day. Add your fats to vegetables, beans, breads, or other foods for flavor.
Snacks & sweets 5 a week	1 medium fruit, 1 cup low-fat yogurt, half cup low-fat frozen yogurt, three quarter cup pretzels, 1 Tbs. maple syrup, sugar, jelly, or jam, half cup Jell-O, 3 pieces hard candy, 15 jellybeans	The healthier, the better. If you're more likely to go for the jellybeans than the fresh fruit, keeping your snacks to less than one a day minimizes the damage. The "control" diet had four snacks a day.

SOURCE: DASH clinical study

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The Importance of Population-Wide Sodium Reduction as a Means to Prevent Cardiovascular Disease and Stroke: A Call to Action From the American Heart Association

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AHA Presidential Advisory

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A Call to Action From the American Heart Association

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Blood pressure (BP)-related diseases, specifically, stroke, coronary heart disease, heart failure, and kidney disease, are leading causes of morbidity and mortality in the United States and throughout the world. In the United States, coronary heart disease and stroke are the leading causes of mortality, whereas heart failure is the leading cause of hospitalizations.[1] Concurrently, the prevalence of chronic kidney disease remains high and is escalating.[2,3] The direct and indirect costs of these conditions are staggering, over $400 billion just for cardiovascular disease (CVD) in 2009.[1,4] The human consequences are likewise enormous.

The relation between BP and adverse health outcomes is direct and progressive with no evidence of a threshold, that is, the risk of CVD, stroke, and end-stage kidney disease increases progressively throughout the range of usual BP starting at a level of ≈115/75 mm Hg.[5–7] Overall, elevated BP is the second leading modifiable cause of death, accounting for an estimated 395 000 preventable deaths in the United States in 2005.[8] Worldwide, elevated BP accounts for 54% of stroke and 47% of coronary heart disease events; importantly, about half of these events occur in persons without hypertension.[9]

The 2020 goal of the American Heart Association (AHA) is to improve the cardiovascular heath of all Americans by 20% while continuing to reduce deaths from CVD and stroke by 20%.[4] Two of the key metrics for ideal cardiovascular health are a BP of <120/80 mm Hg and sodium consumption of <1500 mg/d. The purpose of this advisory is 2-fold: first is to highlight the impressive body of evidence that links sodium intake with elevated BP and other adverse outcomes, and second, to serve as a call to action on behalf of the AHA for individuals, healthcare providers, professional organizations, governments, and industry to address this major public health issue. See Table for key points.

The Evidence

Excess intake of salt (sodium chloride) has a major role in the pathogenesis of elevated BP. Excess sodium intake also has BP-independent effects, promoting left ventricular hypertrophy as well as fibrosis in the heart, kidneys, and arteries.[10] Evidence on the adverse health effects of excess sodium intake includes results from animal studies, epidemiological studies, clinical trials, and meta-analyses of trials.[11] To date, >50 randomized trials have tested the effects of sodium reduction on BP in adults. A meta-analysis[12] of these trials documented that a median reduction in urinary sodium of ≈1800 mg/d lowered systolic/diastolic BP by 2.0/1.0 mm Hg in nonhypertensive individuals and by 5.0/2.7 mm Hg in hypertensive individuals. In a subsequent meta-analysis of trials in children, a reduced sodium intake lowered mean systolic/diastolic BP by 1.2/1.3 mm Hg in children and adolescents and lowered systolic BP by 2.5 mm Hg in infants.[13] The benefits of sodium reduction in persons with poorly controlled BP are striking. In a recent trial of patients with resistant hypertension, reducing sodium intake by 4600 mg/d lowered systolic/diastolic BP by 22.7/9.1 mm Hg.[14]

Some of the most persuasive evidence on the effects of sodium on BP comes from rigorously controlled, dose-response trials.[15–17] Each of these trials tested at least 3 sodium levels, and each documented statistically significant, direct, progressive, dose-response relations. The lowest level of sodium intake in

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Table. Key Points

- Elevated blood pressure (BP) is a leading, preventable cause of mortality and morbidity in the United States and throughout the world.
- The relation of BP and adverse health outcomes is direct, progressive, consistent, continuous, independent, and etiologically relevant throughout the range of usual BP starting at a level of approximately 115/75 mm Hg.
- A diverse body of evidence has implicated excess sodium intake in the pathogenesis of elevated BP.
- Independent of its effects on BP, excess sodium intake adversely affects the heart, kidneys, and blood vessels.
- Current intake of sodium greatly exceeds 1500 mg/d, the upper level of intake recommended by the American Heart Association and the 2010 Dietary Guidelines Scientific Advisory Committee.
- The potential public health benefits of sodium reduction are enormous and extend to virtually all Americans.

each trial was ≈1500 mg/d, the level currently recommended by the AHA.[4] Importantly, the BP response to sodium reduction, while direct and progressive, was nonlinear. Specifically, decreasing sodium intake by ≈900 mg/d caused a greater reduction in BP when the starting sodium intake was ≈2300 mg/d than when it was ≈3500 mg/d. The DASH (Dietary Approaches to Stop Hypertension)-Sodium trial, the largest of the 3 major dose-response trials,[18,19] also documented that reduced sodium intake significantly lowered BP in each of the major subgroups studied (ie, nonhypertensive individuals, hypertensive individuals, men, women, African Americans, non–African Americans). The benefits of sodium reduction in non-hypertensive individuals were recently corroborated in the GenSalt feeding study, which documented that lowering sodium intake to ~1500 mg/d reduced BP in ~2,000 Asian adults with mean systolic/diastolic BP <120/80 mm Hg.[20]

Sodium reduction also blunts the age-related rise in BP. Because BP rises with age, about 90% of adults eventually become hypertensive.[21] The DASH-Sodium trial demonstrated that sodium reduction to a level of ≈1500 mg/d lowers BP more in older adults than younger adults.[19] Systolic BP decreased by 8.1 mm Hg in those aged 55 to 76 years, compared with 4.8 mm Hg for adults aged 23 to 41 years. In persons without hypertension, BP decreased by 7.0 mm Hg in those >45 years of age compared with 3.7 mm Hg in those ≤45 years of age. These results demonstrated that sodium reduction can lessen the rise in BP with age[22] and also confirmed the well-documented observation of a reduced age-related rise in BP in isolated populations with low sodium intake.[23] Consistent with this evidence, a major trial in the United States documented that a reduced sodium intake can prevent hypertension by ≈20%.[24]

Evidence supporting a direct relation of sodium intake and CVD is also accumulating. In a recent meta-analysis of observational studies, a higher sodium intake was associated with an increased risk of stroke and likely CVD.[25] To date, 3 trials conducted in general populations have reported the effects of reduced sodium interventions on CVD outcomes. Two of these trials tested lifestyle interventions that focused on reducing sodium intake, and 1 trial tested the effects of a reduced sodium/high potassium salt. In each instance, there was a 21% to 41% reduction in clinical CVD events in those who received a reduced sodium intervention (significant reduction in 2 trials[26,27] and a nonsignificant trend in the third[28]). Hence, direct evidence from trials, albeit limited, is consistent with indirect evidence on the health benefits of sodium reduction.

Independent of its effects on BP, an increased sodium intake has other adverse effects. These include subclinical CVD (ie, left ventricular hypertrophy, ventricular fibrosis, diastolic dysfunction), kidney damage, gastric cancer, and disordered mineral metabolism (ie, increased urinary calcium excretion, potentially leading to osteoporosis).[11] It is well-established that sodium loading suppresses the systemic renin-angiotensin-aldosterone system by inhibiting renin release from the renal juxtaglomerular apparatus. Less well appreciated are findings that sodium loading increases oxidative stress and endothelial dysfunction and promotes mitogenic responses (fibrosis in heart, kidneys, and arteries) resulting in cardiac and vascular remodeling.[10,29–33]

With regard to arterial dysfunction, higher sodium intake is associated with greater increases in large elastic artery stiffness with aging,[34,35] and reducing sodium intake from moderate levels by ≈50% to less than ≈1500 mg/d reduces large elastic artery stiffness in otherwise healthy middle-aged and older adults with elevated systolic BP.[36,37] An acute increase in sodium intake has been shown to impair vascular endothelial function in young adults with normal BP.[38] Among middle-aged and older adults with elevated systolic BP, lower sodium intake is associated with enhanced vascular endothelial function, independent of BP or other risk factors.[39] A low sodium diet of ≈1200 mg/d improves endothelial function in overweight and obese adults with normal BP.[40] These findings have important clinical implications given that stiffening of the large elastic arteries, independent of BP, is a major independent risk factor for CVD and incident cardiovascular events,[41,42] whereas vascular endothelial dysfunction is associated with increased cardiovascular events and CVD mortality.[43,44]

Sodium-induced increases in BP may directly induce renal injury or accelerate kidney disease caused by other conditions such as diabetes mellitus or glomerulonephritis. However, excess sodium intake also has deleterious effects on the kidneys independent of increased BP. Studies in experimental animals and in human beings have shown, for example, that high sodium intake can cause glomerular hyperfiltration and increased albumin excretion, renal oxidative stress, and renal fibrosis independent of BP.[45–47] A direct association between sodium intake and urinary albumin excretion, independent of BP, has been observed in epidemiological studies.[47] In a trial of whites, blacks, and Asians with elevated BP, decreasing sodium intake from an average of ≈3800 mg/d to ≈2500 mg/d significantly reduced 24-hour urinary albumin excretion, an early marker of renal injury.[48] A retrospective analysis of patients with chronic kidney disease, with an average observation period of 3 years, showed that in patients with a sodium intake >4600 mg/d, the rate of decline in creatinine clearance and increase in proteinuria were greater compared with patients with a sodium intake <2300 mg/d, despite similar BP control.[49] Excess sodium intake also attenuates the beneficial effects of many antihypertensive drugs, especially the antiproteinuric effect of blocking the renin-angiotensin system.[50] Thus, there is considerable evidence linking increased sodium intake with kidney injury not only through

increased BP but also by effects that appear to be at least partly independent of BP.[51]

Some sodium intake is required. An Institute of Medicine Committee set 1500 mg of sodium per day as an adequate intake level, primarily to assure nutrient adequacy.[52] Based on the DASH-Sodium trial, it is apparent that Western type diets can provide this level of sodium intake and that such a diet also can provide adequate levels of other nutrients.[53] In 2005, the US Dietary Guidelines for Americans recommended a sodium intake of <2300 mg/d for the general adult population and stated that hypertensive individuals, blacks, and middle-aged and older adults would benefit from reducing their sodium intake even further to 1500 mg/d.[53] Because these latter groups comprise at least 50% of adults and perhaps as high as 70%,[54] and because ≈90% of US adults will develop hypertension over their lifetime, the goal should be 1500 mg/d, as recommended by the scientific advisory of the 2010 Dietary Guidelines Committee.[55] The health benefits apply to Americans in all groups, and there is no compelling evidence to exempt special populations from this public health recommendation. Although clinical research has identified groups that experience greater or lesser BP effects from sodium reduction, there is no practical clinical test to assess sodium sensitivity in individuals. Hence, it is not feasible, from a public health perspective, to classify individuals as sodium-sensitive or not.

A Call to Action

The projected benefits of sodium reduction are substantial. Several studies have estimated the societal benefits of population-wide sodium reduction.[56–58] In the most recent and comprehensive set of projections, Bibbins-Domingo and colleagues[58] quantified the effects of 400 mg/d to 1200 mg/d reductions in sodium intake on a variety of relevant outcomes. A national effort that reduces sodium intake by 1200 mg/d should result in 60 000 to 120 000 fewer coronary heart disease events, 32 000 to 66 000 fewer strokes, 54 000 to 99 000 fewer myocardial infarctions, and 44 000 to 92 000 fewer deaths, and save 194 000 to 392 000 quality-adjusted life-years and $10 to $24 billion in healthcare costs annually. Even if average sodium intake is reduced by just 400 mg/d, the benefits would still be substantial and warrant implementation.

Accomplishing population-wide sodium reduction is similar to achieving other lifestyle modifications, in that a substantial public health approach will be required to facilitate environmental changes that support changes in individual behavior. Indeed, the need for an effective public health approach is even greater for sodium reduction than other lifestyle modifications. For example, in contrast to cigarette smoking, where usage is evident and deliberate by the consumer, the sodium content of our diets is not readily apparent.

More than 75% of consumed sodium comes from processed foods.[59] Even those who read labels are often left without realistic alternatives to high-sodium foods, and those who eat out, a behavior that has increased more than 200% from 1977 to 1995, are subjected to excessive sodium intakes from routinely served, processed foods.[55] Some food items are extremely high in sodium. However, from a public health perspective, the problem of excess sodium intake largely reflects the cumulative intake of common foods that are only moderately high in sodium. Hence, any meaningful strategy to reduce sodium intake population-wide must involve the efforts of food manufacturers, food processors, and restaurant industries, a strategy that is being successfully implemented in other countries. For example, the United Kingdom has a vigorous salt reduction campaign, which has resulted in an estimated population-wide reduction in sodium intake of ≈10%.[60] Ongoing surveillance is necessary to evaluate the progress of such strategies.

Some scientists still question the evidence supporting population-wide sodium reduction. Common arguments include the absence of a major trial with hard clinical outcomes. It is well-known, however, that such trials are not feasible because of logistic, financial, and often ethical considerations. In fact, there is no trial of weight reduction or increased physical activity on hard clinical outcomes, and only 1 definitive trial of smoking cessation therapy on lung cancer.[61] It also has been argued that sodium reduction might be harmful.[62] However, the evidence for harm is unpersuasive, based largely on inferences from cohort studies with major methodological limitations, particularly, incomplete assessment of sodium intake and the potential for reverse causality.[63]

In 2010, the Institute of Medicine issued a report that provides a roadmap for lowering Americans' intake of sodium.[64] It was noted that for >40 years, efforts to reduce sodium intake of the US population have been unsuccessful. This absence of tangible progress reflects the lack of a substantive, multidimensional, environmentally focused strategic plan with measurable outcomes, joint-ownership, and accountability among the many stakeholders. Specifically, given the ubiquity of sodium in the food supply, the prior focus on encouraging individuals to select reduced-sodium products has been insufficient to meaningfully reduce sodium intake and achieve levels consistent with the Dietary Guidelines for Americans. Such efforts must be accompanied by an overall reduction of the level of sodium in the food supply. The Institute of Medicine made a series of recommendations, many of which involved regulatory actions (eg, setting mandatory national standards for the sodium content of foods). Such a strategy extends the voluntary approaches implemented in New York City.[65]

Conclusion

A compelling and still increasing body of evidence supports the imperative for population-wide sodium reduction as an integral component of public health efforts to prevent CVD, stroke, and kidney disease. The potential public health benefits are enormous and extend to virtually all Americans. The AHA is committed to improving cardiovascular health of the whole population, as recently articulated in its 2020 strategic goals.[4] Successful sodium reduction requires action and partnership at all levels—individuals, healthcare providers, professional organizations, public health agencies, governments, and industry. The AHA urges a renewed and intensive focus on this critically important public health issue and looks forward to partnering with public and private organizations to achieve our shared goal of population-wide reduction in sodium intake.

Disclosures

Writing Group Disclosures

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*Significant.

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Omega-6 Fatty Acids and Risk for Cardiovascular Disease: A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention

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Omega-6 Fatty Acids and Risk for Cardiovascular Disease

A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention

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A large body of literature suggests that higher intakes of omega-6 (or n-6) polyunsaturated fatty acids (PUFAs) reduce risk for coronary heart disease (CHD). However, for the reasons outlined below, some individuals and groups have recommended substantial reductions in omega-6 PUFA intake.[1–4] The purpose of this advisory is to review evidence on the relationship between omega-6 PUFAs and the risk of CHD and cardiovascular disease.

Omega-6 PUFAs

Omega-6 PUFAs are characterized by the presence of at least 2 carbon-carbon double bonds, with the first bond at the sixth carbon from the methyl terminus. Linoleic acid (LA), an 18-carbon fatty acid with 2 double bonds (18:2 omega-6), is the primary dietary omega-6 PUFA. LA cannot be synthesized by humans, and although firm minimum requirements have not been established for healthy adults, estimates derived from studies in infants and hospitalized patients receiving total parenteral nutrition suggest that an LA intake of ≈0.5% to 2% of energy is likely to suffice. After consumption, LA can be desaturated and elongated to form other omega-6 PUFAs such as γ-linolenic and dihomo-γ-linolenic acids. The latter is converted to the metabolically important omega-6 PUFA arachidonic acid (AA; 20:4 omega-6), the substrate for a wide array of reactive oxygenated metabolites. Because LA accounts for 85% to 90% of the dietary omega-6 PUFA, this advisory focuses primarily on this fatty acid, recognizing that dietary AA, which can affect tissue AA levels,[5] may have physiological sequelae.[6–8] LA comes primarily from vegetable oils (eg, corn, sunflower, safflower, soy). The average US intake of LA, according to National Health and Nutrition Examination Survey 2001 to 2002 data for adults ≥19 years of age, is 14.8 g/d.[9] On the basis of an average intake of 2000 kcal/d, LA intake is 6.7% of energy. AA (≈0.15 g/d) is consumed preformed in meat, eggs, and some fish.

Omega-6 PUFAs and Inflammation

Arguments for reduced LA intakes are based on the assumption that because CHD has an inflammatory component[10] and because the omega-6 fatty acid, AA, is the substrate for the synthesis of a variety of proinflammatory molecules, reducing LA intakes should reduce tissue AA content, which should reduce the inflammatory potential and therefore lower the risk for CHD. The evidence, derived primarily from human studies, regarding this line of reasoning is examined below.

AA is the substrate for the production of a wide variety of eicosanoids (20-carbon AA metabolites). Some are proinflammatory, vasoconstrictive, and/or proaggregatory, such as prostaglandin E_2, thromboxane A_2, and leukotriene B_4. However, others are antiinflammatory/antiaggregatory, such as prostacyclin, lipoxin A_4,[11] and epoxyeicosatrienoic acids.[12] Epoxyeicosatrienoic acids are fatty acid epoxides produced from AA by a cytochrome P450 epoxygenase. Epoxyeicosatrienoic acids also have important vasodilator properties via

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on November 6, 2008. A copy of the statement is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. LS-1966). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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hyperpolarization and relaxation of vascular smooth muscle cells.[13] Importantly, because the production of AA from LA is tightly regulated,[14] wide variations in dietary LA (above minimal essential intakes) do not materially alter tissue AA content.[15] In tracer studies, the extent of conversion of LA to AA is ≈0.2%.[16]

In studies with vascular endothelial cells, omega-6 PUFA had antiinflammatory properties, suppressing the production of adhesion molecules, chemokines, and interleukins, all key mediators of the atherosclerotic process.[17] In human studies, higher plasma levels of omega-6 PUFAs, mainly AA, were associated with decreased plasma levels of serum proinflammatory markers, particularly interleukin-6 and interleukin-1 receptor antagonist, and increased levels of antiinflammatory markers, particularly transforming growth factor-β.[18] When healthy volunteers were given ≈7 times the usual intake of AA (ie, 1.5 g/d) in a 7-week controlled feeding study, no effects on platelet aggregation, bleeding times, the balance of vasoactive metabolites, serum lipid levels, or immune response were observed.[5–8] Likewise, in a recent study from Japan, AA supplementation (840 mg/d for 4 weeks) had no effect on any metabolic parameter or platelet function.[19] Consistent with this, in observational studies, higher omega-6 PUFA consumption was associated with unaltered or lower levels of inflammatory markers.[20]

Diets high in LA can increase the ex vivo susceptibility of low-density lipoprotein (LDL) to oxidation,[21] and oxidized LDL can promote vascular inflammation.[22] Therefore, oxidized LDL may play some role in the etiology of CHD.[23] However, the extent of LDL oxidation at higher LA intakes (5% to 15% of energy) has not been established, and its clinical relevance is in question owing to the general failure of antioxidant treatments to mitigate CHD risk in most randomized trials.[24] At present, little direct evidence supports a net proinflammatory, proatherogenic effect of LA in humans.[22,25,26]

Omega-6 PUFA Consumption and Other CHD Risk Factors/Markers

The cholesterol-lowering effect of LA is well established from human trials. In a meta-analysis of 60 feeding studies including 1672 volunteers, the substitution of PUFA (largely omega-6, varying from 0.6% to 28.8% energy) for carbohydrates had more favorable effects on the ratio of total to high-density lipoprotein cholesterol (perhaps the best lipid predictor of CHD risk) than any class of fatty acids.[27] Higher plasma PUFA levels are associated with a reduced ratio of total to high-density lipoprotein cholesterol,[28] and epidemiologically, the replacement of 10% of calories from saturated fatty acid with omega-6 PUFA is associated with an 18-mg/dL decrease in LDL cholesterol, greater than that observed with similar replacement with carbohydrate.[29] These findings confirm an LDL-lowering effect of omega-6 PUFA beyond that produced by the removal of saturated fatty acids. Favorable effects of LA on cholesterol levels are thus well documented and would predict significant reductions in CHD risk. Additionally, higher LA intakes may improve insulin resistance[30] and reduce the incidence of diabetes mellitus,[31] and higher serum LA levels are associated with lower blood pressure.[32] Nevertheless, not all studies support a beneficial effect of LA on CHD risk markers. For example, an angiographic study reported a direct association between PUFA intakes and luminal narrowing in women with CHD.[33] However, effects on markers do not always translate into effects on actual clinical end points; thus, it is essential to evaluate the relations between LA consumption and CHD events.

Omega-6 PUFA Consumption and CHD Events: Observational Studies

Ecological Studies

Cross-cultural, cross-sectional, and time-trend studies examining omega-6 PUFA intake and CHD risk demonstrate equivocal results.[34,35] Among the 4584 subjects in the National Heart, Lung, and Blood Institute Family Heart Study, the prevalence of coronary artery disease was ≈66% higher at LA intakes of 1.8% compared with 5.3%.[36] The weaknesses of these study designs for evaluating diet-disease relations are well documented,[37] and most evaluated only total PUFA intake, failing to distinguish between omega-3 and omega-6 PUFAs and their potentially distinct effects. Given these limitations, firm conclusions cannot be drawn from these studies.

Case-Control Studies

In a meta-analysis of 25 case-control studies (including 1998 cases and 6913 controls) evaluating blood/tissue omega-6 PUFA content and CHD events, LA content was inversely associated with CHD risk, whereas AA was unrelated to CHD risk.[38] Even very high LA intakes have been associated with lower risk; in 1 study in Israel,[39] where 25% of the population consumes >12% of energy as omega-6 PUFA, an inverse association was found between adipose LA and acute myocardial infarction after controlling for other omega-6 PUFAs.

Prospective Cohort Studies

These observational studies use the strongest designs, minimizing both selection and recall bias. No significant associations between LA or omega-6 PUFA intake and CHD risk were seen in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study,[40] Lipid Research Clinics study,[41] or Honolulu Heart Program.[42] Modest, nonsignificant inverse associations were observed in the Multiple Risk Factor Intervention Trial,[43] the Irish-Boston Heart Study,[44] and the Health Professionals Follow-Up Study.[45] In the Health Professionals Follow-Up Study, CHD rates were lowest in participants with higher intake of both omega-3 and omega-6 PUFAs,[46] and in the Western Electric Study[47] and the Kupio Heart Study,[48] higher LA intakes or serum levels were associated with lower risk of CHD or total mortality. In the Nurses' Health Study, in which diet was assessed multiple times over 20 years,[49] CHD risk was ≈25% lower comparing the 95th and 5th percentiles of LA intake (7.0% versus 2.8% of energy, respectively). Most prospective cohort studies have not found significant associations between omega-6 fatty acid intakes and ischemic[50–52] or hemorrhagic[50,51,53] stroke or stroke mortality.[54] In 1 prospective study, serum

LA levels predicted lower risk of stroke, particularly ischemic stroke.[55] LA intakes are not associated with risk for cancer.[26] Therefore, observational studies generally suggest an overall modest benefit of omega-6 PUFA intake on CHD risk and no significant effect on stroke or cancer. These studies, some of which included LA intakes of up to 10% to 12% of energy, contradict the supposition that higher omega-6 PUFA intakes increase risk for CHD.

Omega-6 PUFA Consumption and CHD Events: Randomized Controlled Trials

Several randomized trials have evaluated the effects of replacing saturated fatty acids with PUFAs on CHD events.[56–65] Intakes of PUFA (almost entirely omega-6 PUFA) ranged from 11% to 21%. In addition to the inability to double-blind these studies, many had design limitations such as small sample size (n=54),[65] the provision of only ≈50% of meals,[56] outcomes composed largely of "soft" ECG end points,[59,60] randomization of sites rather than individuals with open enrollment and high turnover of subjects,[59,60] use of vegetable oils that also contained the plant omega-3 fatty acid α-linolenic acid,[57,59,60] and simultaneous recommendations to increase fish and cod liver oil use.[58] Nevertheless, a meta-analysis including 6 of these trials[56–60,62–64] indicated that replacing saturated fatty acids with PUFAs lowered the risk for CHD events by 24%.[66] Of the remaining 4 studies, 1 reported a significant 45% reduction in risk,[59] whereas no significant effect was seen in the others.[60,61,65]

These trials tested the effect of replacing saturated fatty acids; no randomized trial has reported the effects of replacing carbohydrate or protein with omega-6 PUFAs on CHD risk. Although limitations are present for each trial, the combined results of these studies and the observational trials provide evidence that replacing saturated fatty acid or refined carbohydrate (eg, sugars, white bread, white rice, potatoes) with omega-6 PUFAs reduces CHD risk. On the basis of the intakes of omega-6 PUFAs used in the randomized trials, metabolic studies, and nonhuman primate studies discussed below, reductions in CHD risk might be expected with omega-6 PUFA intakes of 10% to 21% of energy compared with lower intakes, with no clinical evidence for adverse events.

Recommended Intakes of Omega-6 Fatty Acids

Dietary recommendations for omega-6 PUFAs traditionally focused on the prevention of essential fatty acid deficiency but are now increasingly seeking to define "optimal" intakes to reduce risk for chronic disease, particularly CHD. The Institute of Medicine's Food and Nutrition Board, in their Dietary Reference Intake Report for Energy and Macronutrients,[67] defines an adequate intake of LA as 17 g/d for men and 12 g/d for women (5% to 6% of energy) 19 to 50 years of age, approximately the current median US intake. Both the Dietary Reference Intake Report and the 2005 Dietary Guidelines for Americans[68] support an acceptable macronutrient distribution range (the range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients) of 5% to 10% dietary energy from omega-6 PUFAs. The Third Adult Treatment Panel of the National Cholesterol Education Program recommends PUFA consumption up to 10%, noting that "there are no large populations that have consumed large quantities of polyunsaturated fatty acids for long periods. Thus, high intakes have not been proven safe in large populations; this introduces a note of caution for recommending high intakes."[69] On the other hand, evidence from trials in nonhuman primates has demonstrated cardiovascular benefits and no evidence of harm with LA intakes of 25% of energy for up to 5 years,[70,71] and randomized trials in humans have shown reduced CHD risk with omega-6 PUFA intakes of 11% to 21% of energy for up to 11 years with no evidence of harm.

Other governmental health recommendations for omega-6 fatty acid intakes (on a percent energy basis) are as follows: European Commission, 4% to 8%[72]; Food and Agriculture Organization/World Health Organization, 5% to 8%[73]; British Nutrition Foundation, 6% to 6.5% (maximum, 10%)[74]; the Department of Health and Ageing, Australia and New Zealand, 4% to 5% (maximum, 10%)[75]; and the American Dietetic Association/Dietitians of Canada, 3% to 10%.[76] The American Heart Association places primary emphasis on healthy eating patterns rather than on specific nutrient targets.

Advice to reduce omega-6 PUFA intakes is typically framed as a call to lower the ratio of dietary omega-6 to omega-3 PUFAs.[1–4] Although increasing omega-3 PUFA tissue levels does reduce the risk for CHD,[77,78] it does not follow that decreasing omega-6 levels will do the same. Indeed, the evidence considered here suggests that it would have the opposite effect. Higher omega-6 PUFA intakes can inhibit the conversion of α-linolenic acid to eicosapentaenoic acid,[79] but such conversion is already quite low,[80] and whether additional small changes would have net effects on CHD risk after the other benefits of LA consumption are taken into account is not clear. The focus on ratios, rather than on levels of intake of each type of PUFA, has many conceptual and biological limitations.[81]

Conclusions

This advisory was undertaken to summarize the current evidence on the consumption of omega-6 PUFAs, particularly LA, and CHD risk. Aggregate data from randomized trials, case-control and cohort studies, and long-term animal feeding experiments indicate that the consumption of at least 5% to 10% of energy from omega-6 PUFAs reduces the risk of CHD relative to lower intakes. The data also suggest that higher intakes appear to be safe and may be even more beneficial (as part of a low–saturated-fat, low-cholesterol diet). In summary, the AHA supports an omega-6 PUFA intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for CHD.

Disclosures

Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Scott Grundy	University of Texas Southwestern Medical Center	Donald W. Reynolds Cardiovascular Center,† Merck Project,† Abbott†	None	None	None	None	Merck,* Merck Schering Plough,* AstraZeneca,* Pfizer*	None
Ronald Kauss	Children's Hospital Oakland Research Institute	Abbott Laboratories,* Merck,* Merck/Schering-Plough*	None	None	None	None	Merck,* Pfizer*	None
Neil Stone	Northwestern University	None	None	Unilever*	None	None	Unilever*	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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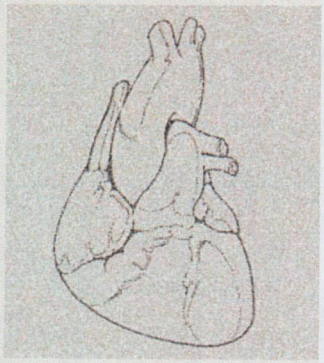
Striking the Right Balance: The Residual Risk of Coronary Artery Disease



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Striking the Right Balance: The Residual Risk of Coronary Artery Disease

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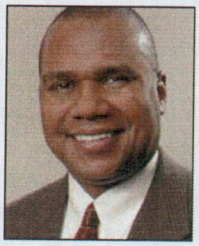
Very active in international, national, and local organizations, including the American College of Cardiology and the American Heart Association, Dr Bittner is on the editorial boards of the *Journal of the American College of Cardiology, American Heart Journal, Cardiology Today,* as well as 6 other publications, in addition to having been a reviewer for almost 40 medical journals. She is a board member of the National Lipid Association and a past president of the Southeast Lipid Association and the Birmingham Cardiovascular Society. Dr Bittner has conducted extensive research on a variety of cardiovascular topics, and she has published over 100 journal articles, dozens of reviews and book chapters, and more than 150 abstracts. She has made hundreds of international, national, and regional presentations. ■

DAVID S. KOUNTZ, MD, FACP



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Dr Kountz has published and lectured extensively on cardiovascular issues, especially in minority populations. In 1998, Dr Kountz was funded by the CDC to study the management of diabetes in managed care. This study, called Translating Research Into Action in Diabetes (TRIAD), has resulted in over 60 publications. More recently, he has served as editorial board chair for MetabolicPulse.org, a CME-accredited Web site providing education on diabetes and related disorders to health care providers. ■

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Dr Miller's major research interests are disorders of lipid and lipoprotein metabolism; molecular studies of high-density lipoprotein cholesterol, triglycerides, and the postprandial response to dietary fat; nontraditional coronary risk factors; and clinical trials to reduce atherosclerosis. He has participated in landmark clinical trials, including AVERT, MIRACL, PROVE-IT, TNT, and COURAGE. Dr Miller is a fellow of the American College of Cardiology and the American Heart Association Council on Arteriosclerosis. He is also an active member of the American Heart Association Council on Epidemiology.

Dr Miller has authored more than 200 original articles, book chapters, and other publications. He is the coauthor of *The Practice of Coronary Disease Prevention* and the recently published *AMA Guide to Preventing and Treating Heart Disease.* Dr Miller is on the program faculty for the Complex Lipid Management Self-Assessment Program, which involves preparation for certification by the American Board of Clinical Lipidology. He is also a member of several editorial boards and a reviewer for numerous journals. Dr Miller is past president of the American Society of Preventive Cardiology and has served on the Program Committee of the AHA Epidemiology and Prevention Council. His research has been supported by the NIH, American Heart Association, and Veterans Affairs Administration. ■

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

Supported by an educational grant from Abbott Laboratories.

Overview

A decade ago, it was envisaged that the treatment of hypercholesterolemia and hypertension would eventually eliminate coronary heart disease; however, that goal has not yet been realized. In 2006, the estimated costs associated with coronary heart disease in the United States exceeded $145 billion. Despite the availability of lipid-lowering agents, cardiovascular disease continues to be one of the leading causes of mortality in the United States and worldwide, owing to a rising incidence of obesity and diabetes, among other factors. This exclusive monograph will revisit coronary heart disease, discuss the underlying risks, and present strategies for prevention and treatment.

Learning Objectives

After completion of this program, participants should be able to:

- Recognize the types and levels of lipids that contribute to increased coronary heart disease risk.
- Differentiate the factors that contribute to residual risk, including high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG).
- Assess the effect of therapies that focus on lowering low-density lipoprotein cholesterol versus therapies that are directed toward managing dyslipidemia as a whole (ie, "the lipid triad") in the form of raising HDL-C and lowering serum TG through single-agent and/or combination treatment.

Release Date: November 2008

Expiration Date: November 2009

Method of Participation

Participants should read the learning objectives and review the monograph in its entirety. After reviewing the activity, they should complete and submit the post-test and evaluation. Upon achieving a passing score of 70% or better on the post-test, a statement of credit will be awarded.

Target Audience

This program is intended for the education of cardiologists, primary care physicians, nurse practitioners, physician assistants, as well as other health care providers involved in the treatment of patients with dyslipidemia.

Accreditation and Designation

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A Promise for Life

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Striking the Right Balance: The Residual Risk of Coronary Artery Disease

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ABSTRACT: Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established independent risk factor for coronary artery disease and is the principal lipid target for risk reduction. Statins lower LDL and other apo B–containing lipoproteins, thereby leading to a 20% to 35% reduction in major cardiovascular events, but do not comprehensively address the multiple lipid abnormalities of atherogenic dyslipidemia. Combination therapy with available lipid agents (eg, statin plus fibrate or statin plus niacin) has been shown to improve lipid profiles in atherogenic dyslipidemia. Even though small clinical trials have suggested clinical benefit using surrogate end points (less coronary lesion progression, less progression of carotid intima-media thickening), definitive outcomes studies are not yet available. Major trials are in progress to determine whether improvement in the atherogenic dyslipidemia will achieve the projected reduction in cardiovascular events, and which combination is associated with the most favorable outcomes.

More than a decade ago, it was envisaged that treating hypercholesterolemia and hypertension, the 2 major risk factors of cardiovascular disease (CVD), would significantly lower the incidence of CVD.[1] Although, as expected, age-adjusted CVD death rates have declined in developed nations, CVD is estimated to be the leading cause of death worldwide, with a significant increase in disease burden in low-income and middle-income countries.[2]

Low-density lipoprotein cholesterol (LDL-C) is strongly related to development and progression of CVD, and lowering of LDL-C lowers the risk of incident and recurrent cardiovascular events and mortality. Current treatment paradigms for the prevention of CVD recommend the use of statin therapy to achieve cholesterol goals, which have shown a significant 30% to 40% reduction in cardiovascular events, as documented in clinical trials.[3,4] Despite the use of optimal statin therapy to lower LDL-C levels, a significant number of patients continue to be at high risk for cardiovascular events. Thus, some have suggested adopting a more comprehensive approach, which includes modification of other lipoprotein fractions to address this burden of "residual risk."[5] This article will review the pathophysiology of atherosclerosis, and provide a comprehensive evidence-based overview of the available treatment options to manage residual risk in patients with dyslipidemia.

PLASMA LIPIDS AND LIPOPROTEINS

There are 4 major types of lipids that circulate in plasma: cholesterol and cholesteryl esters, phospholipids, and triglycerides (TGs).[6] Cells obtain cholesterol either by intracellular synthesis or by reuptake from the systemic circulation.[7] The function of the lipid transport system is to ferry these hydrophobic fat molecules from their sites of synthesis to points of utilization

through the aqueous environment of the plasma.

Because of their hydrophobic nature, cholesterol and other fatty substances are packaged into lipoprotein particles before secretion into plasma.[7] Typically, a lipoprotein particle is composed of a core of TGs and cholesteryl esters that are covered by an envelope of phospholipids and free cholesterol. Based on size, density, lipid, and apolipoprotein content, lipoprotein particles can be separated into distinct classes: high-density lipoprotein (HDL), LDL, very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and chylomicrons.[6] Apolipoproteins, the protein moieties on the outer surface of lipoproteins, provide structural integrity to lipoproteins, activate enzyme systems, and bind or dock to specific receptors.[6,7]

PHYSIOLOGY OF LIPID TRANSPORT

The lipid transport system has 2 main functions: transporting TGs from the gut and liver to muscles or fat tissue for utilization or storage, and transporting cholesterol to sites of utilization for the synthesis of bile acids, steroid hormones, and membrane synthesis.[8] In the exogenous pathway, dietary fat and cholesterol first pass through the intestinal lymphatic circulation, then through the systemic circulation, and finally to the liver by receptor-mediated uptake of chylomicron remnants. Dietary fat, emulsified by bile salts in the gut, is hydrolyzed by pancreatic lipases into constituent free fatty acids and monoglycerides and diglycerides, which are taken up by intestinal cells, the enterocytes.

To facilitate transportation through lymphatic venous circulation, the constituent free fatty acids and glycerides, which are first reassembled into TGs, are transformed into chylomicrons by the addition of apolipoprotein (apo) B48. As the TG-rich chylomicrons pass through the capillary beds, a part of the TG content is removed by the catabolic activity of lipoprotein lipase, leaving the core of the remnant particles containing cholesterol as well as some of the dietary TG to be re-utilized by the liver.[6] In the endogenous pathway of the lipid transport system, TGs synthesized in the liver are assembled into VLDL particles before their secretion into the systemic circulation. The VLDL particles undergo a partial delipidation in a manner similar to the processing of chylomicrons. The resultant VLDL remnants and IDL particles are smaller and enriched in cholesterol. Approximately 50% of remnants are removed from the circulation, while the remainder is converted into LDL particles.[6,7]

The primary function of HDL particles is to transport cholesterol from peripheral tissue to the liver, a process called *reverse cholesterol transport.* This process begins with the uptake of cholesterol from peripheral cells, such as arterial wall macrophages, by nascent cholesterol-poor HDL, which is then converted to mature HDL_2 through the activity of lecithin-cholesterol acyltransferase (LCAT). In addition, a cholesterol ester transfer protein (CETP) mediates a net exchange of TGs for cholesteryl esters to facilitate the transfer of cholesterol from HDL to VLDL remnants.[8] Such bidirectional transfer of constituents between lipoproteins allows the acquisition of specific apolipoproteins and ensures that unused cholesterol from peripheral tissues is transferred to the liver for re-utilization.[8]

PATHOGENESIS OF ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory disorder of blood vessels, which results in asymmetric focal thickenings of the arterial intima.[9] The atheroma is preceded by the formation of a fatty streak consisting of macrophages and some T lymphocytes. The center of the atheroma has a core region with foam cells (cholesterol-rich macrophages) and extracellular lipid droplets, surrounded by a cap of smooth muscle cells and a collagen-rich matrix. T cells, macrophages, and mast cells often infiltrate the lesion and are present around the shoulder region, where the atheroma grows.[9-11]

Myocardial infarction occurs because of complete coronary artery occlusion resulting from atheromatous plaque that is covered by overlying thrombus. It was previously thought that progressive luminal narrowing was the main cause of infarction.[1] However, angiographic studies have identified that destabilization of plaque with overlying occlusive thrombus, rather than progressive stenosis, precipitates ischemia and infarction.[1,12] What might be the cause of coronary thrombosis? Plaque rupture, detectable in 60% to 70% of cases, exposes prothrombotic material from the core of plaques.[13] It is believed that activated immune cells, which are abundant at sites of plaque rupture, produce factors such as inflammatory cytokines, coagulation factors, and vasoactive molecules that destabilize lesions and promote thrombosis.[1]

Endothelial activation. Hypercholesterolemia causes focal activation of the endothelium in large- and medium-sized arteries.[1] The activation of the endothelium starts with the infiltration and retention of LDL, VLDL, and chylomicron remnants in the arterial intima, which initiates an inflammatory response in the arterial wall.[14,15]

There are several mechanisms by which these lipoproteins may cause atherosclerosis. For instance, native LDL can be retained in the intima by aggregation, binding to pro-

teoglycan matrix, and absorption by macrophages. The inflammatory effect of LDL can be modified by glycosylation or oxidation, which facilitates the cholesterol loading of macrophages.[16] Further, it has been recently discovered that apo CIII, a component of some of these lipoproteins, directly stimulates the inflammatory process in vascular tissue.[17,18]

The endothelial cells that are activated by the lipoproteins are responsible for the production of several monocyte adhesion molecules that cause circulating monocytes to adhere at sites of activation.[16] Once recruited, cytokines and other growth factors produced at the site of the inflamed intima induce the differentiation of monocytes into active macrophages—a critical early step in the development of atherosclerosis—and attract collagen-producing smooth muscle cells into the intima.[1]

Formation of atherosclerotic plaques. Scavenger receptors on the surface of activated macrophages enable the uptake of aggregated and modified LDL and remnant VLDL particles.[19] These macrophages transform into foam cells, and accumulate in the intimal space to form a fatty streak.[7] As fatty streaks continue to transform the once-smooth endothelial artery surface into an uneven surface, an *atherosclerotic plaque* is formed. Calcium is also deposited in advanced plaques. However, the pathogenesis of atherosclerosis is much more complex than the initiation and formation of plaques. In an earlier study, Glagov and colleagues[20] have shown that as atherosclerotic plaques develop, arteries enlarge in relation to plaque area due to a compensatory mechanism. Given that lumen stenosis may be delayed until 40% of the internal elastic lamina area is occupied by lesion,[20] evidence of luminal obstruction on coronary angiography is more likely to indicate an advanced lesion. Lower-grade lesions may be more prone to rupture due to intrinsic pro-inflammatory characteristics of the plaque-derived foam cells.[7]

RISK FACTORS FOR ATHEROSCLEROSIS: DYSLIPIDEMIA AND METABOLIC SYNDROME

The *Framingham Heart Study* coined the term "risk factors" for CVD.[8] According to the current NCEP ATP III guidelines, along with elevated LDL-C, a number of lipid and nonlipid factors have been identified that are associated with the development of coronary heart disease (CHD).[21] Two such risk factors, elevated TGs and reduced HDL-C, often occur together and, when both are present, the patient is said to have "atherogenic dyslipidemia." Atherogenic dyslipidemia is prevalent in persons with obesity, insulin resistance, type 2 diabetes, and physical inactivity.[22-24]

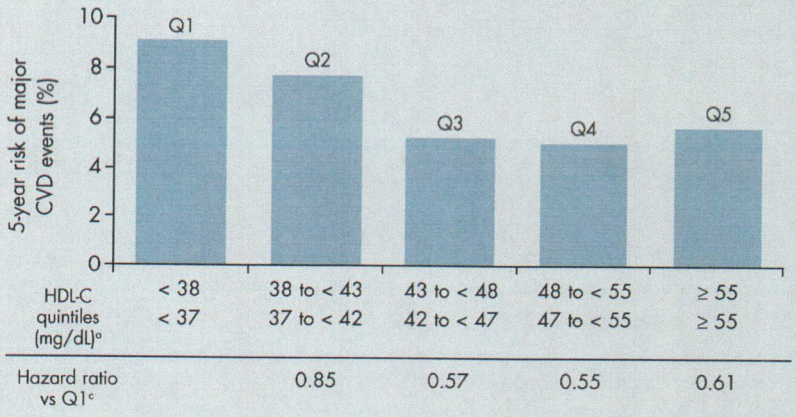
Elevated LDL-C. From the *7-Country Study,* it became evident that cardiovascular mortality was highest in countries with populations that had elevated levels of total serum cholesterol and was lowest in Mediterranean and Asian populations.[25] Furthermore, the study showed a strong and graded relationship between saturated fat intake, serum cholesterol, and the incidence of CHD, whereas dietary cholesterol had a weaker correlation.[25]

In the *Framingham studies,* increased level of LDL-C proved to be a major risk factor for development of CHD. More importantly, however, the Framingham data set showed that a mix of risk factors, when present together, additively increase the risk of CVD.[26]

A contentious issue is the relative strength of LDL-C compared with non-HDL-C and apo B. Non-HDL-C and apo B include not only LDL but also VLDL and VLDL remnants, which are atherogenic and contribute to risk. Thus, non-HDL-C and apo B provide a more complete assessment of risk associated with atherogenic lipoproteins.[27] Nuclear magnetic resonance spectroscopy can be used to estimate lipoprotein particle concentration and measure the size of lipoprotein particles.[27] Although small dense LDL particles are moderately correlated with high TGs, and were thought to contribute independently to CVD,[25] particle size is not an independent predictor of CVD but rather a secondary phenomenon; accumulating data indicate that LDL is related to abnormal TG metabolism.[28]

In this context, data from the *Physician's Health Study* showed that nonfasting TG levels were a better predictor of first myocardial infarction than LDL particle size, and that LDL particle size had no effect beyond that of TGs.[27,28] Moreover, in epidemiological studies that used LDL particle size as a parameter to predict the risk of CHD, there was no consistent pattern that suggested small LDL is an independent contributor of CHD risk, as some have found that large LDL was associated with CVD.[29] This is consistent with the observation that patients with familial hypercholesterolemia have large LDL.

Reduced HDL-C. Population-based studies have consistently shown that a low level of HDL-C is a powerful predictor of increased cardiovascular risk; nonetheless, it remained unclear whether low HDL-C would be a significant risk factor in individuals with LDL-C reduced to very low levels.[30-32] In a post hoc multivariate analysis from the *Treating to New Targets* (TNT) study, HDL-C levels were a significant predictor of major cardiovascular events across the entire study cohort, even when LDL-C was reduced to an on-treatment level of less than 70 mg/dL



[a] On-treatment level (3 months of statin therapy); N = 2661.

[b] Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL.

[c] $P = .03$ for differences among quartiles of HDL-C.

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides

Figure 1 – A post hoc multivariate analysis from the Treating to New Targets (TNT) Study showed that low HDL-C increases CVD risk even if LDL-C levels are well controlled.

with statin therapy.[33] According to the multivariate analysis, patients in the highest quintile of HDL-C (≥ 55 mg/dL) had a lower risk of major cardiovascular events compared with those subjects in the lowest quintile (≤ 37 mg/dL) (hazard ratio, 0.61; 95% CI, 0.38 - 0.97) (**Figure 1**).

The biosynthesis of HDL is complex and requires the synthesis of apo AI and apo AII, the 2 major protein components. Interestingly, in the general population, an inverse relationship has been observed between plasma levels of both apo AI and apo AII and CHD risk.[34] Turnover studies that delineate the rate of metabolism of HDL in plasma have indicated that HDL levels are determined mainly by the clearance rate from plasma of both apo AI and apo AII.[35-37] Apo AI is mainly synthesized in the liver, with a minor contribution from the intestine.[38] Newly synthesized HDL particles—also referred to as pre-beta HDL—are secreted into plasma as disk-like structures containing apo AI and phospholipids. As the disks interact with vascular intima, they take up the cholesterol from macrophages to form mature spherical HDL particles. Based on the genetic studies of Tangier disease, it is evident that ABC-A1—a transport protein involved in the efflux of cellular cholesterol—is a critical participant in the cholesterol loading of nascent HDL and reverse cholesterol transport.[39] The genetic absence of ABC-A1 is associated with low levels of HDL-C and apo AI, and consequently the development of atherosclerosis and CVD early in adult life.

Apo B/apo AI ratio. Several studies have now demonstrated that apolipoprotein concentrations predict future cardiovascular events somewhat more strongly than the lipoprotein cholesterol concentrations. The *Apolipoprotein-Related Mortality Risk Study* (AMORIS) investigated whether apo B and apo AI are better predic-

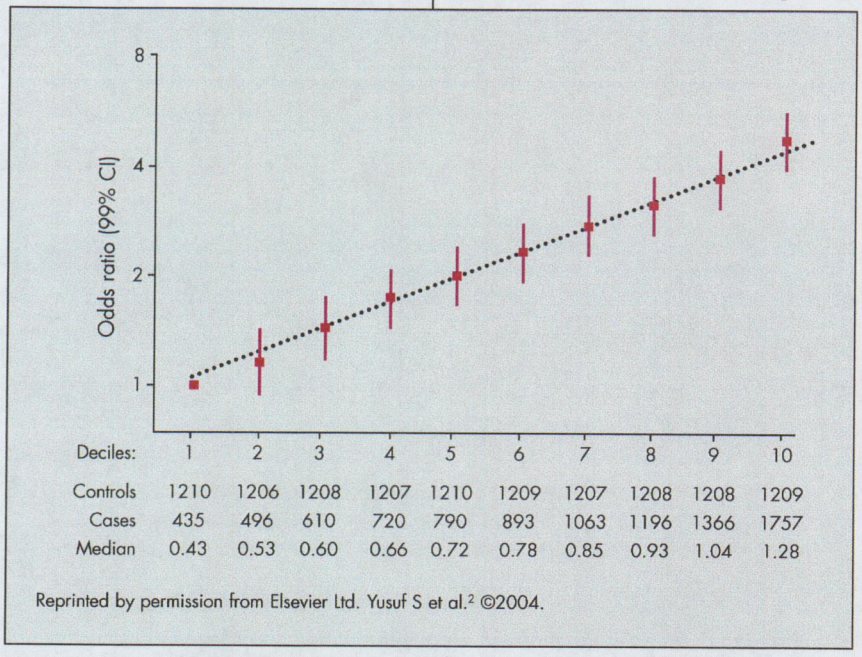
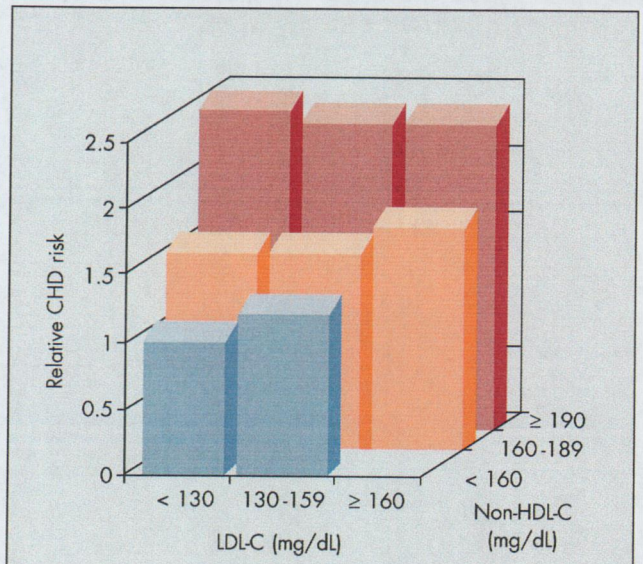


Figure 2 – The INTERHEART study, which assessed the importance of risk factors for coronary heart disease in 52 countries, reported overall odds ratios for individual risk factors in more than 12,000 cases. Raised apo B/AI ratio was found to be one of the strongest risk factors for acute myocardial infarction.

tors of risk of fatal myocardial infarction than total cholesterol and LDL-C.[40] The study, which investigated a large cohort of Swedish men and women, showed that after adjusting for age, cholesterol, and TG content, both apo B and apo B/apo AI ratio were significantly and positively correlated to increased risk of fatal myocardial infarction. In agreement with the Swedish study, data from the *INTERHEART* study clearly identified raised apo B/apo AI ratio as the most important lipoprotein-related risk factor for acute myocardial infarction in men and women across different ethnic groups and geographic regions (**Figure 2**).[2] The *INTERHEART* study, a large, international, case-control study designed to assess the importance of risk factors for CHD in 52 countries, reported overall odds ratios for individual risk factors in 12,461 cases and 14,637 controls after adjusting for age, sex, smoking status, and region. After a multivariate analysis, raised apo B/apo AI ratio emerged as one of the two strongest risk factors for acute myocardial infarction, second only to current smoking status.[2]

Non-HDL-C. Another approach to predict cardiovascular risk is to use non-HDL-C, which is a surrogate estimate of all atherogenic particles in the VLDL, remnants lipoprotein(a), and LDL fractions.[27,41] Thus, non-HDL-C is the cholesterol equivalent of apo B levels, and both parameters are highly correlated to one another and better predictors of CHD risk than LDL-C; the correlation coefficient of non-HDL and apo B is 0.93 - 0.94, compared with 0.84 - 0.85 for LDL-C and apo B.[42] Interestingly, recent prospective studies such as AMORIS[40] and the *Health Professionals Follow-Up Study*[43] have shown that apo B measurement outperforms LDL-C and non-HDL-C in cardiovascular risk stratification. Specifically, in the latter, an increase in CHD was associated with higher apo B levels across all categories of non-HDL-C levels.[43] Given the lack of readily available standardized assays for the measurement of apo B in a clinical setting, non-HDL-C is preferred and recommended as a secondary target of therapy when TG levels are higher than 200 mg/dL.[21] In this context, findings from a recent report by Liu and colleagues, who examined the original data sets from the *Framingham Cohort Study* and the *Framingham Offspring Study,* were in agreement with the earlier findings that non-HDL-C is a better predictor of CHD risk than LDL-C (**Figure 3**).[44]



CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non–high-density lipoprotein cholesterol

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Figure 3 – Non-HDL-C is superior to LDL-C in predicting CHD risk. Within non-HDL-C levels, no association was found between LDL-C and the risk of CHD. In contrast, a strong positive and graded association between non-HDL-C and risk of CHD occurred within every level of LDL-C.

Elevated TGs. Many epidemiological studies that employed meta-analyses have reported a positive correlation between elevated serum TGs and the incidence of CHD,[45,46] though previous multivariate analyses did not always identify TGs as an independent risk factor.[47] Recent data from 29 Western prospective studies with more than 260,000 participants and 10,000 CHD cases have indicated that elevated TGs are indeed a significant risk factor for CVD (**Figure 4**).[48] It is notable that NCEP ATP III guidelines recommend the use of lower cut points for the categorization of TG levels than the ATP II guidelines, thus reflecting a growing concern about even moderate TG elevation. Elevated TGs are thought to increase CHD risk through the atherogenic effects of TG-rich remnant lipoproteins, specifically chylomicrons and VLDL remnants and their high apo CIII content.[49]

An elevated TG level (> 150 mg/dL) is also one of the criteria for the diagnosis of metabolic syndrome.[49] The ATP III guidelines define metabolic syndrome as any 3 of the following 5 clinical features: abdominal obesity (waist > 40 inches for men and > 35 inches for women), elevated TG (> 150 mg/dL), low HDL-C (< 40 mg/dL for men and < 50 mg/dL for women), elevated blood pressure (> 130/85 mm Hg), and elevated fasting glucose (> 110 mg/dL).[21] Several factors may elevate TG levels in the general population. These include overweight/obesity,

physical inactivity, cigarette smoking and excess alcohol intake, consumption of high-carbohydrate diets, diabetes, and renal failure, and a number of medications.[50,51] However, the most common contributing factors are related to lifestyle. The current ATP III guidelines recommend treating hypertriglyceridemia according to its severity and the levels of other lipids. For borderline high TG levels (150 - 199 mg/dL), the goal of therapy is to reduce LDL-C levels with therapeutic lifestyle changes and drug therapy if needed.[21] Lifestyle changes that incorporate weight loss programs and increased physical activity have been shown to be effective in improving insulin sensitivity in patients with insulin resistance, a contributor to hypertriglyceridemia.[49] When TG levels continue to remain high (200 - 499 mg/dL) even after achieving LDL-C goals, the guidelines recommend using non-HDL-C levels as the secondary target for therapy. For very high TG levels (≥ 500 mg/dL), the primary goal of therapy is to prevent pancreatitis by lowering TG levels.[52]

MANAGING DYSLIPIDEMIA: TREATMENT GOALS AND RESIDUAL RISK

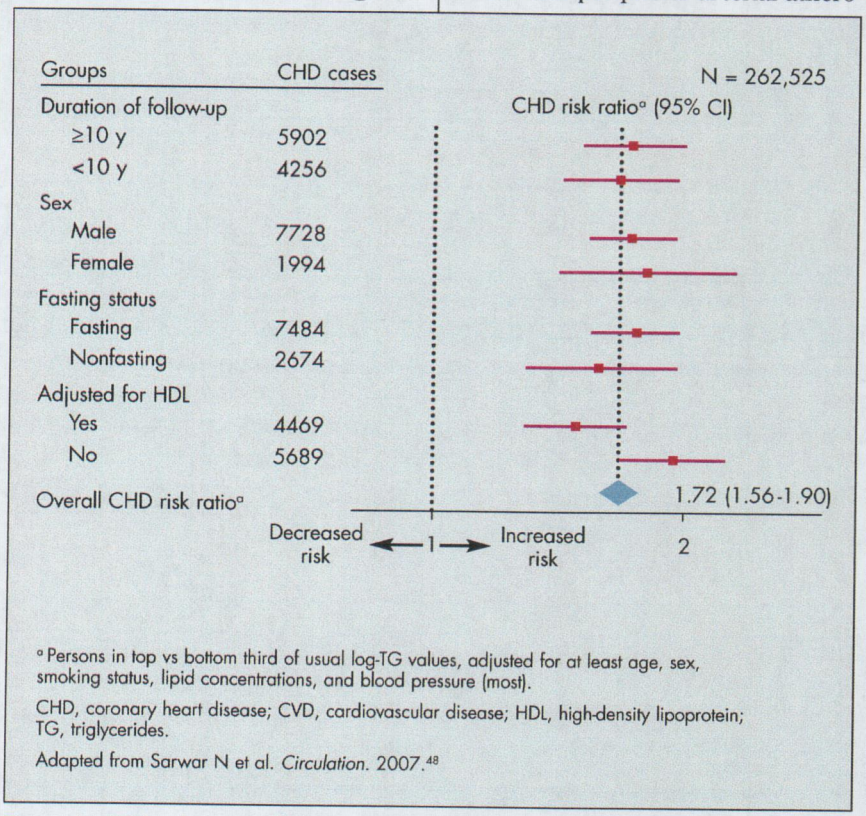
Risk assessment. The NCEP ATP III guidelines recommend risk assessment as the first step in primary prevention of coronary artery disease (CAD). According to the guidelines, individuals are categorized into 3 risk factor groups:

- Those with established CAD or CAD-risk equivalents.
- Those with more than 2 risk factors for CAD.
- Those with no or 1 risk factor.

CAD-risk equivalents include patients with peripheral arterial atherosclerosis, abdominal aortic aneurysm, or diabetes.[53] Others have also included patients with chronic kidney disease in this designation.[53] To estimate the cardiovascular risk, risk factors are first counted, and for those patients with multiple risk factors, the Framingham risk calculator is used to estimate the 10-year cardiovascular risk.[21] Although NCEP ATP III guidelines have recommended a LDL-C goal of less than 100 mg/dL as an optimal level, for those patients who are at very high risk, a further reduction to less than 70 mg/dL is suggested as an option, with a non-HDL-C goal of less than 100 mg/dL. Individuals deemed to be at "very high risk" are those with established CVD and one or more additional risk factors (eg, recent acute coronary syndrome, diabetes, smoking, etc).[52] After LDL-C goals have been met, the guidelines recommend addressing metabolic syndrome as a secondary goal of therapy.

Lifestyle modification. While it is widely accepted that dietary changes can improve LDL-C levels, it is less well appreciated that comprehensive lifestyle modification is critical in the management of patients with multiple metabolic abnormalities or metabolic syndrome. NCEP-ATP III–recommended therapeutic lifestyle changes include reduced intake of saturated fat, trans fat, and cholesterol; increased consumption of plant stanols/sterols and soluble fiber; weight reduction; and increased regular physical activity.[21] Even seemingly modest weight changes can result in significant metabolic benefits.

The importance of lifestyle management is also emphasized in the updated 2006 American Heart Association (AHA) "Diet and Lifestyle Recommendations." Balancing caloric intake and physical activity to achieve and maintain a healthy body weight is a major priority in this scientific statement. The authors recommend a diet rich in vegetables, fruits, and whole



[a] Persons in top vs bottom third of usual log-TG values, adjusted for at least age, sex, smoking status, lipid concentrations, and blood pressure (most).

CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; TG, triglycerides.

Adapted from Sarwar N et al. *Circulation*. 2007.[48]

Figure 4 – TG level is a significant CVD risk factor. Shown here are the results of a recent meta-analysis of 29 studies.

grains that is high in fiber, and consumption of oily fish at least twice a week while limiting the intake of saturated fat to less than 7% of energy, trans fat to less than 1% of energy, and cholesterol to less than 300 mg/d by choosing lean meats, vegetable alternatives, and fat-free (skim) or low-fat (1% fat) dairy products and minimizing intake of partially hydrogenated fats.[54]

In observational studies, both physical fitness and physical activity levels are strongly associated with subsequent cardiovascular events, cardiovascular mortality, as well as noncardiovascular morbidity and mortality. The *Aerobics Center Longitudinal Study* (ACLS) was a prospective study that was designed to examine the association between cardiorespiratory fitness and health, which was broadly defined to encompass all-cause mortality, cause-specific mortality, disease morbidity, and functional health status. The study population included over 14,000 women and 46,000 men who were examined at least once at a preventive medicine clinic from 1970 to 2004. Data from this study evaluated changes in physical fitness and the risk of mortality in men.[55] This analysis, which involved assessment of physical fitness by maximal exercise tests and evaluation of health status at 2 clinical examinations conducted 5 years apart, showed that the highest rate of mortality was observed in men who were unfit at both examinations. As expected, those who were fit at baseline and follow-up had the best prognosis. Importantly, men who improved from unfit to fit status between the first and subsequent assessment had a 44% lower mortality than those who remained unfit at both examinations.[55] While observational in nature, this study suggests that exercise interventions that improve physical fitness could have a major impact on cardiovascular morbidity and mortality.

Another study of relevance is the *Diabetes Prevention Program* (DPP), which was designed to determine whether lifestyle intervention or pharmacotherapy with metformin would prevent or delay the onset of diabetes in persons with impaired glucose tolerance, many of whom had metabolic syndrome. Results from this study showed that lifestyle intervention conferred a marked reduction of 58% in the incidence of type 2 diabetes, a reduction that was significantly greater than that achieved with metformin (31%).[56]

Most recently, the LOOK AHEAD trial published its 1-year results indicating that a comprehensive lifestyle approach is more effective in improving metabolic parameters among patients with diabetes than a traditional diabetes education approach.[57] This study is ongoing and will answer the question whether these metabolic improvements translate into improved morbidity and mortality.

TRADITIONAL PHARMACOLOGICAL APPROACHES

While lifestyle management is critical in all patients at increased cardiovascular risk, many will require pharmacological therapy as well, an approach supported by a large evidence base. Given that the magnitude of reduction in cardiovascular events is related to the extent of LDL lowering, recent intervention trials have used increasing doses of statin therapy to achieve maximal therapeutic benefit. In the *Prospective Study of Pravastatin in the Elderly at Risk* (PROSPER) study, treatment with pravastatin 40 mg/day reduced major coronary events by 19%.[58] In the *Heart Protection Study* (HPS), treatment with simvastatin 40 mg/day resulted in a significant reduction in major cardiovascular events by 24%.[59] In the *Pravastatin or Atorvastatin Evaluation and Infection Therapy* (PROVE-IT), patients hospitalized with acute coronary syndrome were given atorvastatin 80 mg/day or pravastatin 40 mg/day. Death, myocardial infarction, unstable angina, revascularization, or stroke was considered as primary end points. Although both statins were effective in reducing LDL-C levels, atorvastatin at higher dose was more effective in lowering clinical events over two years compared with pravastatin therapy; 26.3% versus 22.4%, respectively.[60] To compare the effects of high and low doses of atorvastatin, in the TNT study, 80 mg/day was compared with 10 mg/day in patients with stable CHD. The study concluded that the higher dose of atorvastatin was significantly effective in providing additional clinical benefits compared with low-dose therapy.[61] To compare the effects of 2 different statins on the risk of cardiovascular events, patients with a history of myocardial infarction in the *Incremental Decrease in End Points Through Aggressive Lipid Lowering* (IDEAL) study received either atorvastatin 80 mg/day or simvastatin 20 mg/day. Interestingly, the intensive lowering of LDL-C with atorvastatin at the highest recommended dose did not yield a significant reduction in the primary outcome of major coronary events compared with the moderate and most widely used dose of simvastatin, although atorvastatin 80 mg did significantly reduce secondary CVD end points.[62]

As recommended LDL cholesterol targets have decreased, it has become increasingly difficult to achieve these goals solely with lifestyle modifications. Of relevance is a recent study that analyzed the data from participants of the 1999 to 2002 NHANES study and demonstrated that 30% of the US adults had LDL-C levels that exceeded their corresponding ATP III goals.[63] More impor-

tantly, 18% of the participants exceeded their LDL-C goal by more than 10%; thus, they were considered unlikely to reach their target LDL without pharmacotherapy.[63] For many, adopting the lower optional LDL-C target would mean large reductions using high-dose statin therapy or combination therapy.

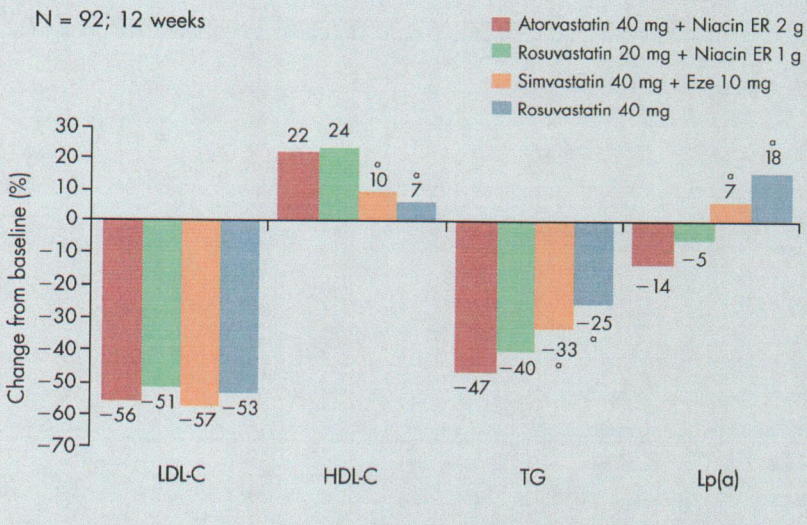
Lowering LDL with statins has significantly reduced CVD risk. A recent meta-analysis of lipid-lowering trials estimated that major coronary events were lowered by 23%, thus leaving a residual risk of 77% for events among treated patients, possibly higher among those at the greatest risk.[4] While high-dose statin therapy may yield additional benefits, a more comprehensive approach targeting other components of the dyslipidemia and addressing non-lipid risk factors is clearly warranted. Additionally, it is important to note that the clinical use of statin therapy depends not only on its ability to reduce LDL-C levels, but also on its tolerability and safety profile. Generally, statins are well tolerated, with myalgias, including rhabdomyolysis, and their effect on liver enzymes the best known and most challenging adverse events.[64] Most statins may occasionally cause myopathy; however, the occurrence has been estimated to be less than 1 in 10,000 patients at standard dose with increasing risk at higher doses.[65]

TARGETING RESIDUAL RISK WITH COMBINATION THERAPY

Combination therapies. In addition to statins, lipid-lowering drugs such as fibrates, niacin, and bile acid sequestrants have proven efficacy in lowering cardiovascular events, although the number of clinical trials that have tested these agents is quite small.[5] Fibrates, which are peroxisome proliferator–activated receptor α (PPAR-α) agonists, affect many genes that influence lipoprotein metabolism and could consequently modulate atherogenesis.[5] Fibrates also exert pleiotropic effects to downregulate proinflammatory genes in vascular cells. While the clinical importance of these effects is speculative, post hoc analyses from some of the fibrate trials do support a role for PPAR-α agonism in patients with diabetes or metabolic syndrome, such as to reduce cerebrovascular disease or microvascular disease of the kidney and retina, vascular conditions that are not related to lipid risk factors.

Analyses of subgroups of patients in several fibrate trials suggest that patients with atherogenic dyslipidemia or diabetes receive greater event reduction compared with those with normal TG and HDL-C levels, or nondiabetics. This effect was especially notable in the older studies such as *Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial* (VA-HIT)[66] and in the *Helsinki Heart Study* (HHS),[67] where a subset of patients with diabetes had a nominally greater risk reduction than patients without diabetes. Furthermore, in the VA-HIT study, the effect of fibrate therapy was less dependent on lipid levels than on the presence or absence of insulin resistance.[66] In the large *Fenofibrate Intervention and Event Lowering in Diabetes* (FIELD) study, patients with type 2 diabetes who were treated with micronized fenofibrate showed significant reduction in total cardiovascular events (a secondary end point) compared with the placebo group.[68] However, it must be noted that fenofibrate treatment did not yield a significant benefit on the primary outcome, which was a combination of CHD events including death or first occurrence of nonfatal myocardial infarction.

Because fibrates appear to have unique benefits in patients with insulin resistance, the combination of statin and fibrate therapy may have the potential to benefit patients with



COMPELL, Comparative Effects on Lipid Levels of Niaspan and Statin Versus Other Lipid-Modifying Therapies Study.

° $P < .05$ vs atorvastatin + niacin ER.

ER, extended release; Eze, ezetimibe, LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; Lp(a), lipoprotein(a).

Adapted from McKenney JM et al. *Atherosclerosis.* 2007.[71]

Figure 5 – Shown here are the lipid effects of niacin ER/statin combination therapy in the COMPELL study.

diabetes.[5] The combined effects of simvastatin and fenofibrate on lipid parameters have been investigated in the *Simvastatin Plus Fenofibrate for Combined Hyperlipidemia* (SAFARI) trial.[69] The combination significantly improved the components of atherogenic dyslipidemia compared with monotherapy. For example, combination therapy increased HDL-C levels by 19% compared with 10% with simvastatin monotherapy (19% vs 10%).[69] Although the risk of myopathy is low with statin monotherapy, a significant increase in rhabdomyolysis has been reported when used in combination with fibrates, particularly with gemfibrozil.[70]

Statins have also been combined with niacin. This combination regimen not only significantly lowers LDL-C levels but also TGs and lipoprotein(a) and it concurrently increases HDL-C levels. Thus, the *COMParative Effects on Lipid Levels of Niaspan and Statin Versus Other Lipid-Modifying Agents* (COMPELL) study was designed to investigate whether a low-to-moderate dose of statins with low-dose niacin extended-release (ER) is an effective combination regimen to lower LDL-C levels (>50%) and non-HDL-C.[71] The study concluded that low-dose niacin ER in combination with low doses of either atorvastatin or rosuvastatin was effective in lowering LDL-C by 50%, an efficacy that was comparable to statin/ezetimibe combination therapy or to rosuvastatin monotherapy at moderate-to-high doses.[71] Interestingly, the efficacy of statin/niacin combination therapy on HDL-C, TGs, and lipoprotein(a) was superior to other therapies (**Figure 5**).[71] A limitation of this study was its inability to evaluate the impact of the lipid changes on measurable cardiovascular end points. Nonetheless, limited outcome data exist at this time.

In the *HDL Atherosclerosis Treatment Study* (HATS), patients who were diagnosed with CHD, in addition to having moderately elevated LDL-C and low HDL-C, were randomized to receive simvastatin alone or simvastatin plus niacin for 2.5 years.[72] At the end of the study, significant regression was noted on serial quantitative angiography, accompanied by 60% to 90% risk reduction in cardiovascular events in the combination treatment group compared with half the efficacy observed in the group that received statin alone.[72] Using a similar combination regimen, in the *Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol* (ARBITER) study, treatment with simvastatin plus niacin ER did not result in significant changes in the carotid intima-media thickness from baseline, whereas with statin monotherapy, a significant progression was noted.[73] Interestingly, in the subsequent 1-year follow-up study during which all patients were treated with the combination regimen, an absolute regression was evident in carotid intima-media thickness.[74] The *Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes* (AIM HIGH) study, which is still recruiting, is specifically designed to ascertain the impact of statin/niacin combination therapy on cardiovascular outcomes (see www.clinicaltrials.gov).

Niacin therapy induces flushing, raises blood glucose levels, raises uric acid levels, and increase liver enzymes.[75] Although clinical trials have failed to show that niacin therapy increases the rate of myalgias over that of placebo, myopathy has been reported in statin and niacin combination therapy.[75] ■

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CME Assessment/Evaluation/Certificate Request

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

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3.	☐	☐	☐	☐	☐
4.	☐	☐	☐	☐	☐
5.	☐	☐			
6.	☐	☐	☐	☐	☐
7.	☐	☐	☐	☐	☐
8.	☐	☐			
9.	☐	☐			
10.	☐	☐	☐	☐	☐

T7A50-MG

(continued) ▶

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

Program Evaluation: So that we may assess the value of this self-study program, we ask that you please complete this evaluation form.

Have the objectives for the activity been met?

1. Recognize the types and levels of lipids that contribute to increased coronary heart disease risk.

☐ Yes ☐ No

2. Differentiate the factors that contribute to residual risk, including HDL-C and TG.

☐ Yes ☐ No

3. Assess the effect of therapies that focus on lowering LDL-C versus therapies that are directed toward managing dyslipidemia as a whole (ie, "the lipid triad") in the form of raising HDL-C and lowering serum TG through single-agent and/or combination treatment.

☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias?

☐ Yes ☐ No

If no, please explain: _____

_____

Please rate the program on the following parameters using a scale of 1 to 5, where 1 = Never, 2 = Not very often, 3 = Sometimes, 4 = Very often, and 5 = Always.

1. Think about how you ***currently*** treat patients for dyslipidemia. How often do you currently use each of the following strategies?

   a. Lifestyle changes (weight loss, diet, exercise) in combination with drug therapy

   5 4 3 2 1 N/A

   b. Single-agent drug therapies directed at managing "the lipid triad," not just lowering LDL-C

   5 4 3 2 1 N/A

   c. Combination drug therapies directed at managing "the lipid triad," not just lowering LDL-C

   5 4 3 2 1 N/A

   d. Fibrate therapy to reduce CVD risk in patients with diabetes and metabolic syndrome

   5 4 3 2 1 N/A

   e. Addition of niacin to statin therapy to reduce residual CVD risk and slow atherosclerosis

   5 4 3 2 1 N/A

2. Based on your completion of this CME supplement, how often do you ***now plan to*** use each of the following strategies when treating patients with dyslipidemia?

   a. Lifestyle changes (weight loss, diet, exercise) in combination with drug therapy

   5 4 3 2 1 N/A

   b. Single-agent drug therapies directed at managing "the lipid triad," not just lowering LDL-C

   5 4 3 2 1 N/A

   c. Combination drug therapies directed at managing "the lipid triad," not just lowering LDL-C

   5 4 3 2 1 N/A

   d. Fibrate therapy to reduce CVD risk in patients with diabetes and metabolic syndrome

   5 4 3 2 1 N/A

   e. Addition of niacin to statin therapy to reduce residual CVD risk and slow atherosclerosis

   5 4 3 2 1 N/A

Effectiveness of this method of presentation:

Excellent	Very good	Good	Fair	Poor
5	4	3	2	1

What other topics would you like to see addressed?

_____

_____

_____

Comments: _____

_____

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CME Post-Test

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

1. **Which of the following mediates the net exchange of triglycerides (TGs) to facilitate the transfer of cholesterol from high-density lipoprotein (HDL) to very low-density lipoprotein (VLDL) remnants?**
   - **a.** Cholesteryl ester transfer protein
   - **b.** Intermediate-density lipoprotein
   - **c.** Apo B
   - **d.** Apo CIII
   - **e.** None of the above

2. **Which of the following contribute(s) to atherogenic dyslipidemia?**
   - **a.** Elevated serum glucose
   - **b.** Elevated TGs
   - **c.** Elevated HDL
   - **d.** Elevated VLDL
   - **e.** All of the above

3. **In using low-density lipoprotein cholesterol (LDL-C) levels to predict cardiovascular risk, which of the following is (are) true?**
   - **a.** Apo B is a better predictor of atherogenic risk than LDL-C
   - **b.** Apo B is a constituent of VLDL and LDL
   - **c.** Small dense LDL particles are moderately correlated with high TGs
   - **d.** LDL particle size is not an independent predictor of cardiovascular disease
   - **e.** All of the above

4. **Which of the following markers is (are) effective predictors of cardiovascular events?**
   - **a.** Non-HDL-C is a better predictor than LDL-C
   - **b.** Non-HDL-C is a better predictor when TGs are elevated > 200 mg/dL
   - **c.** Apo B is a better predictor than non-HDL-C
   - **d.** Raised apo B/apo AI ratio is a strong predictor of myocardial infarction
   - **e.** All of the above

5. **In population-based studies, reduced HDL-C is a significant predictor of cardiovascular events only when LDL-C levels are elevated above 160 mg/dL.**
   - **a.** True
   - **b.** False

6. **According to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP) III guidelines, which of the following clinical features define(s) metabolic syndrome?**
   - **a.** Elevated TG > 150 mg/dL
   - **b.** Reduced HDL-C < 30 mg/dL
   - **c.** Abdominal obesity > 40 inches for men
   - **d.** Elevated LDL-C > 160 mg/dL
   - **e.** Elevated fasting glucose > 110 mg/dL

7. **For patients with elevated TG levels (200 - 499 mg/dL) the recommended guidelines are:**
   - **a.** Achieve LDL-C goals as primary target
   - **b.** Achieve non-HDL-C levels as secondary target
   - **c.** Prevention of pancreatitis
   - **d.** a and b
   - **e.** a, b, and c

8. **In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study, subgroup analysis showed that patients with diabetes benefited significantly more from fibrate therapy than those without diabetes.**
   - **a.** True
   - **b.** False

9. **According to the COMParative Effects on Lipid Levels of Niaspan and Statin Versus Other Lipid-modifying Agents (COMPELL) study, statin/niacin combination regimen is effective in lowering LDL-C levels by more than 50%.**
   - **a.** True
   - **b.** False

10. **According to the American Heart Association guidelines, the recommended daily intake of cholesterol should not exceed:**
    - **a.** 100 mg
    - **b.** 300 mg
    - **c.** 500 mg
    - **d.** 1 g
    - **e.** 5 g