

CardiologyRounds®

www.cardiologyrounds.org

AS PRESENTED IN THE ROUNDS OF THE CARDIOVASCULAR DIVISION
OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

Fish Intake, Contaminants, and Human Health: Evaluating the Risks and the Benefits Part 1 – Health Benefits

By DARIUSH MOZAFFARIAN, MD, DRPH

This two-part report summarizes findings from a recent publication in the *Journal of the American Medical Association*.¹ Part 1 discusses the potential health benefits of fish and fish oil intake. Part 2 discusses the potential health risks and describes optimal intakes for different populations. The Tables and Figures in this report are adapted from *JAMA*, October 18, 2006; 296:1885-99, © 2006, American Medical Association, all rights reserved.

Health effects of fish intake – controversy and confusion

Since low rates of coronary heart disease (CHD) death were observed among Greenland Eskimos consuming high quantities of seafood,² fish has been considered a heart-healthy food. Since that time, the evidence from animal-experimental, observational, and clinical research paradigms has further supported a protective effect of fish consumption on risk of CHD death and identified the long-chain marine n-3 polyunsaturated fatty acids (n-3 PUFAs) – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – as the likely active constituents.³⁻²¹ On the other hand, concern has grown over the potentially harmful effects of mercury, dioxins, and polychlorinated biphenyls (PCBs) present in some fish species.²²⁻²⁹ The public is presented with contradictory messages on the risks and benefits of fish intake, causing confusion over the potential health effects of fish consumption.^{30, 31}

Health benefits of fish intake

Cardiovascular outcomes

CHD death (documented or suspected fatal myocardial infarction [MI]) and sudden death (a sudden pulseless condition of presumed cardiac etiology) are clinically defined conditions. These conditions typically share the final common pathway of fatal ventricular arrhythmia, which is often ventricular fibrillation induced by, or related to, ischemia. A pooled analysis of results from prospective observational studies and randomized clinical trials suggests that fish or fish oil consumption lowers the risk of CHD death and sudden death (Figure 1).^{3-5,7-18,32-38} This effect is not linear. Rather, a threshold effect is apparent: modest intake (up to 250-500 mg/d EPA + DHA) substantially lowers risk, whereas higher intakes confer little additional risk reduction. This threshold effect explains findings seen in Japanese populations.^{18,36,37} Average seafood intake among Japanese people is very high (~900 mg/d EPA + DHA) and, therefore, most of the population is already above the threshold for maximum benefits on CHD mortality. Consequently, rates of CHD death are already very low among the Japanese (eg, 87% lower than comparable Western populations^{10, 18}), and additional fish intake (or fish oil supplementation) produces little further reductions in CHD death. When different types of fish meals have been evaluated, lower risk appears most strongly related to intake of oily fish (containing higher levels of n-3 PUFAs), rather than intake of lean fish.^{11,16} Fish intake may modestly affect other cardiovascular (CV) outcomes, but evidence is not as robust as for CHD death (Table 1).^{18, 37, 39-52}

The n-3 PUFAs influence several CV risk factors.^{19,20,53-68} Changes in these risk factors occur within weeks of intake and likely result from changes in membrane fluidity and receptor responses following incorporation of n-3 PUFAs into cell membranes^{69,70} and from direct binding of n-3 PUFAs to intracellular receptors, which regulate gene transcription.⁷¹ Intake of fish or fish oil is unlikely to affect all clinical CV outcomes equally, due to varying dose-responses and time-responses of the effects of n-3 PUFAs on the risk factors (Figure 2). For example, at typical dietary levels of intake (<500 mg/d EPA + DHA), antiarrhythmic effects predominate, reducing risk of sudden death and CHD death within



BRIGHAM AND
WOMEN'S HOSPITAL



HARVARD
MEDICAL SCHOOL
TEACHING AFFILIATE

Cardiovascular Division (Clinical)

Dale Adler, MD	Jane A. Leopold, MD
Christine Albert, MD	Eldrin Lewis, MD
Michelle Albert, MD	James Liao, MD
Elliott Antman, MD	Peter Libby, MD
Kenneth Baughman, MD	(Division Chief)
Joshua Beckman, MD	Leonard Lilly, MD
Charles M. Blatt, MD	Bernard Lown, MD
Eugene Braunwald, MD	Laura Mauri, MD
Christopher Cannon, MD	Thomas Michel, MD, PhD
Ming Hui Chen, MD	David Morrow, MD
Alanna Coolong, MD	Karen Moulton, MD
Mark Creager, MD	Gilbert Mudge, MD
Akshay Desai, MD	Anju Nohria, MD
Elazer Edelman, MD, PhD	Patrick O'Gara, MD
Andrew Eisenhauer, MD	Marc A. Pfeffer, MD, PhD
Laurence Epstein, MD	(Editor)
David Faxon, MD	Jorge Plutzky, MD
Ming Hui Chen, MD	Jeffrey Popma, MD
Mark Feinberg, MD	Shmuel Ravid, MD
Daniel Forman, MD	Frederic Resnic, MD
Peter Ganz, MD	Paul Ridker, MD
J. Michael Gaziano, MD	Thomas Rocco, MD
Thomas Gaziano, MD	Maria Rupnick, MD, PhD
Marie Gerhard-Herman, MD	Marc Sabatine, MD
Robert Giugliano, MD	Arthur Sasahara, MD
Michael Givertz, MD	Benjamin Scirica, MD
Samuel Z. Goldhaber, MD	Christine Seidman, MD
Thomas B. Graboys, MD	Andrew Selwyn, MD
Howard Hartley, MD	Laurence Sloss, MD
Carolyn Ho, MD	Piotr Sobieszcyk, MD
John Jarcho, MD	Regina Sohn, MD
Paula Johnson, MD	Scott Solomon, MD
Scott Kinlay, MD	Lynne Stevenson, MD
Jamil Kirdar, MD	William Stevenson, MD
James Kirshenbaum, MD	Peter Stone, MD
Bruce Koplan, MD	Michael Sweeney, MD
Raymond Kwong, MD	Usha Tedrow, MD
Michael J. Landzberg, MD	Stephen Wiviott, MD
Richard Lee, MD	Justina Wu, MD

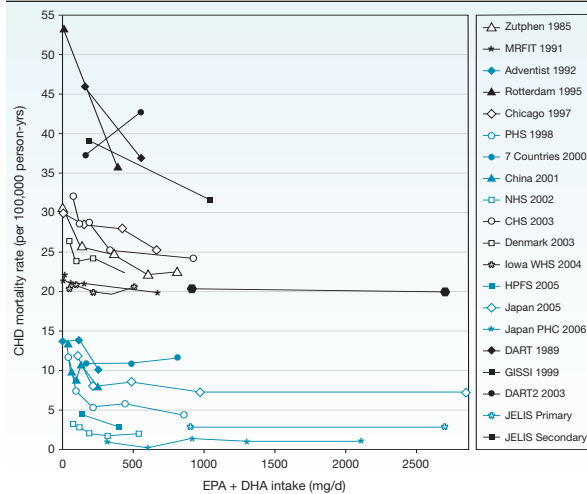
Brigham and Women's Hospital

Fax: (617) 732-5291 Website: www.heartdoc.org

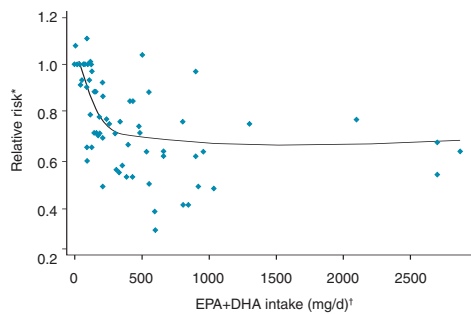
The editorial content of *Cardiology Rounds* is determined solely by the Cardiovascular Division of Brigham and Women's Hospital. This publication is made possible by an educational grant.

Cardiology Rounds is approved
by the Harvard Medical School
Department of Continuing Education
to offer continuing education credit

Figure 1: The relation between fish or fish oil intake and absolute risk of CHD death in prospective cohort studies and randomized clinical trials.



Top panel: CHD mortality rates vary >100-fold across different populations (due to differences in age, prior CHD, and other risk factors), but the relative effects of fish or fish oil intake are consistent. Compared with little or no intake, modest consumption (~250-500 mg/d EPA+DHA) lowers relative risk by 25% or more. At higher levels of intake (eg, in Japanese populations^{18,37}), CHD death rates are already low and do not substantially further reduce with greater intake, suggesting a threshold of effect. Only one study (DART238) found markedly divergent results from this pattern.



Bottom panel: Pooled analysis of prospective studies and randomized trials of fish or fish oil intake and relative risk of CHD death using restricted cubic splines. A significant threshold effect ($p < 0.001$) was evident at intake of ~250 mg/d: between 0 and 250 mg/d, mortality risk was lower by 14.6% (95% CI, 8-21%) per each 100 mg/d greater intake (total risk reduction=36%, 95% CI, 20-50%), while at higher intakes, risk was not further lowered (0.0% change per each 100 mg/d, 95% CI, -0.9-0.8%, $p = 0.94$).

weeks. At higher doses, maximum antiarrhythmic effects have been achieved, but other physiologic effects may modestly impact other clinical outcomes, in some cases requiring years to result in clinical benefits. For instance, the risk of nonfatal MI may not be greatly reduced by lower doses or shorter durations of n-3 PUFA intake, but may be modestly reduced by higher doses or prolonged intake (eg, 1.8 g/d for 5 yrs in the JELIS trial¹⁸).

Differing pathophysiologies of different clinical CV outcomes also result in heterogeneity in the clinical effects of fish or fish oil intake. For example, differing pathophysiologies of primary ventricular fibrillation (often ischemia-induced) vs. recurrent ventricular tachyarrhythmias (ectopic or reentrant) may explain why n-3 PUFAs more strongly reduce the risk of CHD death or sudden death, compared with equivocal effects on recurrent tachyarrhythmias among patients with implantable cardiofibrillators. Similarly, the pathophysiology of chronic development of atherosclerosis is very different from acute plaque rupture/thrombosis or from ventricular arrhythmia and, thus, n-3 PUFAs would be expected to have differing effects on atherosclerotic plaque progression vs. nonfatal MI vs. CHD death/sudden death. When fish is consumed, other foods, such as meats or dairy products, may be replaced in the diet. However, such displacement is very unlikely to account for much of the observed health benefits of fish intake, because the foods replaced would be highly variable for any given meal, among individuals, and across cultures. Furthermore, modest intake of these other foods (1-2 times/week) is not associated with higher CHD risk.⁷²

Total mortality

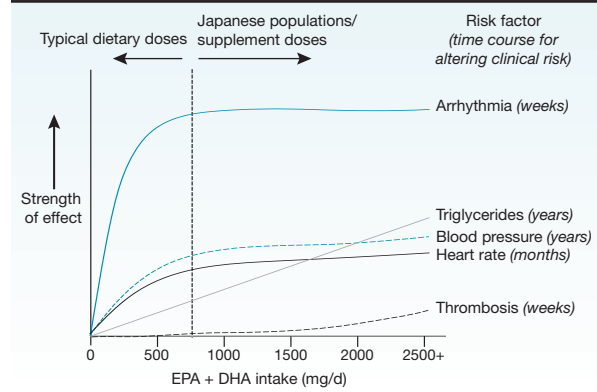
Consumption of fish or fish oil most strongly affects CHD death^{6,10,15-17,19} and is unlikely to appreciably reduce other causes of mortality. Thus, in any given population, the effects of fish or fish oil intake on total mortality would depend on the proportion of mortality due to CHD in that population. Among typical middle-aged populations, one-quarter of all deaths are due to CHD, while in higher risk populations (such as those with prior MI), one-half of all deaths are due to CHD.^{10,73} Thus, given an estimated 36% reduction in CHD death (Figure 1), fish or fish oil intake would be expected to reduce total mortality by between ~9% (36% reduction x 25% CHD deaths) to ~18% (36% reduction x 50% CHD deaths), depending on the population studied, or an average of ~14% in mixed

Table 1: Summary of the evidence for effects of fish or fish oil consumption on CV outcomes

Outcome	Clinical effect	Strength of the evidence	Comments
CHD mortality – CHD death Sudden death	~35% ~50%	Strong Strong	Probable threshold of effect – most risk reduction occurs with modest intake (~250 mg/d EPA+DHA), with little additional benefit with higher intakes (see Figure 1). ^{3-5,7-18,32-38}
Ischemic stroke	~30%	Moderate	Strong evidence from prospective cohort studies; ^{39,40} no RCTs.
Nonfatal CHD – Nonfatal MI Progression of atherosclerosis Post-angioplasty restenosis	? Modest benefit ? Modest benefit ? Modest benefit	Equivocal Equivocal Equivocal	Possible benefits at very high intakes (~2 g/d n-3 PUFAs). ^{18,37} Mixed results in cohort studies ⁴¹ and RCTs. ⁴²⁻⁴⁴ Possible benefits in a meta-analysis of RCTs. ⁴⁵
Recurrent ventricular Tachyarrhythmias	? Modest benefit	Equivocal	Mixed results in three RCTs. ⁴⁶⁻⁴⁸
Atrial fibrillation	~30% +	Limited	Mixed results in two cohort studies; ^{49,50} benefit in one RCT. ⁵¹
Congestive HF	~30%	Limited	Benefit in one prospective cohort study. ⁵²

RCT = randomized clinical trial; HF = heart failure

Figure 2: Schema of dose-responses (colored lines) and time courses for altering clinical events (denoted in italics) of physiologic effects of fish or fish oil intake. The relative strength of effect is estimated from effects of EPA + DHA on each risk factor and on the corresponding impact on CV risk.^{56-58,63-68} For example, the dose-response for anti-arrhythmic effects is initially steep with a subsequent plateau (Figure 1), and clinical benefits may occur within weeks, while dose-response for triglyceride effects is more gradual and monotonic, and clinical benefits may require years of intake. At typical Western levels of intake (eg, <750 mg/d EPA + DHA), the physiologic effects most likely to account for clinical CV benefits include modulation of myocardial sodium and calcium ion channels, reducing susceptibility to ischemia-induced arrhythmia,^{19,20} and reduced left ventricular workload and improved myocardial efficiency as a result of reduced heart rate, lower systemic vascular resistance, and improved diastolic filling.^{53-58,64} At higher levels of intake seen with fish oil supplementation or in Japanese populations^{36,37} (>750 mg/d EPA + DHA), maximum antiarrhythmic effects have been achieved and clinically relevant effects occur on serum triglycerides,⁶³ and possibly, at very high doses, thrombosis.⁶² Potentially important effects on endothelial,⁵⁹ autonomic,⁶⁰ and inflammatory⁶¹ responses are not shown because dose-responses and time-courses of such effects on clinical risk are not well-established. Relationships are not necessarily exclusive; for example, antiarrhythmic effects may be partly mediated by effects on blood pressure or heart rate.



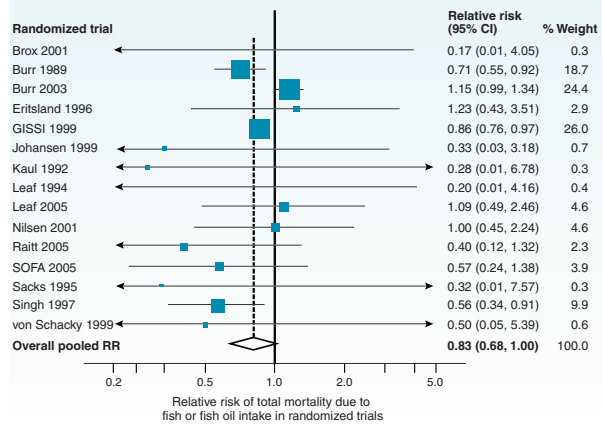
populations. This is consistent with findings in a meta-analysis of randomized clinical trials of fish or fish oil intake in humans, in which fish or fish oil intake reduced total mortality by 17% (among 15 trials, pooled RR=0.83, 95% CI, 0.68-1.00, p=0.046) (Figure 3).¹

This can be compared to the effects of statins on total mortality – 15% reduction – in a meta-analysis of randomized clinical trials (pooled RR=0.85, 95% CI, 0.79-0.92).⁷⁴ Although the magnitude of the mortality benefit, as determined by meta-analyses of randomized clinical trials, is similar for fish or fish oil intake vs. statin therapy, the robustness of the evidence is not as strong for fish or fish oil intake, as evidenced by wider confidence intervals. Nevertheless, an “either/or” comparison is unnecessary: patients with appropriate indications should receive statin therapy, and all patients should receive directed advice to consume 1-2 servings/week of fish – preferably oily fish rich in n-3 PUFAs – to receive the complementary health benefits of both therapies.

Neurologic development

The rapidly developing fetal and infant brain preferentially incorporates DHA into the cell membranes of gray-matter and retinal tissues.⁷⁵ Infants are able to convert shorter-chain n-3 fatty acids, such as alpha-linolenic acid (ALA), to DHA.⁷⁶ However, it is not known whether such conversion is adequate for optimal brain development in the absence of sufficient maternal consumption of DHA.^{77,78} Both observational

Figure 3: The effect of fish or fish oil intake on total mortality in randomized clinical trials. Relative risks and 95% CIs are shown for each trial; the size of the shaded square indicates the trial’s contribution (inverse-variance weight) to the pooled estimate (dotted line) and 95% CI (diamond) determined by random effects meta-analysis. Fish or fish oil intake reduced total mortality by 17% (pooled RR=0.83, 95% CI, 0.68-1.00, p=0.046), with evidence for heterogeneity between trials (p heterogeneity=0.04). If two trials with methodologic concerns,⁹⁸ 101 were excluded, the pooled RR was 0.83 (95% CI, 0.74-0.92, p<0.001) with little evidence for heterogeneity (p heterogeneity=0.75). A recently reported trial of fish oil among the Japanese¹⁸ was not included in the primary analysis due to very high fish intake in the reference group (estimated EPA + DHA intake 900 mg/d) that would obviate mortality benefits of additional fish oil intake. When this trial was added to the secondary analysis, the pooled RR was 0.87 (95% CI, 0.76-0.99, p=0.048; p heterogeneity=0.29).



studies and randomized clinical trials have evaluated the effects of maternal DHA consumption (during gestation or nursing) on early brain development. A variety of outcomes have been assessed, including visual acuity, global cognition, and specific neurologic domains. In a meta-analysis of 14 randomized clinical trials, maternal DHA consumption significantly improved the visual acuity of the child, with improvements seen in a dose-dependent fashion.⁷⁹ Results of studies evaluating general cognitive function have been less consistent, possibly due to differences in neurologic tests utilized,^{75,78,80} nevertheless, in a meta-analysis of 8 randomized clinical trials, each 100 mg/d increase in maternal DHA consumption increased child IQ by 0.13 points (95% CI, 0.08-0.18).⁸¹ In a randomized clinical trial among pregnant women, consumption of cod liver oil from mid-pregnancy (18 weeks) until 3 months postpartum raised mental processing scores, a measure of intelligence, in the children at 4 years age.⁸² These findings are supported by observational studies demonstrating higher behavioral attention scores, visual recognition memory, and language comprehension in infancy when mothers consume greater amounts of DHA or fish during pregnancy.⁸³⁻⁸⁵ Thus, together these studies indicate that maternal consumption of DHA is beneficial for early neurodevelopment.

Other outcomes

Several lines of evidence suggest that fish consumption may favorably affect other clinical outcomes, such as cognitive decline and dementia,⁸⁶ depression and other neuropsychiatric disorders,^{87,88} and asthma and other inflammatory disorders.^{61,89} While these possible effects may prove to be clinically imperative, a review of these and other potential health benefits of fish intake is beyond the scope of this report.

Table 2: Levels of n-3 fatty acids and contaminants in commonly consumed fish, shellfish, and other foods

	EPA + DHA, mg per serving (serving size)	Selenium, µg/g (parts per million)	Mercury, µg/g (parts per million)	PCBs, ng/g (parts per billion)	Dioxins, TEG pg/g (parts per trillion) [†]
FDA action level	n/a	n/a	1.0	2000	none
Fish					
Anchovy	1165 (2 oz)	0.68	<0.05		0.35 (1997-98)
Catfish, Farmed	253 (5 oz)	0.15	<0.05	<50 (1997)	0.52 (1995-97)
Cod, Atlantic	284 (6.3 oz)	0.38	0.10		0.10 (1995-97)
Fish Burger, Fast Food	337 (2.2 oz)	0.17	<0.05	8 (2001)	0.06 (2001)
Fish Sticks, Frozen	193 (3.2 oz)	0.17	<0.05		0.04 (2001)
Golden bass (tilefish),	1,358 (5.3 oz)	0.52	1.45		
Halibut	740 (5.6 oz)	0.47	0.25		1.00 (1995-97)
Herring, Atlantic	1,712 (3 oz)	0.47	<0.05		0.97 (1995-98)
Mackerel, Atlantic	1,059 (3.1 oz)	0.52	0.05		0.60 (1997-98)
Mackerel, King	618 (5.4 oz)	0.47	0.73		
Salmon, Farmed [†]	4,504 (6 oz)	0.41	<0.05	25* (2001-03)	0.61 (2001-03)
Salmon, Wild [†]	1,774 (6 oz)	0.46	<0.05	1.8* (2002)	0.19 (2002)
Sardines	556 (2 oz)	0.53	<0.05	40 (2001-03)	0.31 (2001-03)
Shark	585 (3 oz)	0.34	0.99		
Swordfish	868 (3.7 oz)	0.62	0.98		
Trout	581 (2.2 oz)	0.15	0.07	11 (2002)	0.44 [‡] (2002)
Tuna, Light (Skipjack) [†]	228 (3 oz)	0.80	0.12	45 (2001)	0.02 (1995-98)
Tuna, White (Albacore) [†]	733 (3 oz)	0.66	0.35	100 (2001-03)	0.23 (2001-03)
Shellfish					
Crab	351 (3 oz)	0.40	0.09	6 (2002)	0.55 [‡] (2002)
Scallops	310 (3 oz)	0.28	<0.05		0.16 (1998)
Shrimp	267 (3 oz)	0.40	<0.05	1.1 (2002)	0.09 [‡] (2002)
Other foods					
Beef	0	0.19	0	22 (2001)	0.20 (1995-2001)
Butter	0	<0.05	0	70 (2001)	0.44 (1995-2001)
Cheese	0	0.22	0		0.45 (1995-2001)
Chicken	0	0.23	0	32 (2001)	0.11 (1995-2001)
Eggs	22 (1 egg)	0.23	0	19 (2001)	0.29 (1998-2001)
Milk	0	0.02	0		0.07 (1995-2001)

Average values shown (Mozaffarian and Rimm¹), which may vary due to methodologic, geographic, temporal, and fish-to-fish differences. Values for PCBs and dioxins may overestimate current levels because contaminant levels in most foods, including fish species, are decreasing over time (eg, TEQs decreased by 33%-81% in meats and 66%-77% in salmon and tuna fish between 1995 and 2003^{102, 103}); year of sampling is given in parenthesis.

* Values including the fish skin; levels may be lower in the edible portion.¹⁰⁴

[†] For the same specific species, there are minimal differences in nutritional or contaminant content of canned vs. fresh salmon or tuna. However, different species are typically canned vs. sold fresh. For salmon, differences between species are small compared with differences between farmed and wild salmon. For tuna, canned light (skipjack) tuna and fresh yellowfin/ahi tuna are more similar overall, while canned white (albacore) tuna and fresh bluefin tuna are more similar overall.

[‡] Includes dioxin-like PCBs. TEQ = Toxic equivalence.

Related considerations

Plant sources

Alpha-linolenic acid (ALA, 18:3n-3) is a plant-derived n-3 fatty acid, present in flaxseed, canola, soybeans, and walnuts.⁹⁰ In humans, ALA is converted to EPA in only small quantities and further conversion to DHA is very limited.⁹¹ Consumption of ALA (eg, 2-3 g/d) may reduce CV risk⁹² or improve neurodevelopment, but benefits are less established compared with EPA + DHA. Thus, currently, ALA intake should not be considered a replacement for EPA + DHA intake.

Fish oil supplements

Fish oil capsules are a good source of n-3 PUFAs, containing 20%-80% EPA + DHA, or 200-800 mg EPA + DHA per 1 g capsule.^{93,94} Supplemental doses of fish oil (2-4 g/d) are needed to achieve significant triglyceride lowering.⁶³ However, achieving the major clinical CV benefit – reduction in CHD mortality – appears to require only modest intake, ~250 mg/d EPA + DHA (Figure 1), indicating that this benefit is largely unrelated to triglyceride effects (Figure 2). Because dietary n-3 PUFAs persist in tissue membranes for weeks,⁹⁵ this can be converted to a weekly EPA+DHA intake of ~1500-2000 mg, corresponding to one 3-oz serving/week of farmed salmon,

one 6-oz serving/week of wild salmon or similar oily fish, or more frequent intake of less n-3 PUFA-rich fish (Table 2). Compared with supplements, consumption of fish also provides potentially beneficial protein, vitamin D, and selenium.⁹⁰ Thus, dietary fish consumption can be considered the first line recommendation to prevent CHD death. Nevertheless, most of the benefit is likely related to the n-3 PUFAs in fish and, thus, fish oil capsules are a reasonable alternative for individuals who do not want to consume oily fish or who wish to ensure adequate regular intake of EPA+DHA.

Functional foods

n-3 PUFAs may be added to foods during manufacturing (eg, dairy products, eggs, salad dressings), creating “functional foods.” Many of these foods contain ALA, rather than EPA + DHA. There may be clinical benefit for ALA, but it is less clearly established.⁹² As the number of functional foods containing EPA + DHA increases, consumption of such foods may provide a reasonable alternative for individuals not consuming seafood.⁹⁶

Commercial preparations

Commercially-prepared fried fish from fast food restaurants or supermarket frozen sections^{97,98} are often

made using white-meat fish that are lower in n-3 PUFAs.^{22,97} These fish meals are also often prepared using partially hydrogenated oils (that contain trans fats) and/or oils reused for multiple frying cycles (which introduces oxidative/deteriorative products⁹⁹). Thus, overall, these fish meals may have an unfavorable balance of benefit vs. harm, containing lower amounts of EPA + DHA and higher amounts of trans fats and deteriorative products. Higher CV risk seen with fried fish intake^{16,40,49,52} may relate to this unfavorable balance of benefit vs. harm or to residual factors confounding from other lifestyle factors. Further research is needed; however, it appears unlikely that intake of commercially-prepared fried fish meals lowers CV risk.

Conclusions

Modest consumption of fish, especially species higher in n-3 PUFAs, reduces the risk of CHD death by 36% ($p < 0.001$) in observational studies and randomized clinical trials, and reduces total mortality by 17% ($p < 0.05$) in randomized clinical trials. Fish intake may also favorably affect other clinical outcomes in adults. Intake of 250 mg/d EPA + DHA appears sufficient for primary prevention. DHA also appears beneficial for early neurodevelopment during gestation and infancy. In Part 2 of this report, the evidence for the potential health risks of mercury and PCBs/dioxins is discussed, and the evidence for both benefits and risks is synthesized to describe optimal intakes for different populations.

References

- Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: Evaluating the risks and the benefits. *JAMA* 2006;296:1855-99.
- Bang HO, Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. In: Draper H, ed. *Advances in Nutrition Research*. New York, NY: Plenum Press; 1980:1-22.
- Kromhout D, Bosschiet EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 1985;312:1205-1209.
- Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2:757-761.
- Dolecek TA, Grandits G. Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *World Rev Nutr Diet* 1991;66:205-216.
- Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995;274:1363-1367.
- Kromhout D, Feskens EJ, Bowles CH. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *Int J Epidemiol* 1995;24:340-345.
- Daviglus ML, Stamler J, Orenca AJ, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 1997;336:1046-1053.
- Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998;279:23-28.
- Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447-455.
- Oomen CM, Feskens EJ, Rasanen L, et al. Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. *Am J Epidemiol* 2000;151:999-1006.
- Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol* 2001;154:809-816.
- Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002;287:1815-1821.
- Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002;346:1113-1118.
- Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am J Clin Nutr* 2003;77:319-325.
- Mozaffarian D, Lemaitre RN, Kuller LH, Burke GL, Tracy RP, Siscovick DS. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. *Circulation* 2003;107:1372-1377.
- Mozaffarian D, Ascherio A, Hu FB, et al. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. *Circulation* 2005;111:157-164.
- Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid (EPA) on major cardiovascular events in hypercholesterolemic patients: The Japan EPA Lipid Intervention Study (JELIS). Paper presented at: American Heart Association Scientific Sessions; Nov 17, 2005; Dallas, TX.
- McLennan PL. Myocardial membrane fatty acids and the antiarrhythmic actions of dietary fish oil in animal models. *Lipids* 2001;36 Suppl:S111-114.
- Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation* 2003;107:2646-2652.
- Wang C, Harris WS, Chung M, et al. n-3 Fatty acids from fish or fish-oil supplements, but not (alpha)-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* 2006;84:5-17.
- U.S. Environmental Protection Agency. Mercury Study Report to Congress. Available at: <http://www.epa.gov/mercury/report.htm>. Accessed January 24, 2006.
- U.S. Geological Survey. Mercury in the Environment. Available at: <http://www.usgs.gov/themes/factsheet/146-00/>. Accessed October 25, 2005.
- Committee on the Toxicological Effects of Methylmercury; Board on Environmental Studies and Toxicology; Commission on Life Sciences; National Research Council. *Toxicological Effects of Methylmercury*. Washington, DC: National Academy Press; 2000.
- The Risk Assessment Information System. Toxicity Summary for Mercury. Available at: http://risk.lsd.ornl.gov/tox/profiles/mercury_f_V1.shtml. Accessed January 24, 2006.
- U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition. Seafood Information and Resources. Available at: <http://www.cfsan.fda.gov/seafood1.html>. Accessed January 30, 2006.
- World Health Organization. Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI): WHO Consultation, May 25-29, Geneva, Switzerland; 1998.
- U.S. Environmental Protection Agency. National Center for Environmental Assessment. Dioxin and Related Compounds. Available at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55264>. Accessed March 14, 2006.
- U.S. Environmental Protection Agency. Polychlorinated Biphenyls (PCBs). Available at: <http://www.epa.gov/opptintr/pcb/>. Accessed March 14, 2006.
- Verbeke W, Sioen I, Pieniak Z, Van Camp J, De Henauw S. Consumer perception versus scientific evidence about health benefits and safety risks from fish consumption. *Public Health Nutr* 2005;8:422-429.
- Center for Food Nutrition and Agriculture Policy. University of Maryland. Real Mercury Facts. Available at: <http://www.realmercuryfacts.org/index.htm>. Accessed March 23, 2006.
- Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch Intern Med* 1992;152:1416-1424.
- Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart* 1997;78:450-455.
- Osler M, Andreassen AH, Hoidrup S. No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged, Danish adults. *J Clin Epidemiol* 2003;56:274-279.
- Folsom AR, Demissie Z. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. *Am J Epidemiol* 2004;160:1005-1010.
- Nakamura Y, Ueshima H, Okamura T, et al. Association between fish consumption and all-cause and cause-specific mortality in Japan: NIPPON DATA80, 1980-99. *Am J Med* 2005;118:239-245.
- Iso H, Kobayashi M, Ishihara J, et al. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation* 2006;113:195-202.
- Burr ML, Ashfield-Watt PA, Dunstan FD, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003;57:193-200.
- He K, Song Y, Daviglus ML, et al. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke* 2004;35:1538-1542.
- Mozaffarian D, Longstreth WT, Jr., Lemaitre RN, et al. Fish consumption and stroke risk in elderly individuals: the cardiovascular health study. *Arch Intern Med* 2005;165:200-206.
- Erkkila AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr* 2004;80:626-632.
- Sacks FM, Stone PH, Gibson CM, Silverman DI, Rosner B, Pasternak RC. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. *J Am Coll Cardiol* 1995;25:1492-1498.
- von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999;130:554-562.
- Angerer P, Kothny W, Stork S, von Schacky C. Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries. *Cardiovasc Res* 2002;54:183-190.
- Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on coronary restenosis, intima-media thickness, and exercise tolerance: a systematic review. *Atherosclerosis* 2006;184:237-246.
- Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *JAMA* 2005;293:2884-2891.
- Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation* 2005;112:2762-2768.
- Brouwer IA, Zock PL, Camm AJ, et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA* 2006;295:2613-2619.
- Mozaffarian D, Psaty BM, Rimm EB, et al. Fish intake and risk of incident atrial fibrillation. *Circulation* 2004;110:368-373.
- Frost L, Vestergaard P. n-3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Clin Nutr* 2005;81:50-54.
- Calo L, Bianconi L, Colivicchi F, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol* 2005;45:1723-1728.
- Mozaffarian D, Bryson CL, Lemaitre RN, Burke GL, Siscovick DS. Fish intake and risk of incident heart failure. *J Am Coll Cardiol* 2005;45:2015-2021.
- Charnock JS, McLennan PL, Aberywardena MY. Dietary modulation of lipid metabolism and mechanical performance of the heart. *Mol Cell Biochem* 1992;116:19-25.

54. Kenny D, Wartier DC, Pleuss JA, Hoffmann RG, Goodfriend TL, Egan BM. Effect of omega-3 fatty acids on the vascular response to angiotensin in normotensive men. *Am J Cardiol* 1992;70:1347-1352.
55. Chin JP, Gust AP, Nestel PJ, Dart AM. Marine oils dose-dependently inhibit vasoconstriction of forearm resistance vessels in humans. *Hypertension* 1993;21:22-28.
56. Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: meta-regression analysis of randomized trials. *J Hypertens* 2002;20:1493-1499.
57. Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL, Katan MB. Effect of fish oil on heart rate in humans: A meta-analysis of randomized controlled trials. *Circulation* 2005;112:1945-1952.
58. Mozaffarian D, Gottdiener JS, Siscovick DS. Intake of tuna or other broiled or baked fish vs. fried fish and cardiac structure, function, and hemodynamics. *Am J Cardiol* 2006;97:216-222.
59. Nestel PJ. Fish oil and cardiovascular disease: lipids and arterial function. *Am J Clin Nutr* 2000;71:228S-231S.
60. Christensen JH. n-3 fatty acids and the risk of sudden cardiac death. Emphasis on heart rate variability. *Dan Med Bull* 2003;50:347-367.
61. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep* 2004;6:461-467.
62. Kristensen SD, Iversen AM, Schmidt EB. n-3 polyunsaturated fatty acids and coronary thrombosis. *Lipids* 2001;36 Suppl:S79-82.
63. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr* 1997;65:1645S-1654S.
64. Dallongeville J, Yarnell J, Ducimetiere P, et al. Fish consumption is associated with lower heart rates. *Circulation* 2003;108:820-825.
65. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-1847.
66. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol* 1998;81:7B-12B.
67. Kannel WB, Kannel C, Paffenbarger RS, Jr., Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 1987;113:1489-1494.
68. Jouven X, Zureik M, Desnos M, Guerot C, Ducimetiere P. Resting heart rate as a predictive risk factor for sudden death in middle-aged men. *Cardiovasc Res* 2001;50:373-378.
69. Clandinin MT, Cheema S, Field CJ, Garg ML, Venkatraman J, Clandinin TR. Dietary fat: exogenous determination of membrane structure and cell function. *Faseb J* 1991;5:2761-2769.
70. Feller SE, Gawrisch K. Properties of docosahexaenoic-acid-containing lipids and their influence on the function of rhodopsin. *Curr Opin Struct Biol* 2005;15:416-422.
71. Vanden Heuvel JP. Diet, fatty acids, and regulation of genes important for heart disease. *Curr Atheroscler Rep* 2004;6:432-440.
72. Hu FB, Stamper MJ, Manson JE, et al. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. *Am J Clin Nutr* 1999;70:1001-1008.
73. Anderson RN, Smith LB. Centers for Disease Control and Prevention, Division of Vital Statistics. National Vital Statistics Reports. Deaths: Leading Causes for 2002. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr53/nvsr53_17.pdf. Accessed March 29, 2006.
74. Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *Br J Clin Pharmacol* 2004;57:640-651.
75. Lewin GA, Schachter HM, Yuen D, Merchant P, Mamaladze V, Tsertsvadze A. Effects of omega-3 fatty acids on child and maternal health. Agency for Healthcare Research and Quality (AHRQ). *Evid Rep Technol Assess (Summ)* 2005;1-11.
76. Uauy R, Mena P, Wegher B, Nieto S, Salem N, Jr. Long chain polyunsaturated fatty acid formation in neonates: effect of gestational age and intrauterine growth. *Pediatr Res* 2000;47:127-133.
77. Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients) Washington D.C.: The National Academies Press; 2002/2005.
78. McCann JC, Ames BN. Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. *Am J Clin Nutr* 2005;82:281-295.
79. Uauy R, Hoffman DR, Mena P, Llanos A, Birch EE. Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. *J Pediatr* 2003;143:S17-25.
80. Simmer K. Longchain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database Syst Rev* 2001:CD000376.
81. Cohen JT, Bellinger DC, Connor WE, Shaywitz BA. A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. *Am J Prev Med* 2005;29:366-374.
82. Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* 2003;111:e39-44.
83. Oken E, Wright RO, Kleinman KP, et al. Maternal fish consumption, hair mercury, and infant cognition in a U.S. Cohort. *Environ Health Perspect* 2005;113:1376-1380.
84. Colombo J, Kannass KN, Shaddy DJ, et al. Maternal DHA and the development of attention in infancy and toddlerhood. *Child Dev* 2004;75:1254-1267.
85. Daniels JL, Longnecker MP, Rowland AS, Golding J. Fish intake during pregnancy and early cognitive development of offspring. *Epidemiology* 2004;15:394-402.
86. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Fish consumption and cognitive decline with age in a large community study. *Arch Neurol* 2005;62:1849-1853.
87. Peet M, Stokes C. Omega-3 fatty acids in the treatment of psychiatric disorders. *Drugs* 2005;65:1051-1059.
88. Young G, Conquer J. Omega-3 fatty acids and neuropsychiatric disorders. *Reprod Nutr Dev* 2005;45:1-28.
89. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. *Chest* 2006;129:39-49.
90. U.S. Department of Agriculture. Agricultural Research Service. USDA National Nutrient Database for Standard Reference - Release 18 (2005). 2006.
91. Williams CM, Burdge G. Long-chain n-3 PUFA: plant v. marine sources. *Proc Nutr Soc* 2006;65:42-50.
92. Mozaffarian D. Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence. *Altern Ther Health Med*. 2005;11:24-30; quiz 31, 79.
93. Chee KM, Gong JX, Rees DM, et al. Fatty acid content of marine oil capsules. *Lipids* 1990;25:523-528.
94. U.S. Food And Drug Administration, Center for Drug Evaluation and Research. Omacor: Consumer Drug Information Sheet - Approval Label. Available at: <http://www.fda.gov/cder/foi/label/2004/216541bl.pdf>. Accessed April 5, 2006.
95. Brown AJ, Pang E, Roberts DC. Persistent changes in the fatty acid composition of erythrocyte membranes after moderate intake of n-3 polyunsaturated fatty acids: study design implications. *Am J Clin Nutr* 1991;54:668-673.
96. Patch CS, Tapsell LC, Mori TA, et al. The use of novel foods enriched with long-chain n-3 fatty acids to increase dietary intake: a comparison of methodologies assessing nutrient intake. *J Am Diet Assoc* 2005;105:1918-1926.
97. Shim SM, Lasrado JA, Dorworth LE, Santerre CR. Mercury and omega-3 fatty acids in retail fish sandwiches. *J Food Prot* 2005;68:633-635.
98. DietFacts.com. Helping you choose healthful foods. Available at: <http://www.dietfacts.com/>. Accessed April 4, 2006.
99. Warner K. Impact of high-temperature food processing on fats and oils. *Adv Exp Med Biol* 1999;459:67-77.
100. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.
101. Singh RB, Niaz MA, Sharma JP, et al. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival-4. *Cardiovasc Drugs Ther* 1997;11:485-491.
102. U.S. Department of Agriculture. Food Safety and Inspection Service. Dioxins and Dioxin-Like Compounds In the U.S. Domestic Meat and Poultry Supply. Available at: http://www.fs.is.usda.gov/PDF/Dioxin_Report_0605.pdf. Accessed March 24, 2006.
103. Gomara B, Bordajandi LR, Fernandez MA, et al. Levels and trends of polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (PCBs) in Spanish commercial fish and shellfish products, 1995-2003. *J Agric Food Chem*. 2005;53:8406-8413.
104. Thanun J. Great Lakes Indian Fish & Wildlife Commission. Tribally sold Lake Superior fish easily meet FDA restrictions for chemical contaminants. Available at: http://www.glifwc.org/pub/summer00/fish_contaminants.htm. Accessed March 25, 2006.



Dr. Dariush Mozaffarian obtained his undergraduate degree from Stanford University and his MD from Columbia College of Physicians and Surgeons. He completed his Internal Medicine residency at Stanford University and his Cardiology fellowship at the University of Washington. He also obtained a Masters in Public Health from the University of Washington and a Doctorate in Epidemiology from Harvard. He holds appointments in the Department of Medicine at Harvard Medical School and in the Department of Epidemiology at the Harvard School of Public Health. His primary research interests are the effects of dietary habits on cardiovascular health and disease, including coronary heart disease, sudden death, heart failure, and atrial fibrillation. He has authored numerous original publications on these topics. He is particularly interested in the effects of dietary fats, especially omega-3 fatty acids (found in seafood and plant sources) and trans fatty acids (found in partially hydrogenated oils). He has also elucidated cardiovascular effects of other dietary factors, such as dietary fiber, refined carbohydrates, and saturated fats. His research efforts are funded by multiple grants from the National Institutes of Health.

Disclosure: Dr. Dariush Mozaffarian has no conflicts of interest in association with the contents of this issue.

Brigham and Women's Hospital,
Cardiovascular Division website:

www.heartdoc.org

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Corporation

© 2006 Brigham and Women's Hospital, Boston, Massachusetts, which is solely responsible for the contents. The opinions expressed in this publication do not necessarily reflect those of the publisher or sponsor, but rather are those of the author based on the available scientific literature. Publisher: **SNELL Medical Communication Inc.** in cooperation with Brigham and Women's Hospital, Boston, Massachusetts. *Cardiology Rounds* is a registered trade mark of SNELL Medical Communication Inc. All rights reserved. The administration of any therapies discussed or referred to in *Cardiology Rounds* should always be consistent with the recognized prescribing information as required by the FDA. **SNELL Medical Communication Inc.** is committed to the development of superior Continuing Medical Education.