Editorial

On the Reanalysis of the GISSI-Prevenzione

Alexander Leaf, MD

The reanalysis\(^1\) of the results of the GISSI-Prevenzione secondary prevention trial appearing in this issue of Circulation greatly increases the importance of this large, well-conducted clinical trial. The original publication of the GISSI-Prevenzione\(^2\) reported that when 11,323 patients surviving a very recent myocardial infarction (MI) were randomized to 1.0 g daily of a concentrate of fish oil n-3 polyunsaturated fatty acids (PUFAs, \(n=2835\)), vitamin E (300 mg daily, \(n=2830\)), both (\(n=2830\)), or no treatment (\(n=2828\)) on top of usual pharmacological treatment and lifestyle, significant reductions in mortality were observed over the 42 months of follow-up. However, probably two or three features of the outcome drew the attention of the investigators. These were (1) the very early separation of the mortality curves (or probability of mortality) between the subjects receiving the n-3 supplement versus the control groups, (2) the absence of any reduction in plasma cholesterol levels, and (3) the finding that the major factor in the mortality reduction by n-3 PUFAs resulted from a striking 45% reduction in sudden cardiac deaths, which had not been a stated primary end point for the GISSI-Prevenzione trial.

Indeed, an early reduction in mortality has become a hallmark of the beneficial effects of n-3 PUFAs on coronary heart disease. This relationship is further strengthened when the benefit occurs in the absence of a reduction in cholesterol levels. Both were noted by Burr and associates in their 1989 publication of the Death and Reinfarction Trial\(^3\) and in the Lyon Heart Study by DeLorgeril et al\(^4\) in 1994. So the GISSI Investigators wisely decided that a careful time-course analysis of the results of GISSI-Prevenzione was warranted, and their resulting present publication adds greatly to the importance of their investigations.

See p 1897

The authors point out that the GISSI-Prevenzione was conducted in a population that fully adopted intensive preventive interventions. This would include the touted cardiac benefits of the Mediterranean diet.\(^5,6\) But because the diet benefits would apply to both the control and the experimental groups, one may ask if there is a way that some characteristic of the Mediterranean diet might benefit the subjects receiving the fish oil supplement more than the controls? I think there may be.

There has been much discussion among investigators studying the effects of polyunsaturated fatty acids on health, regarding the possible importance of the n-6/n-3 PUFA ratio. This ratio in its least essential form is reduced to the ratio of n-6 arachidonic acid (AA) to the n-3 eicosapentaenoic+docosahexaenoic acids (EPA+DHA, respectively), which are physiologically the most important representatives of their two classes of polyunsaturated fatty acids. AA is the source of the well-known arachidonic acid cascade including prostaglandins, leukotrienes, lipoxines, and epoxygenase products—many of which have been shown to be potent regulators of cell functions. Oxygenation by the same cyclooxygenase, lipoxygenase, and epoxygenase enzymes, however, results in a different series of products when EPA is a competitive substrate for these enzymes. Several of the products of EPA have actions that prevent or oppose the equivalent products of AA. A couple of examples, commonly cited, are the production of a potent vasoconstrictor and platelet activator, thromboxane B\(_2\), from AA and a decrease in thromboxane B\(_2\) when EPA is available to compete with AA for the cyclooxygenase, resulting also in only a small production of a physiologically mostly inactive thromboxane B\(_3\) from EPA. The adverse effects of thromboxane B\(_2\) are counteracted by the fact that the prostacyclins produced from AA or EPA equally prevent platelet aggregation and are potent vasodilators. These effects of the EPA prostaglandins would convert the circulation from a vasoconstrictive and platelet aggregatory state from thromboxane B\(_2\) to a vasodilatory, non-thrombotic state by EPA. This very favorable outcome results from the opposing action of n-3 EPA to n-6 AA.\(^6\) Another often cited antagonizing action of n-3 PUFAs to excess n-6 PUFAs is to the production of highly inflammatory leukotriene B\(_4\) from AA by the comparable but largely inactive leukotriene B\(_\text{3}^\text{a}\), as well as a reduction of leukotriene B\(_4\) produced when EPA is a competitive substrate to AA for lipoxygenase.\(^6\) A not commonly known, but additional example relevant to this discussion, is that all the prostaglandins we tested (except prostacyclin) produced from AA are proarrhythmic, whereas the equivalent prostaglandins derived from EPA are not.\(^7\)

The discussion in the preceding paragraph was to make the point that n-6 AA, when in excess in the diet and in our bodies, unbalanced by n-3 EPA+DHA may increase coronary atherosclerosis and sudden cardiac arrhythmic deaths. A corollary of this statement is that actions, which will reduce the n-6 PUFAs and decrease the ratio of AA/EPA+DHA should promote the antiarrhythmic effects of n-3 PUFAs and reduce total mortality from coronary heart disease. The Mediterranean diet includes the use of olive oil, which replaces the plant seed oils. The latter dominate the intake of

\(^1\)Reanalysis 1 of the results of the GISSI-Prevenzione secondary prevention trial appearing in this issue of Circulation greatly increases the importance of this large, well-conducted clinical trial.

\(^2\)The original publication of the GISSI-Prevenzione reported that when 11,323 patients surviving a very recent myocardial infarction (MI) were randomized to 1.0 g daily of a concentrate of fish oil n-3 polyunsaturated fatty acids (PUFAs, \(n=2835\)), vitamin E (300 mg daily, \(n=2830\)), both (\(n=2830\)), or no treatment (\(n=2828\)) on top of usual pharmacological treatment and lifestyle, significant reductions in mortality were observed over the 42 months of follow-up. However, probably two or three features of the outcome drew the attention of the investigators. These were (1) the very early separation of the mortality curves (or probability of mortality) between the subjects receiving the n-3 supplement versus the control groups, (2) the absence of any reduction in plasma cholesterol levels, and (3) the finding that the major factor in the mortality reduction by n-3 PUFAs resulted from a striking 45% reduction in sudden cardiac deaths, which had not been a stated primary end point for the GISSI-Prevenzione trial.

\(^3\)The study was conducted in a population that fully adopted intensive preventive interventions. This would include the touted cardiac benefits of the Mediterranean diet.

\(^4\)The authors point out that the GISSI-Prevenzione was conducted in a population that fully adopted intensive preventive interventions. This would include the touted cardiac benefits of the Mediterranean diet.

\(^5\)But because the diet benefits would apply to both the control and the experimental groups, one may ask if there is a way that some characteristic of the Mediterranean diet might benefit the subjects receiving the fish oil supplement more than the controls? I think there may be.

\(^6\)There has been much discussion among investigators studying the effects of polyunsaturated fatty acids on health, regarding the possible importance of the n-6/n-3 PUFA ratio.

\(^7\)The discussion in the preceding paragraph was to make the point that n-6 AA, when in excess in the diet and in our bodies, unbalanced by n-3 EPA+DHA may increase coronary atherosclerosis and sudden cardiac arrhythmic deaths. A corollary of this statement is that actions, which will reduce the n-6 PUFAs and decrease the ratio of AA/EPA+DHA should promote the antiarrhythmic effects of n-3 PUFAs and reduce total mortality from coronary heart disease. The Mediterranean diet includes the use of olive oil, which replaces the plant seed oils. The latter dominate the intake of...
polysaturated fatty acids in North America and northern European countries. Olive oil with 77% monounsaturated oleic acid makes very little contribution to AA. Plant seed oils, the common cooking and table oils (eg, corn, sunflower, safflower, cotton seed, and soy bean oils) are the sources of n-6 fatty acids in our diets. Corn, safflower, and sunflower oils average nearly 70% n-6 fatty acids with no n-3 fatty acids. The Mediterranean diet, which replaces n-6 vegetable seed oils with very low n-6 PUFA olive oil, may augment or amplify the effects of the n-3 PUFAs in the supplemented cohort as compared with the controls. The controls will also have olive oil replacing n-6 PUFAs, but lack the supplementary intake of n-3 PUFAs, so their ratio of AA/EPA + DHA is not so much reduced. To obtain maximal cardiovascular benefit from intake of n-3 PUFAs, it seems the concomitant intake of n-6 PUFAs must be reduced and n-3 PUFAs increased. This dual requirement was noted by DeLorgeril et al in their Lyon Heart Study. Today in the US, the ratio of n-6 to n-3 PUFAs is estimated to be some 15/1 to 20/1 or higher. The optimal ratio appears to be closer to 1/1, which has been roughly estimated to be the ratio during the 2 million or so years when our hunter-gather forebears were adapting their genes to their environment including their diet.

The available sources of n-3 fatty acids in our diets are from marine vertebrates, but stem from the ability of single cell phytoplankton and algae to convert the parent n-6 fatty acid, linoleic acid, to the parent n-3 fatty acid, α-linolenic acid, which enter the food chain of marine life and is further elongated and desaturated to produce the fish oil fatty acids EPA and DHA. As sources of edible fish in the oceans are being depleted by overfishing and the market price of fish keeps rising, one may ask where the dietary n-3 PUFAs will come from in the future. Farmed fish seem to be providing an increasing share of fish in today’s markets, but the feeding requirement of some 3 kg of fish or fish entrails to produce 2 kg of fish, makes this seem an unsustainable source of n-3 fatty acids. The temptation to augment the diets of the farmed fish with n-6 or other fatty acids will reduce the n-3 PUFA requirement of some 3 kg of fish or fish entrails to produce 2 kg of fish, makes this seems an unsatisfactory source of n-3 fatty acids. The temptation to augment the diets of the farmed fish with n-6 or other fatty acids will reduce the n-3 PUFA content in the final fish product. In this regard, a recent discovery by my brilliant young colleague Jing X. Kang may prove a major breakthrough. He has expressed the cDNA encoding a n-3 fatty acid desaturase obtained from the roundworm C. elegans in a cultured mammalian cardiomyocyte. When these rat heart cells were fed n-6 fatty acids in culture, their content of the n-3 desaturase quickly converted the n-6 fatty acids to the corresponding n-3 PUFAs. Thus, n-6 linoleic acid was converted to n-3 α-linolenic acid and AA was converted to EPA so that at equilibrium the ratio of n-6 to n-3 PUFAs was very close to 1/1. The importance of a n-6/n-3 ratio of these PUFAs of approximately 1.0 in order to attain maximal benefit from n-3 PUFAs, he demonstrated in another context by expressing the n-3 desaturase in a human breast cancer cell line. Again, as in the rat cardiomyocytes, the n-6 PUFAs were quickly converted to their n-3 counterparts with an equilibrium ratio of n-6/n3 PUFAs of approximately 1.0. The functional consequence of this was that the cancer cells expressing the n-3 desaturase underwent apoptotic death, whereas the control cancer cells with a high n-6/n-3 ratio continued to proliferate. This discovery raises the potential of transfecting the cells of animals, fowl, and of edible plants with the cDNA of the roundworm n-3 fatty acid desaturase to convert their content of n-6 PUFAs to n-3 PUFAs. We could thus achieve a ratio approximating 1.0 by consuming foods with such a ratio without the public having to make stringent changes in their diets.

References

On the Reanalysis of the GISSI-Prevenzione
Alexander Leaf

Circulation. 2002;105:1874-1875
doi: 10.1161/01.CIR.000015344.46176.99
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/16/1874