*European Heart Journal* (2000) **21,** 949–952
doi:10.1053/euhj.1999.1971, available online at http://www.idealibrary.com on IDEAL®

## *Hotline Editorial*

# The results of the GISSI-Prevenzione trial in the general framework of secondary prevention

A comment on the recent 'fast track' publication of the results of the fourth trial of the GISSI group[1] provides an interesting opportunity for a broader reflection on the so-called dietary component of secondary prevention, which so far has run largely in parallel with the pharmacological component.

Let us first summarize briefly the main answers provided by GISSI-Prevenzione to the original hypothesis of testing the pharmacological role of n-3 polyunsaturated fatty acids and vitamin E (i.e. substances usually consumed through diet) in the framework of a formal, controlled clinical experiment. GISSI-Prevenzione was a multicentre, open-label design, clinical trial in which 11 324 patients with recent ($\leq$3 months) myocardial infarction were randomly allocated to four treatment groups: n-3 PUFA alone, vitamin E alone, n-3 PUFA and vitamin E combined, or no supplement (control) and followed for 3·5 years. Daily doses of n-3 PUFA, as a 1 g capsule containing 850 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters, and 300 mg vitamin E, given as one capsule of synthetic $\alpha$-tocopherol, were used. In the end, GISSI-Prevenzione recruited a relatively low-risk population, with 16% of patients aged 70 years or older, and 14% with an echo-documented ejection fraction of 40% or less. Patients were compliant to dietary recommendations and during the study the intake of healthy foods was remarkably high. Most patients received recommended preventive treatments (anti-platelet drugs 92%, beta-blockers 44%, and inhibitors of angiotension-converting enzyme 46%). Statins were not supported by definitive data on efficacy when the trial was started; however, at the end of the study almost half of the patients were receiving cholesterol-lowering drugs. Most importantly, dietary habits and preventive interventions were maintained during follow-up and well-balanced across the four randomized groups.

The results of GISSI-Prevenzione indicate that in patients who have had a myocardial infarction, n-3 PUFA supplements, but not the moderate dose of synthetic vitamin E, reduced long-term complications of myocardial infarction to a clinically important extent. In particular, the combined primary end-point of death, non-fatal myocardial infarction, and non-fatal stroke were significantly reduced by n-3 PUFA treatment; relative risk reduction (RRR) was 15%, and the 95% confidence interval (CI) was increased from 2% to 26%. All the benefit seen in the combined end-point, however, was attributable to the reduction of total mortality (relative risk reduction 20%, 95% CI 6% to 23%), the rate of non-fatal cardiovascular events (myocardial infarction and stroke) being unchanged. In secondary analyses, n-3 PUFA significantly reduced the risk of cardiovascular death (RRR 30%, 95% CI 13% to 44%), coronary death (RRR 35%, 95% CI 16% to 49%), and sudden death (RRR 45%, 95% CI 24% to 60%).

Patients receiving vitamin E and controls did not differ significantly for the combined primary end-point (RRR 11%, 95% CI −3% to 23%), total mortality (RRR 14%, 95% CI −2% to 28%), and non-fatal cardiovascular events (RRR −2%, 95% CI −28% to 19%). An indication of a possible beneficial effect of vitamin E was provided, however, in the secondary analyses of the individual components of the causes of death, for which the increasing benefit (all cardiovascular deaths: RRR 23%, 95% CI 3% to 39%; coronary deaths: RRR 25%, 95% CI 4% to 41%; sudden death: RRR 35%, 95% CI 11% −52%) was similar to the picture for n-3 PUFA.

The results for combined treatment compared with controls for the primary combined end-point and for total mortality did not differ from those obtained with n-3 PUFA alone.

What are the implications of GISSI-Prevenzione results, and how could these be read in the broader framework of secondary prevention strategies? Although it is not brand new, the first point which needs to be underlined is the research approach: what was needed was an adequately sized controlled trial to provide an answer to questions raised by epidemiological evidence, tantalizing positive clinical results, and borderline significant findings[2–15]. The adoption of a population-oriented approach, with a naturalistic design, was specifically appropriate for the testing of interventions where dietary-derived drugs are

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assessed in addition to (and as substitutes for) correct dietary habits. While the most popular, and already widely used vitamin E (which is claimed to be an important antioxidant)[16–21] failed to reach statistically significant results (consistent with the more recently reported findings of the HOPE trial)[22], n-3 PUFA is the first pharmacological equivalent of a dietary component shown to decrease, in a clinically significant manner, the pre-defined hard end-points of morbidity and mortality.

As to the relevance and comparability of GISSI-Prevenzione results, it is worth noting that for every 1000 patients with myocardial infarction per year up to 5·7 lives can be saved with previous n-3 PUFA treatment (1 gram daily). Such a result is comparable to the one observed in the LIPID trial[23], where 5·2 lives could be saved per 1000 hypercholesterolaemic, coronary heart disease patients treated with pravastatin for 1 year (which corresponds to 192 patients treated for 1 year to save one life).

GISSI-Prevenzione results were obtained in a population already exposed to the protective effects of the Mediterranean diet, with more than 70% of the patients ingesting one or more servings of fish per week, irrespective of the randomized treatments. Therefore, the effects of n-3 PUFA could be tentatively considered to be additive with respect to those observed in the Lyon Diet Heart trial[12]. The pattern of effects seen in GISSI-Prevenzione (namely, reduction of overall mortality with no decrease in the rate of non-fatal myocardial infarction), in addition, does not come in isolation and resembles closely the one observed in the DART trial as well as in observational studies[6,7,15].

According to the above, it could confidently be said that n-3 PUFA treatment should be considered a recommended new component of secondary prevention. It is worth underlining that if these results did document a significant advantage in the Italian population, whose low risk for coronary heart disease is well-known, GISSI-Prevenzione results could be even more relevant for other populations with less favourable dietary habits. The importance of this combined/additive effect is further suggested by the preliminary analyses (to be submitted in final form for publication) of the interplay between diet and n-3 PUFA: there is an interesting direct correlation between size of the effect and 'correctness' of background diets.

It can be anticipated that a conceptual barrier must be overcome: A 'dietary drug' should be combined with 'dietary advice'. It will be interesting to monitor (as soon as the drug is registered) the degree of acceptance of the evidence. Cardiologically (and mechanistically) interesting points to be explored are suggested by the results of the secondary analyses on the causes of death. In particular, the striking reduction of sudden deaths observed with n-3 PUFA is not unexpected because the pathophysiological basis of the clinical and epidemiological suggestions in favour of a more direct cardiac effect of n-3 PUFA has been explored in a wealth of experimental, animal, human, and in-vitro[24–37] studies, which together support an important role for n-3 PUFA on arrhythmogenesis. Studies in humans, for instance, suggest increased heart rate variability and almost a halving of frequent ventricular ectopy in patients treated with n-3 PUFA as compared to controls[28–30], whereas the results of a case-control study conducted by Siscovick *et al.* suggest an inverse association between the risk of primary cardiac arrest and the level of n-3 PUFA intake from seafood[31].

According to the above, experimental and clinical research should establish that the antiarrhythmic effect is the more natural candidate to support the efficacy of n-3 PUFA. It is finally useful to underline that, with respect to the doses used in experimental and basic research, the pharmacological regimen of GISSI-Prevenzione is by far the lowest ever tested. Besides the interest in a trial which, with its hard facts, contradicts many pharmacological and biochemical expectations (pointing to the need for much higher dosages to guarantee efficacy), the indication for lower dosages is certainly not irrelevant, particularly from the point of view of clinical tolerability and economic burden.

A final comment on vitamin E data. Following the encouraging results of several, well-conducted, large-size prospective epidemiological studies and after the disappointing, unexpected results on $\beta$-carotene[38–39], vitamin E has been found to be the favourite antioxidant candidate for coronary heart disease prevention. Although contradictory, the results of the CHAOS trial further reinforced expectations of benefit[5,40,41]. With a daily regimen of 400–800 mg vitamin E in patients with angiographically proven coronary atherosclerosis, CHAOS showed a striking, significant 77% relative decrease of risk in non-fatal myocardial infarction, even though paralleled by a not significant 22% increase in all deaths. Another gloomy result came from the ATBC trial, which was conducted among 29 133 male cigarette smokers in Finland, which showed no cardiovascular benefit with low-dose (50 mg daily) vitamin E treatment after 6 years of follow-up[38]. However, the vitamin E results should not be viewed as cancelling out the 'anti-oxidation hypothesis', but more properly as 'not positive'[16]. The lack of benefit with vitamin E, however, is corroborated by the results of the HOPE trial and therefore the confirmation/refutation of the

'antioxidant hypothesis' has to wait for the results of ongoing clinical trials, as well as of meta-analyses which are obviously around the corner.

In conclusion, at variance with the orientation of a scientific scenario largely dominated by the 'cholesterol-heart hypothesis', GISSI-Prevenzione indicates that n-3 PUFA (virtually devoid of any cholesterol-lowering effect) is a relevant pharmacological treatment for secondary prevention after myocardial infarction.

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