Perspectives on n-3 PUFAs: primary prevention, antiarrhythmic effects, congestive heart failure

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(Key Words: n-3 PUFA, arrhythmias, primary prevention, congestive heart failure.)

From an impressive array of contributions, which have spanned the subject from basic science to randomized trials to a series of epidemiological findings and recommendation, the meeting has been provided with a unique opportunity of confronting the most up-to-date information:

• on the comprehensive pharmacological and clinical profile of n-3 PUFAs;
• on their role as dietary components as well as on the increasingly clear identity as a well-defined ‘drug’;
• even more interestingly, on the contexts in which they should be carefully assessed, so that their impact can produce the most reliable and relevant results.

The format of the meeting was not planned to produce a formal ‘consensus’ (at least according to the meaning which this term has assumed specifically over the years: a position, or a statement, reached through standardized procedures of confrontation and discussion of evidence, controversial data and opinions, pros and cons). However, the intensive debate which has accompanied all the presentations has suggested and allowed the formulation of a series of statements which could be assumed to represent at least a widely shared background, and which could be used as a baseline for future developments. The points reproduced in Table 1 may be seen as a reasonable summary of the overall philosophy of the meeting and of the issues which have been scored as the most relevant, to be taken into account and to be pursued in future research and developments.

There is no doubt that to look, briefly but with very concrete proposals, into the future is a coherent way to conclude a consensus meeting, which was convened around a large population trial. The results of that trial have been specifically instrumental in supporting a substantial change of viewpoint on n-3 PUFAs: from substances acting on the balance of lipids leading to atherosclerotic and thrombotic complications and morbimortality, to drugs which could have its specific target on a more therapeutically ‘orphan’ condition, namely severe arrhythmias leading to sudden death. The physiological and experimental background of this ever-more-clearly emerging profile (which does not eliminate nor contradict the other, mainly epidemiological, documented mechanisms of action and of cardiovascular protection) does not need further comment, following the major contribution proposed by Alexander Leaf. The strength of the hypotheses is further confirmed by the fact that at least two major trials are ongoing on the ‘naturally experimental’ clinical condition represented by patients with implantable cardiac defibrillators (ICD).

The experience of the GISSI–Prevenzione trial, with documentation of a remarkable safety record and of a possibly higher than expected tolerability of the much lower dose adopted for a population-wide use, suggests however that there are at least two populations and two objectives which could be targeted to test the broader clinical and epidemiological relevance of n-3 PUFAs:

(1) patients who have not yet suffered a cardiovascular events, and who are usually classified as the candidates for primary prevention strategies;
(2) patients at the other extreme of the spectrum of morbidity and of the need for interventions, namely those who have developed cardiac failure and can be still considered, despite the impressive therapeutic advances of the last decade, among those with one of the worst short–medium term prognosis.

For both populations, the perspective of having a tool that possibly reduces the risk of sudden death, documented by the efficacy profile of n-3 PUFAs in the GISSI–Prevenzione study which is consistent with the
Large-scale clinical trials as the backbone of research projects on basic mechanisms are fatal and which therefore occur in the world at specifically those (ischaemic? arrhythmic?) events which, given that, despite general prevention measures, no successful interventions on MI and post-MI patients, relatively limited public health impact of the highly epidemiological literature consistently underlines the large — before they could become hospital events. The hospitalization (about 50% of all cardiac deaths) taking place before reduction has been so far obtained in those deaths profile, bring to the fore the issue of possibly decreasing lar events, but with a documented cardiovascular risk and promising. People without a history of cardiovascular events, but with a documented cardiovascular risk profile, bring to the fore the issue of possibly decreasing specifically those (ischaemic? arrhythmic?) events which are fatal and which therefore occur in the world at large — before they could become hospital events. The epidemiological literature consistently underlines the relatively limited public health impact of the highly successful interventions on MI and post-MI patients, given that, despite general prevention measures, no reduction has been so far obtained in those deaths (about 50% of all cardiac deaths) taking place before hospitalization[5]. An even stronger and abiding issue can be found in the many reports on major (and highly successful) trials which have tested the currently recommended treatments of cardiac failure, from the classical ACE inhibitors, to beta-blockers, to spironolactone[2–6].

Sudden death, which is specifically decreased by beta-blocking agents, contributes an important fraction of events to the still unsatisfactory prognosis of patients with left ventricular dysfunction and heart failure (Fig. 1).

The GISSI group has decided therefore that the most natural — and due — development of the findings of the GISSI–Prevenzione study will be the activation of two new large-scale trials, focused on primary prevention and heart failure respectively.

Figures 2 and 3 provide a very schematic plan of the studies, which have already been adopted in principle, and whose protocols are being formally drafted and are being assessed in terms of feasibility and timing. The numbers of patients to be recruited clearly suggests that, once more, a truly epidemiological or population approach is considered to be the ‘natural’ framework where the impact, if any, of a new treatment must be

Table 1 Summary of issues discussed in the meeting

1. The importance of dietary habits as a whole
   Epidemiological evidence on the specific causal role of n-3 PUFAs (alpha-linolenic acid, EPA, DHA) in determining background rates of cardiovascular population mortality and on the importance of the ‘competition’ of n-6 and n-3 across various populations.

2. Dietary habits and public health recommendations
   The incorporation of the existing knowledge into dietary recommendations and related public health campaigns/interventions must be pursued, with a well balanced focus on what should be ‘increased’ and what should be ‘decreased’ (quantities vs ratios).

3. Transferability of research findings
   While pursuing general lifestyle modifications (i.e. dietary habits), and waiting for inputs from genetic epidemiology, it is important to redefine scenarios for transferring epidemiological knowledge into clinical interventions (experimental and outcome research) i.e. with measurable results: (a) on the short term; (b) in target populations (at specific risk).

4. Consistency between epidemiology, DART — diet, GISSI — drug
   Recent data from clinical epidemiological studies and randomized controlled clinical trials consistently indicate that small differences/modifications/doses of (dietary) n-3 PUFAs suffice to decrease heart disease mortality.

5. Pharmacological knowledge
   There is a need to reconcile the pharmacological-mechanistic knowledge on the effects of n-3 PUFAs with most recent clinical epidemiological findings which in the past were: (a) mainly lipid-centred; (b) focused on atherothrombotic effects; (c) based on high doses.

6. New pharmacological hypotheses
   Most compelling recent clinical, epidemiological, and experimental evidence favours a role of low-dose n-3 PUFAs for clinical applications in (a) determining benefit without clear effects on lipid and atherosclerosis; (b) reducing CHD mortality, rather than the incidence of MI; (c) producing favourable results early after MI; (d) via an effect on sudden cardiac death, to be investigated directly in populations at high predefined cardiovascular risk. It is important to stress that strategies of research focused on the revised pharmacological profile of n-3 PUFAs must be always seen/pursued in addition, not as an alternative, to dietary measures/recommendations.

7. The need of clinical trials
   Controlled, large-scale trials seem today to be mandatory, specifically because of: (a) the substance which is tested (cultural besides medical considerations); (b) the target populations (already the subject/object of intensive medical interventions); (c) the need for good evidence in other countries.

8. Main research areas worth to be investigated with priority
   (a) Shift from dietary to pharmacological studies with low-dose n-3 PUFAs; (b) efficacy of different dosages of n-3 PUFAs (1 g vs 2–3 g), if feasible; (c) experimental groups and populations at high risk of fatal arrhythmic complications (e.g. patients with CHF, patients with implantable cardiac defibrillator); (d) populations with different characteristics and at high risk of cardiovascular mortality, where the preventive efficacy (and safety) of n-3 PUFAs must be further explored, with emphasis (also) on the comparison of efficacy in different populations.

9. Large-scale clinical trials as the backbone of research projects on basic mechanisms
   The scenarios of planning/implementing this type of trials seem to be also the most suitable for nested or companion studies aimed at exploring basic mechanisms of action and redefining the role and relevance of biomarkers.
tested. The tradition and the results obtained so far in the two areas are certainly promising in terms of feasibility. In primary prevention, the network of general practitioners who have recently concluded another large-scale trial, the Primary Prevention Project (PPP)\[7\], appears to be a reliable 'core' resource for conducting a trial, which will base the criteria of recruitment on the cardiovascular risk chart produced as a fall-out of the trial. The rather long, and highly successful, surveillance network of cardiological centres, which are already prospectively monitoring heart failure patients seen in their routine practice, provides a very suitable and efficient baseline for testing a new treatment on the top of the best available treatments, none of which has as a specific target arrhythmias and sudden death\[8\].

It is stimulating to conclude a meeting looking for consensus on what is known (which is already a lot) by underlining, with new studies already in an advanced stage of planning, that possibly the therapeutic life of n-3 PUFAs is just starting. At the same time, it is equally important to stress that (for the GISSI–Prevenzione as well as for the other results presented and discussed in this meeting) the experimental controlled testing of a therapeutic tool is framed in an epidemiologically oriented strategy\[9\]. The 'null hypothesis' is by definition the rule for both trials. The meeting has provided all the reasons to say that it is worth trying its falsification.

References


