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Saving Lives Post-MI: Highly Purified Omega-3 PUFAs for the Prevention of Sudden Death

H. Rupp1, C.-N. Verboom2, B. Jäger2

Opportunities still exist to improve prognosis and survival after myocardial infarction (MI). In particular there is a substantial mortality attributable to sudden death, a mode of death that has proved until now resistant to therapeutic intervention. In the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico)-Prevenzione study, use of highly purified omega-3 polyunsaturated fatty acids (omega-3 PUFAs) at a dose of 1 g/day was associated with a substantial reduction in the all-cause mortality of post-MI patients. This reduction was the result of a large and statistically significant reduction in risk of sudden death, with these survival benefits emerging early in the course of the 3.5-year study and being additive to the benefits of conventional secondary preventive therapies. OMACOR, a pharmaceutical formulation of highly purified omega-3 PUFAs, has been approved for use in post-MI patients on the basis of the results of GISSI-Prevenzione.

Several lines of evidence indicate that the clinical benefits of highly purified omega-3 PUFAs may be attributed to anti-arrhythmic qualities. Evidence for this mechanism of benefit is discussed in this review.

OMACOR is an effective and well tolerated medication that complements established post-MI medications. This agent should be considered part of the standard treatment strategy for MI survivors. J Clin Basic Cardiol 2002; 5: 209–14.

Key words: myocardial infarction, highly purified omega-3 PUFAs, clinical trial, arrhythmias, GISSI, sudden death

Despite considerable progress in the management of myocardial infarction (MI) in the past two decades [1–3], this condition continues to represent one of the major causes of death and morbidity throughout the developed world; its incidence is also increasing in developing nations [4–6]. Sudden death is one of the largest intractable threats to the well being of the MI survivor. The absence of any reliable warning symptoms, combined with its diffuse pathology and abrupt onset, mainly outside hospital, make sudden death an unusually difficult condition to anticipate and prevent [4, 5]. Experience with anti-arrhythmic drugs has been at best contentious and at worst clearly harmful [6]. Successful intervention specifically directed against this threat has been limited to use of implantable defibrillators in closely defined high-risk subgroups (Fig. 1). Only a small number of high-risk but clinically stable patients are suited to management by these means and the technology is not applicable to more general preventive efforts. A widespread use of these expensive devices would be prohibited by the current limited healthcare budgets. Similar constraints apply to public access defibrillation (PAD), which suffers additionally from the fact that the number of incidents at or near any given location is likely to be very low. (For a discussion of developments in PAD see Sotoodehnia et al. [5] and Weaver and Peberdy [7].)

With most instances of sudden death occurring out of hospital in persons who are not eligible for implantation of a defibrillator, population-based preventive measures are essential if substantial reductions are to be achieved in this form of mortality. The availability of an easily administered therapy of proven efficacy in preventing sudden death post-MI would therefore represent a considerable advance in the management of “the single most important cause of death in the industrialized world” [6]. Such a therapy has in fact been available for several years but has not become an established part of the routine therapeutic regimen for MI survivors. A more vigorous dissemination of this treatment could be expected to yield great health dividends to patients and to society.

The product in question, OMACOR, is a preparation of highly purified and concentrated omega-3 polyunsaturated fatty acids (omega-3 PUFAs) containing 90 % omega-3 PUFAs per 1 g. Almost all the PUFA content (84 %) of OMACOR is docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). OMACOR, administered at a dose of 1 g/day, has been approved for secondary prevention post-MI based on the findings of the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico)-Prevenzione study.

The GISSI-Prevenzione Study

GISSI-Prevenzione was an investigator-led multicentre study undertaken to examine the impact of highly purified omega-3 PUFAs, vitamin E, or the combination of omega-3 PUFAs plus vitamin E on outcomes post-MI in the context of contemporary preventive practice. Primary results of the study and informative ancillary analyses and commentaries have been published in the peer-reviewed literature [8–10].

Figure 1. Incidence of sudden death and numbers of sudden death events in different patient populations. Acronyms in arrows identify clinical trials in high-risk patients in which implantable cardioverter-defibrillators (ICDs) have been shown to have survival benefits. (From Myerburg RJ et al. Circulation 1998; 97: 1514–21; with additions)
Any patient with a recent MI (≤ 3 months) was eligible to participate in GISSI-Prevenzione provided he or she had no condition associated with poor short-term prognosis (eg cancer), no known contraindications to the study medications or congenital coagulation defect, and was competent to give informed consent and comply with the requirements of the study [8]. Drugs for secondary prevention (eg antplatelet drugs, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors and cholesterol lowering drugs) were prescribed according to prevailing standard practice. In addition, patients were encouraged to adhere to recommended preventive measures, including a Mediterranean-style diet with a high content of fruit, fish and fibre, and a relatively low content of saturated fats [8].

A total of 11,323 patients were recruited and randomised at 172 centres, making GISSI-Prevenzione one of the largest studies in secondary prevention. Approximately 2,800 patients were randomised to each of four treatment groups, comprising:

- Highly purified omega-3 PUFAs, administered at a dose of 1 g/day, comprising 84 % EPA and DHA
- Vitamin E, administered as alpha-tocopherol (300 mg/day)
- Highly purified omega-3 PUFAs plus vitamin E
- Control (usual care)

Treatments were administered open-label with ascertainment of prospectively defined endpoints by a blinded Endpoint Validation Committee. This PROBE (Prospective Randomized Open with Blinded Endpoint adjudication) format has been used in other major cardiovascular trials (eg the HOT [Hypertension Optimal Treatment]-study [11]).

Patients’ selected baseline characteristics appear in Table 1 (for a comprehensive summary of demographic details see [8]).

Noteworthy features of the study population included the relatively low proportions of elderly patients (17 % aged > 70 years) and patients with low ejection fraction (14 % with ejection fraction < 0.40) or evidence of active ischaemia during stress testing. This was, overall, a relatively low-risk post-MI population, with an annualised mortality rate in the control group of less than 3 % [9]. Use of recommended preventive therapies at baseline was generally high, particularly in the case of antplatelet agents (> 80 % throughout follow-up). Use of lipid-lowering drugs was low initially (< 5 %) but increased substantially (> 40 % at completion of follow-up) during the trial in response to the publication of the results of several pivotal trials of statins. Usage increased in a comparable manner in all treatment groups, so this trend is unlikely to have influenced the results of GISSI-Prevenzione. Adherence to the advised diet, as represented by patient-reported consumption of sentinel foodstuffs, was high throughout the study and tended to improve with duration of follow-up [8]. End-of-study vital status was recorded for 99.9 % of participants, yielding more than 38,000 patient-years of data during an average 3.5 years of follow-up.

Endpoints of GISSI-Prevenzione

The study had two primary endpoints [8]:

1. Cumulative rate of all-cause mortality, non-fatal MI and non-fatal stroke
2. Cumulative rate of cardiovascular mortality, non-fatal MI and non-fatal stroke

Secondary efficacy analyses included inspection of all components of the primary endpoints and the principal causes of death. Fatal endpoint definitions were based on a nested classification (Fig. 2). Non-fatal MIs and non-fatal strokes were diagnosed on the basis of prespecified criteria. Statistical comparisons emphasised four-way analysis, in which any treatment assignment could be compared with any other. Outcomes were analysed according to the principles of intention-to-treat.

Results of GISSI-Prevenzione

Substantive effects on the primary endpoints were observed only with highly purified omega-3 PUFAs. Vitamin E had no significant effect on either of the primary endpoints of GISSI-Prevenzione, and there was no indication of clinical synergism with combination therapy. The failure to demonstrate a benefit with vitamin E in GISSI-Prevenzione has since been repeated in the Heart Outcomes Prevention Evaluation (HOPE) trial [12] and the Heart Protection Study [13].
**Effects of Highly Purified Omega-3 PUFAs**

In contrast to the negative findings with vitamin E, highly purified omega-3 PUFAs significantly reduced the risk of experiencing a primary endpoint event in GISSI-Prevenzione. Compared with controls, the risk reduction for the endpoint of all-cause mortality plus non-fatal MI and non-fatal stroke was 15–16% (P = 0.02) and the risk reduction for cardiovascular death plus non-fatal MI and non-fatal stroke was 20–21% (P = 0.006) [8–10]. Analysis of cause-specific mortality revealed that the reduction in risk of a primary endpoint event with highly purified omega-3 PUFAs was due to a reduction in fatal events, most notably a 45% reduction in the risk of sudden death (P = 0.0006) (Fig. 3) [8, 9].

Blinded, retrospective time-to-event analysis revealed an early effect of highly purified omega-3 PUFAs in reducing the risk of sudden death, with a large (53%) and statistically significant (P = 0.048) benefit apparent after only 4 months (Fig. 4) [9]. The reduction in sudden death at 3 months, although not statistically significant (P = 0.058) accounted for more than half of the reduction in total mortality at that time (41% risk reduction for all-cause mortality; P = 0.037). By the end of follow-up, the reduction in sudden death was highly statistically significant (P = 0.0006) and accounted for 59% of the total survival benefit of highly purified omega-3 PUFAs versus controls.

Further analysis of the GISSI-Prevenzione database indicates that the survival benefit of highly purified omega-3 PUFAs was greater (though not significantly so) in patients who were most closely compliant with the Mediterranean diet [14]. The pragmatic interpretation of these data is that dietary modification is advantageous post-MI but that highly purified omega-3 PUFAs confer additional benefit: highly purified omega-3 PUFAs therefore represent an essential element in any comprehensive preventive strategy irrespective of dietary habits [14].

**Tolerability and Safety**

Highly purified omega-3 PUFAs were very well tolerated during GISSI-Prevenzione. Gastrointestinal disturbances and nausea were the only adverse events reported during the study, and the rate of discontinuation for treatment-related adverse events was 3.8% [8]. Numbers of deaths due to non-cardiovascular causes were similar in both the omega-3 PUFA group and the control group. These data provide assurance that no substantive non-cardiovascular safety concerns are associated with the long-term use of highly purified omega-3 PUFAs.

**Other Evidence that Omega-3 PUFAs Prevent Sudden Death**

GISSI-Prevenzione is the largest reported clinical trial to show a survival benefit of highly purified omega-3 PUFAs in post-MI patients. This result is corroborated, however, by other clinical trials’ data. The findings of the Diet and Reinforcement (DART) study [15], in particular, provide strong corroboration of the outcomes data from GISSI-Prevenzione.

DART was a clinical trial of factorial design conducted in 2033 non-diabetic men (aged < 70 years) who had recently recovered from an MI [15]. After 2 years of follow-up a significant survival benefit was recorded in men who had been instructed to augment their intake of omega-3 PUFAs. The magnitude of the treatment effect seen in DART (29% reduction in all-cause mortality) was broadly congruent with the results of GISSI-Prevenzione (21% reduction in all-cause mortality), and was attributed to an early effect of omega-3 PUFAs on reducing sudden death [15]. The survival benefit in DART was not accompanied by any effect on risk of non-fatal events, an outcome exactly in conformity with the results of GISSI-Prevenzione. Reports from observational studies are also supportive of the conclusion that omega-3 PUFAs prevent sudden death [16–19].

**Omega-3 PUFAs and Other Secondary Preventive Drugs**

It is beyond the scope of this review to undertake detailed comparison of the nature and magnitude of the survival benefit of omega-3 PUFAs in GISSI-Prevenzione relative to other drugs used for secondary prevention. (Separate appraisals of these other agents have been published [20–26].) However, an instructive and revealing comparison has been published in a recent report of the Task Force on Sudden Cardiac Death of the European Society of Cardiology (ESC) [6] and is reproduced in Table 2 exactly as originally published: the reasons for emphasising this fact will shortly be made apparent.

Two aspects of this table deserve attention. First, the effect size of omega-3 PUFAs on sudden death (based on GISSI-Prevenzione) is the largest on record from a controlled trial. Furthermore, the effect size on reduction in risk of all-cause
mortality, which is the most robust and unequivocal of clinical outcomes (without necessarily being in every instance the most informative), is also among the largest reported. It should be borne in mind that the nature and conduct of GISSI-Prevenzione was such that these benefits were seen in patients already highly compliant with dietary modification and receiving contemporary best practice in secondary preventive medication. It may therefore be concluded with some confidence that the benefits of highly purified omega-3 PUFAs are an additional survival benefit to patients beyond what may be achieved with conventional therapies and alterations to lifestyle and diet.

The other point to consider is the title of the original table and the classification of omega-3 PUFAs within the table. The title, which specifies 'agents/interventions without direct cardiac electrophysiological properties', almost certainly misrepresents the true status of omega-3 PUFAs at the dose used in GISSI-Prevenzione, as will be discussed later in this article. The description of omega-3 PUFAs at the dose given in GISSI-Prevenzione as 'lipid lowering agents' is certainly erroneous. The GISSI-Prevenzione investigators have confidently refuted the assumption, inherent in that classification, that omega-3 PUFAs exercised their influence on clinical outcomes via effects on blood lipids [27]: the report of the primary results documented no substantive effects on any lipoprotein fraction that could explain the improvements seen in prognosis and none compatible with the results of trials of authentic lipid-lowering drugs [eg see 24, 26, 28, 29]. In particular, the triglyceride-lowering effect of higher doses of omega-3 PUFAs (≥ 4 g/day) was not seen in GISSI-Prevenzione.

The current view of how omega-3 PUFAs prevent sudden death is conveyed in the statement "...DHA or EPA ... protects the heart cell locally from participating in the genesis and propagation of ventricular tachycardia, which can result in cardiac arrest and sudden death. This protective effect ... depends on the unique ability of these n-3 fatty acids [omega-3 PUFAs] to stabilize all contractile heart cells electrically..." [30]. In short, these agents act at the level of the cardiomyocytes to reduce susceptibility to arrhythmogenesis.

<table>
<thead>
<tr>
<th>Drug category</th>
<th>No. of patients</th>
<th>Relative risk of death (95 % CI)</th>
<th>Relative risk of SCD (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During MI</td>
<td>100,963</td>
<td>0.94 (0.80–0.98)</td>
<td></td>
</tr>
<tr>
<td>After MI</td>
<td>15,104</td>
<td>0.83 (0.71–0.97)</td>
<td>0.80 (0.70–0.92)</td>
</tr>
<tr>
<td>Aldosterone receptor blockers</td>
<td>1,663</td>
<td>0.70 (0.60–0.82)</td>
<td>0.71 (0.54–0.95)</td>
</tr>
<tr>
<td>Lipid lowering agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>30,817</td>
<td>0.71 (0.64–0.80)</td>
<td></td>
</tr>
<tr>
<td>n-3 polyunsaturated fatty acids</td>
<td>31,232</td>
<td>0.70 (0.56–0.86)</td>
<td>0.55 (0.40–0.74)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>81,908</td>
<td>0.94 (0.90–0.98)</td>
<td>N.a.</td>
</tr>
<tr>
<td>Magnesium</td>
<td>61,860</td>
<td>1.02 (0.96–1.08)</td>
<td>N.a.</td>
</tr>
<tr>
<td>Thrombolytics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During MI</td>
<td>58,600</td>
<td>0.82 (0.77–0.87)</td>
<td>N.a.</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After MI</td>
<td>17,187</td>
<td>0.75 (0.71–0.79)</td>
<td>N.a.</td>
</tr>
<tr>
<td>Abciximab*</td>
<td>2,399</td>
<td>0.43 (0.19–0.97)</td>
<td>N.a.</td>
</tr>
<tr>
<td>Oral anticoagulants**</td>
<td>10,056</td>
<td>0.78 (0.69–0.87)</td>
<td>N.a.</td>
</tr>
<tr>
<td>Heparin***</td>
<td>5,130</td>
<td>0.90 (0.62–0.90)</td>
<td>N.a.</td>
</tr>
<tr>
<td>PTCA****</td>
<td>2,606</td>
<td>0.66 (0.46–0.94)</td>
<td>N.a.</td>
</tr>
</tbody>
</table>

* After coronary stenting  
** Significant reduction in mortality in high intensity oral anticoagulant therapy defined as INR > 2.8  
*** Overall data (high and low dosage) in the absence of aspirin  
**** PTCA vs. thrombolytic therapy  
--- Death from all causes tested as one of more combined parameters accounting for the study’s primary endpoint

** The ESC Task Force report [6] included a separate table summarising the effects on sudden death of drugs considered to have direct cardiac electrophysiologic effects. Beta-blockers were the only class to show any beneficial effect on risk of sudden death. Only in patients with confirmed heart failure – a group largely absent from GISSI-Prevenzione – did the effect size of the risk reduction with beta-blockers compare favourably with that achieved in GISSI-Prevenzione: in less selected post-MI populations the benefit of beta-blockade was only about half of that seen with highly purified omega-3 PUFAs. These are in themselves striking comparisons that highlight the potential impact of highly purified omega-3 PUFAs post-MI. When, in addition, it is recalled that all the other classes of electrophysiologically active drugs considered by the ESC Task Force had either no effect or substantially increased the risk for sudden death it becomes apparent that highly purified omega-3 PUFAs therapy addresses successfully an important aspect of post-MI therapy that otherwise has been resistant to medical manipulation.

** How do Omega-3 PUFAs Save Lives Post-MI?**

The current view of how omega-3 PUFAs prevent sudden death is conveyed in the statement "... DHA or EPA ... protects the heart cell locally from participating in the genesis and propagation of ventricular tachycardia, which can result in cardiac arrest and sudden death. This protective effect ... depends on the unique ability of these n-3 fatty acids [omega-3 PUFAs] to stabilize all contractile heart cells electrically..." [30]. In short, these agents act at the level of the cardiomyocytes to reduce susceptibility to arrhythmogenesis.

There is abundant evidence that omega-3 PUFAs exert multiple actions potentially relevant to secondary prevention, including competitive inhibition of the production of thromboxane A2 and leukotriene B4 [31], inhibition of platelet aggregation [32] and thrombus formation [33–35], and inhibition of local inflammatory processes implicated in plaque rupture, including expression of endothelial adhesion molecules and leukocyte chemotaxis [36]. The pharmacology of omega-3 PUFAs is characterised by dose-dependence, however, and the actions described are reliably demonstrated only at doses several times larger than the 1 g/day used in GISSI-Prevenzione. Even then the scale of the effects does not always compare especially favourably with that of other secondary preventive agents. None of these effects can therefore be regarded as a plausible explanation for the survival benefit seen with highly purified omega-3 PUFAs in GISSI-Prevenzione. Similarly, there is no evidence that highly purified omega-3 PUFAs materially inhibit myocardial fibrosis or ventricular dilatation post-MI and hence no reason to ascribe the results of GISSI-Prevenzione to such a mechanism. It may also be noted that anti-remodelling effects have been documented with ACE inhibitors and beta-blockers and there is no basis for thinking that omega-3 PUFAs when used at a dose of 1 g/day would augment these effects to any clinically pertinent degree.

By contrast, anti-arrhythmogenic effects are seen when omega-3 PUFAs are used at this dose. Such actions, exerted ‘downstream’ from the development of ischaemia and fibrosis, may...
be expected to reduce the propensity to develop arrhythmia in the infarcted heart, with a commensurate impact on sudden death. This mechanism is consistent with preclinical observations and the clinical outcomes data of GISSI-Prevenzione, and identifies a unique position for highly purified omega-3 PUFAs in the spectrum of preventive therapy (Fig. 5).

Extensive investigation of the electrophysiological effects of omega-3 PUFAs supports the conclusion that these agents have anti-arrhythmic properties [37–53]. Useful reviews of research in this area have been published by Leaf and Kang [49–51]. Salient findings of this research may be summarised as follows:

- The anti-arrhythmic action of highly purified omega-3 PUFAs resides exclusively in the free acid form.
- The anti-arrhythmic action of highly purified omega-3 PUFAs cannot be attributed to limitation of infarct size in preclinical models.
- The anti-arrhythmic action of highly purified omega-3 PUFAs is due to molecule-specific inhibition of transmembrane ion channels; comparable effects are not seen with other fatty acids. Evidence for this inhibitory effect is most coherent for sodium channels [46], but potassium [52] and calcium channels [43] may also be targets for omega-3 PUFAs.

The primary effect of omega-3 PUFAs on these membrane channels is to prolong the inactivation state. Depolarisation thresholds are raised following exposure of cardiomyocytes to omega-3 PUFAs. Leaf and colleagues have proposed that this is achieved by location of omega-3 PUFAs molecules at key sites adjacent to the transmembrane channel. It is hypothesised that the orientation of omega-3 PUFAs within cell membranes brings the negatively charged carboxyl terminal into proximity with a positively charged region of the alpha-subunit of the ion channel [46, 51]. A more general alteration of the phospholipid arrangements in cell membranes appears to be excluded by the results of in vitro experiments which indicated that only a low (< 0.01) molar ratio of omega-3 PUFAs to phospholipid was required in sarcolemma for achieving electrical stabilisation [53]. The possibility that the microenvironment of ion channels is modified by the incorporation of omega-3 PUFAs cannot be excluded by these observations, but would not necessarily be incompatible with the theory of Leaf et al.

Future Directions

Study of heart rate variability (HRV) is likely to be a central theme in further research into the basis of the clinical outcomes of GISSI-Prevenzione. A detailed discussion of HRV is beyond the scope of the present review but, at risk of oversimplifying a complex topic, aspects of HRV relevant to the findings of GISSI-Prevenzione may be identified.

1. The term HRV refers to regular, repeated fluctuations in the ECG pattern, which may be quantified and expressed according to agreed definitions [54].
2. Low or reduced HRV is associated with poor prognosis and an increased risk for sudden death [55–58].
3. Several interventions associated with improved prognosis post-MI have also been linked with increases in HRV [56], including parenteral omega-3 PUFAs [59]; observational data also favour a role for omega-3 PUFAs in increasing HRV [eg 60, 61].

Some cautionary observations need to be added to this summary. HRV is generally considered to be a product of the interplay between the two domains of the autonomic nervous system and there is no comprehensive explanation of how omega-3 PUFAs might affect either sympathetic or parasympathetic activity. It is plausible, nonetheless that an increase in HRV may be one pathway through which omega-3 PUFAs may reduce the risk of arrhythmogenesis and thus prevent sudden death. It is also conceivable that measurement of changes in HRV may be a practical way to monitor the response to omega-3 PUFA therapy in the absence of a suitable widely available assay for the PUFA content of cell membranes.

A study is in preparation to investigate whether omega-3 PUFAs influence HRV and to relate any such changes to clinical status [62].

The benefits of omega-3 PUFAs in the prevention of sudden death may extend in both directions from the post-MI population studied in GISSI-Prevenzione. In the US Physicians’ Health Study, an epidemiological survey, a strong inverse correlation was shown between plasma levels of omega-3 PUFAs and risk of sudden death after 17 years of follow-up of men with no history of coronary disease [17]. These data hint at a possible role for omega-3 PUFAs in the prevention of sudden death in an unselected population with no defining clinical history. Such a possibility is currently being evaluated in a large clinical trial [14, 63].

Omega-3 PUFAs may also be expected to exert arrhythmia-preventing actions in patients with dilated hearts. Experimental observations indicate that enlargement of the ventricles is associated with the activation of ion channels and the emergence of heterogeneity of action potential duration, which may be expected to dispose toward arrhythmia even in the absence of detectable ischaemia. Certainly, absolute rates of sudden death in post-MI patients increase as ejection fraction declines, so an initiative directed at sudden death is highly desirable. This category of patients was largely excluded from GISSI-Prevenzione but a full-scale randomised trial of highly purified omega-3 PUFAs in patients with heart failure is being prepared and will provide important information about the clinical relevance of this therapy in heart failure [63].

Conclusions

The results of GISSI-Prevenzione identify highly purified omega-3 PUFAs as a substantial and important element in the medical management of patients who survive an MI. The treatment benefits, which include a reduction in all-cause mortality, are considerable and arise predominantly from a reduction in sudden death, which has proved resistant to other forms of medical intervention. Moreover, the treatment

![Figure 5](image_url)

**Figure 5.** Highly purified omega-3 PUFAs occupy a unique niche among post-MI medications, being the only therapy to target directly the electrical instability of the myocardium.
regimen is simple – a single 1 g capsule per day – and is associated with a notably low incidence and severity of side effects: the risk-benefit ratio for this treatment is unquestionably in favour of its widespread use in post-MI patients. The potential role of omega-3 PUFAs in secondary preventive therapies was recognised as relatively low risk for a study post-MI. Even so, the number needed-to-treat for 1 year to prevent one death (NNT) was low (164) and compares favourably with that of several established secondary preventive therapies. The NNT would become still smaller in a population with a higher absolute event rate. Health-economic considerations are also favourable to the use of omega-3 PUFAs [64]. There are thus persuasive, even compelling, reasons for omega-3 PUFAs to be used widely as an integral part of the management strategy for post-MI patients.

Two large clinical studies are being developed to investigate and define the role and application of omega-3 PUFAs in patients with overt cardiac dysfunction and in patients with no defining prior cardiac or coronary history [63]. The outcome of these studies may have a profound impact on the use of omega-3 PUFAs as well as revealing more about the epidemiology of sudden death in both these populations.

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