Review article

Statin alternatives or just placebo: an objective review of omega-3, red yeast rice and garlic in cardiovascular therapeutics

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Keywords: *statin; omega-3, red yeast rice; garlic; cardiovascular therapeutics*

Objective The aim of this review is to objectively access the trial evidence on the role of omega-3, red yeast rice and garlic in preventing clinical cardiovascular events. Given the large number of clinical trials favoring statin use in cardiovascular disease, it is important to see if evidence is available for these supplements and whether they could replace statin therapy.

Data source A PubMed search was conducted using the keywords 'trial, omega-3, red yeast rice, xuezhikang, garlic, cholesterol, cardiovascular, outcomes'; the resulting trials were reviewed together with the references quoted in the papers obtained.

Study selection The studies selected are prospective, randomized, placebo-controlled studies with predefined clinical cardiovascular end-points recruiting at least 2000 patients, with a follow-up over 2 years.

Results Modest dose omega-3 fatty acid has been shown in GISSI-P (11 324 patients, follow-up 3.5 years) to produce a reduction in sudden death of 45%, and in cardiac death of 35%, acting probably via an anti-arrhythmic effect. In JELIS (18 645 patients, follow-up 4.6 years), high dose omega-3 given to Japanese patients on a high fish diet and already on statin treatment produced further benefit with a 19% reduction of nonfatal cardiovascular outcomes; fatal cardiac events are not affected. CCSPS (4870 patients, follow-up 4 years), a secondary prevention trial using xuezhikang, a commercial red yeast rice preparation, produced a 46% reduction in nonfatal myocardial infarction and coronary death. There has been no trial to show that garlic reduces clinical cardiovascular outcomes. A rigorous trial with constant assessment of chemicals in the study material in 192 patients found that over a 6-month follow-up, raw garlic and 2 commercial preparations do not significantly affect lipid levels.

Conclusions Omega-3 in modest doses reduces cardiac deaths, and in high doses reduces nonfatal cardiovascular events. Red yeast rice reduces adverse cardiac events to a similar degree as the statins. It is unlikely that garlic is useful in preventing cardiovascular disease.

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Despite the overwhelming evidence favoring prescription drug therapy, the public is keen on herbal and dietary medicine, sales of which in the United States are estimated at $4 billion annually.[1] A telephone survey in 2002 revealed that 18.8% of 8470 subjects had used herbal or other natural products in the preceding week.[2] Over 20% of adults on prescription medication also use dietary supplements, although most do not report this to their doctors.[3] It is thus important that medical doctors objectively analyze the evidence on herbal and dietary medicine so that they can confidently guide patients in its usage. The evidence favoring statin therapy in preventing cardiovascular events is highly convincing, with over 200 000 patients randomized in prospective randomized controlled trials around the world.[4,5] To objectively assess the role of dietary products in cardiovascular disease, it is important to seek out similar prospective, randomized, long term trials with clinical end-points. Omega-3 fatty acids (eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)), red yeast rice (RYR) and garlic are chosen for this review since they are commercially available as oral supplements and have been promoted for their cardiovascular protective effects.

A three step PubMed search was conducted using the keywords: (1) 'trial, omega-3, cholesterol, cardiovascular, outcomes'; (2) "trial, red yeast rice, xuezhikang, cholesterol, cardiovascular, outcomes" and (3) 'trial, garlic, cholesterol, cardiovascular, outcomes'. The results were supplemented by reviewing references quoted in the papers obtained.

As there have been numerous well conducted large clinical statin trials, the studies on supplements should be of equivalent quality in order to be taken seriously. Thus, studies highlighted here are prospective, rigorously conducted, randomized, placebo-controlled trials with predefined clinical cardiovascular end-points recruiting at least 2000 patients, with a follow-up over 2 years. It is not the intention to perform a meta-analysis by statistically integrating the trials since to do a post-hoc analysis carries the risk of statistically manufacturing data when none exist. By objectively reviewing the individual clinical trials with an open mind, this paper seeks to

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derive practical lessons from their results.

OMEGA-3 FATTY ACIDS

Epidemiological evidence reveals that communities consuming large amounts of fish have lower cardiac deaths. The Japanese, who consume an average of one serving of fish per day, have a cardiac death rate of 2.5 per 1000 person-years, compared to a rate of 17 per 1000 person-years in Italians.[6] Within the same community, those eating more fish are better off. A 30-year follow-up in Chicago showed that men who consume 35 g or more of fish daily had a 38% lower risk of heart disease mortality.[7] Similarly, amongst 85 000 women followed for 16 years, those taking fish 2 to 4 times a week had a 31% lower risk of death from heart disease compared to those rarely eating fish.[8]

Randomized controlled trials on omega-3 supplements with clinical cardiovascular end-points suffer from poor methodology, inadequate follow-up or small numbers recruited. Two meta-analyses, each done by the same primary authors and pooling 48 trials with 36 913 patients, suggested that omega-3 fatty-acids are not useful in reducing clinical cardiovascular outcomes.[9,10] However, these meta-analyses did not differentiate between dietary intervention trials from those using oral omega-3 supplements. Significant heterogeneity was noted in the study design, background diet and end-point definition of the various studies pooled into the meta-analyses. A more rigorous meta-analysis reviewing only trials lasting over 1 year found omega-3 to reduce total mortality, myocardial infarction (MI) and sudden cardiac death for both secondary (11 trials, 19 403 patients) and primary prevention (1 trial, 13 578 patients).[11] There appears to be sound logic in the recommendations of healthcare societies for cardiac patients to consume 1 g DHA and EPA daily.[12,13]

In the GISSI-Prevenzione trial, 11 324 patients who recently had a MI were randomized daily to 1 g omega-3, 300 mg vitamin E, both or none and followed up for 3.5 years.[14] The primary end-point was death, non-fatal MI and non-fatal stroke. In comparing the 2836 patients only on omega-3 with the 2828 controls, treatment significantly reduced the primary end-point (*RR* 0.85, 95%*CI* 0.74–0.98), total mortality (0.80, 0.67–0.94) and cardiovascular death (0.70, 0.56–0.87). Trigyceride levels of patients on omega-3 decreased significantly compared to controls (–3.4% vs +1.4%, *P*=0.0001). Vitamin E had no significant effect on lipid levels or outcomes. The Japanese JELIS trial recruited 18 645 hyper-cholesterolemic patients and randomized 9326 to 1.8 g of EPA as well as 10–20 mg pravastatin or 5–10 mg simvastatin, with the control group of 9319 receiving just statin treatment.[15] After a mean follow-up of 4.6 years, EPA supplement significantly reduced unstable angina (0.76, 0.62–0.95, *P*=0.014) and non-fatal coronary events (0.81, 0.68–0.96, *P*=0.015) leading to a significant reduction of the primary end-point of major coronary events (0.81, 0.69–0.95, *P*=0.011). This study is especially relevant in demonstrating that omega-3 has an additive protective effect even in patients already on stain therapy. Furthermore, it shows that even when fish consumption is high, supplementation adds further cardiovascular protection. There was no difference in the total, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol levels in the two groups, although triglycerides were significantly lower in the EPA group compared to control (change from baseline –9% vs –4%, *P* <0.0001).

There is some evidence that omega-3 can effect the atherosclerotic process. An angiographic study on 233 patients given omega-3 supplements (6 g/d for 3 months and then 3 g/d for 21 months) found treatment to significantly reduce coronary atherosclerosis progression and induce more regression compared to those on placebo.[16] Clinical cardiovascular events occurred in 2 patients on omega-3, and 7 in the placebo group, a difference which did not reach statistical significance (*P*=0.10). Triglycerides were lower in the omega-3 group, although LDL cholesterol was elevated. A meta-analysis of different anti-lipidemic agents involving 97 studies, with 276 116 patients found that only statins and omega-3 significantly reduced total mortality (statins 0.87, 0.81–0.94; omega-3 0.77, 0.63–0.94) and cardiac mortality (statins 0.78, 0.72–0.84; omega-3 0.68, 0.52–0.90).[17] This occurred despite the fact that total cholesterol was not altered with omega-3 treatment, unlike the case with statins. Thus, cardiovascular protection from omega-3 is probably not related to its influence on lipid levels. Omega-3 reduces sudden cardiac death in patients with a prior MI, and also in healthy individuals.[18,19] As this protection comes on early and with low dose supplements, it has been attributed to an anti-arrhythmic effect produced when the ratio of n-3 to n-6 polyunsaturated fatty acid is elevated.[20] High doses also appear to reduce cardiac events, but mainly nonfatal events, raising the possibility of omega-3 having an effect on the atherosclerotic lesion, whether through anti-inflammatory or plaque regression consequences.[16,21]

The lessons from the two clinical omega-3 trials

Table 1 shows that the reduction in primary end-point in GISSI-P of 15% (*P* = 0.023) was driven by the reduction in cardiac death of 35% (*P* <0.001) and in sudden death of 45% (*P* <0.001); there was no reduction in nonfatal cardiovascular events (*RR* 0.96, 95%*CI* 0.76–1.21).[18] The marked reduction in sudden death and cardiac death suggests that a daily modest dose of 1 g omega-3 prevents mortality via an anti-arrhythmic effect. As total and LDL cholesterol levels in both the placebo and omega-3 groups rose during this trial, treatment with omega-3 does not have a significant impact on lipid levels and does not exert a statin-like action.

All patients in JELIS were also on statins and so the

Table 1. Clinical outcomes in the GISSI-Prevenzione trial: highly significant reduction in coronary mortality with no reduction of non-fatal MI with low dose omega-3 (1 g) daily

Variables	*RR*	95% *CI*	*P* value
Primary end point*	0.85	0.74–0.98	0.023
Non-fatal CV events	0.91	0.70–1.18	0.473
Cardiac death	0.65	0.51–0.82	0.001
Sudden death	0.55	0.39–0.77	0.001

*Primary end point: composite of death, non-fatal MI & non-fatal stroke. CV: cardiovascular.

protection demonstrated with omega-3 is additive to that obtained from statin therapy alone. JELIS used a high dose regime of 1.8 g omega-3, in a Japanese population that already has a high baseline serum omega-3 levels from high fish consumption.[22] Amongst controls, cardiac death rate per 1000 person-years was 17 in GISSI-P but only 2.5 in JELIS.[6] This lower cardiac death rate in the JELIS control is due to the higher fish consumption amongst the Japanese, and is compatible with the trial results of GISSI-P which show omega-3 supplement to reduce sudden death. In the JELIS trial, there was a lowering of non-fatal cardiac events in patients on the high dose omega-3 regime (Table 2). Thus, high dose omega-3 still provides further additive cardiovascular protection, against non-fatal outcomes. Although there is a fear of mercury contamination from high fish ingestion, it has been suggested that the benefit from fish and omega-3 intake is more than any potential adverse effect arising from contaminants.[23]

Table 2. Equivalent primary end-point reduction in GISSI-P and JELIS trials

Variables	GISSI-P	JELIS
Number of patients	11 324	18 645
Follow-up (years)	3.5	4.6
Dose of omega-3 (g)	1	1.8
Primary end-point (*RR* (95% *CI*))*	0.85	0.81
	(0.74–0.98)	(0.69–0.95)
Non-fatal cardiac events (*RR* (95% *CI*))	0.96	0.81
	(0.76–1.21)	(0.68–0.96)
Cardiac death (*RR* (95% *CI*))	0.65	1.06
	(0.51–0.82)	(0.55–2.07)

GISSI-P: Gruppo Italiano per lo Studio della sopravvivenzanell' Infarto. Miocardico-Prevenzione. JELIS: Japan EPA Lipid Intervention Study. *Primary end-point in GISSI-P: death, non-fatal myocardial infarction (MI), non-fatal stroke. Primary end-point in JELIS: major coronary event including sudden cardiac deaths, fatal and non-fatal MI, unstable angina, angioplasty, stenting and bypass grafting.

RED YEAST RICE (RYR)

RYR is the fermented product obtained after red yeast (*Monascus purpureus*) is grown on rice. It had been used in China for centuries as a food flavoring as well as a medicinal product.[24] Recent studies have shown RYR to contain lovastatin, amongst other possibly useful compounds, and numerous studies have suggested a beneficial lipid lowering effect from commercial preparations of this traditional supplement.[24-27] In a meta-analysis involving 9625 patients in 93 randomized trials, 3 different commercial preparation of RYR produced a mean reduction in total cholesterol of 0.91 mmol/L, LDL-cholesterol of 0.73 mmol/L, triglyceride of 0.41 mmol/L and a mean rise in HDL-cholesterol of 0.15 mmol/L.[28]

A large, randomized, placebo-controlled trial with clinical end-points involving xuezhikang, a commercial RYR preparation, has produced impressive results comparable to the statin studies.[29] The China Coronary Secondary Prevention Study (CCSPS) recruited 4870 patients with a prior MI and baseline cholesterol between 4.40–6.47 mmol/L. They were randomized to xuezhikang 0.6 g twice daily or matching placebo and followed for a mean of 4 years. The primary end-point of non-fatal MI and fatal coronary events was significantly reduced in the treatment group (0.54, 0.44–0.66, P <0.0001). Cardiovascular mortality (0.68, 0.52–0.88, P=0.0048) and total mortality (0.66, 0.52–0.82, P=0.0003) were also significantly reduced. Changes in plasma lipids were less impressive, with a reduction in total cholesterol of 10.3%, LDL-cholesterol of 14.7% and a rise in HDL-cholesterol of 4.2%. The calculated number needed to treat (NNT) to prevent a primary end-point over the trial duration is 21; this is comparable to the NNT in the various secondary prevention statin trials that range from 19 to 56.[30] This marked clinical event reduction with xuezhiang treatment, occurring despite only modest lipid level changes, is in keeping with an analysis of the AFCAPS-TEXCAPS trial using lovastatin which found on-treatment LDL-cholesterol to be unrelated to risk of clinical cardiovascular outcomes.[31] Subsequent sub-group analyses of CCSPS, published in the English medical literature, confirm the reduction of cardiovascular outcomes amongst diabetics and in the elderly.[32,33]

Trials outside China have also shown the lipid lowering and anti-inflammatory properties of xuezhikang.[34] It is tempting to attribute the cardiovascular benefit of RYR to lovastatin, since all preparations contain this clinically proven useful statin. Yet only 0.8% of xuezhikang is lovastatin.[35] Thus in CCSPS, the treated group received about 10 mg of lovastatin daily, well below the dose of 20–40 mg used in the AFCAPS-TEXCAPS trial. It may well be that other manocolins present in xuezhikang also have cardio-protective effects, in addition to that produced by lovastatin (manocolin K). It has been shown that the cardioprotective effect of statins in Japanese occurs at lower doses than in Western populations.[36-38] Thus it is also possible that the low dose 10 mg lovastatin found in xuezhikang is sufficient to produce the reduction of cardiac events amongst Chinese patients studied in the CCSPS trial.

Different commercial preparations of RYR have different concentrations of manocolins, and some even contain a toxic by-product of yeast fermentation, citrinin.[39] Before RYR can be routinely recommended for cardiovascular prevention, strict regulations have to be enforced to ensure that available products are standardized and

efficacious. Consumers feel that herbal products are safer than pharmaceutical drugs, but the reality may be that the unregulated usage of herbal products, with different manufacturers producing differing amounts of active and toxic constituents, is a far more risky practice.

GARLIC

Garlic (*Allium sativum*) use in cardiovascular therapeutics has an even longer history than RYR, with records dating back over 3000 years to ancient Egypt.[40] Numerous animal studies have shown garlic to have a cholesterol lowering effect, but human studies on the effects of garlic have produced inconsistent results.[41-44] A meta-analysis of 45 randomized trials had suggested that garlic may have a hypolipidemic effect at 3 months, but not at 6 months of usage.[45] However, the randomization, blinding and methodology of many of the trials reviewed were poor and there was inadequate definition of the specific biologically active constituent of the various forms of garlic ingested. The active chemical in garlic is allicin, which is produced when raw garlic is crushed, allowing the enzyme alliinase to act on the stable precursor alliin. Commercial garlic preparations have been found to produce unexpectedly low amounts of active allicin, and this could account for the absence of a demonstrable lipid lowering effect in some studies.[46]

A recent randomized trial sought to overcome these problems by including treatment with raw garlic, and extensively characterizing the chemicals in the garlic supplements used before and throughout the trial.[47] This Stanford University study recruited 192 patients with LDL-cholesterol between 3.36–4.91 mmol/L and randomized them to 1 of 4 treatment arms using raw garlic, powdered garlic (garlicin), aged garlic extract (Kyolic) or placebo. After 6 months, there was no significant difference in the LDL-cholesterol levels in the 4 groups (raw garlic +0.01 mmol/L, powdered garlic +0.08 mmol/L, aged garlic extract +0.005 mmol/L, placebo –0.10 mmol/L). There was also no difference in the HDL-cholesterol, triglycerides and total cholesterol-HDL ratio. This trial was well conducted with patient retention of nearly 90% in all arms, monthly blood lipid assay, assessment of the chemicals in the study material throughout the trial duration and patient adherence assessment by weekly logs and tablet count. Chemical characterization ensured that adequate levels of the active allicin were studied in the 3 treatment groups. In fact, the dosage used in the 2 commercial garlic supplements was several times above that recommended by the manufacturers. No serious adverse effects were noted in the groups using garlic, although bad odor was noted in over half those on raw garlic treatment.

It is pertinent to note that there has been no clinical cardiovascular event trial with garlic therapy, such as is available with omega-3 and RYR. The negative result from the Stanford study, together with the absence of any evidence of clinical event reduction, means that at present garlic treatment can not be recommended for hyperlipidemia or for patients at risk of cardiovascular events.

CONCLUSION

Results from large prospective placebo-controlled clinical trials must be analyzed seriously when judging the value of any treatment intervention. The two omega-3 trials have together recruited over 30 000 patients and confirm the value of both modest and high dose supplementation in reducing adverse cardiac events. Thus, it is reasonable to recommend 1–1.8 g omega-3 daily to reduce clinical cardiovascular events especially in patients with established ischemic heart disease. It is interesting to postulate that modest dose omega-3 reduces arrhthymic events, while higher doses may work via an anti-atherosclerotic process to reduce nonfatal events. However, more clinical trials or animal experiments are needed to test these hypotheses.

The CCSC trial showed that reduction of cardiovascular events in secondary prevention using the RYR preparation, xuezhikang, is equivalent to that obtained from the landmark 4S statin trial (Table 3). It is pertinent to ask whether the benefit of xuezhikang comes from the 10 mg lovastatin it contains especially since recent reports have shown that lower lipid levels reached with higher statin doses produce more reduction in cardiovascular outcomes.[48-52] However, a review of the AFCAPS-TEXCAPS trial, which also involved lovastatin, showed no correlation between on treatment LDL-cholesterol levels with clinical cardiovascular outcomes.[31] By reducing C-reactive protein and inflammation, statin therapy has been reported to reduce clinical cardiovascular events independent of the effect on lipid levels.[53,54] There is also good evidence that statins reduce endothelial dysfunction and enhance vasodilatation.[55,56] It could well be that lovastatin (manocolin K) acts more via non-lipid lowering mechanisms, thereby explaining the marked cardiovascular protection with modest lipid reduction. It may also be possible that the cardiovascular protection of RYR in fact arises from the other manocolins present, and not just from lovastatin. A third possibility is that Asians may indeed respond to lower statin doses than that used in the conventional trials with Caucasian patients.[36-38] Further trials are necessary to resolve these issues.

An objective review of the trial evidence confirms the value of omega-3 and RYR in reducing clinical cardiovascular events. The evidence favoring omega-3 is highly convincing but RYR could be more confidently recommended if another large randomized clinical trial, preferably in a non-Chinese population, could reproduce the results of CCSPS. Garlic probably does not significantly affect lipid levels and has no evidence supporting a role in reducing clinical outcomes. The trials have confirmed that supplements are safe, with

Table 3. The reduction in adverse clinical outcome with xuezhikang in CCSPS and 4S study

Variables	CCSPS	4S
Number of patients	4870	4444
Follow-up (years)	4	5.4
Study product	1.2 g xuezhikang	5 – 40 mg simvastatin
Primary end-point	CHD death non-fatal MI	total mortality
Relative risk (95% *CI*)	0.54 (0.44–0.66)	0.70 (0.58–0.85)
NNT	21	25
Change from baseline		
Total cholesterol	–13.2%	–25%
LDL cholesterol	–20.2%	–35%
Triglycerides	– 15%	–10%

CCSPS: China Coronary Secondary Prevention Study. 4S: Scandinavian Simvastatin Survival Study. CHD: coronary heart disease. MI: myocardial infarction. NNT: number needed to treat. LDL: low density lipoprotein.

an adverse effect profile similar to placebo. Nevertheless fears of mercury and industrial contamination of fish stock are increasing.[57,58] While proper purification processes may help ensure that prescription preparations are safer, both omega-3 supplements and RYR are widely available in non-prescription forms which may differ in content and impurities.[39,59] The involvement of regulatory bodies is needed to ensure that the standardization and manufacturing processes of herbal products are as strict as those with pharmacological drugs. Only then can these supplements have a routine role in clinical practice.

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