ORIGINAL ARTICLE

Simvastatin vs Therapeutic Lifestyle Changes and Supplements: Randomized Primary Prevention Trial

DAVID J. BECKER, MD; RAM Y. GORDON, MD; PATTI B. MORRIS, RD; JACQUELINE YORKO, MED; Y. JEROLD GORDON, MD; MINGYAO LI, PHD; AND NAYYAR IQBAL, MD, MSCE

OBJECTIVE: **To compare the lipid-lowering effects of an alternative regimen (lifestyle changes, red yeast rice, and fish oil) with a standard dose of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin).**

PATIENTS AND METHODS: **This randomized trial enrolled 74 patients with hypercholesterolemia who met Adult Treatment Panel III criteria for primary prevention using statin therapy. All participants were randomized to an alternative treatment group (AG) or to receive simvastatin (40 mg/d) in this open-label trial conducted between April 1, 2006, and June 30, 2006. The alternative treatment included therapeutic lifestyle changes, ingestion of red yeast rice, and fish oil supplements for 12 weeks. The simvastatin group received medication and traditional counseling. The primary outcome measure was the percentage change in low-density lipoprotein cholesterol (LDL-C). Secondary measures were changes in other lipoproteins and weight loss.**

RESULTS: **There was a statistically significant reduction in LDL-C levels in both the AG (–42.4%±15%) (*P*<.001) and the simvastatin group (–39.6%±20%) (*P*<.001). No significant differences were noted between groups. The AG also demonstrated significant reductions in triglycerides (–29% vs –9.3%; 95% confidence interval, –61 to –11.7; *P*=.003) and weight (–5.5% vs –0.4%; 95% confidence interval, –5.5 to –3.4; *P*<.001) compared with the simvastatin group.**

CONCLUSION: **Lifestyle changes combined with ingestion of red yeast rice and fish oil reduced LDL-C in proportions similar to standard therapy with simvastatin. Pending confirmation in larger trials, this multifactorial, alternative approach to lipid lowering has promise for a subset of patients unwilling or unable to take statins.**

Trial Registration: clinicaltrials.gov identifier: NCT0042

***Mayo Clin Proc.* 2008;83(7):758-764**

AG = alternative treatment group; CI = confidence interval; CK = creatine kinase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RYR = red yeast rice; TC = total cholesterol; TG = triglycerides

Overwhelming scientific evidence shows that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are beneficial to patients for primary prevention of coronary artery disease.[1] Although the safety of these medications is established,[2] adherence can be troublesome. As many as 40% of patients who receive a prescription for a statin are thought to take it for less than 1 year.[3,4] Possible reasons include the cost of these medications, adverse effects, poor explanations of their benefits by physicians, and patients' reluctance to take prescription or long-term medications.[5] It is difficult to estimate the number of patients who seek alternative therapies to statins, and most do not discuss this choice with their physicians.[6,7]

We have used a combination of fish oil and red yeast rice (RYR) as an alternative regimen for hyperlipidemia. This regimen is nonprescription, is readily available, and seems to be tolerated with few adverse effects. However, to date, no data show a benefit to patients.

The primary purpose of this study was to test whether an "alternative" regimen reduced serum low-density lipoprotein cholesterol (LDL-C) in a primary prevention population. Specifically, the efficacy and safety of RYR, fish oil, and therapeutic lifestyle changes (alternative regimen) was compared to those of a standard dose of a cholesterol-lowering agent (simvastatin, 40 mg/d) and traditional diet and exercise counseling.

PATIENTS AND METHODS

Patients were recruited from a cardiology practice in suburban Philadelphia, PA. The trial was approved by the Institutional Review Board of Chestnut Hill Healthcare, and written informed consent was obtained from all participants. All authors had complete access to the primary data.

Men and women aged 18 to 80 years with known or newly detected hypercholesterolemia were eligible for enrollment if they met the Adult Treatment Panel III guidelines.[8] Inclusion criteria included baseline LDL-C of 130 mg/dL or more (to convert to mmol/L, multiply by 0.0259) and 2 or more cardiovascular risk factors or baseline LDL-C between 160 and 210 mg/dL for patients with no or 1 risk factor. Risk factors included age (men >45 years or women >55 years or postmenopausal), hypertension requiring medical treatment, high-density lipoprotein cholesterol (HDL-C) less than 40 mg/dL, current cigarette smoking,

From the Division of Cardiology, Chestnut Hill Hospital, University of Pennsylvania Health System, Philadelphia (D.J.B., R.Y.G., P.B.M., J.Y.); Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA (Y.J.G.); Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia (M.L.); and Division of Endocrinology, Philadelphia VA Medical Center/University of Pennsylvania, Philadelphia (N.I.).

This study was sponsored by an unrestricted grant from the State of Pennsylvania.

Address reprint requests and correspondence to David J. Becker, MD, 1722 Bethlehem Pike, Flourtown, PA 19095 (dbeckerchcardiology@hotmail.com).

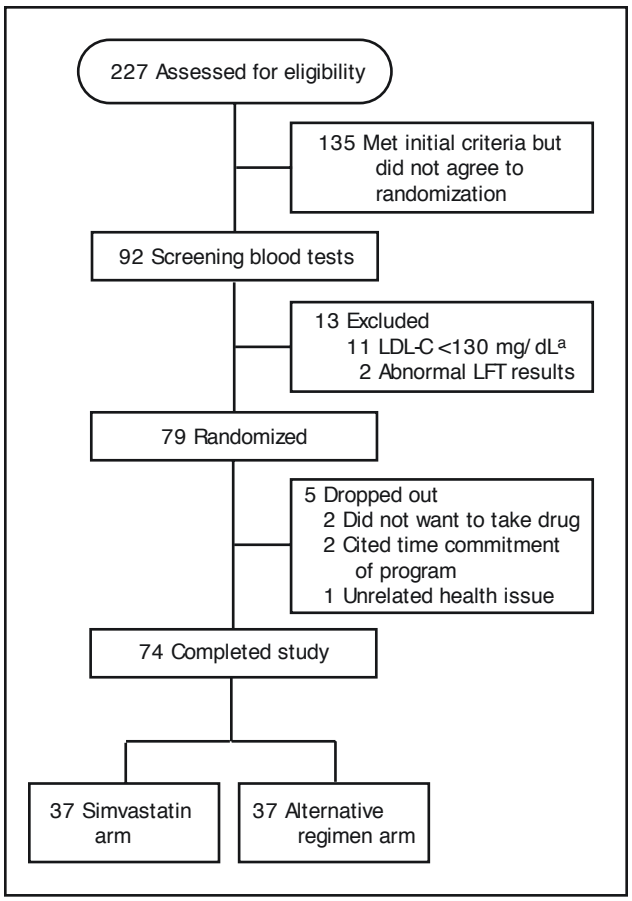

FIGURE. Flow of participants through trial. LDL-C = low-density lipoprotein cholesterol; LFT = liver function test.
[a] SI conversion factor: To convert LDL-C to mmol/ L, multiply by 0.0259.

diabetes mellitus, or family history of premature coronary artery disease.

Exclusion criteria included known coronary artery disease or a procedure to treat such disease (angina pectoris, myocardial infarction, percutaneous transluminal angioplasty, or coronary artery bypass grafting), triglyceride (TG) levels at baseline testing higher than 400 mg/dL, use of warfarin, severe liver or kidney disease, an orthopedic condition that would prevent aerobic exercise, or other systemic disease.

Randomization and Intervention

The flow of participants through the trial is shown in the Figure. Patients were recruited between December 1, 2005, and March 31, 2006. Of the 227 eligible patients, 135 met the initial screening criteria but chose not to participate. Ninety-two patients signed the informed consent form and were screened. Thirteen patients failed screening, most because LDL-C levels were less than 130 mg/dL. A total of 79 patients were eligible to be randomized to the treatment

TABLE 1. **Analysis of Fish Oil**[a]

Component	Quantity (mg/capsule)
Eicosapentaenoic acid (EPA)	351
Docosahexaenoic acid (DHA)	280
Fatty acids	1006
n-3 Polyunsaturated	747
n-6 Polyunsaturated	48
Monounsaturated	157
Saturated	54

[a] Two bottles of 200 capsules/bottle were sent for analysis.

phase. Before the trial began, 3 patients dropped out of the simvastatin group, and 2 patients dropped out of the alternative treatment group (AG). Of the 79 patients randomized, 74 were included in the analysis. By using a computer-generated simple randomization list, patients were allocated to either the simvastatin group or the AG. Men and women were separately randomized to ensure equal numbers in both groups. The study was conducted between April 1, 2006, and June 30, 2006. No patients were lost to follow-up.

Group 1 patients received simvastatin (40 mg/d) and traditional counseling regarding diet and exercise in the form of preprinted material. These handouts were based on American Heart Association diet and lifestyle recommendations. Group 2 received fish oil and RYR supplements. The fish oil (Res-Q 1250; N3 Oceanic, Palm, PA) was purchased directly from the manufacturer, and each patient took 3 capsules twice daily (Table 1). The RYR (Res-Q LDL-X, 600-mg [by weight] capsules, N3 Oceanic) was also purchased directly from the manufacturer. Each capsule had a total monacolin content of 5.3 mg, of which 2.53 mg was monacolin K (lovastatin) (Table 2). Two strengths of RYR were used. If the initial LDL-C measurement was higher than 160 mg/dL, a total dose of 3.6 g was given in 2 divided doses. If the initial LDL-C measurement was 160 mg/dL or less, a total dose of 2.4 g was given in 2 divided doses. No other medications were adjusted other than discontinuation of prestudy statin therapy.

Group 2 patients were also enrolled in a 12-week multidisciplinary lifestyle program that involved weekly $3^1/_2$-hour meetings. The group was taught about the importance of lifestyle changes by a board-certified cardiologist. Participants learned about coronary plaque formation, preventive measures, and standard cardiac testing techniques. In addition to the cardiologist, the team consisted of a dietitian, exercise physiologist, and several alternative or relaxation practitioners. A certified dietitian taught basic principles of nutrition and encouraged the group to follow a Mediterranean diet that was modified by reducing saturated fat and by limiting total fat to less than 25% of daily caloric intake. Sugars and simple carbohydrates were restricted, and participants were taught how to count calories,

TABLE 2. **Analysis of Red Yeast Rice**[a]

Component	Quantity (mg/capsule)
Total monacolins	5.3
Monacolin JA	0.0267
Monacolin J	0.00413
Monacolin XA	0.0558
Monacolin KA	1.96
Monacolin LA	0.0190
Monacolin X	0.0760
Monacolin K (lovastatin)	2.53
Monacolin L	0.122
Monacolin M	0.0285
Dihydromonacolin K	0.473
Other	
Citrinin	None detected (1000 ppm detection limit)

[a] Three bottles of 120 capsules/bottle were sent for analysis.

although there was no formal caloric restriction. An exercise physiologist instructed the group to gradually increase exercise to 5 to 6 times per week. Aerobic exercise was encouraged and included walking, swimming, or jogging for 30 to 45 minutes at a time. Patients in this group were exposed to relaxation methods including yoga and tai chi.

Adherence to the program was documented by the study coordinators at the weekly meetings. Patients in both treatment groups received a 30-day supply of medication at each of 3 monthly visits, and pill counts were performed to ascertain adherence. Although the 2 groups ran concurrently, there was no contact between them during the study.

Outcomes and Follow-up

The primary efficacy parameter was percentage change from baseline levels of LDL-C. The secondary parameters included percentage change from baseline levels of HDL-C and TG at 12 weeks. A fasting blood sample was drawn from all study participants for lipid profile, liver function tests, and creatine kinase (CK) levels at baseline and at the end of the study (week 12). If patients in either group experienced severe muscle pain during the study, CK level was obtained, and supplements or simvastatin was withheld for 2 days until the laboratory result was available. The dose of simvastatin or RYR was halved if patients continued to experience symptoms but had a normal CK level.

Laboratory Analyses

Serum laboratory analyses were performed by Laboratory Corporation of America (LabCorp, Burlington, NC). The lipid panel (total cholesterol [TC], LDL-C, HDL-C, and TG) and serum glucose levels were determined enzymatically.

Laboratory analysis of the fish oil (Table 1) and RYR capsules (Table 2) was performed by ConsumerLab (www.consumerlab.com, White Plains, NY). We provided the testing facility with 400 capsules of fish oil and 360 capsules of RYR. The commercial laboratory randomly selected 20 capsules of each product, made this sample into a single composite, and then analyzed the composite for total content of each chemical. The results were then calculated and reported to us on a per capsule basis (Tables 1 and 2). Variability estimates for these samples based on how the facility performed its analysis are unavailable.

The fish oil capsules were assessed by gas chromatography. The RYR was tested for its amount of individual and total monacolins by high-performance liquid chromatography. Citrinin was analyzed using thin-layer chromatography. The identity of the products was not disclosed to the laboratory that performed the testing.

Statistical Analyses

The primary end point was percentage change of LDL-C from baseline levels. A sample of 35 patients was required for each group for an 80% power and an α level of .05 to detect a 20% difference in the percentage change between the 2 groups assuming an SD of 30%.

Statistical analyses included mean ± SD of baseline characteristics by treatment group, a between–treatment group comparison at baseline, a within–treatment group comparison for the percentage change from baseline, and a between–treatment group comparison for the percentage change from baseline for all variables. The between–treatment group comparison at baseline was performed using a 2-sample *t* test, and the within–treatment group comparison at baseline and at week 12 was performed using a 1-sample *t* test. Multiple linear regression, with treatment group included as a factor and adjusting for baseline weight, was used for between–treatment group comparison. Analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC). All tests were 2-sided; $P<.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Baseline characteristics of patients randomized to each group are shown in Table 3. There were 20 women and 17 men in each treatment group. Fifteen patients (41%) in the simvastatin group and 12 patients (32%) in the AG were receiving a statin (which was stopped at least 30 days before initial blood testing and randomization) before the study. The mean age was 55.9±8.4 years in the AG and 59.3±9.6 years in the simvastatin group. No statistically significant differences between the baseline groups were apparent other than borderline significance of weights. The

TABLE 3. **Baseline Characteristics by Treatment Group**[a]

Variable	Alternative (n=37)	Simvastatin (n=37)	*P* value
Age (y)	55.9±8.4	59.3±9.6	.11
Weight (kg)	87.7±15.5	80.8±14.6	.05
Body mass index[b]	30.0±5.0	28.0±5.2	.09
Hip circumference (cm)	111.5±11.3	109.6±11.2	.47
Waist circumference (cm)	101.4±12.9	97.5±12.6	.20
Blood pressure (mm Hg)			
Systolic	132.8±16.6	127.1±12.1	.10
Diastolic	80.9±9.3	78.6±7.7	.27
Fasting glucose (mg/dL)[c]	101.4±21.6	101.8±26.0	.94
Lipids (mg/dL)[d]			
Total cholesterol	238.5±25.6	241.2±28.4	.67
LDL-C	154.2±22.5	157.1±23.5	.59
HDL-C	56.8±13.0	59.6±13.7	.36
LDL-C/HDL-C	2.9±0.9	2.8±0.8	.50
Triglycerides	137.5±69.7	121.5±67.8	.32
Creatine kinase (U/L)	143.5±109.4	129.5±63.4	.50

[a] Data are expressed as mean ± SD unless otherwise indicated. LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.
[b] Calculated as the weight in kilograms divided by the height in meters squared.
[c] SI conversion factor: To convert glucose value to mmol/L, multiply by 0.055.
[d] SI conversion factor: To convert cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride value to mmol/L, multiply by 0.0113.

mean weight in the AG was 87.7±15.5 kg, and in the simvastatin group, 80.8±14.6 kg (95% confidence interval [CI], –0.1 to 14.0; *P*=.05). Because of this difference, we adjusted for baseline weight when comparing the lipid, blood pressure, and glucose levels after treatment in the AG and simvastatin group.

Effects on Plasma Lipids and Lipoproteins

Table 4 shows the changes from baseline in the 2 treatment groups. Weight decreased by 4.7±2.4 kg (–5.5%) in the AG (*P*<.001) and by 0.3±2.2 kg (–0.4%) in the simvastatin group (*P*=.42). Mean difference between the 2 groups was –4.4 kg (95% CI, –5.5 to –3.4 kg; *P*<.001). Body mass index also decreased significantly more in the AG than in the simvastatin group (95% CI, –1.9 to –1.2; *P*<.001). No significant differences in systolic blood pressure (95% CI, –7.0 to 7.2 mm Hg; *P*=.59), diastolic blood pressure (95% CI, –6.1 to 4.0 mm Hg; *P*=.89) or fasting glucose (95% CI, –11.2 to 5.2 mg/dL; *P*=.57) appeared between the groups.

In the AG, all lipid values except HDL-C declined significantly from baseline. (TC, –78.5±32.6 mg/dL [–32.4%±11.8%]; *P*<.001; LDL-C, –66.8±28.9 mg/dL [–42.4%±14.8%]; *P*<.001; and TG, –50.8±65.1 mg/dL [–29.2%±36.3%]; *P*<.001) In the simvastatin group, all lipid values except HDL-C declined significantly from baseline (TC, –66.5±36.8 mg/dL [–27.3%±14.9%]; *P*<.001; LDL-C, –63.7±33.5 mg/dL [–39.6%±20.2%; *P*<.001; TG, –14.4±37.8 mg/dL; –9.3%±30.9%; *P*=.03). The HDL-C level decreased 2.9±9.7 mg/dL (–4.3%±16.3%; *P*=.08) in the AG and increased 0.4±6.3 mg/dL (+1.4%±11.0%; *P*=.70) in the simvastatin group. The difference between groups was not statistically significant (95% CI, –7.1 to 0.5; *P*=.21).

Between-group analysis revealed a reduction in LDL-C of 3.1 mg/dL greater in the AG than in the simvastatin group that was not statistically significant (95% CI, –17.6 to 11.4; *P*=.59). There was also no significant difference in

TABLE 4. **Change of Variables From Baseline by Treatment Group**[a]

	Alternative (n=37)			Simvastatin (n=37)			Comparison of groups	
Variable	Change from baseline	% change	*P* value	Change from baseline	% change	*P* value	Mean difference (95% CI)	*P* value
Weight (kg)	–4.7±2.4	–5.5±2.8	<.001	–0.3±2.2	–0.4±2.7	.42	–4.4 (–5.5 to –3.4)	<.001
Body mass index[b]	–1.6±0.9	–5.5±2.8	<.001	–0.1±0.8	–0.4±2.7	.52	–1.5 (–1.9 to –1.2)	<.001
Hip circumference (cm)	–4.0±5.5	–3.4±4.7	<.001	–1.3±2.6	–1.2±2.4	.005	–2.7 (–4.6 to –0.6)	.02[c]
Waist circumference (cm)	–4.3±5.4	–4.3±4.9	<.001	–1.8±3.1	–1.7±3.1	.002	–2.5 (–4.6 to –0.5)	.02[c]
Blood pressure (mm Hg)								
Systolic	–6.9±14.6	–4.2±11.4	.007	–7.0±16.0	–5.5±13.0	.01	0.1 (–7.0 to 7.2)	.59[c]
Diastolic	–6.9±11.4	–7.5±13.3	.001	–5.8±10.4	–7.1±12.9	.02	–1.1 (–6.1 to 4.0)	.89[c]
Fasting glucose (mg/dL)[d]	–1.1±18.6	0.9±20.4	.72	1.8±16.5	2.0±17.8	.51	–3.0 (–11.2 to 5.2)	.57[c]
Lipids (mg/dL)[e]								
Total cholesterol	–78.5±32.6	–32.4±11.8	<.001	–66.5±36.8	–27.3±14.9	<.001	–12.1 (–28.2 to 4.1)	.15[c]
LDL-C	–66.8±28.9	–42.4±14.8	<.001	–63.7±33.5	–39.6±20.2	<.001	–3.1 (–17.6 to 11.4)	.59[c]
HDL-C	–2.9±9.7	–4.3±16.3	.08	0.4±6.3	1.4±11.0	.70	–3.3 (–7.1 to 0.5)	.21[c]
Total cholesterol/HDL-C	–1.3±1.0	–28.0±17.6	<.001	–1.2±0.9	–27.8±15.4	<.001	–0.1 (–0.5 to 0.4)	.73[c]
Triglycerides	–50.8±65.1	–29.2±36.3	<.001	–14.4±37.8	9.3±30.9	.03	–36.4 (–61.1 to –11.7)	.003[c]

[a] Data are expressed as mean ± SD unless otherwise indicated. LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.
[b] Calculated as the weight in kilograms divided by the height in meters squared.
[c] Groups are compared by adjusting for baseline weight.
[d] SI conversion factor: To convert glucose value to mmol/L, multiply by 0.055.
[e] SI conversion factor: To convert cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride value to mmol/L, multiply by 0.0113.

the ratio of TC to HDL-C (95% CI, –0.5 to 0.4; *P*=.73). However, there was a significant decrease in TG in the AG compared with the simvastatin group, with a mean difference between groups of –36.4 mg/dL (95% CI, –61.1 to –11.7; *P*=.003)

Adherence

Adherence was excellent, and there were no dropouts in either arm. Average attendance of study participants was 90% at each of the lifestyle sessions, and adherence and adverse effects were reported to the study coordinator using standard adverse reporting forms.

Safety and Adverse Events

In the simvastatin group, 3 patients experienced musculoskeletal symptoms. One completed the protocol, taking 40 mg of simvastatin daily until the end of the study. Two patients stopped their simvastatin regimen for 3 days, per protocol. Their CK levels were normal, and they completed the study taking 20 mg/d. One patient had transaminase elevations that were more than 2 times the upper limit of normal on the 12-week blood sample and reported generalized fatigue but completed the protocol.

In the AG, one patient had a baseline CK level of 232 U/L, which increased to 1532 U/L on routine testing at the completion of the study. He was completely asymptomatic, was engaged in vigorous exercise the night before his blood test, and was taking 3 capsules of RYR twice daily. After the study was completed, medication and exercise were stopped, and his CK level returned to normal. Two patients noted heartburn that resolved when they were switched to equivalent doses of a liquid form of fish oil (ResQ 1250 liquid) from the same manufacturer.

DISCUSSION

The primary purpose of this clinical trial was to compare the effects of an alternative regimen (a combination of RYR, fish oil, and therapeutic lifestyle changes) with the effects of a standard dose of a statin and traditional diet and exercise counseling on LDL-C levels. We observed a similar reduction in serum LDL-C levels in both groups. Members of the AG also had a substantial reduction in TG and lost more weight. The ratio of TC to HDL-C decreased equally in both groups. Finally, the HDL-C decreased in the AG and increased slightly in the simvastatin group, but this difference was not statistically significant.

Last year, 18.9% of US adults used natural products with unproven efficacy,[9] many taken without their physician's knowledge or consent. Alternative therapies for hyperlipidemia that have been studied and remain controversial include policosanol, chromium, eggplant extract, garlic, and guggulipids.[10-15] If these results are confirmed in larger trials, the regimen used in this trial (although demanding in terms of commitment and cost) could offer an option for patients who refuse therapy with statins.

Red yeast rice, also called hong qu, is a Chinese herbal medication first described in the Tang Dynasty in 800 AD. It is made by fermenting the yeast *Monascus purpureus* over red rice and is both a garnish for food and a traditional medication. Red yeast rice contains naturally occurring lovastatin and 9 different substances called monacolins that could inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase. Results of the current study support findings from previous studies with RYR that demonstrated a positive effect.[15-17] The dose of RYR in our study (2.4-3.6 g/d) was equivalent to a daily lovastatin dose of 10 to 15 mg (Table 2), less than the established therapeutic dose (20-40 mg).[16]

Fish oil has been reported to decrease the risk of death, cardiac death, and coronary events in patients who have had myocardial infarction.[17,18] It might have an antiarrhythmic effect,[19] and recent reviews have shown no increased risk of bleeding.[20,21] The TG-lowering effects of fish oil have been established[22] and could be responsible for the results observed in the current study. Weight loss could also have contributed to the significantly lower TG levels in the AG.[23]

Lifestyle changes (eg, Mediterranean diet,[24,25] exercise,[26] and weight loss[27,28]), an important aspect of the current trial, are likely multifactorial and have been shown to reduce the risk of recurrent cardiac events. In our study, blood pressure decreased significantly in both groups. This effect was expected in the AG, which lost weight and engaged in exercise, but was somewhat unexpected in the simvastatin group, which was randomized to usual care. A recent review suggested that statins have a beneficial effect on blood pressure, although the mechanism is unknown.[29] Limitations of the current trial include brief course (12 weeks), single site, unblinded (design precluded effective masking), and limited scope. The design of the trial also prevented delineation of the relative contribution of each component of the alternative therapy. Thus, we were unable to evaluate the lipid-lowering effects of the therapeutic lifestyle changes alone, without the supplements. Larger future studies should address these issues. Nevertheless, the study was randomized, had no dropouts, had excellent adherence in both groups, and yielded statistically significant changes in unambiguous outcome measures—serum LDL-C levels and weight loss. Additional concerns in the AG included elevated CK values in 1 asymptomatic patient (attributed to vigorous exercise,[30] the statinlike properties of RYR, and their enhanced effect in combination[31,32]) and the possible HDL-C–lowering effects of RYR. We expected the HDL-C to increase in the AG because members

adopted an exercise program. The unexpected, but not statistically significant, reduction in HDL-C levels could be partially explained by the diet followed by our patients that was low in saturated fats.[33,34] The decrease in HDL-C levels could have been related to the supplements. Despite the small decrease in HDL-C levels, the ratio of TC to HDL-C (an excellent index of cardiac risk)[35-37] decreased equally in both groups.

Our study was designed to test a comprehensive and holistic approach to lipid lowering. The excellent adherence in the AG was undoubtedly related to the intensive follow-up, education, and support provided for this group. Long-term adherence to the alternative regimen remains to be determined, but previous studies involving diet and exercise have unfortunately found a high rate of recidivism.[38-40]

Another possible limitation of the study is the legal status of RYR as an herbal supplement. In 2001, the US Food and Drug Administration determined that the RYR product Cholestin was a drug, not a dietary supplement, and asked companies to reformulate products to remove RYR.[41] In fact, since completion of the current study, N3 Oceanic has replaced the RYR in Res-Q LDL-X with a "phytosterol ester complex and policosanol." Policosanol was recently found to be no better than placebo in reducing lipid levels.[10]

However, RYR remains widely available in stores and on the Internet. Although the chemical composition of RYR was known and controlled in the current study, composition of various products and the batch consistency between lots from the same source make recommending unregulated supplements difficult. Heber et al[42] found varying levels of monacolins in different preparations of RYR and suggested standardized manufacturing practices to ensure equivalence of active ingredients. We concur that there is an ongoing need for the Food and Drug Administration to address regulation of nutritional supplements.

Taking RYR without a physician's supervision could also have unknown risks. The lovastatinlike component could cause myopathy or transaminase elevations, and a potentially dangerous metabolite, citrinin, can form in poorly manufactured preparations. Further, the safety of combining RYR and fish oil has not yet been studied in a large population.

A final issue with our study concerns the association of lipid lowering with cardiovascular outcomes. Statin drugs have a beneficial effect on lipid levels but also decrease cardiovascular events and mortality because of their pleiotropic effects (ie, improved endothelial function, antithrombotic and antioxidant effects, anti-inflammatory properties, and stabilization of atherosclerotic plaque).[43,44] Although the alternative regimen in this study lowered LDL-C similarly compared with simvastatin, we have no evidence that our regimen will lead to a reduction in cardiovascular events. The recent Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial showed that size of reductions in LDL-C levels was not necessarily associated with rate of progression in vascular disease.[45] Our small, short-term study did not and could not evaluate reduction in cardiovascular morbidity and mortality, which is clearly the most important outcome.

CONCLUSION

In this single-center, small, randomized study, RYR and fish oil (when taken with a commitment to make lifestyle changes) had LDL-C lowering effects similar to those of a standard dose of simvastatin. In addition, the lifestyle modification arm showed significant reductions in TG and weight. These results are intriguing and show a potential benefit of an alternative, or naturopathic, approach to a common medical condition, hyperlipidemia. A larger, multicenter trial with longer follow-up is necessary, and the effects on cardiovascular outcomes will need to be established in the future. The risks of this alternative therapy need to be balanced against a possible therapeutic benefit for a subset of motivated patients who are willing to adopt strict lifestyle changes and take over-the-counter supplements.

REFERENCES

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7-22.

2. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation*. 2006 Dec 19;114(25):2788-2797. Epub 2006 Dec 11.

3. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA*. 1998;279(18):1458-1462.

4. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Med J Aust*. 1996;164(4):208-211.

5. Braunstein JB, Cheng A, Cohn G, Aggarwal M, Nass CM, Blumenthal RS. Lipid disorders: justification of methods and goals of treatment. *Chest*. 2001;120(3):979-988.

6. Dalen JE. "Conventional" and "unconventional" medicine: can they be integrated [editorial]? *Arch Intern Med*. 1998;158(20):2179-2181.

7. Kessler RC, Davis RB, Foster DF, et al. Long-term trends in the use of complementary and alternative medical therapies in the United States. *Ann Intern Med*. 2001;135(4):262-268.

8. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497.

9. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data*. 2004 May 27;343:1-19.

10. Berthold HK, Unverdorben S, Degenhardt R, Bulitta M, Gouni-Berthold I. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. *JAMA*. 2006;295(19):2262-2269.

11. Knox J, Gaster B. Dietary supplements for the prevention and treatment of coronary artery disease. *J Altern Complement Med*. 2007;13(1):83-95.

12. Szapary PO, Wolfe ML, Bloedon LT, et al. Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial. *JAMA*. 2003;290(6): 765-772.

13. Praca JM, Thomaz A, Caramelli B. Eggplant (*Solanum melongena*) extract does not alter serum lipid levels. *Arq Bras Cardiol*. 2004 Mar;82(3): 269-276. Epub 2004 Apr 5.

14. Caron MF, White CM. Evaluation of the antihyperlipidemic properties of dietary supplements. *Pharmacotherapy*. 2001;21(4):481-487.

15. Ulbricht C, Basch E, Szapary P, et al. Guggul for hyperlipidemia: a review by the Natural Standard Research Collaboration. *Complement Ther Med*. 2005 Dec;13(4):279-290. Epub 2005 Sep 23.

16. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: two-year efficacy and safety follow-up. *Am J Cardiol*. 1994;74(7):667-673.

17. Marchioli R, Barzi F, Bomba E, et al, GISSI-Prevenzione Investigators. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation*. 2002;105(16):1897-1903.

18. Lee JH, O'Keefe JH, Lavie CJ, Marchioli R, Harris WS. Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc*. 2008;83(3):324-332.

19. Brouwer IA, Zock PL, Camm AJ, et al, SOFA Study Group. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA*. 2006;295(22):2613-2619.

20. Bays HE. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol*. 2007 Mar 19;99(6A)35C-43C. Epub 2006 Nov 28.

21. Harris WS. Expert opinion: omega-3 fatty acids and bleeding—cause for concern? *Am J Cardiol*. 2007 Mar 19;99(6A):44C-46C. Epub 2006 Nov 29.

22. Harris WS, Bulchandani D. Why do omega-3 fatty acids lower serum triglycerides? *Curr Opin Lipidol*. 2006;17(4):387-393.

23. Tuomilehto J, Lindström J, Eriksson JG, et al, Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344(18): 1343-1350.

24. Trichopoulou A, Orfanos P, Norat T, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. *BMJ*. 2005 Apr 30; 330:991. Epub 2005 Apr 8.

25. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6):779-785.

26. Gielen S, Schuler G, Hambrecht R. Exercise training in coronary artery disease and coronary vasomotion. *Circulation*. 2001;103(1):E1-E6.

27. Himeno E, Nishino K, Okazaki T, Nanri H, Ikeda M. A weight reduction and weight maintenance program with long-lasting improvement in left ventricular mass and blood pressure. *Am J Hypertens*. 1999;12(7):682-690.

28. Sartorio A, Lafortuna CL, Marinone PG, Tavani A, La Vecchia C, Bosetti C. Short-term effects of two integrated, non-pharmacological body weight reduction programs on coronary heart disease risk factors in young obese patients. *Diabetes Nutr Metab*. 2003;16(4):262-265.

29. Sarafidis PA, Kanaki AI, Lasaridis AN. Statins and blood pressure: is there an effect or not? *J Clin Hypertens (Greenwich)*. 2007;9(6):460-467.

30. Schiff HB, MacSearraigh ET, Kallmeyer JC. Myoglobinuria, rhabdomyolysis and marathon running. *Q J Med*. 1978;47(188):463-472.

31. Thompson PD, Gadaleta PA, Yurgalevitch S, Cullinane E, Herbert PN. Effects of exercise and lovastatin on serum creatine kinase activity. *Metabolism*. 1991;40(12):1333-1336.

32. Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Staggers J, Guyton JR. Lovastatin increases exercise-induced skeletal muscle injury. *Metabolism*. 1997;46(10):1206-1210.

33. Lefevre M, Champagne CM, Tulley RT, Rood JC, Most MM. Individual variability in cardiovascular disease risk factor responses to low-fat and low-saturated-fat diets in men: body mass index, adiposity, and insulin resistance predict changes in LDL cholesterol. *Am J Clin Nutr*. 2005;82(5):957-963.

34. Berglund L, Oliver EH, Fontanez N, et al. HDL-subpopulation patterns in response to reductions in dietary total and saturated fat intakes in healthy subjects. *Am J Clin Nutr*. 1999;70(6):992-1000.

35. Hsia SH, Pan D, Berookim P, Lee ML. A population-based, cross-sectional comparison of lipid-related indexes for symptoms of atherosclerotic disease. *Am J Cardiol*. 2006 Oct 15;98(8):1047-1052. Epub 2006 Aug 28.

36. Frontini MG, Srinivasan SR, Xu JH, Tang R, Bond MG, Berenson G. Utility of non-high-density lipoprotein cholesterol versus other lipoprotein measures in detecting subclinical atherosclerosis in young adults (The Bogalusa Heart Study). *Am J Cardiol*. 2007 Jul 1;100(1):64-68. Epub 2007 May 11.

37. Real JT, Chaves FJ, Martínez-Usó I, García-García AB, Ascaso JF, Carmena R. Importance of HDL cholesterol levels and the total/HDL cholesterol ratio as a risk factor for coronary heart disease in molecularly defined heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2001;22(6):465-471.

38. Schmidt-Trucksäss. Effects of exercise on plasma lipoproteins [letter]. *N Engl J Med*. 2003;348(15):1494-1496.

39. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med*. 2002;347(19): 1483-1492.

40. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005;293(1): 43-53.

41. Moore RJ. Letter to Sonia Rodriguez, Mason Viamins. May 5, 2001. US Department of Health and Human Services Web site. http://www.fda.gov/ohrms/dockets/dailys/01/Jun01/061101/let0494.pdf. Accessed May 20, 2008.

42. Heber D, Lembertas A, Lu QY, Bowerman S, Go VL. An analysis of nine proprietary Chinese red yeast rice dietary supplements: implications of variability in chemical profile and contents. *J Altern Complement Med*. 2001; 7(2):133-139.

43. Corsini A, Ferri N, Cortellaro M. Are pleiotropic effects of statins real? *Vasc Health Risk Manag*. 2007;3(5):611-613.

44. Davignon J. Cardioprotective and other emerging effects of statins. *Int J Clin Pract Suppl*. 2004 Oct;143:49-57.

45. Kastelein JJ, Akdim F, Stroes ES, et al, ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008 Apr 3;358(14):1431-1443. Epub 2008 Mar 30.