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**Laffin LJ, Bruemmer D, Garcia M, Brennan DM, McErlean E, Jacoby DS, Michos ED, Ridker PM, Wang TY, Watson KE, Hutchinson HG, Nissen SE. Comparative Effects of Low-Dose Rosuvastatin, Placebo, and Dietary Supplements on Lipids and Inflammatory Biomarkers. J Am Coll Cardiol. 2023 Jan 3;81(1):1-12.**

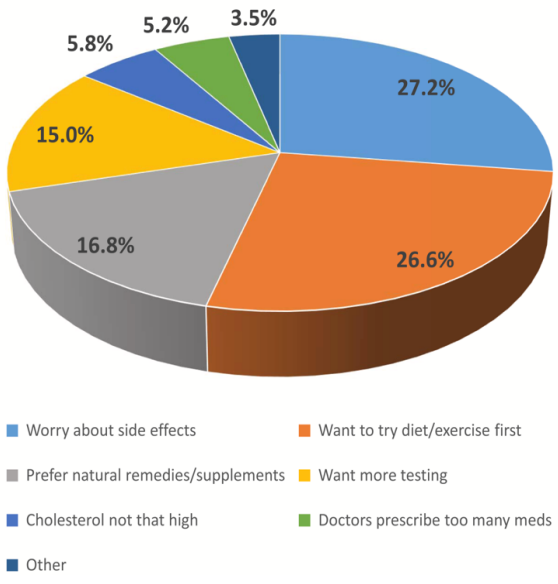
## What We Know, Think We Know, or Are Starting to Know

It is now concretely established that LDL-cholesterol is the primary causal risk factor for the initiation, development, and progression of atherosclerosis in humans [1,2]. While the incidence of cardiovascular disease [CVD] events tend to occur later in life, atherosclerosis is a chronic, progressive process that begins early in life [1,2].

Striking evidence of this characteristic is found in individuals with a genetic condition known as Familial Hypercholesterolaemia [FH], of which there are two genetic variant types: heterozygous and homozygous [3]. In FH, a genetic mutation in the LDL-receptor gene leads to a loss of function in the LDL-receptor that is responsible for clearing cholesterol from the circulation, resulting in elevated circulating LDL-C [3]. Individuals with homozygous FH may have LDL-C levels over 500mg/dL [13mmol/L] from birth and develop – indeed may die of – atherosclerotic CVD before the age of 20 if untreated [3].

It is also possible to have genetic variants that increase the expression of the LDL-receptor, leading to greater clearance of LDL-C from the circulation [4]. Individuals with genetically lower LDL-C levels from birth have a 3-fold lower risk of coronary heart disease for each 10mg/dL [1mmol/L] lower LDL-C compared to those only lowering LDL-C with pharmacotherapy later in life [4]. For example, for someone starting a statin later in life to achieve the same 55% lower risk of CHD as someone born with genetically lower LDL-C levels would require that they achieve a 116mg/dL [3mmol/L] reduction in LDL-C [4].

Collectively, the evidence is now strongly converging in favour of lowering LDL-C as early in life as it is identified to be elevated [see this recent Research Lecture on this topic]. However, there are some barriers to achieving this in clinical practice. Statins have a reputation for causing side effects, despite the evidence that the risk of side effects occurring is just as likely on a placebo [5–7]. As a result, primary non-adherence, defined as never starting to take a statin following prescription [as opposed to forgetfulness], may be as high as 20% [8].



Surveys among patients characterised by primary non-adherence indicate [see **pie chart** above] that ~17% prefer natural supplements, while ~27% want to try diet and exercise first [9]. While diet and exercise are encouraged as part of overall CVD risk management, those seeking to lower LDL-C through dietary supplements are faced with the overall lack of quality evidence in support of popular supplements [10].

However, there is little evidence comparing dietary supplements directly against pharmacotherapy in a well-controlled intervention trial. The present study compared a statin to six dietary supplements commonly considered beneficial for heart health.

## The Study

The SPORT [Supplements, Placebo, or Rosuvastatin Study] trial was conducted as a randomised, single-blind, controlled trial. To be included in the trial, participants were required to be free of CVD and not currently taking statins or dietary supplements to lower LDL-C, be aged between 40–75-years, and have an LDL-C between 70–189mg/dL [1.8–4.8mmol/L].

Eligible participants were randomised to one of six intervention groups or a placebo group [seven groups in total]:

- **Statin**: 5mg/d of rosuvastatin.
- **Fish Oils**: 2,400mg/d of "Nature Made" fish oils with mixed EPA and DHA.
- **Garlic Extract**: 5,000mcg allicin from "Garlique" brand.
- **Cinnamon**: 2,400mg/d from the "Nutriflair" brand.
- **Turmeric**: 4,500mg/d of a curcumin and black pepper [10mg] from the "BioSchwartz" brand.
- **Red Yeast Rice [RYR]**: 2,400mg/d from the "Azaro Nutrition" brand.
- **Placebo**: Tablet similar in appearance to rosuvastatin.

The duration of the intervention was 28-days. Participants had fasting blood samples taken at baseline and again on day 28, and outcomes were analysed as the difference in measures between baseline and end of the study.

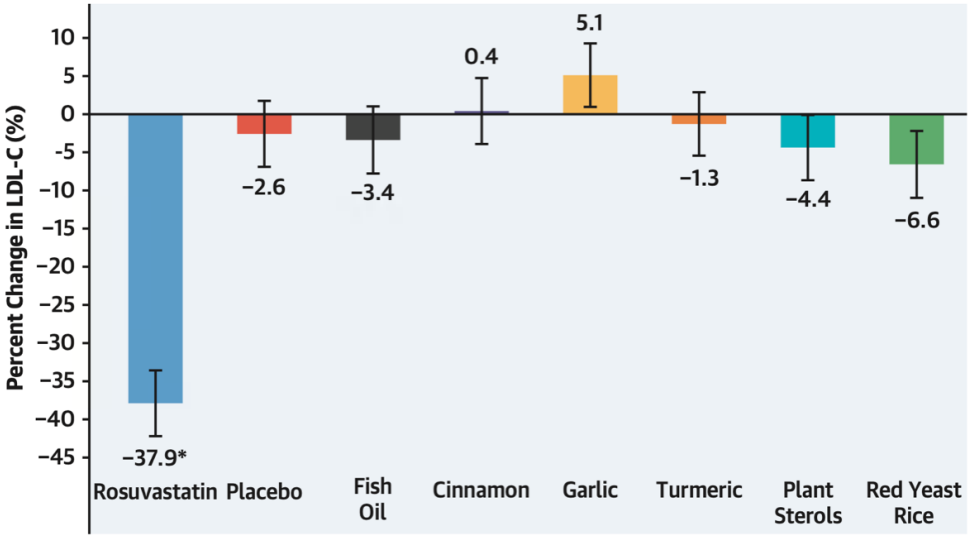
The primary outcome was change in LDL-C on the statin compared to the placebo and each of the dietary supplements. Secondary outcomes included high-sensitivity C-reactive protein [hs-CRP, a marker of systemic inflammation], total cholesterol [TC], HDL-C, and triglycerides.

**Results:** 199 participants were randomised, of which 190 completed the study with both baseline and follow-up outcome measures. Average age of participants was 64-years, 59% were female, and 89% were classified as non-Hispanic White ethnicity. Average baseline LDL-C levels were 128mg/dL [3.3mmol/L].

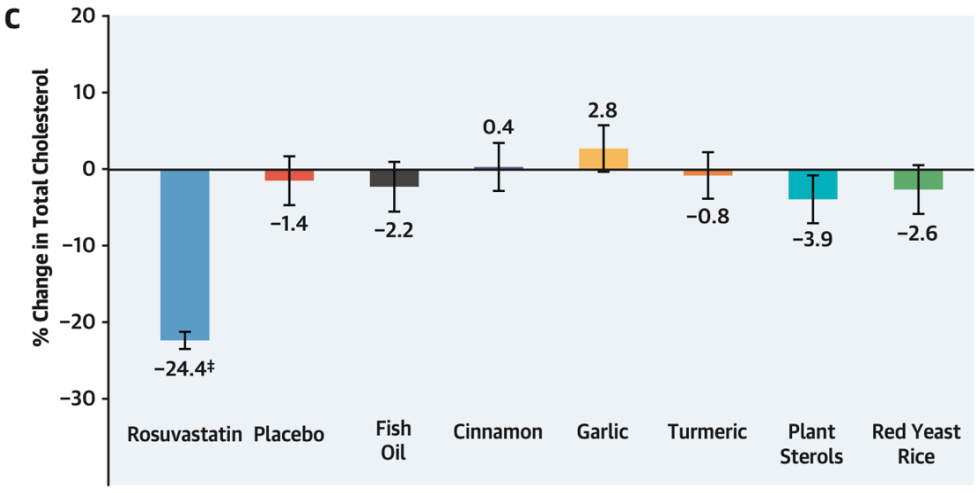
***Primary Outcome – Change in LDL-C*:** Over 28-days, rosuvastatin lowered LDL-C by 37.9%; fish oils by 3.4%; turmeric by 1.3%; plant sterols by 4.4%, and RYR by 6.6%. Garlic led to an increase in LDL-C of 5.1%, while LDL-C was unaffected by cinnamon. There was a 2.6% reduction in LDL-C in the placebo group.

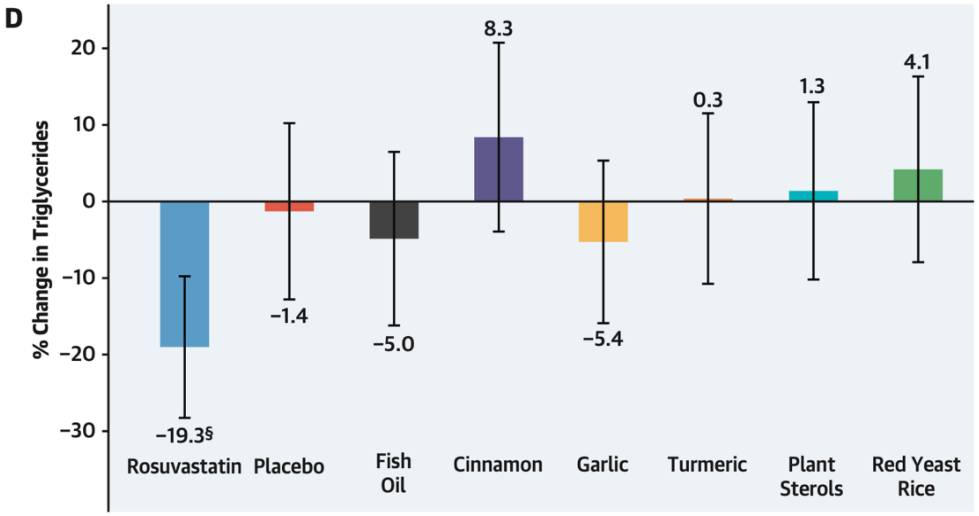
Thus, in comparing the magnitude of LDL-C lowering of rosuvastatin to the dietary supplements, rosuvastatin lowered LDL-C by 31.3–38.3% compared to the supplements.

The **figure** below illustrates the percentage change from baseline of each of the treatments over the 28-day study period of the trial.




***Secondary Outcomes***: None of the treatments had any significant effect on hs-CRP. Rosuvastatin decreased TC and triglycerides by 24.4% and 19.3%, respectively. Dietary supplements had no significant effect on either TC or triglycerides. The **figure** below illustrates the changes in TC and triglycerides from each treatment during the study.



## The Critical Breakdown

**Pros:** The study addressed an important research question for which evidence is currently lacking. The study aim was clearly stated, and the design was strong with computer-generated randomisation, placebo control, and blinding of investigators. The participants were balanced for sex. The supplements were repackaged into unlabelled containers to provide to participants, but as the shape and size of the pills differed the participants were not officially deemed to be blinded [although for all intents and purposes likely were]. The primary and secondary outcomes were clearly stated. The study was sufficiently powered for the primary outcome of change in LDL-C from rosuvastatin. The statistical analysis was based on intention-to-treat, including all participants who were randomised, although practically all but 9 participants included in this analysis completed both baseline and follow-up measures. Finally, adherence to taking the prescribed treatments was high.

**Cons:** The study duration was more reflective of the time-course of statin effectiveness, as 4-weeks is approximately the timeframe in which the maximum achieved reduction in LDL-C from statins would be expected [(11)]. Further, although highly powered to detect the effect of rosuvastatin, the sample sizes for each dietary supplement group may have been too small to detect more robust effects. The study was also ~90% White participants, which is not representative of the wider U.S. population from which the participants were sampled. The main limitation of this study is that arguably it somewhat "strawmanned" the comparative supplements [more under ***Key Characteristic***, below]. There were no nutrition scientists listed among the research team, and arguably a more collaborative approach could have resulted in a better design for the supplemental interventions. Finally, diet was not assessed and while this may not affect the signal from rosuvastatin, it could be relevant for the placebo and dietary supplement groups.

## Key Characteristic

The design and analysis of the present study provided a comparison not only of a statin against dietary supplements, but also a comparison of all intervention treatments against a placebo. This is useful because we would obviously expect a drug designed specifically for the purposes of lowering LDL-C to exert a much greater effect on that primary outcome in 4-weeks.

However, none of the dietary supplements significantly lowered LDL-C even compared against the placebo. And while this finding is not encouraging, as alluded to as the main limitation of the present study, there are legitimate questions to ask about the choice of supplemental interventions. Turmeric [curcumin] has primarily been used in interventions in patients with type-2 diabetes where LDL-C was a secondary outcome, and actual magnitude of effect is weak [(12,13)]. The effect of cinnamon on LDL-C is moistly noise and higher quality trials do not support much impact on LDL-C [(14)].

The brand of omega-3 used for this supplement was a generic "fish oil", and of the 2,400mg of fish oil just 720mg was the long-chain omega-3's EPA and DHA. This is far below the ~3,000mg dose at which significant triglyceride-lowering effects of EPA and DHA are observed, and there is also little impact of omega-3's on LDL-C [(15)].

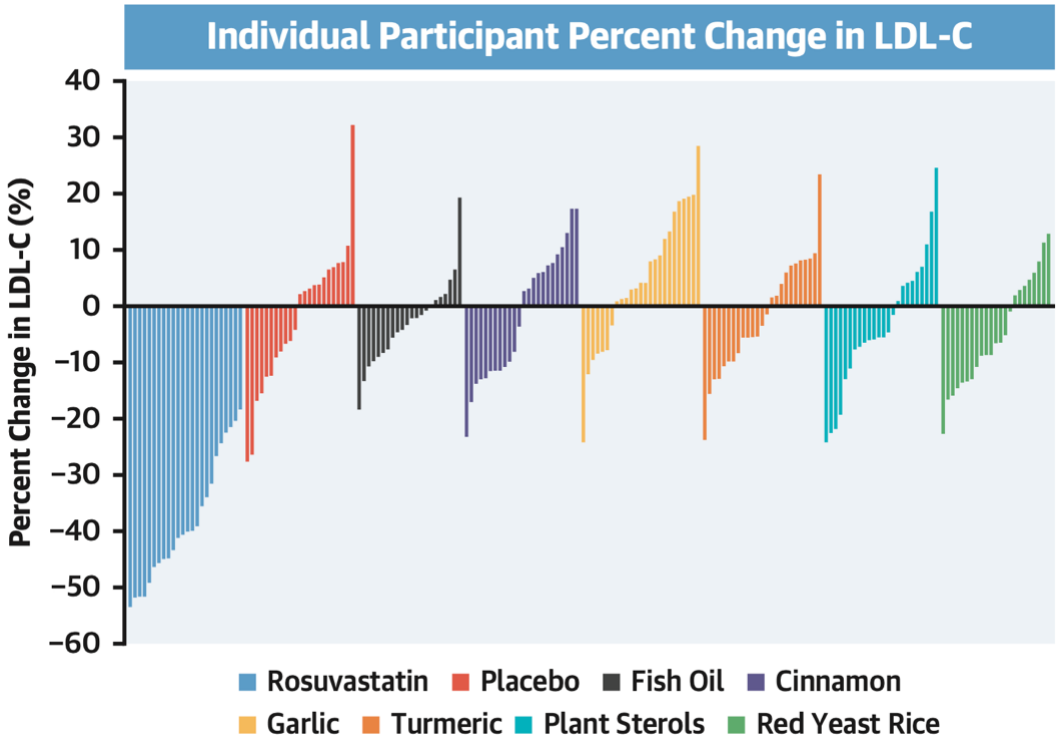
Plant sterols were also underdosed at 1,600mg/d relative to the well-established minimum of 2,000mg and over for lowering of LDL-C up to 8% from plant sterols

specifically [16]. And the supplement used for RYR does not have any information on levels of the main active ingredient that lowers LDL-C, namely monacolin K [17].

Overall, the choices of dietary supplements have poor justifications, with weak rationale for some [e.g., turmeric and cinnamon], underdosing for others [e.g., omega-3 and plant sterols], or missing key information on active ingredients [e.g., RYR].

## Interesting Finding

The inter-individual variation in LDL-C response to rosuvastatin compared to the dietary supplements, and indeed the placebo group, was striking for the fact that the variation in response to rosuvastatin was in the context of a minimum average ~18% reduction in LDL-C. And half of participants assigned to rosuvastatin had a reduction in LDL-C of 40% or over. The **figure** below demonstrates each individual LDL-C response to the respective treatments.




However, it should be noted that the unifying mechanism of both lipid-lowering drugs and key dietary modifications, i.e., replacing saturated with polyunsaturated fats, is upregulating LDL-receptor expression and enhancing clearance of cholesterol from the circulation [18]. This is not necessarily the case with, e.g., omega-3 EPA, which appears to act on plaque morphology [we covered this in a previous Research Lecture], or plant sterols which act on intestinal cholesterol uptake and recycling [19].

Thus, while directly lowering LDL-C may not always be a pathway through which certain dietary supplements may benefit cardiovascular risk, for someone with a need to lower LDL-C a dietary supplement may be no guarantee of benefit.

## Relevance

Recall that in the evaluation of any intervention, there are three key criteria that we consider: *efficacy* [i.e., the capacity to produce a desired effect], *effectiveness* [i.e., does this desired effect actually occur in real-life contexts], and *safety* [i.e., does the treatment produce any adverse effects]. For lowering LDL-C, the efficacy and effectiveness of lipid-lowering therapies, including statins, is established beyond doubt [(10)].

However, there have been safety questions in relation to statins, which is reflected in the fact that of all major chronic disease drugs, lipid-lowering drugs show the highest level of primary nonadherence, i.e., patients never start on the drug [(8).] The single most important reason for this hesitancy is potential for side effects [(9)]. But statin trials never showed higher rates of adverse effects compared to placebo [(6,7)], and up to 90% of self-reported side effects may be attributable to the "nocebo effect" [i.e., an self-reported experience due to negative expectations] [(5)].

While efficacy, effectiveness, and safety would all be strongly in favour of lipid-lowering drugs, however, this does not mean there is no potential role for nutritional interventions. The replacement of saturated with unsaturated fats, polyunsaturated fats in particular, is the single most influential dietary modification to lower LDL-C [(20,21)]. And this dietary modification reduces coronary heart disease event and mortality risk [(22,23)].

But if these findings relate to diet, what of dietary supplements? The evidence on the whole suggests weak efficacy and effectiveness, at least of commercially available supplements. The most promising is purified EPA in ethyl ester form, which is an entirely different intervention to the triglyceride-based generic fish oil supplement used in this study. And this trial underdosed plant sterols, which is fairly inexcusable given wider available knowledge [(16,19)].

The case of RYR in this study is perhaps a good example of why dietary supplements are unreliable. The active ingredient in RYR, monocolin K, is chemically identical to the statin, lovastatin. Yet to be effective in lowering LDL-C a product must have a 5–10mg monacolin K [which may lower LDL-C by 30mg/dL [~0.8mmol/L] [(17)]. The product in the present study has no information on this active ingredient.

## Application to Practice

We didn't need this study to tell us that rosuvastatin is an excellent drug for lowering LDL-C: the JUPITER trial told us that loud and clear [(24)]. However, the implications of this study for statins extend beyond our scope of practice, at least for those of us who are not prescribing medical professionals.

Nevertheless, given cardiovascular disease remains a leading cause of mortality, nutrition professionals should have current knowledge of where available dietary supplements may, and may not, be advisable in the context of cardiovascular health. And this is a rare study that stacks common dietary supplements against a frontline drug, which is highly relevant given statin hesitancy and the expression in survey data that patients may want to try diet, lifestyle, and natural supplements.

The present study in fact lends support to the "food first" approach, and for lowering LDL-C specifically the most efficacious, effective, and safe dietary intervention is to replace saturated with unsaturated fats.

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