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Cost-effectiveness of dietary supplement ingredients versus generic statins for LDL reduction

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ABSTRACT

Background: While statin therapy is the preferred treatment for hyperlipidemia, literature supports the low-density lipoprotein (LDL) lowering effects associated with red yeast rice, berberine, and *Silybum marianum*. Dietary supplements may be perceived as a more affordable alternative to prescription medication.
Objective: We determined cost-effectiveness of generic pravastatin versus single-ingredient dietary supplements in relation to LDL lowering effect.
Methods: Data from meta-analyses and systematic reviews was extracted to calculate pooled weighted mean LDL differences amongst generic pravastatin and single ingredient dietary supplements. The effect was then divided by average 30-day costs and compared amongst agents.
Results: The greatest difference was seen in pravastatin 40 mg [MD -57.88 mg/dL (95%CI: - 64.80 to −50.96)], followed by pravastatin 10 mg [MD -41.30 mg/dL (95%CI: 63.30 to - 19.40)], red yeast rice [MD -25.39 (95%CI: −32.98 to −17.81)], berberine [MD -15.13 (95%CI: −21.78 to −8.48)], and *Silybum marianum* [MD -9.51 mg/dL (95%CI: −22.13 to - 0.10)]. were divided by mean difference to calculate cost per mg/dL reduction in LDL. Cost-effectiveness was greatest for pravastatin 10 mg [$0.66/mg/dL LDL reduction (range: $0.39 to $1.13)], followed by pravastatin 40 mg [$0.74/mg/dL LDL reduction (range: $0.66 to $0.84)], berberine [$0.81/mg/dL LDL reduction (range: $0.56 to $1.44)], red yeast rice [$0.84/mg/dL reduction (range: $0.67 to $1.13)], and *Silybum marianum* [$0.88/mg/dL LDL reduction (range: $0.38 to $82.02)].
Conclusion: Pravastatin is most cost-effective in each scenario whether or not prescription insurance is utilized.

1. Introduction

Statin therapy is the cornerstone of hyperlipidemia treatment given proven risk reduction of atherosclerotic cardiovascular disease (ASCVD) events through suppression of low-density lipoprotein (LDL) concentrations. While generic statins are associated with lower cost as compared to other prescriptions, over the counter products may entice patents to mitigate chronic conditions for less expense. A survey of 20,214 adults shows those without health insurance are more likely to use dietary supplements [odds ratio 1.23 (95%CI: 1.06 to 1.43)].[1] In a survey of 584 adults using dietary supplements, 20.6% reported use for "cholesterol" reduction.[2] Red yeast rice, berberine, and *Silybum marianum* have significant literature supporting LDL reduction.[3–6] Consumer perception is that dietary supplements are less expensive than prescription medication. However, it is unclear how dietary supplements compare to generic statin medications in terms of overall cost-effectiveness.

This study assessed the cost-effectiveness of generic pravastatin versus three dietary supplements in patients with and without insurance.

2. Methods

2.1. LDL effects

A robust literature search for the most recent systematic reviews with meta-analyses was completed via PubMed. LDL effects of targeted single dietary supplement ingredients (red yeast rice, berberine, *Silybum*

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marianum) or pravastatin in randomized controlled trials (RCTs) were assessed. The search strategy included (red yeast rice OR berberine OR Silybum marinarium or Pravastatin) AND (hyperlipidemia OR LDL OR cholesterol OR hypercholesterolemia OR lipids) with a filter for "meta-analysis". The most recent meta-analysis for each agent was included. We reran analyses of any literature pooling various control trials to only include placebo-controlled trials. Analyses were also rerun to exclude multi-ingredient RCTs or in the case of pravastatin, if it was used with another therapy. RCTs that only provided LDL reduction as percentage were also excluded if unable to determine average and standard deviations in mg/dL. Studies reporting mmol/L values were converted to mg/dL using OmniCalculator (https://www.omnicalculator.com/health/cholesterol-units).

We extracted data from the individual RCTs before conducting our own meta-analyses. DerSimonian-Laird random effects model in Stats-Direct version 2.8.0 (London, England) was utilized to account for potential clinical and methodological heterogeneity. An I^2 value above 50% was considered high statistical heterogeneity in which we required three or more RCTs to be pooled.

2.2. Monthly costs

GoodRx (https://www.goodrx.com/search) was utilized to determine the retail price of generic pravastatin in United States dollars as of 7/18/2023 at five different chain pharmacies. Prices are out-of-pocket costs patients pay without any coupons or insurance coverage. GoodRx queries included 30 tablets of either pravastatin 10 mg or 40 mg to derive the price per 30-day. We then assessed the 30-day supply cost for patients with co-payments which the average co- for a tier-1 generic in the US is $6.06, and for patients with co-insurance paying 20% of the total cost.[7,8]

We determined the cost of the first five products containing the dietary supplement ingredients found online and independently third-party verified by USP, NSF, or ConsumerLabs. Searches started at Amazon.com and branched out to major chain pharmacies before looking at other sites. The cost of a bottle was divided by the number of contained dosage forms to derive the cost per unit. Using the suggested daily dose, the number of units used per day was multiplied by 30 to derive cost. The average dose of red yeast rice in RCTs was 2346 mg, so we identified the whole number of pills for each product that was closest to 2400 mg. The average dose of berberine in RCTs was 989 mg, so we identified the whole number of pills for each product that was closest to 1000 mg. For *Silybum marianum* (Milk Thistle Seed Extract, where the active ingredient Silymarin is concentrated), the RCTs used an average total daily dose of 420 mg. In general, 1000 mg of Milk Thistle is equivalent to 250 mg of *Silybum marianum* seed extract, so we identified the whole number of pills for each product that got closest to 420 mg of *Silybum marianum* or 1000 mg of Milk Thistle.

2.3. Calculating the cost per mg/dL reduction in LDL

The average 30-day cost of each product was divided by the mean difference in LDL that each ingredient provided in our pooled analysis versus placebo. The upper and lower limit of the LDL reduction 95% confidence interval was used to derive the range of prices paid per mg/dL reduction in LDL. The average $6.06 monthly amount was used as the cost for both pravastatin 10 mg and 40 mg to assess price in patients with generic co-payments.[7] Cost was calculated as 20% of the GoodRx price for both pravastatin 10 mg and 40 mg products in patients with co-insurance.[8] We again applied the mean difference in LDL and the upper and lower limit calculations to derive the cost per mg/dL reduction. If the lower limit for LDL impact was greater than zero, we set the limit at a reduction of −0.1 mg/dL for purposes of the calculation.

3. Results

Baseline data was extracted from within systematic reviews providing the evidence base for LDL lowering with each assessed product for the RCTs that compared single active ingredient products versus placebo as displayed in Supplemental Table 1.[9–32] We calculated the pooled weighted mean differences (MD) for LDL in the active groups versus the placebo groups over varying follow-up periods ranging from 8 to >24 weeks with negative numbers representing greater LDL reductions as displayed in Fig. 1. The weighted mean differences for LDL reduction was greatest for pravastatin 40 mg [MD -57.88 mg/dL (95% CI: −64.80 to −50.96)] followed by pravastatin 10 mg [MD -41.30 mg/dL (95%CI: −63.30 to −19.40)], red yeast rice [MD -25.39 (95%CI: −32.98 to −17.81)], berberine [MD -15.13 (95%CI: −21.78 to −8.48)], and *Silybum marianum* [MD -9.51 mg/dL (95%CI: −22.13 to −0.10)]. Statistical heterogeneity is high although the directions of effect were consistent with the main difference being in the magnitude of effect across RCTs.

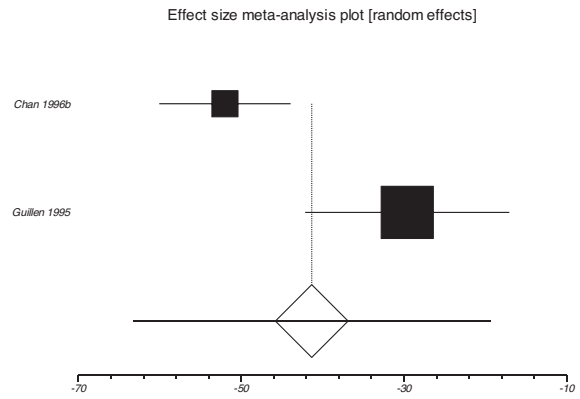
The mean average costs and corresponding standard deviations for a 30-day supply of each product are listed in Table 1. Cost was greatest for pravastatin 40 mg, followed by pravastatin 10 mg, red yeast rice, berberine, and *Silybum marianum*. Cost-effectiveness as seen in Table 2 was greatest for pravastatin 10 mg and least for *Silybum marianum*. People with a standard prescription insurance co-pay would pay less per mg/dL reduction in LDL for pravastatin 40 mg [$0.10/mg/dL LDL reduction (range: $0.09 to $0.12)] than pravastatin 10 mg [$0.15/mg/dL LDL reduction (range: $0.10 to $0.31)] but people with 20% co-insurance would pay less for pravastatin 10 mg [$0.12/mg/dL LDL reduction (range: $0.08 to $0.26)] than pravastatin 40 mg [$0.15/mg/dL LDL reduction (range: $0.13 to $0.17)]. In all scenarios, the cost-effectiveness is greatest for people with prescription drug coverage receiving pravastatin than any out-of-pocket purchase of pravastatin or dietary supplement.

4. Discussion

In the absence of prescription coverage, pravastatin 10 mg and 40 mg were the most cost-effective therapy at $0.66 and $0.74per mg/dL reduction in LDL, respectively. Pravastatin was the chosen comparator given generic availability, modest LDL reduction, and proven ASCVD risk reduction. Equipotent out-of-pocket expenses for lovastatin and simvastatin are similar to pravastatin allowing for a general class assessment. Berberine was the most cost-effective dietary supplement at $0.81 per mg/dL reduction in LDL followed by red yeast rice and *Silybum marianum* at $0.84 and $0.88/mg/dL, respectively. Pravastatin is more cost advantageous when standard copayment or coinsurance is used.

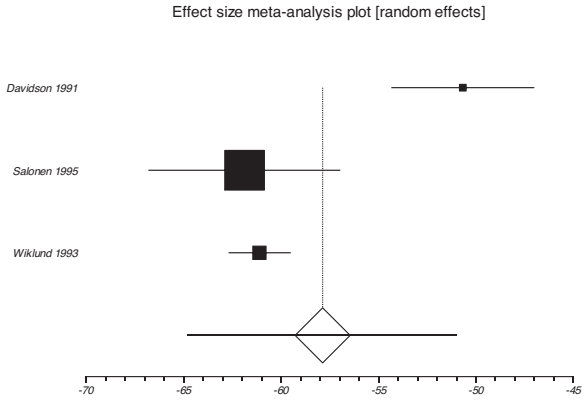
Cost-effectiveness transcends simply reducing LDL cholesterol. There are no studies validating the reductions in negative health outcomes for dietary supplement use in patients with elevated LDL cholesterol. In contrast, the Cholesterol and Recurrent Events (CARE) and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trials were multicenter double-blind trials in subjects with a past medical history (PMH) of acute myocardial infarction (MI) randomized to receive either pravastatin 40 mg or placebo to assess ASCVD events.[33,34] CARE results included a reduction in ASCVD events by 24%, r bypass surgery by 26%, and coronary angioplasty by 23% in those receiving pravastatin vs. placebo ($p < 0.05$ for each).[33] Similarly, LIPID showed that compared to placebo, pravastatin reduced ASCVD events by 29%, stroke by 19%, MI by 29%, and coronary revascularization need by 20% ($p < 0.05$ for each).[34] Additionally, the LIPID trial identified a significant 22% reduction in overall mortality in pravastatin users ($p < 0.001$).[34] A meta-analysis of 27 statin trials with a median follow-up of ~5 years found a 21% reduction in ASCVD events for every 18 mg/dL reduction in LDL [RR 0.79 (95% CI 0.77 to 0.81)].[35] This relationship between LDL reduction and ASCVD event reduction was sustained when extended to ezetimibe and PCSK9-inhibitors but other LDL lowering

1A. Pravastatin 10mg vs. Placebo



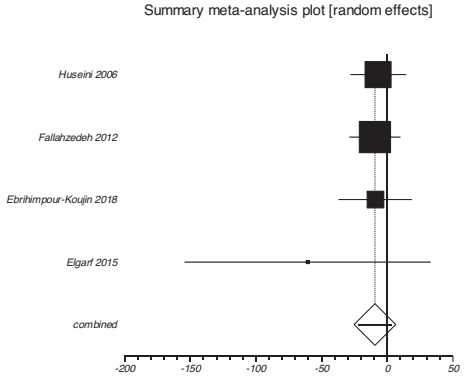
I^2 = NA

1B. Pravastatin 40mg vs. Placebo



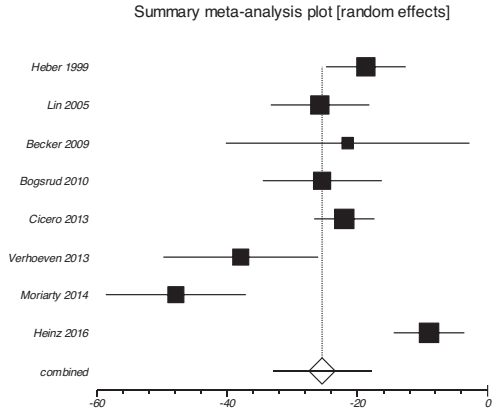
I^2 = 93%

1C. Silybum Marianum vs. Placebo



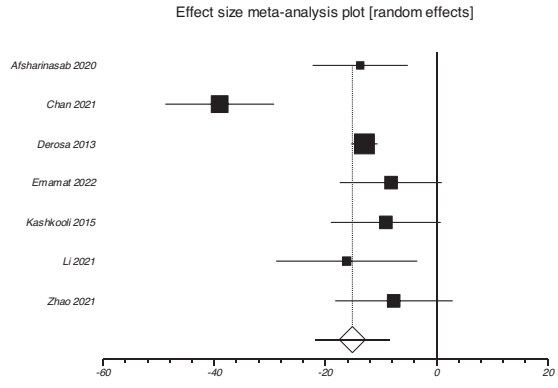
I^2 = 0%

1D. Red Yeast Rice vs. Placebo



I^2 = 87.0%

1E. Berberine vs. Placebo



= 79.9%

Fig. 1. Pooled mean difference for LDL reductions (in mg/dL) with pravastatin vs. placebo and dietary supplements vs. placebo.

Table 1
Total Costs for 30-Day Supplies.

Medication/Ingredient	Cost, $ (Mean ± SD)
Pravastatin 40 mg	43.00 ± 14.46
Pravastatin 10 mg	25.00 ± 15.17
Red yeast rice	20.13 ± 11.34
Berberine	12.20 ± 2.81
Silybum marianum	8.40 ± 4.40

Table 2
Costs per mg/dl Reduction in LDL.

Medication/ Ingredient	Out-of-pocket Costs ($/mg/dL) [Average (range)]		
	No insurance	Insurance copay	Co-insurance
Pravastatin 10 mg	0.66 (0.39–1.13)	0.15 (0.10–0.31)	0.12 (0.08–0.26)
Pravastatin 40 mg	0.74 (0.66–0.84)	0.10 (0.09–0.12)	0.15 (0.13–0.17)
Berberine	0.81 (0.56–1.44)	–	–
Red yeast rice	0.84 (0.67–1.13)	–	–
Silybum marianum	0.88 (0.38–84.02)	–	–

drug classes have not yet demonstrated ASCVD event reductions.

This study solely reviewed single ingredient dietary supplement products to isolate individual results, and only placebo-controlled trials were included to strengthen assessment of treatment effects. The prices utilized were based on five different manufacturers and only products independently verified were included in the study. Generic pravastatin prices were collected from five pharmacies via GoodRx to determine the most generalizable out-of-pocket expenses based upon insurance coverage or lack thereof. We utilized 30-day supply quantities based upon available data and given this is the commonly prescribed quantity dispensed within the United States. Generic prices do not change readily over time so it is assumed that such costs could extrapolate to longer periods if desired. Data from previous meta-analyses was verified before conducting a pooled data analyses and a random effects model was utilized to account for possible heterogeneity.

While efforts were taken to minimize biases, this study still had several limitations. First, we relied on trials identified in meta-analyses which may have resulted in missed data from more recent RCTs. However, meta-analyses evaluating dietary supplements were all published in the last decade. Second, statistical heterogeneity was identified in some of our analyses which could be due to differences in dosing regimens, durations of therapy, product formulation, baseline LDL levels, and patient populations. However, the same direction of effect was observed in each study with the only difference being the magnitude. Third, pravastatin was the only prescription medication compared to natural products despite the various other agents available for hyperlipidemia. This study aimed to represent generic pricing and efficacy of a low-moderate intensity statin. Equipotent doses of generic lovastatin, and simvastatin are similar in cost. Fourth, we did not account for the costs of managing potential adverse effects given lack of consistent reporting in the RCTs. Finally, we did not factor costs associated with office visits, which could be up to $150. It is possible that a patient could forego an office visit and choose a dietary supplement. The cost of a yearly office visit ($150) spread out over 12 months increases the monthly cost of pravastatin therapy by $12.50/month. Still, the cost of pravastatin 10 mg and 40 mg without insurance is still attractive at $0.99 and $0.95 per mg/dL reduction in LDL. However, it is unlikely that a patient would know they had hypercholesterolemia in the absence of an office visit.

Lipid reductions generally peak within about four weeks and effects are then carried forward as long as therapy is continued. This does not mean that people might not have a slow LDL transient increase over time given underlying dietary controls but those increases would have also occurred in those not receiving a therapy and would not change the reduction in LDL with therapy versus those without.

5. Conclusion

Pravastatin therapy is more cost-effective than dietary supplements in reducing LDL despite prescription insurance coverage.

CRediT authorship contribution statement

C. Michael White: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ava Sedensky:** Writing – original draft, Resources, Investigation, Data curation. **Dakota Sicignano:** Writing – original draft, Resources, Investigation, Data curation. **Katelyn J. Galli:** Writing – review & editing, Visualization, Data curation.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rcsop.2024.100428.

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