Review

The Effect of Adding Plant Sterols or Stanols to Statin Therapy in Hypercholesterolemic Patients: Systematic Review and Meta-Analysis

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Objective: To characterize the effect of plant sterols/stanols on serum lipids in hypercholesterolemic patients on concurrent statin therapy, we conducted a meta-analysis of randomized controlled trials.

Methods: A systematic literature search of MEDLINE, EMBASE, Cochrane CENTRAL, and the Natural Medicines Comprehensive Database was conducted from the earliest possible date through May 2008. Trials were included in the analysis if they were randomized controlled trials evaluating the use of plant sterols/stanols in combination with statins in hypercholesterolemic patients that reported efficacy data on total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, or triglycerides. The weighted mean difference (WMD) of the change from baseline (in mg/dL) with 95% confidence interval (CI) was calculated as the difference between the mean in the plant sterol/stanol groups and the control groups, using a random-effects model.

Results: Eight studies (n = 306 patients) met the inclusion criteria. Upon meta-analysis, the use of plant sterols/stanols in combination with statin therapy significantly lowered total cholesterol (WMD, −14.01 mg/dL [95% CI, −18.66 to −9.37], $p < 0.0001$) and LDL cholesterol (WMD, −13.26 mg/dL [95% CI, −17.34 to −9.18], $p < 0.0001$) but not HDL cholesterol or triglycerides.

Conclusions: Based upon the current literature, we can only say that plant sterols/stanols, when administered in addition to statins, favorably affect total and LDL cholesterol with 95% confidence. Randomized trials examining the impact of plant sterols/stanols in combinatation with statins on patient morbidity and mortality are needed.

INTRODUCTION

Elevated serum lipids, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, as well as decreased high-density lipoprotein (HDL) cholesterol are associated with an increased risk for the development of coronary heart disease (CHD) [1]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines recommend a number of dietary modifications such as decreasing the intake of saturated fat (<7% of daily calories) and dietary cholesterol (<200 mg/day) while increasing intake of viscous soluble fiber (≥5–10 g/day) and plant sterols or stanols (2 g/day) to help achieve treatment goals [1].

Plant sterols and stanols are plant steroids with a chemical structure and cellular function similar to that of human cholesterol. Plant sterols and stanols have lower bioavailability than dietary cholesterol and can displace cholesterol from mixed micelles in the intestine, reducing the absorption of dietary cholesterol [2].

A previous meta-analysis of randomized trials evaluated the ability of foods containing plant sterols or stanols to alter

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Abbreviations: CI = confidence interval, HDL = high-density lipoprotein, LDL = low-density lipoprotein, WMD = weighted mean difference.

serum lipid levels [3]. The meta-analysis found that foods containing plant sterols or stanols were able to reduce LDL cholesterol by a mean of 6.7% at doses of 0.7–1.1 g/day and by as much as 11.3% at doses ≥2.5 g/day.

Until recently, there was a paucity of data evaluating plant sterols or stanols in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) in hypercholesterolemic patients. As many patients are already receiving statins to reduce LDL cholesterol, but are not achieving NCEP goals, it is important to better quantify the additional LDL cholesterol–lowering benefit achieved with adjuvant plant sterol or stanol ingestion.

Therefore, we performed a meta-analysis of randomized controlled trials of plant sterols or stanols in combination with statins to better characterize their impact on serum lipids in patients with hypercholesterolemia.

METHODS

A systematic literature search of MEDLINE, EMBASE, Cochrane CENTRAL, and the Natural Medicines Comprehensive Database was conducted from the earliest possible date through May 2008. A search strategy was performed using the Medical Subject Headings and the following text key words: sterol, stanol, sitosterol, sitostanol, beta-sitosterol, beta-sitostanol, phytosterol, phytostanol, stanol ester, sterol ester and simvastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin, lovastatin, rosuvastatin, statin, HMG-CoA reductase inhibitor, hydroxymethylglutaryl coenzyme A reductase inhibitor, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, in combination with lipids, cholesterol, hypercholesterolemia, hypercholesterolemic, hyperlipidemia, hyperlipidemic, low-density lipoproteins, high-density lipoproteins, LDL, HDL, and triglycerides. For our MEDLINE search, we used the Cochrane Collaboration's Highly Sensitive Search Strategy sensitivity-maximizing version [4]. The McMaster University Health Information Research Unit search strategy was used for the EMBASE search [5]. No language restrictions were imposed. In addition, a manual search of references from primary or review articles was performed to identify relevant trials.

Trials were included in the analysis if they were randomized controlled trials evaluating the use of plant sterols or stanols in combination with statins in hypercholesterolemic patients that reported efficacy data (suitable for calculation of change from baseline) on at least one of the following lipid endpoints: (1) total cholesterol, (2) LDL cholesterol, (3) HDL cholesterol, or (4) triglycerides. Both parallel and crossover trials were eligible for inclusion. To be included, crossover studies needed to have at least a 2-week washout period or, if the washout was shorter or absent, needed to measure lipid levels at least 4 weeks after therapies had been switched. This allows for the effect of the previous therapy to dissipate, the effects of the newer therapy to manifest, and patients to reach new steady-state lipid levels. We included trials individually evaluating multiple treatment arms by including each pairwise comparison separately, but with the repeated placebo groups' sample size divided out evenly among the comparisons. Three investigators (J.M.S., R.T., C.I.C.) reviewed potentially relevant articles independently and abstracted necessary data, with differences resolved through discussion. When applicable, efforts were made to contact investigators for clarification or additional data.

The mean change in lipid parameters from baseline was treated as a continuous variable and the weighted mean difference (WMD) was calculated as the difference between the mean in the plant sterol/stanol and control groups. Accepted statistical methods were used to impute change scores as suggested by Follmann and colleagues [6]. We conducted subgroup analyses to determine whether plant stanols or sterols had differing effects on lipid parameters and whether the use of concomitant dietary modification affected plant sterol/stanol efficacy. We also conducted sensitivity analyses to assess whether study design characteristics or the inclusion of a study enrolling patients with familial hypercholesterolemia had an effect on our results. A DerSimonian and Laird random-effects model was used to calculate the WMD and 95% confidence intervals (CIs) [7]. Statistical heterogeneity was addressed using the I^2 statistic. Visual inspection of funnel plots and Egger's weighted regression statistics were used to assess for the presence of publication bias. Statistics were performed using StatsDirect, version 2.5.8 (StatsDirect, Cheshire, England).

RESULTS

Study Characteristics

A total of eight randomized controlled trials (n = 306 patients) met all inclusion criteria [8–15]. All 8 trials [8–15] reported useable data for total and LDL cholesterol while 7 trials [8–12,14,15] reported useable data for HDL cholesterol and triglycerides (Fig. 1). All trials enrolled patients with mild-to-moderate hypercholesterolemia and randomized them to be treated with either plant sterol/stanol (dosing range: 1.8–6 g/day) or control for a period of 4–14 weeks (Table 1). Five trials were double-blinded [8,9,11–13], one single-blinded [10], one open-label [15], and one was unclear in reporting the extent of blinding [14]. Five were parallel trials [9–11,13,15] and 3 were crossover trials [8,12,14]. Only 4 studies required patients to undergo concurrent dietary modification [8,11,12,15]. The use or absence of use of dietary modification was similar between plant sterol/stanol– and control-treated patients in each trial; however, one trial provided what appeared to be more intensive dietary counseling to the plant

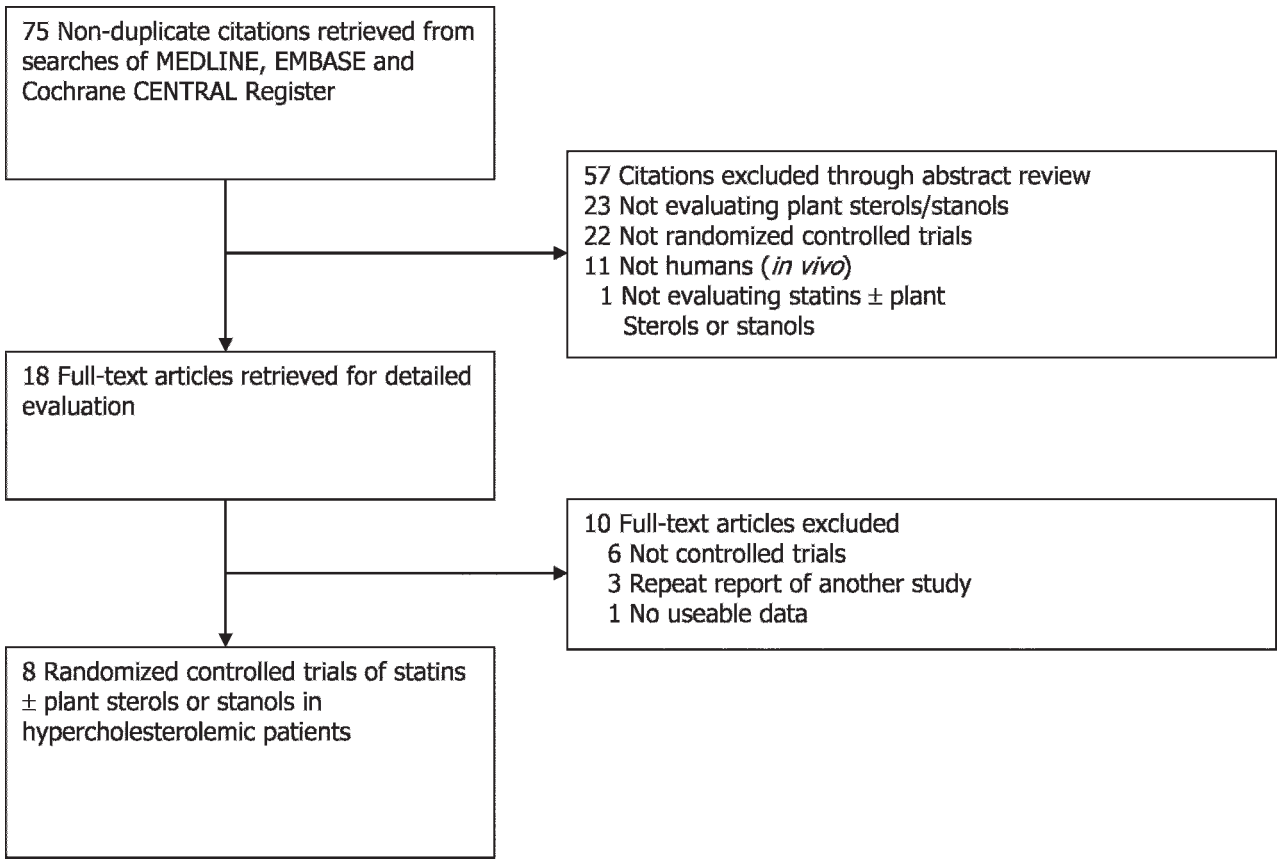

Fig. 1. QUOROM flow diagram of study identification, inclusion, and exclusion.

sterol/stanol group compared to the control group, although no dietary modification was mandated in either group [10]. Manufacturers of plant sterol/stanol products funded 2 trials [12,13]; research foundations funded 4 trials [8,9,11,14], an academic institution funded 1 trial [10] and one did not state the source(s) of study funding [15].

Quantitative Data Synthesis

Upon meta-analysis, the use of plant sterol or stanols added to statin therapy significantly lowered total cholesterol (WMD, −14.01 mg/dL [95% CI, −18.66 to −9.37], $p < 0.0001$) and LDL cholesterol (WMD, −13.26 mg/dL [95% CI, −17.34 to −9.18], $p < 0.0001$), but not HDL cholesterol or triglycerides ($p > 0.10$ for all) as compared with statin use alone (Fig. 2). No statistical heterogeneity was observed in any of the lipid endpoint analyses ($I^2 = 0\%$ for all).

Review of funnel plots (not shown) and the Egger's weighted regression statistic p values suggested a low potential for publication bias for the total cholesterol, LDL cholesterol, and HDL cholesterol analyses ($p > 0.31$ for all). Both an asymmetrical funnel plot and the Egger's p value ($p = 0.02$) for triglycerides suggested a higher likelihood of publication bias. The funnel plot suggested that at least one study to the right of the composite effect line may not have been included in our analysis.

Subgroup and sensitivity analyses are presented in Table 2. No noteworthy changes in our meta-analysis' conclusions were seen in any of these analyses.

DISCUSSION

Our meta-analysis of 8 randomized controlled trials [8–15] evalutating the addition of plant sterols/stanols at doses of 1.7–6 g/day to statin therapy in hypercholesterolemic patients showed significant lowering of both total cholesterol (14 mg/dL) and LDL cholesterol (13 mg/dL) as compared with a statin alone. No significant impact on either HDL cholesterol or triglycerides was seen. Subgroup analyses revealed no significant difference in lipid lowering when plant sterols versus stanols were used or whether or not diet modification was present. According to the NCEP ATP III 2004 update [16], a 1-mg/dL decrease in LDL cholesterol reduces a patient's relative risk of having a coronary event by approximately 1%. Thus, the LDL cholesterol reductions seen in our meta-analysis with sterols/stanols above and beyond that achieved with statins is likely clinically important.

Table 1. Characteristics of Included Randomized, Controlled Trials of Statins Plus Plant Sterols or Stanols in Patients with Hypercholesterolemia

Reference (n)	Study Design	Baseline Lipids (mg/dL)[a]	Follow-up	Statin Dosing
Fuentes, 2008 [8] (n = 30)	Double-blinded, crossover (no washout)	TC = 229 LDL-C =154 HDL-C = 53 TG = 91	4 wk	Atorvastatin or simvastatin 40 mg/day for at least 8 wk prior
Fuentes, 2008 [8] (n = 30)	Double-blinded, crossover (no washout)	TC = 229 LDL-C =154 HDL-C = 53 TG = 91	4 wk	Atorvastatin or simvastatin 40 mg/day for at least 8 wk prior
De Jong, 2008 [9] (n = 41)	Double-blinded, parallel	TC = 222, 207; 210 LDL-C = 138, 133; 124 HDL-C = 50, 61; 59 TG = 172, 115; 137	16 wk	Stable doses of atorvastatin, simvastatin, or pravastatin
Cabezas, 2006 [10] (n = 20)	Single-blinded, parallel	TC = 251; 282 LDL-C = 174; 201 HDL-C = 40; 49 TG = 195;151	6 wk	Atorvastatin or simvastatin 80 mg/day for at least 6 months prior
Goldberg, 2006 [11] (n = 26)	Double-blinded, parallel	TC = 193; 197 LDL-C = 112;119 HDL-C = 51;44 TG = 151;171	6 wk	Stable statin dose for at least 90 days prior
Cater, 2005 [12] (n = 10)	Double- blinded, crossover (no washout)	Baseline values not reported (LDL-C had to be between 100 and 129 mg/dL)	8 wk	Stable doses of atorvastatin or simvastatin for least 60 days prior
Blair, 2000 [13] (n = 141)	Double-blinded, parallel	TC = 232; 233 LDL-C = 147; 149 HDL-C = 52; 53 TG =162; 151	14 wk	Stable doses of atorvastatin, pravastatin, simvastatin, or lovastatin for at least 90 days
Gylling, 1996 [14] (n = 8)	Blinded (single- or double-unclear), crossover (no washout)	Baseline values not reported (total cholesterol had to be >232 mg/dL)	7 wk	Previously statin-naïve, pravastatin 40 mg started at randomization
Richter, 1996 [15] (n = 30)	Open-label, parallel	TC = 290; 305 LDL-C = 212; 229 HDL-C = 52; 49 TG = 155; 127	12 wk	Maximally tolerated dose of lovastatin (56.5 ± 25.0 mg/day) started during a 16-week run-in period

[a] Presented as plant sterol and/or stanols value(s) at baseline; placebo value(s) at baseline.

[b] Diet modifications (or lack thereof) were applied equally to the plant sterol or stanols groups and placebo groups except for Cabezas et al. [10], where the stanol ester group received ''intensive dietary education'' and the control group received only a ''healthy eating'' leaflet and answering of questions.

AHA = American Heart Association, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, MUFA = monounsaturated fatty acids, PUFA = polyunsaturated fatty acids, TC = total cholesterol, TG = triglycerides.

Unfortunately, many patients receiving statin therapy are not reaching the LDL cholesterol goals. Foley and colleagues demonstrated that only 48% of patients reached their LDL cholesterol goal following initiation of a statin, and of those who required further dose titration, only an additional 14% achieved their goals [17]. Thus, most patients may require either increased doses of their statin or additional drug therapy in an attempt to reach their goal. The addition of plant sterols and stanols to statin therapy may provide the additional cholesterol lowering needed to reach LDL cholesterol goals.

Plant sterols and stanols have been shown to alter serum lipid levels by decreasing intestinal cholesterol absorption by 26–36%; however, a compensatory increase in cholesterol synthesis of 38–53% is seen [18]. This increase in cholesterol biosynthesis may be attenutated by the concurrent use of a statin [14]. Simons and colleagues showed that LDL cholesterol reductions attributable to plant sterols were similar when plant sterols were used either alone (~8%) or added to statin therapy (~6%), suggesting an additive rather than synergistic effect [19]. This reduction in LDL cholesterol is similar to that seen by doubling the dose of a statin. The results of our meta-analysis support this theory, with additional reductions in both total and LDL cholesterol seen when plant sterols/stanols were added to existing statin therapy.

A similar relationship is seen between ezetimibe and statins. Similar to plant sterols/stanols, ezetimibe lowers

Table 1. Extended.

Plant Sterol/Stanol Dosing and Dosage Form	Control Group	Concurrent Diet Modification[b]
2.5 g/day sterol ester margarine (90% sitosterol; cholestanol 2%; stigmasterol 2%; lathosterol 3%; campesterol 1.5%; lanosterol 0.5%; and others 1%)	<0.5 g/day plant sterol from control diet	280–300 mg/day cholesterol, <30% fat, <10% saturated fat, 6% PUFA, 12% MUFA, 55% carbohydrates, and 15% protein
2.5 g/day sterol ester margarine (90% sitosterol; cholestanol 2%; stigmasterol 2%; lathosterol 3%; campesterol 1.5%; lanosterol 0.5%; and others 1%)	<0.5 g/day plant sterol from control diet	150 mg/day cholesterol, <30% fat, <10% saturated fat, 6% PUFA, 12% MUFA, 55% carbohydrates, and 15% protein
2.5 g/day sterol ester margarine (49% sitosterol ester; 31% campesterol ester; 16% stigmasterol ester) or 2.5 g/day stanol ester margarine (69% sitostanol ester; 31% campestanol ester)	30 g/day (220 g/week) of margarine containing 40% fat and no added plant sterol	No change in habitual diet other than margarine use
3 g/day of plant stanol (5.1 g/day of stanols esters) margarine (Benecol)	30–35 g/day (250 mg/week) of margarine containing 62% fat and no added plant stanol (Becel)	Dietary education only
1.8 g/day of stanols as a dried stanols/lecithin complex in tablet form	Placebo tablet containing starch	AHA Heart Healthy Diet (cholesterol <300 mg/day, 25–35% fat, <7% saturated fat, <1% trans fat)
3 g/day of plant stanol (5.1 g/day of stanols esters) margarine (Benecol)	24 g/day of matching canola oil–based placebo margarine with an average fat content of 18 g and no added plant stanol	Cholesterol <300 mg/day, saturated fat <10% of daily calories
3 g/day of plant stanol (5.1 g/day of stanols esters) margarine (Benecol)	24 g/day of matching canola oil–based placebo margarine with an average fat content of 18 g and no added plant stanol	No change in habitual diet other than margarine use
3 g/day sitostanol margarine (228 mg/100 g campesterol, 921 mg/100 g campestanol, 1138 mg/100 g sitosterol, 11,400 mg/100 g sitostanol)	Matching canola oil–based margarine containing 209 mg/100 g campestanol and 288 mg/100 g sitosterol	No change in habitual diet other than margarine use
6 g/day beta-sitosterol orally	No oral plant sterol	Cholesterol-lowering diet as recommended by the European Atherosclerosis Society (reduction of total fat to <30% of energy, of which less than 1/3 is saturated)

cholesterol by inhibiting cholesterol absorption within the brush border of the small intestine by approximately 54% [20,21]. When added to prior statin therapy, ezetimibe lowers total cholesterol and LDL cholesterol by an additional 16% and 24%, respectively [22].

Although not evaluated in our meta-analysis, a few safety concerns may exist regarding the increased intake of plant sterols and stanols. Patients with inherited phytosterolemia have a defect in intestinal cholesterol transport proteins, causing a hyperabsorption of plant sterols [23]. These patients are known to develop premature atherosclerosis and CHD due to the increased absorption of plant sterols [24]. Further study is need to determine whether there is a risk of atherosclerosis in normal patients taking increased amounts of plant sterols through dietary supplementation [25,26]. Since plant stanols are absorbed into the bloodstream to a lesser extent than plant sterols, the preferential use of plant stanols as a dietary supplement to lower cholesterol might be warranted [27]. Although plant sterols and stanols were only indirectly compared, we found that they had similar effects on lipid parameters, further supporting the preferential use of plant stanols over plant sterols. In addition, plant sterol and stanol use has been assoicated with decreases in carotenoids [3] (e.g., beta-carotene) that may be associated with increased risk of CHD [28], although the true extent of this increased risk, if any, requires further evaluation.

There are some limitations of the meta-analysis. When performing a meta-analysis, the potential for publication bias is always a concern. A visual inspection of our analyses funnel plot's and Egger's weighted regression statistics revealed a low level of publication bias for all endpoints with the exception of triglycerides. Inspection of the funnel plot for triglyceride analysis suggests that a trial to the right of the effect line may exsist but is not included and therefore, our analyses may be

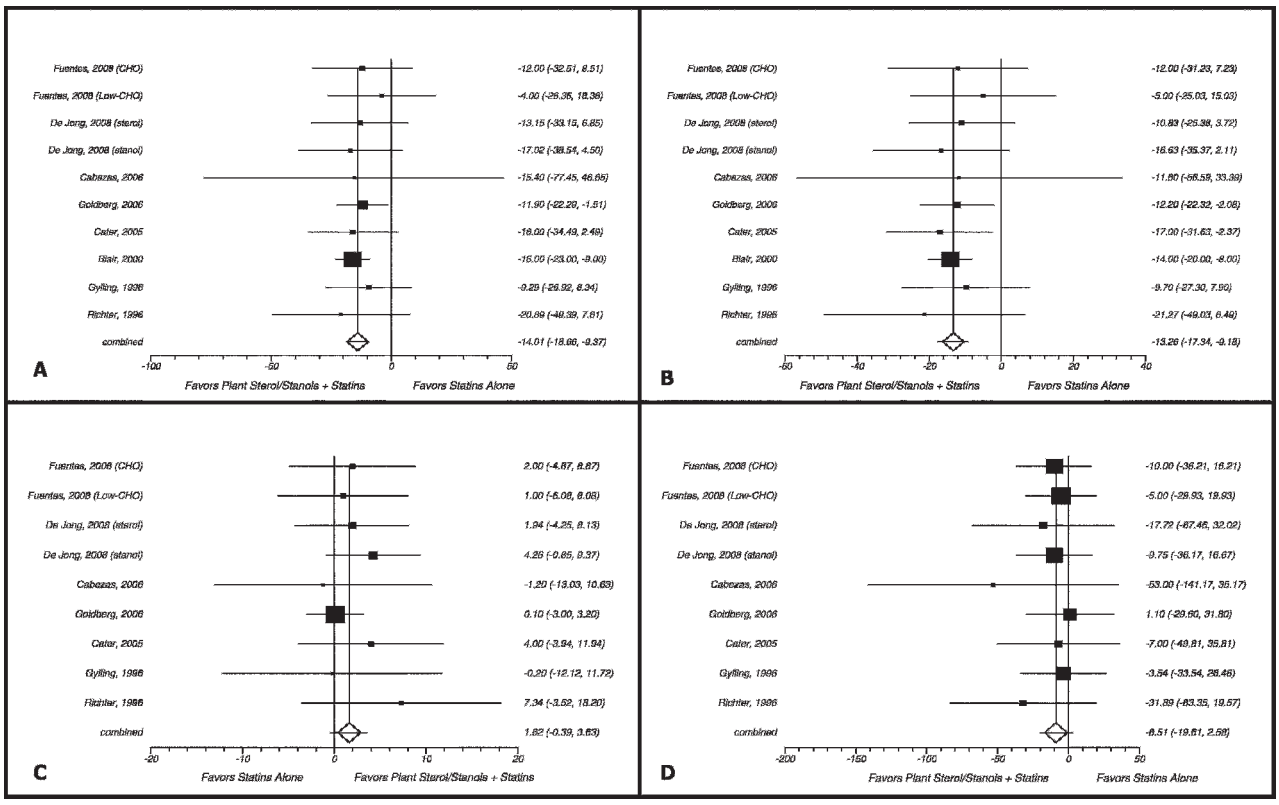

Fig. 2. Forest plots depicting the effect of plant sterols or stanols on (A) total cholesterol, (B) low-density lipoprotein cholesterol, (C) high-density lipoprotein cholesterol, and (D) triglycerides. All results reported as weighted mean differences (in mg/dL) and 95% confidence intervals.

overestimating the effect of plant sterols and stanols on triglyceride levels. This potential bias is not overly concerning, since plant sterols and stanols did not seem to have a significant impact on triglyceride levels in the base-case analysis. The inclusion of crossover trials without adequate washout periods may also be a limitation. To minimize the effect of insufficient washout periods, we only included crossover trials that evaluated lipid levels after a minimum of 4 weeks to allow

Table 2. Results of Meta-Analysis of Randomized Controlled Trials Evaluating Plant Sterols or Stanols in Addition to Statins in Patients with Hypercholesterolemia[a]

	Total Cholesterol (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)
All studies	−14.01 (−18.66, −9.37)	−13.26 (−17.34, −9.18)	1.49 (−0.57, 3.56)	−8.97 (−19.75, 1.80)
Stanol studies only	−14.60 (−19.61, −9.59)	−13.89 (−18.32, −9.46)	1.46 (−0.90, 3.81)	−7.07 (−20.92, 6.77)
Sterol studies only	−12.03 (−21.89, −2.19)	−10.98 (−19.37, −2.59)	2.26 (−1.10, 5.62)	−11.72 (−26.81, 3.37)
Excluding crossover studies	−14.97 (−20.25, −9.68)	−13.64 (−18.26, −9.02)	1.32 (−1.10, 3.75)	−12.07 (−28.12, 3.98)
Excluding studies not double-blinded	−14.16 (−19.07, −9.26)	−13.29 (−17.56, −9.03)	1.40 (−0.77, 3.57)	−7.73 (−19.70, 4.24)
Excluding Cabezas et al. (2006) [10]	−14.00 (−18.66, −9.35)	−13.27 (−17.37, −9.17)	1.57 (−0.52, 3.67)	−8.26 (−19.12, 2.60)
Studies evaluating plant sterols or stanols with diet modification	−12.32 (−19.82, −4.82)	−12.95 (−19.86, −6.04)	1.17 (−1.26, 3.60)	−7.39 (−21.46, 6.69)
Studies evaluating plant sterols or stanols without diet modification	−15.07 (−20.98, −9.15)	−13.42 (−18.48, −8.36)	2.34 (−1.59, 6.27)	−11.22 (−28.00, 5.54)
Excluding study of patients with familial hypercholesterolemia	−14.60 (−19.49, −9.72)	−13.70 (−17.97, −9.42)	1.49 (−0.79, 3.76)	−9.86 (−23.29, 3.57)

[a] A DerSimonian and Laird random-effects model was used in calculating the weighted mean difference and its 95% confidence interval (CI).

To convert values for cholesterol from mg/dL to mmol/L, multiply by 0.0286; to convert values for triglycerides from mg/dL to mmol/L, multiply by 0.01129.

HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

steady-state concentrations to be reached. Sensitivity analysis was also performed and demonstrated that excluding the crossover studies did not impact the effect of plant sterols and stanols on lipid levels. Additional potential limitations involve the inclusion of trials that were not double-blinded, enrolled patients with familial hypercholestrolemia, and provided more intense diet modification education to patients in the treatment group than to patients in the control group. However, upon sensitvity analysis excluding such trials, the lipid-lowering ability of plant sterols and stanols remained consistent.

CONCLUSION

Based on the current literature, it appears that plant sterols and stanols have an additive beneficial effect on total cholesterol and LDL cholesterol when administered in addition to statin therapy. Prospective randomized trials examining the impact of plant sterols and stanols in combinatation with statins on patient morbidity and mortality are needed.

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