Fiber-Multivitamin Combination Therapy: A Beneficial Influence on Low-Density Lipoprotein and Homocysteine

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Proven effective alternative and adjunctive therapies for lipid lowering could be beneficial for patients with hyperlipidemia. We evaluated a 90% soluble fiber for its ability to alter lipid, lipoprotein, and homocysteine levels in the setting of coadministered folate and B vitamins. Patients (n = 119) were randomized to either the fiber and vitamin combination, or placebo. Fasting lipid, glucose, and homocysteine concentrations, and body mass index (BMI) were obtained at baseline and weeks 4 and 8. Both between-group (Wilcoxon rank-sum test) and within-group (paired *t* test) comparisons were used to evaluate treatment effects. After 6 weeks of a diet therapy (National Cholesterol Education Program [NECP] Step I) run-in period, subjects in both groups had similar low-density lipoprotein cholesterol (LDL-C) levels (159 mg/dL *v* 158 mg/dL). The treated group showed a 7.1% ± 11.6% reduction by 4 weeks, which was maintained at 8 weeks (7.9% ± 11.0%). Placebo patients had a slight increase in LDL-C values over the same period (+2.4% ± 11.7%), for a 10.3% difference between groups. The treatment effect was statistically significant both between groups (*P* < .001) and within the active-treatment group (*P* < .001) after the 8-week intervention. Apolipoprotein B (ApoB) levels in a representative subset of the treated group (n = 53) decreased by 20% (*P* = .004). The fiber blend neither raised triacylglycerol (TG) (*P* = .95) nor lowered high-density lipoprotein cholesterol (HDL-C) levels (*P* = .54), and lowered homocysteine (active, 9.8 to 8.7/μmol/L, *P* = .02; placebo, 9.4 to 9.2 /μmol/L, *P* = .98). Thus, a significant LDL-C lowering effect, with parallel Apo B reduction, was demonstrated for this fiber/vitamin combination. No adverse changes on TG or HDL-C levels were noted, and folate/B vitamin benefits attributed to homocysteine reduction were preserved. Concurrent administration of fiber and vitamins represents a preventive approach that may reduce the need for concomitant lipid-lowering therapies or serve as an adjunct therapy.

PRODUCTS ENRICHED with fiber have been reported to lower serum cholesterol levels and improve glucose concentrations in diabetics. Vitamins in addition to or incorporated with foods have resulted in the lowering of homocysteine serum concentrations. Given that the combination of various dietary supplements into one product could enhance benefits and overall compliance, it is important to establish the efficacy of their joint administration.

Fibers can reduce low-density lipoprotein cholesterol (LDL-C) concentrations by 5% to 10%; however, this often occurs with concurrent elevation in triacylglycerol (TG), reductions in serum high-density lipoprotein cholesterol (HDL-C) concentrations,[1] and frequent gastrointestinal side effects.[2] When provided separately or in combination, folic acid, vitamin B_6, and vitamin B_{12} can reduce homocysteine plasma concentrations. However, fiber may modify B_6 bioavailability.[3,4] The influence of vitamin supplementation when coadministered with fiber has not been determined. Finally, it has been suggested that fiber products reduce glucose serum concentrations when provided to diabetic subjects, but it is not clear whether similar reductions occur in nondiabetic patients.

We chose to examine the potential of a combined fiber and vitamin preparation to lower LDL-C concentrations. Secondarily, we tested whether the supplementation of B vitamins in conjunction with fiber would provide the expected reduction in homocysteine levels. Finally, we examined HDL-C and TG changes, as well as possible glucose modification, that occur with daily fiber use.

MATERIALS AND METHODS

Subjects

Potential study subjects were eligible to participate if they were ≥ 18 years of age, had no known cardiovascular disease, and had a fasting LDL-C concentration ≥ 130 mg/dL. No concurrent lipid-lowering therapy or statin during the previous 30 days was permissible. Subjects were required to follow the National Cholesterol Education Program (NCEP) Step I diet for the duration of the investigation, and to avoid any intentional dramatic changes in diet. Female participants could not be pregnant (negative pregnancy test at screening) or breastfeeding, and agreed to use reliable contraception for the duration of the investigation.

Ineligibility criteria included established thyroid, liver, or renal disease; insulin-dependent diabetes mellitus; poorly controlled non–insulin-dependent daibetes mellitus (fasting blood glucose ≥ 200 mg/dL); vasculitis; human immunodeficiency virus infection; dysphagia or swallowing disorders; poorly controlled hypertension (systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 105 mm Hg); and known cardiovascular or unstable cardiac disease. Persons with known allergies to any ingredients in either the active or placebo study compounds were also excluded. Subjects were not included in the study if fasting LDL-C concentration fell to less than 130 mg/dL after the NCEP Step I diet 6-week run-in period. Finally, if the LDL-C concentration did not stabilize (within 15% variance) between the week 3 and week 6 pre-randomization diet-only follow-up clinic visits, the individual was excused from the trial prior to randomization. Those subjects who remained eligible for the trial after the 6-week diet therapy run-in were randomized (n = 119) to receive either placebo or fiber blend in a double-blind parallel fashion. All randomized subjects continued to follow the NECP Step I diet for the next 8 weeks and add 2 servings per day of their assigned study compound.

Prospective subjects were recruited by advertisement in internal hospital communications and community newspapers. All subjects provided informed consent to participate in this investigation, which was approved by the Cleveland Clinic Foundation Institutional Review Board.

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Clinical Parameters Monitored

Following screening for eligibility, a fasting blood sample was collected at defined intervals during the investigation. Blood parameters monitored included comprehensive lipid and metabolic panels, as well as blood counts and homocysteine concentrations. Subjects were also weighed and asked to report any adverse events or side effects at each visit, and underwent periodic physical examinations. Based on the LDL-C findings, a post-hoc analyses of apolipoprotein B (ApoB) was performed on archived samples, permitting a convenience sample of 55 patients (26 treatment, 29 placebo) at randomization, 8 weeks, and 16 weeks.

Diet and Stool Studies

Dietary intake was collected in a diet log completed by the subject and analyzed with The Food Processor software program, version 7.40 (ESHA Research, Salem, OR). Three-day stool records were collected for each subject on 4 occasions. Subjects recorded frequency and consistency for each entry over 3 days (no bowel movement, diarrhea/loose, soft, firm/normal, constipated, or no record).

Fiber Blend Composition and Dosage

The fiber tested was Bios Life 2 (Rexall Sundown, Boca Raton, FL), which provides 4.0 g of soluble fiber and 0.5 g of insoluble fiber per serving (guar gum, locust bean gum, pectin, oat fiber, gum acacia, and barley fiber), along with 1,000 IU vitamin A as β carotene, 30 IU vitamin E, 60 mg vitamin C, 2.7 mg thiamine, 36 mg niacin, 3.1 mg riboflavin, 120 μg folic acid, 3.6 mg vitamin B_6, 9 μg vitamin $B_{12,}$ 30 μg biotin, 100 mg calcium, 0.9 mg zinc, 54 μg chromium, and 4.2 μg selenium. The placebo consisted entirely of insoluble fiber, provided as a combination of purified cellulose and carboxymethylcellulose (Valentine Enterprises, Lawrenceville, GA). These powders were of identical appearance, color, odor, and flavor. Both were dispensed as identical single-serving packets of powder to be mixed with 8 oz of water and consumed within 30 minutes of a meal, twice per day. Subject compliance was estimated from the number of unused packets returned by the study subject at each scheduled study-related clinic visit. The participants attended the clinic 4 and 8 weeks after randomization for observation and follow-up.

Sample Size Calculation

Sample size estimates were calculated to provide 90% power at an α level of 0.05. With these assumptions, 50 patients were required in each group to detect a treatment effect of a 10% reduction in LDL (compared to no change in the placebo group) with a standard deviation of 15%. An additional 10 patients per group were recruited to allow for the probability that some patients would withdraw from the study.

Statistical Methods

Lipid, glucose, homocysteine, BMI, and dietary data are presented as median and interquartile ranges because distributions did not uniformly meet normality assumptions. The primary endpoint was LDL-C response from the start of the study to the end of the blinded phase. The starting concentration is calculated as the average LDL-C concentration from the screening and randomization visits because these 2 visits determined eligibility based on the LDL-C criterion. The response is described as percentage change from the start concentration to the concentration at the end of the blinded phase.

Differences between the treatment and placebo groups were evaluated first at each time period by univariate comparisons using Wilcoxon rank-sum tests.[5] Changes within groups over time were evaluated with paired *t* tests at each follow-up visit after randomization. This strategy was employed for the primary outcome (LDL-C) and secondary outcomes (total cholesterol [TC], ApoB, HDL, TG, glucose, and homocysteine). In addition, for the primary outcome, a repeated-measures mixed model was developed using treatment group as a fixed effect and subjects as random effects.[6] The treatment and time main effects were adjusted for age and gender, and a time by treatment interaction was included.

Mean caloric intake, fiber and soluble fiber intake, calories from fat, protein, carbohydrate, and alcohol intake were calculated for each subject based on diet logs. Between-group comparisons were made at randomization and the end of the blinded phase with unpaired *t* tests. Changes in diet over time were evaluated within groups using paired *t* tests. As with dietary habits, stool consistency was compared between groups with unpaired *t* tests and within groups by paired *t* tests.

RESULTS

A total of 137 subjects expressed interest in participating in the study at the time of the initial visit. Of these, 119 met all of the inclusion criteria and were randomized. Ninety-nine patients (50 treatment, 49 placebo) completed all visits through the end of the blinded phase. Of the 20 patients (10 treatment, 10 placebo) who dropped out of the study, gastrointestinal issues were the most commonly cited clinical reason (n = 7; 2 treatment, 5 placebo). Logistics issues accounted for 10 dropouts (6 treatment, 4 placebo). LDL-C at randomization was not different between those who finished the study (153 mg/dL) and those who did not (158 mg/dL). Baseline characteristics of the 99 patients who completed the study are listed in Table 1.

LDL-C Response

Patients randomized to the treatment group had a slightly lower (but not statistically significant) LDL-C concentration at the screening visit (159 mg/dL *v* 169 mg/dL). After the 6-week diet lead-in, the 2 groups showed virtually identical LDL concentrations (159 mg/dL *v* 158 mg/dL). By the time of the interim visit (4 weeks after randomization), the treatment group demonstrated significantly lower LDL-C than the placebo group (147 mg/dL *v* 162 mg/dL, $P = .02$). That trend continued through the next 4 weeks to the end of the blinded phase (145 mg/dL *v* 163 mg/dL, $P = .003$). Therefore, the LDL-C response at the end of the blinded phase was –7.9% ± 11.0% for the treatment group compared to +2.4% ± 11.7% for the placebo group ($P < .001$). Twelve percent (n = 6) of treatment subjects experienced an LDL reduction of greater than 20% compared to 2% (n = 1) in the placebo group ($P = .05$). The LDL:HDL ratio decreased 9.2% ± 11.9% in the treatment group ($P < .001$), but did not change significantly (-2.0% ± 12.7%, $P = .27$) in the placebo group. The mixed model confirmed that the treatment and time main effects were statistically significant (Fig 1). At the end of the labeled open retail treatment phase of the study, the 2 groups (n = 96, all on active treatment at this point) had begun to converge with regard to LDL-C concentrations (145 mg/dL *v* 156 mg/dL, $P = .09$).

Secondary Endpoints

TC, ApoB, HDL-C, TG, glucose, and homocysteine were secondary endpoints. Table 2 shows that TC mirrored the LDL-C response, with significant differences between the treatment and placebo groups appearing at the time of the interim visit, continuing through the end of the blinded phase, and converging by the end of the open treatment phase. The percent

Table 1. Presentation Characteristics of Patients Who Completed the Study Through the End of the Blinded Phase

	Treatment	Placebo	*P* Value
n	50	49	—
Age (yr)	49 (40-60)	51 (43-58)	.51
Female	16 (32%)	21 (43%)	.26
Non-white	6 (12%)	1 (2%)	.15
TC (mg/dL)	237 (221-262)	242 (228-260)	.67
LDL (mg/dL)	159 (144-178)	158 (148-178)	.83
HDL (mg/dL)	48 (42-62)	48 (42-61)	.81
TG (mg/dL)	146 (94-198)	140 (111-185)	.96
LDL:HDL	3.2 (2.6-3.8)	3.3 (2.7-3.9)	.67
Glucose (mg/dL)	83 (75-91)	82 (75-92)	.99
BMI	27.8 (25.3-30.7)	27.3 (24.7-29.4)	.62
Homocysteine	9.8 (7.8-11.8)	9.4 (8.4-10.4)	.49
Systolic blood pressure (mm Hg)	119 (111-128)	120 (110-131)	.57
Diastolic blood pressure (mm Hg)	81 (72-86)	80 (75-89)	.82

NOTE. Continuous measures presented as median and interquartile range, categorical measures presented as number and percentage.

change in TC from randomization to the end of the blinded phase was –5.7% ± 8.8% for the treatment group compared to +3.1% ± 11.3% for the placebo group ($P < .001$).

At 8 weeks, the treatment group had dropped to a median ApoB of 110 mg/dL, while the placebo group remained at 135 mg/dL ($P = .005$). The correlation between change in LDL-C and change in ApoB (end of blinded phase) was 0.27 ($P = .006$). The correlation for the changes between the end of the blinded phase and the end of the open-label phase was not significant ($r = 0.14$, $P = .30$). Because ApoB was only measured in a subsample, a bias could have been incorporated. However, lipid concentrations (TC, LDL-C, HDL-C, TG) and homocysteine were similar for those with and without ApoB measures at each visit. Further, baseline ApoB measures were similar between the treatment (139 mg/dL) and placebo (135 mg/dL) groups ($P = .75$).

Plasma homocysteine was measured at randomization and at

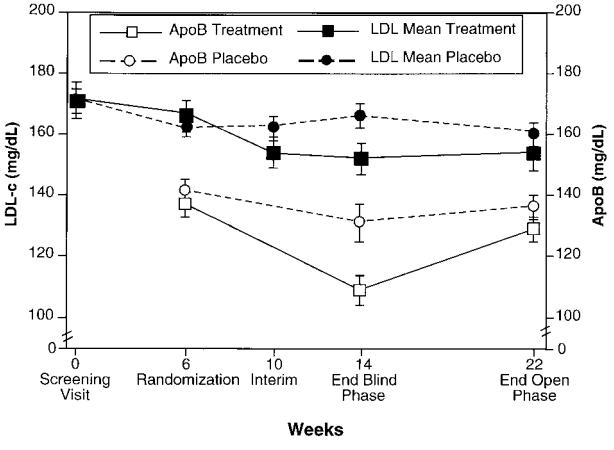

Fig 1. LDL response (mean ± SEM) by median and interquartile range by placebo (P) and treatment (T) groups.

Table 2. Median and Interquartile Range (IQR) for Outcomes at Each Time Period

	Treatment (n = 50)		Placebo (n = 49)	
	Median	IQR	Median	IQR
LDL (mg/dL)				
Screening	159	144-182	169	148-184
Randomization	159	144-178	158	148-178
Interim	147	127-163	162	143-178
EOB	145	134-165	163	143-181
EOO	145	130-166	156	138-178
TC (mg/dL)				
Screening	238	222-268	247	229-271
Randomization	237	221-262	242	228-260
Interim	225*†	210-238	245	227-259
EOB	227*†	202-251	246	230-279
EOO	233†	211-261	237	217-264
HDL (mg/dL)				
Screening	50	44-60	51	42-61
Randomization	48	42-62	48	42-61
Interim	51	43-58	49	42-60
EOB	51	45-59	51†	43-63
EOO	53	44-59	51†	45-64
TG (mg/dL)				
Weeks	122	88-174	137	100-171
Randomization	146	94-198	140	111-185
Interim	123	103-160	127	96-176
EOB	119	89-177	122	104-162
EOO	130	102-205	132	102-159
Weight (kg)				
Weeks	85	74-93	80	72-89
Randomization	85	75-93	80	71-89
Interim	84	70-92	80	72-90
EOB	84	72-93	81	72-88
EOO	83	72-92	79	71-90
GLU (mg/dL)				
Randomization	83	75-91	82	75-92
Interim	83	75-89	86	80-92
EOB	83	76-90	85	77-91
EOO	85	77-91	82	77-90
ApoB (mg/dL)				
Randomization	139 (n = 26)	123-150	135 (n = 29)	130-152
EOB	110*†	89-121	135	114-153
EOO	134	115-138	133	117-155
HCY (mmol/L)				
Randomization	9.8	7.8-11.8	9.4	8.4-10.4
EOB	8.7†	7.6-10.0	9.2	8.3-10.9

NOTE. Data are shown for the screening visit, randomization (which is the combined data for visits 2 and 3), the interim visit (4 weeks after randomization), the end of the blind phase (8 weeks after randomization), and the end of the open phase (16 weeks after randomization).

Abbreviations: IQR, interquartile range; EOB, end of blinded phase; EOO, end of open-label phase; GLU, glucose; HCY, homocysteine.

*$P < .05$ for between-group difference.

†$P < .05$ for within-group difference (*v* value at randomization).

the end of the blinded phase. Both the treatment and placebo groups were similar at randomization (9.8 mg/μmol/L *v* 9.4 mg/μmol/L, $P = .49$). The treatment group showed a significant reduction over 8 weeks, with the median plasma homocysteine dropping to 8.7 mg/μmol/L ($P = .02$). The placebo group showed no change (8-week plasma homocysteine, 9.2 mg/μmol/L; $P = .98$).

Between-group differences never exhibited statistical significance for HDL-C or TG (Table 2). HDL-C increased modestly for both groups (treatment group, +2.3% ± 11.3%; placebo group, +5.1% ± 9.9%; $P = .19$) as did glucose (treatment, +2.7% ± 15.0%; placebo, +4.0% ± 18.2%; $P = .70$). TG concentrations decreased somewhat in the treatment group (-5.3% ± 23.7%), while increasing slightly in the placebo group (+4.3% ± 42.5%), but the difference was not statistically significant ($P = .17$).

The treatment and placebo groups showed similar baseline dietary habits for soluble fiber, fat calories, saturated fat, protein, and alcohol (Table 3). However, total caloric intake, total fiber, and carbohydrate intake were different at randomization. The only statistically significant change in dietary pattern from randomization to the end of the blinded phase was a decrease in soluble fiber intake for the treatment group ($P = .04$). A similar, though not statistically significant, tendency was seen in the placebo group ($P = .09$). This result precludes fiber being associated with the test product itself.

Including baseline dietary fiber intake (ie, not associated with test product) in the mixed models for LDL-C response does not dampen the observed treatment effect. Similarly, incorporating the change in soluble fiber intake does not affect the primary conclusions that LDL-C concentrations were significantly reduced in the treatment group. Neither fiber intake ($P = .49$) nor change in soluble fiber intake ($P = .61$) from the diet alone were significantly related to LDL-C reduction in these models. Stool consistency was not different between groups at randomization ($P = .98$) or at the end of the blinded phase ($P = .54$). Moreover, there was no change over time within the treatment ($P = .99$) or placebo groups ($P = .86$).

DISCUSSION

In this preliminary, double-blind randomized clinical trial, we found a high soluble fiber mixture, supplemented with a full complement of vitamins, to reduce LDL-C by 10% compared to placebo, without adverse effects on HDL-C or TG concentrations. The LDL:HDL ratio significantly improved, and ApoB levels decreased in a representative subsample. The expected modest reduction in homocysteine was observed. Such a supplement could represent a valuable agent in the growing demand for nonsystemic cardiovascular prevention therapies.

Table 3. Median and Interquartile Range for Diet Parameters at Baseline (1) and End of Blind Visit (2) With Between-Group *P* Values

	Treatment	Placebo	*P* Value*
Calories1	1,952 (1,696-2,462)	1,855 (1,372-2,189)	0.06
Calories2	2,047 (1,575-2,607)	1,741 (1,415-2,114)	0.13
Fiber1	23 (17-32)	19 (14-24)	0.03
Fiber2	20 (16-27)	16 (13-24)	0.05
Soluble fiber1	3.3 (2.1-4.9)	3.4 (2.0-4.4)	0.60
Soluble fiber2	3.0 (1.9-4.9)	2.9 (1.8-4.9)	0.94
Fat calories1	596 (439-802)	468 (362-668)	0.10
Fat calories2	644 (435-804)	563 (438-695)	0.36
Saturated fat1	166 (129-258)	143 (98-222)	0.14
Saturated fat2	195 (111-288)	163 (131-217)	0.53
Protein1	83 (69-110)	78 (62-89)	0.15
Protein2	81 (61-108)	73 (66-90)	0.30
Carbohydrate1	270 (205-329)	217 (169-300)	0.03
Carbohydrate2	258 (213-329)	222 (172-279)	0.04
Alcohol1	0 (0-10)	0 (0-11)	0.99
Alcohol2	0 (0-13)	0 (0-13)	0.89

NOTE. Calories, fat calories and saturated fat are reported as calories, while the remaining parameters are reported as grams.

*Wilcoxon rank-sum tests.

In the 49 subjects of the treatment group, this fiber supplement produced an average 7.9% reduction in LDL-C from baseline, during a concurrent 8-week period in which the placebo group LDL-C increased 2.4%. The observed 17-mg/dL LDL-C reduction was consistent with the 1-g soluble fiber per 2.2 mg/dL LDL-C decrease expected based on a recent meta-analysis.[7] The reduction was already observed at the mid 4-week point, which was then subsequently maintained for the additional 4 weeks. Twelve percent of the treatment group achieved 20% or better LDL-C reduction, and the patients appeared to tolerate the supplement without a change in gastrointestinal activity. ApoB decreased coordinately ($r = .27$) with the LDL-C concentrations. In fact, there was a suggestion that ApoB decreased more than LDL-C, leading perhaps to a less dense LDL-C particle and thereby less cardiovascular toxicity.[8] Hunninghake et al[9] recently reported a fiber product that similarly demonstrated an overall 9% LDL-C decrease from placebo, with a companion article[10] indicating an ApoB decrease that evaporated by the 15th week. In addition, the observed LDL-C lowering diminished by the 9th week of fiber intake, all consistent with our own data. We found ApoB and LDL-C lowering markedly diminished if not lost by the 16th week. Compliance appears to be the most likely basis for these outcomes, but it remains possible that some biologic tolerance is a contributing factor. The specific type of fiber is potentially relevant in this regard, as psyllium has only modest effects on ApoB.[11]

Multiple fiber products[1] have provided LDL-C lowering, and mild HDL-C/TG changes. Meta-analyses of 8 controlled trials related to psyllium suggested a 7% average reduction in LDL-C, along with subtle 1% to 3% increases in TG and decreases in HDL-C. Guar gum/pectin combination therapy provided 7% to 8% reductions in LDL, with LDL-C:HDL-C ratio reductions of 6% to 9%[10] and no clear change in HDL-C or TG. This is consistent with the 9% reduction in the LDL-C:HDL-C ratio we observed. While there was no clear tendency for a reduced HDL-C or increased TG in our current study, a downward trend in TG was observed during the blinded phase. Bile acid sequestrants, which target bile acid absorption and are thought to parallel the physiologic action of fiber products, do produce significant increases in TG concentrations.[12] The basis for relatively little change in TG concentrations with fiber compared to bile-absorbing resins remains unclear.

The incorporation of 240 μg of daily folic acid, along with 18 μg of vitamin B_{12} and 7.2 mg vitamin B_6, into the fiber preparation resulted in a modest but anticipated reduction in homocysteine. Given the reported influence of fiber on the absorption of Ca^{2+},[13] beta-carotenoids,[14] and fat-soluble vitamins,[15] as well as vitamin B_6[3,4] via the intestinal system, we thought it prudent to address this issue. At low baseline concentrations of homocysteine with an average 500 μg folate

dose, we might have expected a nearly 20% decrease, rather than the 10% decrease observed.[16] However, we can still reasonably conclude that supplementation with these B vitamins modestly promotes homocysteine changes, even in the setting of fiber coadministration, consistent with reports suggesting fiber does not alter vitamin B_6.[17,18] Given the supplemental folic acid included today in many typical fortified food items, it is noteworthy that a modest trend was still observed. In addition, serum glucose concentrations did not change, suggesting little influence on glucose intestinal uptake and metabolism in nondiabetic subjects.

The recent NCEP Adult Treatment Program guidelines strongly support the use of fiber to lower elevated LDL concentrations.[19] We demonstrate that this fiber-vitamin mixture attains the LDL reduction anticipated, while permitting the homocysteine-related benefit of B vitamins. Long-term studies should be undertaken to preclude ultimate tolerance to this agent. Such a product, if taken regularly, could reduce cardiovascular risk on a population basis and potentially decrease the need and/or dose for lipid-lowering prescription drugs.

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