The Role of Nutraceutical Supplements in the Treatment of Dyslipidemia and Dyslipidemia-induced Vascular Disease

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Disclosure

MARK HOUSTON, MD, MS, MSc has indicated that he is an independent contractor/consultant for Biotics, Itamar, Spectracell, Boston Heart Lab, Cleveland Heart Lab, Designs for Health, Thorne and AC Grace. He is on the review panel/board for Designs for Health, and receives grants from private industry for Biotics, DFH, Thorne and Neogenis.
OBJECTIVES

• Review the scientific data and human clinical trials related to nutritional supplements for the treatment of dyslipidemia and dyslipidemia-induced vascular disease.

• Review the 38 mechanisms involved in dyslipidemia-induced cardiovascular disease.

• Review the effects of nutritional supplements on serum lipids as measured by advanced lipid testing, their proposed mechanisms of action and their role in the treatment of dyslipidemia and dyslipidemia-induced cardiovascular disease.
Key References
Nutritional Supplements and Dyslipidemia

The Arterial Wall

Lumen

Intima
- endothelium
- connective tissue

Media
- smooth muscle
- protein matrix of elastin/collagen
- internal elastic lamina

Adventitia
- strong, fibrous tissue to maintain vessel shape

Mechanism Of Model

- Infinite Insults
  - Oxidative Stress
  - Immune Dysfunction
  - Inflammation

Finite Responses
Cardiovascular Disease

Dyslipidemia  Inflammation  Oxidative stress  Immune dysfunction  Endothelial dysfunction  Cardiomyocyte and vascular dysfunction  Decreased CV function, CHD/MI
Lipoproteins and Atherosclerosis
It Matters What You Have

- Particle movement
  - Gradient driven

- Enhanced macrophage uptake
  - Modified or retained lipoproteins

- Lipoprotein particle
  - Binding to proteoglycans
  - Dendritic cells VADCs

- Enhanced endothelial dysfunction
- Colony-stimulating factors
- Oxidative modification
- Endothelial cells

- Adhesion molecules HSP 60, TLRs and NODs
- PAI-1
- MCP-1
- Tissue factor

- Particle retention

- Extensively modified LDL
- Mildly modified LDL
Atherosclerotic Plaque Formation

- Imflammation ruptures plaque
- Foam cells build plaque
- Foam cell
- Oxidized LDL
- Dense LDL
- RLP
- HDL 2b
- HDL 3
- Lp(a)
- Monocyte cell
- Damaged endothelium cells
- Arterial intima
- Arterial lumen
- HDL removes excess lipids

HDL removes excess lipids.
Reasons that patients or health care providers chose non-pharmacologic treatment of dyslipidemia

1. Intolerable adverse effects of dyslipidemia drugs (myalgias, fatigue, gastrointestinal).
2. Contraindications or allergic response to drugs (liver, muscle, rash, angioedema).
3. Perceptions of adverse effects of drugs.
5. Personal preference for nutritional approaches and nutritional supplement therapies.
Cardiovascular benefits in RCCT with hard clinical endpoints is unproven except for:

- Niacin: Vitamin B 3
- Marine lipids: Omega-3 fatty acids
- Red yeast rice (RYR)
- Mediterranean diet
- Fiber
The Mammalian Cell Mevalonate Cholesterol Pathway and PP (pyrophosphates)

- HMG-CoA Reductase
- Mevalonate-PP Decarboxylase
- Squalene Synthase
- Squalene Epoxidase
- Squalene
- Acetyl-CoA
- Acetoacetyl-CoA
- HMG-CoA
- Mevalonate
- Mevalonate-PP
- Isopentenyl-PP
- Geranyl-PP
- Farnesyl-PP
- Dimethylallyl-PP
- Isopentenyl Adenosine
- Dolichols
- 2-cis Geranylgeranyl-PP
- All Trans Geranylgeranyl-PP
- Ubiquinone
- GG transferase II
- Prenylated Proteins
- Tocotrienols

Drugs and Nutrients:
- Pantethine, Sesame, EGCG
- Omega 3FA, Citrus Bergamot
- Garlic, Curcumin, GLA
- Plant Sterols, Soy, Lycopene
- Policosanol
- Red Yeast Rice
- Statins
- Policosanol
- Red Yeast Rice
- Statins

- Pantethine, Sesame, EGCG
- Omega 3FA, Citrus Bergamot
- Garlic, Curcumin, GLA
- Plant Sterols, Soy, Lycopene

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- Omega 3FA, Citrus Bergamot
- Garlic, Curcumin, GLA
- Plant Sterols, Soy, Lycopene
Niacin meta-analysis of lipid effects, CVD and CHD

Eleven trials of 9959 patients.
Reduction in composite endpoints of any CVD by 34%.
Reduction of major CHD event by 25%. No change in CVA.
Magnitude of on-treatment HDL difference, between treatment arms, was not significantly associated with the magnitude of the effect of niacin on clinical outcomes.
Niacin’s reduction in CVD events may occur through mechanisms that are not reflected by changes in HDL, such as antioxidant, anti-inflammatory, anti-immune and anti-thrombotic activity a reduction in MPO (myeloperoxidase), CAMs (cell adhesion molecules) and cytokines as well as increased adiponectin and improvement in endothelial function.
Niacin meta-analysis of lipid effects and CHD

J Am Coll Cardiol 2013:61(4):440
Nutrition Reviews 2012;70:357; Curr Opin Lipidol 2013;24:475
Therapeutic Advances in Cardiovascular Disease 2011;5:227
Current Opinion in Cardiology 2010 Nov 1, J Clin Lipidology 2011;5:368
NEJM 2009;361:2113 Am Heart J 2011;161:538

Average changes in lipids in the dose range of 1 to 4 grams/day

TC: 20 – 25% decrease.

LDL and APO B: 10 – 25% decrease. Also decreases LDL-P, oxLDL and increases LDL size.

Reduces Lp(a).

Increases RCT (reverse cholesterol transport) and CEC (cholesterol efflux capacity) by passive diffusion, ABCG-1 and SR-B1).

TG: 20 – 25% decrease with decrease in VLDL size.

HDL and APO A-1: 15 – 35% increase with increase in HDL size, increase in HDL 2 by up to 16% increase in HDL-P by up to 16% and improves HDL function.

Adverse Effects: hyperglycemia, hyperuricemia, gout, hepatitis, flushing, rash, pruritus, hyperpigmentation, hyper-homocysteinemia, gastritis, PUD, bruising, SVT and palpitations.
Niacin Lowers PCSK 9 levels

Khera AV. Am J Cardiol 2015;115:178-182

- PCSK9 levels are increased in a dose-dependent fashion with statin therapy compared with placebo (placebo, mean increase 7%; 95% CI, –7 to 21; atorvastatin 10 mg/day, mean increase 19%; 95% CI, –5 to 42; atorvastatin 80 mg/day, mean increase 27%; 95% CI, 12-42; $P=.02$ vs. placebo).

- In a second study, 70 patients with carotid atherosclerosis were randomly assigned simvastatin 20 mg/day, simvastatin 80 mg/day or simvastatin 20 mg/day plus extended-release niacin 2 g/day for 12 months.

- PCSK9 levels increased with statin therapy (simvastatin 20 mg/day, mean change 13%; 95% CI, –14 to 40; simvastatin 80 mg/day, mean change 41%; 95% CI, 27-76; $P<.0001$), but that PCSK9 decreased with combination simvastatin/niacin therapy (mean change –13%; 95% CI, –3 to –23).

- In a third, open-label lipid kinetics study, 19 people with dyslipidemia were treated with atorvastatin 10 mg/day for 4 weeks, followed by the addition of fenofibric acid 135 mg/day for 8 weeks, and then the further addition of extended-release niacin 2 g/day for 10 weeks.

- Adding fenofibric acid led to a 23% (95% CI, 10-36) increase in PCSK9 ($P=.001$), but the addition of niacin resulted in a subsequent 17% (95% CI, –19 to –5) decrease in PCSK9 ($P=.004$), according to the researchers. A positive association between changes in PCSK9 levels and changes in LDL levels ($P=.006$) induced by the addition of niacin was found.
Prolonged combination lipid therapy is associated with reduced carotid intimal-media thickness: 20 years of FATS-OS Trial

J Clinical Lipidology 2014;8:489-493

- Combination therapy with statin, colestipol and niacin had better lipid profiles (p<0.001) and lower CIMT(carotid intimal medial thickness) (P<0.001) than those patients on statins alone.
- Also reduction in carotid plaque and volume of lipid rich necrotic core was better with niacin.
Niacin combination therapy with statin or bile acid resin on lipoproteins and CVD

Am J Cardiology 2014;113:1494

- 107 subjects evaluated with niacin in combination with statin (simvastatin) or bile acid resin (colestipol) with advanced lipid testing and coronary angiography.

- Improved angiographic findings correlated with LDL-P, dense LDL, IDL and VLDL but not with HDL, HDL fractions or large LDL.

- Niacin combination therapy decreases LDL-P, dense LDL, IDL, VLDL and increases HDL. CHD stenosis as measured by angiography and CHD event rate correlate with all except the HDL levels and subfractions of HDL.
- Niacin remains an efficacious agent for the treatment of dyslipidemia and prevention of CVD as single therapy, with statins and other lipid-lowering agents with a relatively low side effect profile. Neither the HPS 2 THRIVE nor the AIM HIGH studies provide any convincing evidence for not using niacin in the appropriate clinical situation.
- The vast majority of clinical trials with niacin or niacin with other anti-lipid agents show significant reductions in CVD, CHD and carotid atherosclerosis.
- In patients not taking statins or those with high LDL levels at baseline (over about 85 mg/dl), high TG over 200 mg/dl and HDL-C < 32 mg/dl, HPS2-THRIVE study results are not likely to be applicable.
- The addition of laropiprant may well have caused harm in the treatment arm, and the conclusions relating to both safety and efficacy cannot be attributed to niacin alone.
- The available evidence strongly suggests that individuals who are not adequately treated on a statin alone can safely benefit from niacin's additive effect on LDL reduction, LDL particle number reduction, increase in LDL size, increase in HDL, HDL 2b, HDL particle number, HDL function, reverse cholesterol transport and triglyceride reduction.
- Patients with CVD and dyslipidemia with HDL < 32 mg/dl and triglyceride > 200 mg/dl may benefit from extended –release niacin added to intensive statin based LDL-C lowering therapy.
- Niacin may have non-lipoprotein actions that are clinically important to prevent and treat CVD and CHD.
- Niacin remains in important agent for the treatment of dyslipidemia and the prevention and treatment of CVD, CHD and carotid atherosclerosis.
IHN (inositol hexanicotinate) which is often referred to a non-flush niacin, is not effective in dyslipidemia compared to placebo and is not recommended.
Red yeast rice
Am J Cardiol 2008;101:1689-93
Clin Med 2006;1:4
J Clin Lipidology 2010;119:374

- 5000 Chinese patients with previous myocardial infarction received Xuezhikang, an extract of red yeast rice (RYR) at 600 mg for 4.5 years vs placebo.
- Primary end point was myocardial infarction and death.
- LDL decreased 17.6% with RYR (p< 0.001) and HDL increased 4.2 % ( p<0.001).
- 10.4 % incidence of primary end point in placebo vs. 5.7% in RYR group (p<0.001). A RRR of 45% and absolute reduction of 4.7% in RYR treated group.
- Cardiovascular mortality decreased 30% ( p<0.005).
- Total mortality decreased 33% ( p<0.0003).
- No change in cerebrovascular accident.
Red yeast rice (RYR) 22 clinical trials review

- **Lipid Effects**: Monacolines are the active ingredients, which inhibit cholesterol synthesis via HMG-CoA reductase (13 natural statins). The statin content is evaluated by NMR. Also contains sterols (B-sitosterol, campesterol, stimasterol, sapogenin), isoflavones, isoflavone glycosides, flavonoids and monounsaturated fatty acids. Contains over 30 pigments and unsaturated FA, ergosterol, amino acids, alkaloids and trace elements.

- **At a dose of 2400 mg at night**
  - Reduces LDL ~ 22%
  - Reduces TC ~ 17%
  - Reduces TG ~ 12%
  - HDL - No change or increase
  - Lowers MMP 2 and 9 (28%), leptin, insulin resistance, hsCRP (24%), TF (tissue factor), NADPH oxidase, thrombosis, caveolin-1, TNF alpha and A-II.
  - Reduces NAFLD (non alcoholic fatty liver disease).
  - Increases eNOS, FMD (flow mediated vasodilation), adiponectin
  - Decrease AAA (abdominal aortic aneurysm)
Red Yeast Rice (RYP) 22 clinical trials review

- Decreases nonfatal MI, total CHD events, revascularization and total deaths.
- No adverse effects or events. (liver, muscle etc).
- Citrinin – Toxic fermentation by product (mycotoxin from penicillium and aspergillus) may induce renal failure and is mutagenic in animals. Must avoid low quality RYR.
- Alternative treatment to statin induced myalgias.
- Effective with plant sterols, berberine HCL, niacin, omega 3 fatty acids and other supplements.
- Dose range: 800 to 4800 mg per day of high quality standardized RYR.
Xuezhikang (XZK) is an extract of fermented red yeast rice. A total of 116 adults with dyslipidemia but no coronary heart disease, with baseline non-high-density lipoprotein cholesterol (non-HDL-C) levels of approximately 208 mg/dL and low-density lipoprotein cholesterol (LDL-C) levels of approximately 175 mg/dL were randomized to either placebo or XZK 1200 or 2400 mg daily and treated for 12 weeks. (1200 mg = 12 mg Lovastatin)

**RESULTS:** A majority of the patients were white (53.4%) or Asian (37.1%). Daily XZK 1200 mg and 2400 mg for 4 to 12 weeks resulted in statistically significant (P < .001) and clinically meaningful decreases in non-HDL-C (~24% reduction) and LDL-C (~27% reduction) compared with placebo. XZK treatment at either dose enabled approximately 50% of subjects to reduce their LDL-C levels by ≥ 30%. Doubling the XZK daily dose from 1200 to 2400 mg at treatment week 8 caused an additional 4.6% reduction in LDL-C. Significant benefits were also observed across secondary efficacy variables, including total cholesterol (TC-18%), apolipoprotein B (Apo B)(21%), triglycerides,(8%) HDL-C and APO A-1( increased 5%), the TC/HDL-C ratio, and the Apo B/Apo A-I ratio, at treatment week 8 or 12. XZK was safe and well tolerated. Safety and tolerability profiles were similar across treatment groups. Most adverse events were gastrointestinal. 3-5 % had muscle spasm or myalgia. No subject experienced myopathy or markedly elevated liver transaminases or creatine kinase.

**CONCLUSION:** Xuezhikang significantly reduced non-HDL-C and LDL-C, and was well tolerated.
PLANT STEROLS

Nutrition Reviews 2011;69:371
J Nutr 2009;139:271
Nutrition 2013;29:96
Curr Opin Lipidol 2013;24:12

- Plant Sterols: B-sitosterol, campesterol, stigmasterol, stanols. Improve serum lipids
  - TC decreased 8%
  - LDL decreased 10%
  - HDL and TG - no change
- Dose dependent decrease in the incorporation of dietary and biliary cholesterol into micelles, reducing cholesterol absorption and increasing bile acid secretion.
- Reflex upregulation of hepatic LDL receptors.
- Anti-inflammatory: reduce CRP, IL6, TNF alpha, PLA 2(phospholipase A) and fibrinogen.
- Interaction with ABCG8 and ABCG 5 that directs cholesterol back into the intestinal lumen.
- Modulate signaling pathways.
PLANT STEROLS

Nutrition Reviews 2011;69:371
J Nutr 2009;139:271
Nutrition 2013;29:96
Curr Opin Lipidol 2013;24:12

- Reduction of Apo B 48 secretion of intestinal and hepatic cells.
- Suppresses HMG COA reductase and suppress CYP7A1.
- Interfere with SREBP (steroid receptor binding protein).
- Promote reverse cholesterol transport (RCT).
- Decreases fat soluble vitamin absorption.
- Reduce atherosclerosis progression, IMT and improves plaque regression.
- Mixed data with CVD reduction.

4S trial and PROCAM trial: increased risk of CV events in hyper-absorbers taking statin drugs.
Dallas Heart Study and EPIC-Norfolk trial did not confirm any evidence of CV events.

- Dose: 2 to 2.5 grams / day
- Meta-analysis 84 trials showed that 2.15 grams per day reduced LDL by 8.8% and lowers CVD and CHD.
- Effective in combination with statins and selected nutritional supplements for dyslipidemia (Red yeast rice, berberine, omega 3 fatty acids, niacin).
• Mixed soluble fibers reduce TC, LDL and TG.
• Average reduction in LDL is 2.2 mg/dL per one gram of fiber in RCCT.
• Reduce CVD and CHD. Each 10 grams of fiber/day reduced CHD events by 14% and CHD death by 27%.
• Types: pectin, psyllium, B-glucan, oat bran, guar gum, rye, glucomannan, nori, kombu.
• Alter hepatic cholesterol metabolism and synthesis by lowering hepatic cholesterol pools and shifting in bile acid synthesis and thus less for VLDL and LDL. Decreases acyl-coenzyme A cholesterol: acyltransferase activity.
• Alter processing of lipoproteins in intravascular compartment by upregulating hepatic LDL receptors.
• Increase catabolism of lipoproteins.
• Decrease VLDL synthesis, reduce conversion of VLDL to LDL.
• Reduces CETP activity.
• DOSE: 30 to 50 grams per day of total fiber and at least 10 grams of soluble fiber.
4 grams of combined EPA and DHA:

1. Net decrease in concentration of all atherogenic particles such as non-HDL cholesterol, apolipoprotein B 100 and LDL particle number (LDL-P) across most all LDL levels. (p<0.01).

2. May have slight increase in LDL mostly in those with lowest LDL level less than 80 mg/dl, but decreased in those with higher LDL over 100 mg/dl but still beneficial (see above).

3. Increase conversion of dense small LDL B to larger LDL A by .25nm (DHA especially) (p<0.002).

4. Reduce TG (30%-40%), VLDL, VLDL particles and VLDL size.

5. Lowers Apo CIII (inhibits lipoprotein lipase) thus enhancing delipidation of TG rich lipoproteins and increasing the fractional rate of VLDL conversion to LDL particles.

6. Increase total HDL with increase in HDL-P and HDL size. HDL 3 decreases 7% (DHA), HDL 2b increases 29% (DHA).
Effects of omega 3 fatty acids on serum lipids
Am J Card 2010;105:1409, J of Nutriton 2008;138:30

4 grams of combined EPA and DHA:

1. Decrease fatty synthesis and increase in fatty acid oxidation.
2. Improves insulin sensitivity, increases insulin levels 18%-27%, reduces or does not change fasting glucose or AIC even in high doses in normal patients.
3. Decreases lipoprotein associated phospholipase A2 levels (Lp-PLA2). Is anti-inflammatory, anti-thrombotic, natural PPAR agonist, improves heart rate variability (HRV), lowers HR, increase eNOS / NO, improves ED, reduces BP (DHA>EPA), decreases atrial fibrillation (?) and arrhythmias, reduces growth of atherosclerotic plaque with more well-formed fibrous caps and fewer thin wall caps.
Optimal dosing and ratios of omega 3 FA with GLA and gamma/delta tocopherols

- EPA to DHA ratio: 3:2.
- GLA at 50% of total dose of DHA and EPA (1:2 ratio).
- Gamma/delta tocopherol at 100 mg per 1000 mg DHA/EPA/GLA with no more than 20% as alpha tocopherol. (membrane oxidation)

Lowers TG (40%), LDL (12%) and BP. GLA with omega 3 FA is better in reducing LDL.
Decreases inflammation, lowers hsCRP and arachidonic acid.
Estimated 43% reduction in 10 year risk of MI.

GLA converts to DGLA which is anti-inflammatory (PGE1, 15OH-DGLA, 15-SOH eicosatrienoic acid.
GLA depletes DHA and EPA.
EPA and DHA deplete GLA and DGLA and decrease conversion to AA.
Combination of GLA with DHA and EPA increase DGLA and EPA and decreased AA.
Japan EPA lipid intervention study (JELIS trial)

Lancet 2007;369:1090
Atherosclerosis 2008; 200: 135
Stroke 2008;39:2952

- 18,645 patients. Mean 4.6 year follow up.
- Randomized to statin plus 1.8 grams of EPA vs statin alone.
- 19 % RRR in major coronary events and non fatal myocardial infarction.
- 20% RRR in stroke.
Krill Oil and Dyslipidemia

Dose related changes in lipids with krill oil.
DHA and EPA are in form of double chain phospholipid structure.
Also contains Vitamin E, A, D and astaxanthin.
ORAC is 48 times that of fish oil.
TG reduced: 1.0 gram 11 %, 1.5 grams 12 %, 2.0 grams 27.6 % and 3.0 grams 26.5 %.
LDL reduced: 1.0 gram 32%, 1.5 grams 35%, 2 grams 37% and 3 grams 39%.
HDL increased: 1 gram 44%, 1.5 grams 43 %, 2 grams 55% and 3 grams 60%.

Study never replicated and the data is in question.
Krill Oil and Triglycerides

Nutrition Research 2014;34:126

- Krill has DHA and EPA in PL form
- May result in higher tissue levels of DHA and EPA?
- RDBPC study of 300 subjects with TG 150-499 mg/dl.
- Krill oil at 0.5, 1.0, 2.0 and 4.0 grams per day for 12 weeks
- No significant change in TC, LDL or HDL
- TG reduction at 12 weeks
  - 0.5 gm: 23 mg/dl (10%) NS
  - 1.0 gm: 9.1 mg/dl
  - 2.0 gm: 16 mg/dl
  - 4 gm: 2.1 mg/dl
  - placebo: 6.4 mg/dl

The reduction at 12 weeks was not significant in any group and was less than that at 6 weeks.

Krill oil is not recommended at this time.
Monounsaturated Fatty Acids Olive Oil

Reduce LDL (5-10%) and TG(10-15%).
Decrease oxLDL and oxLDL receptor
Increase HDL(5%).
Up-regulate genes involved in reverse cholesterol transport (RCT). ATPA1, SRA B 1, PPAR, CD 36. Directly related to the polyphenol content.
Reduces CD40L gene expression, MCP-1, IL-23, ADR B2, IL-8 R, ICAM, VCAM, TNF alpha and interferon gamma.
Reduce CHD and MI by 30% (Mediterranean diet) especially with EVOO and nuts.
Reduce oxidation, inflammation, thrombosis and many of the proatherogenic molecular mechanisms in CVD and CHD.
Improve ED and reduce BP
Related to polyphenol contents. Also to tyrosol and hydrotyroxosol in urine.
Recommend EVOO at 40 grams per day(4 tablespoons)
Inhibit cholesterol synthesis by post-transcriptionally suppressing HMG-CoA reductase activity by two post-transcriptional actions.

1. Increased controlled degradation of reductase protein.
2. Decreased efficiency of translation of HMG-CoA reductase mRNA.

Lipid reductions at 12 weeks diet + gamma/delta tocotrienol extract (p < 0.05) (Nutr Biochem 1997; 8:290)

- ↓ TC 17%, ↓ LDL 24%, ↓ APO-B 15%, → HDL and Apo A-1 and lower Lp(a) 17%.
- ↓ PF4 (platelet factor) 14%, ↓ TxB (thromboxane B) 31%.
- ↓ BS.

- Take with evening meal to increase absorption.
- Variable response rate (50% of patients).
- Endogenous increase in GGPP (geranyl-geranyl pyrophosphate) and mitochondrial CoQ10.
- Synergistic with statins with additional 10% reduction in LDL. (J Nutr Biochem 2001;12:318).
- **DOSE:** 200 mg of gamma / delta tocotrienols taken at night with food at least 12 hours after consumption of any tocopherols.
PCSK9 (Serum proprotein convertase subtilisin/kexin 9)

- Berberine HCL down-regulates PCSK9 and increases activity of LDL-R for hepatic removal of LDL-C.
- Additive with statins in LDL reduction.
- More effective than ezetimibe in lowering LDL-C.

Curr Opin Lipidol 2012;23:511; JAMA 2012;308:2497
Curr Opin Lipidol 2013;24:251; Current Opin Lipidol 2013;24:307
Curr Opin Lipidol 2014:25:387
Berberine HCL

- Alkaloid present in plant roots, rhizomes, stem barks.
- Over 3 months TC decreases 29%, LDL 25% and TG 35%.
- Meta-analysis of 11 trials in 874 subjects showed significant reductions in TC (23.5 mg/dL), LDL (25 mg/dL), TG(44 mg/dL) and increase in HDL similar to above studies.
- Suppresses the PCSK9 expression.
- Increases hepatic LDL R (mRNA and protein) 2.6 to 3.5 fold by inhibiting transactivation of PCSK9 mRNA expression by HNF1 alpha. Post-transcriptional mechanism dependent on ERK but independent of SREBP.
- Reduces cholesterol absorption /increases biliary excretion of LDL.
- Inhibits HMG-CoA reductase.
Berberine HCL

- Stimulates AMPK, reduces insulin resistance and decreases FBS and HBAIC, decreases FA synthesis, increases FA oxidation, delays adipocyte differentiation, promotes weight loss, reduces CHO absorption from GI tract, alters GI flora.
- LPS translocation is blunted.
- Increases EPCs (endothelial progenitor cells), increases eNOS and NO, lowers BP, reduces ED, decreases CECs (circulating endothelial cells), decreases microparticles.
- Lowers NFκb and Th1 cytokines, increases SOD (superoxide dismutase), lowers ROS (radical oxygen species) reduces ACE (angiotensin converting enzyme), lowers NADPH oxidase.

- Additive reduction in LDL, TC and TG with ezetimibe, RYR and phytosterols. Upregulation of LDL R with statins.

- Dose: 500 mg qd to bid of berberine HCL.
Citrus Bergamot

- 1000 mg per day lowers LDL 36%, TG 39% and increases HDL 40% in 30 days. Increases LDL and HDL size, decreases remnant particles, decreases NAFLD and reduces BS.
- Active ingredients are naringin, neoeriocitrin, neohesperidin, poncerin, rutin, neodesmin, rhoifolin, melitidine and brutelidine. Very high polyphenols.
- Inhibits HMG COA reductase. Additive with statin
- Reduce ROS and reduces oxLDL, LOX-R, MDA and PBK phosphorylation.
- Increase cholesterol bile acid excretion.
- Sterol like properties and binds to ACAT receptor.
Lycopene (Acyclic Carotenoid)

- Inhibits HMG CoA reductase.
- Inhibits Rho A.
- Increases PPAR gamma activities
- Increases liver X receptor alpha (LXR-a) activities.
  (nuclear receptors activated by oxysterols involved in lipid homeostasis).
- Forms heterodimer to stimulate RXR (retinoid X receptor).
- Improves ED.
- Decreases NFκB signaling and decreases inflammation.
- Protective role in inhibiting carotid IMT and plaque formation.
Lycopene (Acyclic Carotenoid)

J of Nutritional Biochemistry 2011;22:971
J of Nutritional Biochemistry 2011;23:8-17
J of Nutritional Biochemistry 2013;24:163 and 428
J of Hypertension 2012;31:521

- Enhances ABCA1 expression, reverse cholesterol transport, apoA1 expression, reduces intracellular cholesterol and cholesterol in lipid domains, alters membrane-induced cellular signal transduction.
- Disrupts caveolin-1- nitric oxide binding to increase NO.
- Two unconjugated double bonds reduce ROS.
- Increases HDL 2 and 3, improves HDL functionality.
- Upregulates Nrf2.
- Reduces SAA (serum amyloid A).
- Decreased CETP.
- Increases PON 1 and decreases oxLDL.
- Reduces inflammation and helps immunomodulation.
- Dose 10-20 mg per day
Lycopene Inhibits the Proliferation of LNCaP Cells

Lycopene

Cytoplasm

Translocation

Nucleus

PPARγ

LXRα

PPARγ

RXR

LXRα

RXR

ABCA1

apoA1

HDL

RCT

Cell Proliferation

Cholesterol
Luteolin inhibits transendothelial migration of monocytes and formation of lipid-laden macrophages

Nutrition 2012;28:1044
J of Hypertension 2013;31:521

- Blocks monocyte-endothelium interactions by inhibiting the cytokine associated monocyte induction of integrin –B2.
- Improves endothelial function.
- Blocks MMP 9.
- Reduces PDGF.
- Decreases NFkB signaling and inflammation.
- Dose 10 mg per day.
Garlic and serum lipids: meta-analysis

39 trials in dyslipidemia.
TC reduced 17 mg/dl.
LDL reduced 9 mg/dl and decrease oxLDL.
HDL increased 1.5 mg/dl.
Results in 2 months.
Reduces coronary calcium and plaque progression in humans on statins in DBPC trial of 23 patients over one year on aged garlic at 1200 mg per day. Aged garlic CAC: 7.5+/− 9.4% vs placebo 22.2+/−18.5%.
Improves ED and PWV (pulse wave velocity).
Aged garlic was most effective 600 mg bid (CV formulation).
PANTETHINE


- Pantethine is the disulfide derivative of pantothenic acid and is metabolized to cystamine (SH).

28 Clinical human trials with 646 patients.
- Lowers TC 15% (up to 20.5% at 9 months).
  Lowers LDL 20% and APO B (up to 27.6% at 9 months).
  Increased HDL 8% and APO A-I.
  Lowers TG 33% (up to 36.5% at 9 months).
  - Inhibition of fatty acid synthesis and beta oxidation.
  - Inhibits HMG-CoA reductase.
  - Reduce lipid deposition/ fatty streaks in aorta and coronary arteries.
  - Reduces intimal thickening in the aorta and coronary arteries.
  - Reduces peroxidation of LDL-C.

- Additive to statins, niacin and fibrates.
  Compared to fibrates it has similar changes in serum lipids.

Dose is 450 mg bid.
Peak effect is at 4 months in most, but may be up to 6-9 months.
Probiotics and Lipids
Dig Dis 2013;31:278; Mayo Clinic Pro 2014;89:107; Br J Nutrition 2012;017:1505; Eur

- 100 trillion bacteria in human microbiome (10x that of human cells).
- Lactobacillus reuteri improves lipids (increase fecal excretion via bile salt hydrolase and hepatic catabolism via FXR).
- Reduced LDL and AP0 B 9%, lowers hs CRP and fibrinogen and increases vitamin D.
- Dose: 100 mg per day.
40 grams of dietary sesame reduces LDL-C by 9%, decreases TG and increases HDL.

- Increases catalase, GPx, GSH and SOD,
- Increases vitamins A, C and E.
- Inhibits intestinal absorption.
- Increased biliary excretion.
- Decreased HMG-CoA reductase activity.
- Upregulates LDL receptor gene.
- Upregulates cholesterol 7-alpha hydroxylase gene expression.
- Upregulates SREBP-2 genes.
SOY

38 studies using 31 – 47 grams soy protein / day dose related and proportional to initial cholesterol levels.
- ↓TC 2- 9.3%
- ↓LDL 4-12.9%
- ↑HDL 0- 2.4%
- ↑TG 0- 10.5%

Micellar lipid content and absorption decreased.
Fiber, isoflavones, phytoestrogens improve lipid profile.
Best reduction in dyslipidemic vs. normal.
Most reduction with enriched isoflavones and fermented soy.
Reduce HMG-COA reductase, SREBP, increase LDL receptors, and increases the antioxidant enzymatic activity of catalase and SOD.
Pomegranate juice/seeds

- Increases PON 1 in serum and binding to HDL and PON 2 in macrophages.
- Anti-oxidant.
- Decreases oxLDL.
- Removes oxLDL and other oxidized lipids in serum and arterial wall.
- Reduces glycosylated LDL.
- Reduces carotid IMT.
- POM contains flavonols, flavanols, anthocyanins, proanthocyanidins, ellagitannins and gallotannins, organic and phenolic acids, sterols, triterpenoids, alkaloids, fiber and pectin.
- 1 cup of seeds per day or 6 ounces of juice
Catechins, especially EGCG, improve lipid profile, interfere with micellar solubility of cholesterol in GI tract and reduce absorption.

- Reduce FA synthase gene.
- Increase AMPK.
- Inhibit HMG COA reductase.
- Increase mitochondrial energy expenditure.
- Reduce oxidation of LDL and increase PON 1 (paraoxonase) which protects lipoproteins from oxidation.
- Upregulates the LDL receptor.
- Decreases APO-B lipoprotein secretion from cells.
- Improves FMD and ED.
- Mimics insulin action by activating similar pathways and increases PI3K to regulate gluconeogenesis.
- Reduces body fat.
- Suppresses mRNA expression of proinflammatory cytokines and enhances IRS-1 expression.
- In a rat study: TC reduced 37% (p < 0.05). Non HDL cholesterol reduced 25% (p < 0.05).
- Human Study: EGCG green tea extract at 224-674 mg per day or 60 oz green tea per day reduced LDL 13% and decreased postprandial TG by 15 to 29% and decreased remnant particles.
- Reduce CHD and CVD
- Dose: 500 mg BID of EGCG or 60 to 100 ounces of green tea/day
EGCG stimulates NF-E2 related factor 2 (Nrf2) and heme-oxygenase-1 (HO-1) via caveolin–1 displacement.

- EGCG activates Nrf2 and increased HO-1 expression and cellular production of bilirubin and decreased inflammation and improved oxidative defense.
- Displaces caveolin-1-nitric oxide binding (displacement) and increases nitric oxide, reduces endothelial inflammation and improves endothelial function.
Gamma Oryzanol

Asia Oceania J Obs Gyn 1984;10:317

- Phytosterol in rice bran and rice bran oil
- 10 triterpene and sterol ferulates.
- Reduces LDL by 10-42 % in human studies.
- Inhibits cholesterol uptake into intestinal cells.
- Inhibits HMG-CoA reductase.
- Dose 100 mg tid with food.
CO-ENZYME Q-10 (CO-Q-10) (UBIQUINONE)

Arterioscler Thromb Vasc Biol 2014;34:00; Advances in Therapy 1998; 15:218
Mol Aspects Med 1997; 18:S137; Int J Cardiol 1999; 68:23
Atherosclerosis 1997; 129:119

- Minimal effect on serum lipids, but reduces VLDL and increases HDL and AP0-A1 in animal models and some human studies.
- ROS scavenging and reduction in oxidative stress.
- Decreased oxLDL.
- Reduces inflammation.
- Reduce Lp(a).
- Reduces progression of atherosclerosis in animals.
- Dose 100 mg per day.
RESVERATROL
Smoliga JM et al. Mol Nutr Food Research 2011;55:1129-1141
NEJM 2009;360:1141

- Reduce LDL oxidation and potent antioxidant.
- Inhibit ACAT activity and CE formation.
- Improve ED and vasodilation.
- Increase nitric oxide.
- Increase excretion of bile acids and sterols.
- Reduce atherosclerosis in animals.
- Reduce TC, TG and LDL.
- Ischemia preconditioning in cardiac muscle.
- Modulate SIRT aging genes.
- Reduce proteinuria.
- Reduces inflammation: iNOS, COX-2, NFKb, AP-1.
- Increase PON 1 (paraoxonase) activity.
- Reduce NADPH oxidase, CD36 SR uptake of oxLDL, CD 36 signaling, cell adhesion and actin polymerization.
N Acetyl Cysteine (NAC)

NEJM 2009;360:1144

- Reduces NADPH oxidase, CD36 SR uptake of oxLDL into macrophages, CD36 signaling, cell adhesion and actin polymerization via ROS and adhesion kinase.
CURCUMIN


- Phenolic compounds in turmeric and curry.
- Induces changes in expression of genes involved in cholesterol homeostasis such as LDL-receptor mRNA, HMG CoA reductase, SREBP, cholesterol 7 alpha hydroxylase, PPAR and LXR.
- Reduce oxidative stress.
- Reduces ox LDL uptake into macrophages.
- Increases cholesterol efflux.
- Reduces SR-A and increased ABC A1, ABCG-1 and SR-B1.
- Alters gene expression of CAMs and transendothelial migration via NFkB.
- Decreases foam cell formation and atherosclerosis.
- Human study at 500 mg /day in 10 patients increased HDL 29% and decreased total cholesterol by 12%.
- Human study of 30 patients on 1 gm/day lowered TG (p<0.009), no change in TC, LDL, HDL.
- Meta-analysis 172 subjects lowered HSCRP (p<0.004.)
- Meta-analysis of 133 patients in five studies. No effect on TC, LDL, TG or HDL. Broad range of changes in heterogeneous population.
Quercetin
Nutrition Research 2013;33:136

- Upregulates PPAR gamma, LXR alpha and ATP binding cassette transporter A1 (ABCA-1) genes.
- Increases HDL and Apo A1.
- Increases cholesterol efflux.
- Decreases CDC 36 and SR-A gene expression on macrophage scavenger receptors.
Purified palmitoleic acid for the reduction of high-sensitivity C-reactive protein and serum lipids: A double-blinded, randomized, placebo controlled study. 

- Purified palmitoleic acid (16:1; omega-7) has shown lipid-lowering and anti-inflammatory benefits in open label, epidemiologic, and animal studies.
- First randomized controlled trial of purified palmitoleic acid supplementation in humans.
- Adults with dyslipidemia and evidence of mild systemic inflammation (high-sensitivity C-reactive protein [hs-CRP] between 2 and 5 mg/L) were randomly allocated to receive either 220.5 mg of cis-palmitoleic acid (n = 30) or an identical capsule with placebo (1000 mg of medium chain triglycerides, n = 30) once per day for 30 days. Participants were asked to maintain their current diet. Serum lipids and hs-CRP were drawn at baseline and study completion.

**RESULTS:** At 30 days, there were significant mean (95% confidence interval [CI]) reductions in CRP (-1.9 [-2.3 to -1.4] mg/L), triglyceride (-30.2 [-40.2 to -25.3] mg/dl), and low-density lipoprotein (LDL) (-8.9 [-12.0 to -5.8] mg/dl), and a significant increase in high-density lipoprotein (HDL) (2.4 [1.5, 3.3] mg/dl) in the intervention group compared with control. These changes equated to 44%, 15%, and 8% reductions in CRP, triglyceride, and LDL respectively, and a 5% increase in HDL compared with control.

**CONCLUSIONS:** Purified palmitoleic acid may be useful in the treatment of hypertriglyceridemia with the beneficial added effects of decreasing LDL and hs-CRP and raising HDL. Further study is needed to elucidate mechanisms and establish appropriate human doses.
Clinical Trial

Hypertension Institute Nashville, TN

• 2 month open label study of 30 patients age 30 to 82 with dyslipidemia.

• Administered 4 capsules BID of:
  – Pantethine
  – plant sterols
  – EGCG
  – Gamma delta tocotrienols.

• LPP advanced lipid testing for all lipid parameters.
• TC decreased 14% (p< 0.0001).
• LDL-C decreased 14% and LDL-P decreased 25% (p< 0.003).
• VLDL decreased 20% (p < 0.05).
• Small dense LDL particles type III and type IV decreased 25% (p< 0.02).
• Diastolic blood pressure fell (p< 0.05).
• RYR at 2400 mg at night.
• Niacin B3 at 500 mg per night.

– Additional 20 % reduction in TC and LDL for total reduction of 34%.
– Additional 10 % reduction in LDL-P and in LDL particle type III and IV for total reduction of 35%.
– Additional 7 % reduction in VLDL for total reduction of 27%.
– Increase in HDL 10% (HDL 2).
Natural Treatment Rivals Drug Therapy For Dyslipidemia

- Combination of Portfolio diet, exercise, weight reduction, red yeast rice, phytosterols, berberine, gamma delta tocotrienols, EGCG, pantethine and niacin.

- TC and LDL reductions of 50% with reductions in VLDL, TG, ILDL, LDL-P, increase in LDL particle size, HDL, HDL size, HDL-P and HDL function.
38 mechanisms to decrease dyslipidemia-induced vascular damage, atherosclerosis and coronary heart disease.
Treating the numbers and beyond the numbers

Metabolic approach for prevention and treatment of dyslipidemia-induced vascular disease.
An integrated medicine model
Decrease endothelial permeability, gap junctions, endothelial dysfunction and improve endothelial repair.

Increase nitric oxide bioavailability.

Beets, arginine/citrulline, vitamin D, vitamin C, aged garlic, quercetin, Co enzyme Q 10, lycopene, luteolin, omega 3 fatty acids, polyphenols, flavonoids and flavonoid-rich foods, cacao, tea and catechins, EGCG, MUFA, berry anthocyanins, orange juice and hesperidin, wine polyphenols, red yeast rice, niacin, berberine.

Reduce A-11 effects, increase EPCs, BP control, optimize vascular laminar flow, reduce inflammation, oxidative stress and immune dysfunction.

Modify caveolae, caveolin-1, lipid rafts, membrane microdomains, unesterified cholesterol and cholesterol crystals.

Lycopene, red yeast rice, niacin, omega-3 FA, EGCG.
New Functional And Metabolic Medicine Approach To The Treatment Of Dyslipidemia

- Modify PRR activation -TLR (TLR 2 and 4) and NODs as well as MYD 88 from DAMP, which is primarily modified LDL.
- Niacin, lycopene, curcumin, quercetin, pomegranate, EGCG, pantethine, resveratrol, MUFA, aged garlic, sesame, gamma/delta tocotrienols, reduce saturated fatty acids like stearate and palmitic acid, reduce glucose (especially with simultaneous intake of saturated FA).
- Decrease cholesterol crystals, LDL phospholipids, oxLDL, Apo-B and 7 ketosteroids that activate PRR-NLRP-3 (NODs).
- Omega 3 FA and statins.

New Functional And Metabolic Medicine Approach To The Treatment Of Dyslipidemia


Decrease LDL burden to 55 mg/dl with inhibition of HMG CoA reductase and other mechanisms. This level of LDL decreases LDL particle number and Apo-B, reduces potential downstream inflammation.

Red yeast rice, berberine, plant sterols, omega 3 FA, niacin, lycopene, sesame, citrus bergamot, pantethine, EGCG, soy, flax seed, MUFA, aged garlic, resveratrol, curcumin, gamma/delta tocotrienols, GLA, soluble fiber.
• Increase eNOS and nitric oxide.

• Arginine/citrulline, beets, beet juice and extract, dark green leafy vegetables, niacin, lycopene, berberine, omega 3 FA, EGCG, resveratrol, flax seed, COQ 10, R lipoic acid, NAC, taurine, pycnogenol, grape seed extract, pomegranate,
HMG CoA reductase inhibition.

- RYR, berberine, omega 3 FA, plant sterols, lycopene, pantethine, citrus bergamot, gamma delta tocotrienols, sesame, EGCG, garlic, curcumin, GLA, soy, gamma oryzanol (rice brain phytosterol).

Decrease LDL particle number (LDL-P).

- Niacin (lowers LDL-P more than LDL)
- Omega 3 fatty acids
- Red yeast rice
- Berberine
• Reduce cholesterol absorption.

• **Plant sterols**, berberine, **soy (micelles)**, sesame, EGCG**(micelles)**, flax seeds, garlic, fiber.

• **Increase cholesterol bile excretion**.

• Berberine, **plant sterols**, citrus bergamot, fiber, probiotics, sesame, resveratrol.
• Decrease ApoB.
• RYR, berberine, plant sterols, niacin, omega 3-FA, EGCG.

• Decrease LDL modification: glycation, oxidation, glyco-oxidation and acetylation.
• MUFA (EVOO), EGCG, niacin, catechins, curcumin, quercetin, pantethine, resveratrol, red wine, grape seed extract, various flavonoids, pomegranate, tangerine extract, aged garlic, sesame, gamma/delta tocotrienols, lycopene, gamma/delta tocopherols, polyphenols, oleic acid, glutathione, citrus bergamot, co-enzyme Q -10, gamma oryzanol.
New Functional And Metabolic Medicine Approach To The Treatment Of Dyslipidemia

• Inhibit LDL glycation specifically.
• Carnosine, pomegranate, histidine, myricetin, kaempferol, rutin, morin, organosulfur compounds.

• Increase LDL size from small dense type LDL B (type 3 and 4) to large type LDL A.
• Niacin, omega 3 FA and plant sterols.

• Modify LDL composition of bioactive lipid components and protein-based damage-associated molecular patterns (DAMPs) like ApoB.
• Omega 3 FA, MUFA, pomegranate, reduce inflammation, oxidative stress and immune dysfunction.

• Upregulate LDL receptor.

• Berberine (PCSK9), niacin (PCSK9), plant sterols, EGCG, sesame, tocotrienols, curcumin,, soy.

• Regulate sortilins and SORLA that regulate intracellular processing and secretion of LDL.

• Deactivate the LOX-1 receptor on endothelial cells, VSMC and macrophages and soluble s-LOX products.

• Reduce hemodynamic stress (BP, PP ).
Decrease modified LDL macrophage uptake via CD 36 SR-scavenger receptor and NADPH oxidase (70% of vascular LDL foam cells).

Resveratrol, NAC (n-acetyl cysteine), berberine, curcumin, quercetin, lycopene and luteolin.

Decrease native LDL macrophage uptake by pinocytosis-mediated mechanism (30% vascular LDL foam cells). Decrease infections, inflammation and modified LDL levels.

Decrease LDL signaling with cytokines, chemokines, CAMS and monocyte-endothelial interactions. Plant sterols and sterolins, lycopene, luteolin.
New Functional And Metabolic Medicine
Approach To The Treatment Of Dyslipidemia

- Decrease macrophage recruitment and subendothelial migration.
- Reduce inflammation and immune responses.
- Alter macrophage phenotype from M1 to M2 anti-inflammatory
- Omega-3 FA and downstream resolvins and protectins, plant sterols, sterolins and glycosides – phytosterolins such as BSS(betasitosterols) and BSSG( betasitosterolins).
- Modify signaling pathways.
- Plant sterols and sterolins.
• Increase reverse cholesterol transport.

• Lycopene, niacin, plant sterols, curcumin, quercetin, glutathione, resveratrol, anthocyanadins, flavonoids, co enzyme Q 10.

• Increase HDL and change to larger HDL size to 2b

• Niacin, omega 3-FA, pantethine, red yeast rice, MUFA, resveratrol, curcumin, pomegranate, citrus bergamot, co enzyme Q 10, lycopene.
• Improve HDL function.

• Niacin, quercetin, pomegranate, EGCG, lycopene, resveratrol, glutathione. Reduce inflammation, oxidative stress and autoimmune dysfunction,

• Increase ApoA 1: Niacin, co enzyme Q 10

• Increase PON 1 and PON 2.

• Quercetin, pomegranate, EGCG, lycopene, resveratrol, glutathione.
• Reduce inflammation.
• Omega-3 FA, curcumin, quercetin, niacin, flax seed, MUFA, plant sterols, resveratrol, glutathione, lower hs CRP.

• Reduce oxidative stress: Anti-oxidants

• Modulate immune dysfunction.
• Plant sterols and sterolins, BSS and BSSG, lycopene

• Decrease VLDL and TG
• Omega 3 fatty acids, niacin, red yeast rice, pantethine, citrus bergamot, flax seed, MUFA, resveratrol, Co enzyme Q 10, fiber.
• Reduce foam cell and fatty streak formation.

• Resveratrol, NAC, reduce inflammation and oxidative stress, modulate Th 1/Th 2 balance with phytosterolins BSS and BSSG.

• Reduce trapping of foam cells in subendothelium and actin polymerization with cell adhesion among foam cells.

• Resveratrol, NAC, reduction of ROS / RNS, decrease adhesion kinase.
Lipoprotein (a)  Lp(a)

- Niacin dose related: 2 grams per day (21%-39% decrease)
- NAC: 500-1000 mg bid
- Carnitine: 2 grams (8-21%)
- Vitamin C: 9 grams per day (27% decrease)
- Proline (500 mg) with Lysine (1000 mg) per day
- Inhibit PCSK9: Berberine 500 mg bid
- CoQ10 100 mg qd
- Omega 3 FA 5000 mg qd
- Flax seed 1 cup/day
- Gamma delta tocotrienols 200 mg hs
- L-arginine 5 grams per day
- Monoclonal antibodies (30-40%, sex hormones, thyromimetics and thyroid hormone, ASA 81 mg, reduce IL -6 and inflammation, antisense oligonucleotides and apheresis.)
Stabilize plaque and reduce plaque burden with lack of progression or reversal.

- Omega-3 FA, vitamin K2 MK7, aged garlic, curcumin, quercetin, reduce LpPLA-2.

- Reduce LpPLA-2.
- Omega-3 FA and niacin.
Other agents to consider with less clinical human data

- Chia seeds
- Flax seeds
- Artichoke leaf
- Gamma oryzanol (rice bran phytosterol)
- Co-enzyme Q 10
- Vitamin C
- Palmitoleic acid
Agents that are not supported in clinical trials in humans

- Policosanol
- Guggulipid
- Inositol hexanicotinate
Nutritional Supplement Treatment for Dyslipidemia

Final Recommendations

- Red yeast rice  2400 to 4800 mg at night with food
- Plant sterols   2.5 grams per day.
- Berberine 500 mg per day to twice per day.
- Niacin (nicotinic acid B3) 500 to 3000 mg per day as tolerated pretreated with quercetin, apples, ASA. Take with food and avoid alcohol. Never interrupt therapy.
- Omega-3 fatty acids with EPA/DHA at 3/2 ratio  4 grams/day with GLA at 50% of total EPA and GLA and gamma/delta tocopherol.
- Gamma delta tocotrienols  200 mg hs.
- Aged garlic standardized 600 mg twice per day.

Nutritional Supplement Treatment for Dyslipidemia
Final Recommendations

- Pantethine 450 mg BID
- MUFA 20 to 40 grams per day (EVOO 4 tablespoons per day)
- Lycopene 20 mg per day
- Luteolin 10 per day
- Trans resveratrol 250 mg per day
- NAC 500 mg twice per day
- Carnosine 500 mg twice per day
- Citrus bergamot 1000 mg per day
- Quercetin 500 mg twice per day
- Probiotics standardized 15 to 50 billion organisms BID
- Curcumin 500-1000 mg twice per day
- EGCG 500-1000 mg BID or 60-100 ounces of green tea per day
- Pomegranate one cup of seeds/day or 6 ounces of juice per day.