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 45 mechanisms involved in dyslipidemia-induced cardiovascular disease.

• Review the mechanism of action of nutritional supplements.

• Review nutritional supplement combinations for dyslipidemia treatment.

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, Vibrant America Lab, Designs for Health, Thorne, Primal MD, TA Sciences and AC Grace. He receives grants from private industry for Biotics, DFH, Thorne and Neogenis.

Key References

Nutritional Supplements and Dyslipidemia


Particle movement
Particle retention
Reduction in composite endpoints of any CVD by 34%.
Gradient driven
Enhanced
CHD stenosis as measured by angiography and CHD event rate reduced with
Lipoprotein particle
Lower CIMT (carotid intimal medial thickness) \((P < 0.001)\) than those patients on
Antioxidant, anti-inflammatory, anti-immune, anti-thrombotic activity, reduction
Niacin's reduction in CVD events may occur through mechanisms that are not
Magnitude of on-treatment HDL difference, between treatment arms, was not

Eleven trials of 9959 patients.

• 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 (phosphoproteins)

Overview

• Niacin meta-analysis of lipid effects, CVD and CHD
  Therapeutic Advances in Cardiovascular Diseases 2011;3:277
  Current Opinion in Cardiology 2014;30:3-6, 2011;2:388
  With West Dean Thomas, P. 425-429: 2012;3:497
  NEJM 2009;360:2119-2129
  Am Heart J 2011;161:129

• Eleven trials of 9959 patients.
• Reduction in composite endpoints of any CVD by 54%.
• Reduction in major CHD event by 25%. No change in CVA.
• CHD stenosis as measured by angiography and CHD event rate reduced with niacin in combination with statin, simvastatin or bile acid resin (colestipol) \((P=0.015)\) (Am J Cardiology 2014;113:1494).
• Lower CMI (cardiac nitric arterial thickness) \((P<0.001)\) than those patients on
  statins alone, reduction in carotid plaque and volume of lipid-rich necrotic core
  was better with niacin. 20 years of FATS-OS Trial J Clinical Lipidology 2014;8:489-493).
• 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.
• Anti-oxidant, anti-inflammatory, anti-immune, anti-thrombotic activity, reduction
  in MPO (neutrophil oxidases), CRMs (cell adhesion molecules), cytokines.

Reasons that patients or health care providers chose non-pharmacologic treatment of dyslipidemia

1. Intolerable adverse effects of dyslipidemia drugs (myalgias, fatigue, liver and 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.

Niacin meta-analysis of lipid effects, CVD and CHD

- Panthenol, Sesame, EGCG
- Omega 3FA, Citrus Bergamot
- Plant Sterols, Soy, Lycopene
- Pantethine, Sesame, EGCG
- All Trans Geranylgeranyl-PP Deacetylase
- Geranylgeranyl-PP Synthase
- Mevalonate, Farnesyl, Dimethylallyl-PP
- Acetyl-CoA
- HMG-CoA
- Acetoacetyl-CoA
- Dimethylallyl-PP
- Isopentenyl-PP
- Geranyl-PP
- Farnesyl-PP
- Dolichol
- Tocotrienols
- Tissue factor PAI-1
- MCP-1
- Adhesion molecules
- Dendritic cells VADCs
- Monocyte
- Macrophage
- Macrophage foam cells
- Endothelial cells
- Modified or retained lipoproteins
- Enhanced macrophage uptake

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• Niacin's reduction in CVD events may occur through mechanisms that are not reflected by changes in HDL.
• Anti-oxidant, anti-inflammatory, anti-immune, anti-thrombotic activity, reduction
  in MPO (neutrophil oxidases), CRMs (cell adhesion molecules), cytokines.
  Increased adiponectin and improvement in endothelial function.
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**.
- **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 improvement in HDL function.

**Adverse Effects:**
- Hyperglycemia, hyperuricemia, gout, hepatitis, flushing, rash, pruritus, hyperpigmentation, hyper-homocysteinemia, gastritis, PUD, bruising, SVT and palpitations.

**NIACIN vs IHN (Inositol Hexanicotinate)**

J of Clinical Lipidology 2015;7:14

- **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**


- 5000 Chinese patients with previous myocardial infarction received an extract of red yeast rice (RYR) at 600 mg for 4.5 years vs placebo.
- Primary end point was MI 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 33% (p=0.0003).
- No change in cerebrovascular accident.

**Effects of Red Yeast Rice (RYR) in patients with dyslipidemia: A multicenter, randomized, placebo-controlled study in US and China.**

- 116 adults with dyslipidemia but no coronary heart disease, with baseline non-HDL-C levels of 208 mg/dL and LDL-C of 175 mg/dL. Randomized to placebo or RYR 1200 or 2400 mg daily for 12 weeks.
- **RESULTS:** LDL-C (~27% reduction) and non-HDL-C (~24% reduction (p<0.001) at 1200 mg and 32% reduction in LDL at 2400 mg. Decreased TC-18%, Apo B-21%, triacylglycerols-8% and HDL-C and Apo A-1 increased 5%.
- Safety and tolerability profiles good (gastrointestinal, 3.5% had muscle spasm or myalgia, no myopathy, no increases in liver transaminases or creatine kinase.)
### Red Yeast Rice (RYR) 22 clinical trials review

**Comprehensive Ther Med 2012;5:45-83; Shang Q et al. 2012; April 30th; 24/8/2016**

Red Yeast Rice (RYR) 22 clinical trials review

#### Side Effects

- Monacolins are the active ingredients, which inhibit cholesterol synthesis via HMG-CoA reductase (13 natural statins). The statin content is evaluated by HMB. Also contains sterols (B-sitosterol, campesterol, stigmasterol, hopantriol), tocotrienols, lutein, flavonoids, glycodelin, and monomethylated fatty acids. Contains over 20 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%
- Decrease abdominal aortic aneurysm.
- Interfere with SREBP (steroid receptor binding protein).
- LDL decreased 10%
- Reduces NAFLD (non alcoholic fatty liver disease).
- Decreases nonfatal MI, total CHD events, revascularization and total deaths.
- Decreases fatal MI, total CHD events, revascularization and total deaths.
- Decreases postprandial glucose and insulin levels.
- Decreases blood pressure.
- Decrease in C-reactive protein (CRP) and IL-6.
- Decrease in lipids and triglycerides.
- Decrease in LDL-P and HDL-S.
- Interfere with SREBP (sterol regulatory element-binding protein).
- Reduces SREBP-2 mRNA.

#### 4 grams of combined EPA and DHA:

- Decreases fat soluble vitamin absorption.
- Increases HDL cholesterol.
- Decrease abdominal aortic aneurysm.

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### PLANT STEROLS


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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Reduces LDL</td>
<td><strong>Reduction of Apo A IV secretion of intestinal and hepatic cells.</strong></td>
</tr>
<tr>
<td>Reduces TG</td>
<td><strong>Suppresses HMG-CoA reductase and suppresses CYP7A1.</strong></td>
</tr>
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<td><strong>Interacts with SREBP (sterol receptor binding protein).</strong></td>
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</tr>
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</tr>
<tr>
<td>Reduces TG</td>
<td><strong>Reduces atherosclerosis progression, MS and improves plaque regression.</strong></td>
</tr>
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<td>Reduces LDL</td>
<td><strong>Mixed data with CV outcomes.</strong></td>
</tr>
<tr>
<td>Reduces TG</td>
<td><strong>4S trial and PROCAM trial: increased risk of CV events in hyper-absorbers taking statins daily.</strong></td>
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<tr>
<td>Reduces LDL</td>
<td><strong>Dallas Heart Study and EPIC-Norfolk trial did not confirm any evidence of CV events.</strong></td>
</tr>
<tr>
<td>Reduces TG</td>
<td><strong>Dose: 2 to 2.5 grams / day.</strong></td>
</tr>
<tr>
<td>Reduces LDL</td>
<td><strong>Meta-analysis of trials showed that 2.15 grams per day reduced LDL by 8.8% and lowers LDL and CHD.</strong></td>
</tr>
<tr>
<td>Reduces LDL</td>
<td><strong>Effective in combination with statins and selected nutritional supplements for dyslipidemia (Red yeast rice, berberine, omega 3 fatty acids, etc).</strong></td>
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#### 4 grams of combined EPA and DHA:

- **Reduces fatty synthesis and increases in fatty acid oxidation.**
- **Improves insulin sensitivity, increases insulin levels 18%-27%, reduces or does not change fasting glucose or AIC even in high doses in normal patients.**
- **Decreases lipoprotein associated phospholipase A2 levels (Lp-PLA 2) in anti-inflammatory, anti-thrombotic natural (PPAR agonist).**
- **Improves heart rate variability (HRV), lowers HR, increases eNOS / NO, improves LDL reduces BP (DHA-EPA) decreases arterial fibillation (7) and arrhythmias, reduces growth of atherosclerotic plaque with more well-formed fibrous caps and fewer thin wall caps.**
- **RCCT: Reduces CV events and death, CHD, primary and secondary prevention of MI, CVA, total mortality and sudden death.**
- **Reduces CHD progression, stent and CARG occlusion (DART: Omega Therapeutics Trial – European Heart Study in Females).**

### Effects of omega 3 fatty acids on serum lipids

**Am J Card 2010;105:1409; J of Nutriton 2008;138:30**

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**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 1500 mg DHA/EPA/GLA with no more than 30% as alpha tocopherol. 

Lowered TG (30%), LDL(12%) and BP. GLA with omega 3 FA is better in reducing LDL. Decreases inflammation, lowers hsCRP and arachidonic acid. Estimated 45% reduction in 10 year risk of MI.

GLA converts to DGLA which is anti-inflammatory (PGE1, 15OH-DGLA, 15-S OH eicosatrienoic acids). 
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.

### Krill Oil and Dyslipidemia

- A 12-week, three-month, crossover, randomized study. Total cholesterol levels between 194 and 344 mg/dL, 120 patients (30 patients per group) were randomly assigned to one of four groups.
  - 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 33%, 1.5 grams 37%, and 2 grams 35%.
  - HDL increased: 1.0 gram 5%, 1.5 grams 5%, 2 grams 55% and 3 grams 60%.
  - Study never replicated and the data is in question.

- Gamma/delta tocopherol at 100 mg per 1000 mg DHA/EPA/GLA.
- Take with evening meal to increase absorption.

↓↓ ↓↓

Reduce CHD and MI by 30% and DM by 40% (Mediterranean diet) especially with EVOO and nuts.

### 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 (RCTX, ATPA, SRA B1, 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 35% and DM by 40% (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 hydroxytyrosol in urine.
- Recommend EVOO at 40 grams per day(4 tablespoons)

### TOCOTRIENOLS

- Inhibit cholesterol synthesis by post-transcriptionally suppressing HMG-CoA reductase activity by two independent mechanisms: 1. Increased controlled degradation of reductase protein. 2. Decreased efficiency of translation of HMG-CoA reductase mRNA.

↓↓ ↓↓

Loss reductions: 4.12 weeks diet + gamma/delta tocotrienol extract ( p < 0.05)

- TG: 17%, 4 LDL 24%, 4 APO-B 19%, → HDL and APO A-1 and lower LDL: 17%, 
- LDL to HDL ratio 1:3.4, 
- HDL(8%).
  
- Take with evening meal to increase absorption.
- Variable response rate (50% of patients).
- Endogenous increase in GPP (geranylgeranyl pyrophosphate) and mitochondrial CoQ10.
- Dose: 200 mg of gamma / delta tocotrienols taken at night with food at least 12 hours after consumption of any tocopherols.

### Japan EPA lipid intervention study (JELIS trial)

- 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.

### 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 HNF4 alpha. Post-transcriptional mechanism dependent on ERK but independent of SREBP.
- Reduces cholesterol absorption increases biliary excretion of LDL.
- Inhibits HMG-CoA reductase.

### Krill Oil is not recommended at this time.
**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.

**Berberine HCL**
- Stimulates AMPK, reduces insulin resistance and decreases FBS and HBAC, 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 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. Uptregulation 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 SAA.
- Active ingredients are naringin, neoeicitrin, neohesperidin, poncirin, 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)**
- Enhances ABCA1 expression, reverse cholesterol transport, apoA1 expression, reduces intracellular cholesterol and cholesterol in lipid domains, alters membrane-induced cellular signal transduction.
- disrupts caseolin-1 nitric oxide binding to increase NO.
- Two unconjugated double bonds reduce ROS.
- Increases HDL 2 and 3, improves HDL functionality.
- Uregulates NFkB.
- Reduces SAA (serum amyloid A).
- Decreased CETP.
- Increases PON1 and decreases oxLDL.
- Reduces inflammation and helps immunomodulation.
- Dose 10-20 mg per day.
Garlic and serum lipids: meta-analysis

- 39 trials in dyslipidemia.
- TC reduced 17 mg/dl.
- LDL reduced 8 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 DBPCT trial of 23 patients over one year on aged garlic at 1200 mg per day. Aged garlic CAC: 7.5%22.2±18.5% vs placebo.
- 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 coenzyme A (CoA).
- 28 Clinical human trials with 546 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 4% and APO A-I.
- lowers TG 33% (up to 36.5% at 9 months).
- Inhibits fatty acid synthesis and beta oxidation.
- Increases catalase, GPx, GSH and SOD.
- Reduces carotid IMT.
- Increases vitamins A, C and E.
- Increases PON 1 in serum and binding to HDL and PON 2 in arterial wall.
- 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.
- Uregulates LDL receptor gene.
- Uregulates cholesterol 7-alpha hydroxylase gene expression.
- Uregulates SREBP-2 genes.

Probiotics and Lipids

- 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 APO B 9%, lowers hs CRP and fibrinogen and increases vitamin D.
- Dose: 100 mg per day.

Sesame

- 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.
- Uregulates LDL receptor gene.
- Uregulates cholesterol 7-alpha hydroxylase gene expression.
- Uregulates SREBP-2 genes.

Pomegranate juice/seeds

- Increases PON 1 in serum and binding to HDL and PON 2 in macrophages.
- Anti-oxidant.
- Decreases oxLDL.
- Reduces oxLDL and other oxidized lipids in serum and arterial wall.
- Reduces oxidized LDL.
- POM contains flavonoids, flavanols, anthocyanins, proanthocyanidins, ellagitannins and gallotannins, organic and phenolic acids, sterols, tripenoids, alkaloids, fiber and pectin.
- 1 cup of seeds per day or 6 ounces of juice

Green tea and EGCG

- Catechins, especially EGCG, improve lipid profile, interfere with sterol absorbtion of monosaturated oil (unrefined and reduce absorption).
- Upregulates LDL receptor gene.
- Inhibits HMG-CoA reductase.
- Inhibits intestinal absorption.
- Decreases APO-B lipoprotein secretion from cells.
- Mimics insulin action by activating similar pathways and increases PI3K to regulate gluconeogenesis.
- Reduces body fat.
- Suppresses NF-kappaB expression of proinflammatory cytokines and enhances IRS-1 expression.
- In a rat study: TG reduced 35% (p < 0.05). Non-HDL cholest erol reduced 25% (p < 0.05).
- Human trial: EGCG from jasmine (L. japonica) used (500 mg/kg diet) vs green tea per day.
- Decreased postprandial TG by 15 to 20% and decreases remnant particles.
- Reduces COX and JNK.
- Dose: 300 mg BID of EGCG or 60 to 100 ounces of green tea/day.
CO-ENZYME Q-10 (CO-Q-10) (UBIQUINONE)

- Minimal effect on serum lipids, but reduces VLDL and increases HDL and Apo-A1 in animal models and some human studies.
- Promotes macrophage cholesterol efflux (RCT) by regulation of ABCG1 signaling pathway.
- 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.

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.

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Houston MC and Sparks W.

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Clinical Trial

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- 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).

Study Product With RYR and Niacin Extended

Hypertension Institute Nashville, TN
Houston MC and Sparks W.

- 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).

Table 2. Baseline and 4-month clinical characteristics of the proprietary lipid supplement (LC) and placebo groups

<table>
<thead>
<tr>
<th>Proprietary Lipid Supplement (LC)</th>
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</tr>
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<tbody>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>116.3±7.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>136.7±9.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78.5±7.0</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64.1±6.3</td>
</tr>
</tbody>
</table>

Second Clinical Trial Proprietary Lipid Lowering Nutritional Supplement (LC)

Hypertension Institute Houston, August 2015

- DPRPC Clinical Trial of 40 patients
- Nutritional supplement ingredients

Table 2. Baseline and 4-month clinical characteristics of the proprietary lipid supplement (LC) and placebo groups
68 patients were screened for the study.

40 patients were randomized.

Proprietary Supplement: LC group 20 patients randomized.

LipoCardia group 20 patients completed.

Placebo group 20 patients randomized.

Placebo group 20 patients completed.

Treatment for 4 months.

Figure 2

Total Cholesterol

LDL-C

VLDL-C

Figure 3

Total Cholesterol

Figure 4

LDL-P

Non-HDL-C

HDL-P

Figure 5

OxLDL

Apoe

TG

Figure 6

Decreased all:

hs CRP

TNF alpha

IL-6

Supplement Fig 2

Coenzyme Q10
Supplement Fig 3

Second Clinical Trial Proprietary Lipid Lowering Nutritional Supplement (LC)
Hypertension Institute Houston August 2015

- Total cholesterol decreased from 232.55 mg/dl to 214.17 mg/dl at 4 months with LC but increased from 246.65 mg/dl to 258.58 mg/dl with placebo.
- LDL-C fell from 166.2 mg/dl to 133.73 mg/dl with LC vs. 164.1 mg/dl to 165.9 mg/dl with placebo.
- VLDL-C decreased from 21.62 mg/dl to 15.84 mg/dl with LC and increased from 22.58 mg/dl to 27.54 mg/dl with placebo.
- The ANCOVA analysis showed that serum total cholesterol, and LDL-C and VLDL-C concentrations in LC group were significantly reduced as compared with the changes in placebo group (P <0.0001, P <0.001, P <0.0001, respectively).
- OxLDL was significantly decreased in the LC group (51.65 vs. 42.6 mg/dl; P<0.02), whereas no change was found in the placebo group (55.95 vs. 53 mg/dl; P= 0.89).
- ApoB and TG group fell significantly (P = 0.0029 and 0.014 respectively).

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, MUFAs, 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.

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

- 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.

- 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, sesamene, resveratrol.

- Decrease Apo-B.
- 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, sesamene, gamma/delta tocotrienols, lycopene, gamma/delta tocopherols, polyphenols, oleic acid, glutathione, citrus bergamot, co-enzyme Q-10, gamma oryzanol.

- 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.
New Functional And Metabolic Medicine Approach To The Treatment Of Dyslipidemia

- 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.

- Upregulate LDL receptor.
  - Berberine (PCSK9), niacin (PCSK9), plant sterols, EGCG, sesame, tocoferol, 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 macrophage-endothelial interactions.
  - Plant steroids and sterolins.

- 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.

- 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.
New Functional And Metabolic Medicine Approach To The Treatment Of Dyslipidemia

- Reduce foam cell and fatty streak formation.
- Resveratrol, NAC, reduce inflammation and oxidative stress, modulate Th1/Th2 balance with phytosterols 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
- Camiline: 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, antioxidants oligonucleotids and apheresis.

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.