Module II Cardiology 2018

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Dyslipidemia

Nutrition, Nutraceutical Supplements and Integrative Metabolic Medicine Approach

MMI Module 2 2018

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Key References

- Houston MC. The Role of Nutraceutical Supplements in the Treatment of Dyslipidemia. J Clin Hypertens 2012;14(2):121-32
- Houston MC et al. Nonpharmaolcolgic Treatment of Dyslipidemia. Prog Cardiovasc Dis. 2009;52(2):61-94
- Nijjar PS et al. Role of dietary supplements in lowering low-density lipoprotein cholesterol: A review. J of Clinical Lipidology 2010; 4:248-258.
- Mannarino MR et al. Nutraceuticals for the treatment of hypercholesterolemia. European Journal of Internal Medicine 2014;July 2 EPUB.
- Houston, Mark. The role of nutrition and nutritional supplements in the treatment of dyslipidemia. Clinical Lipidology 2014;9(3): 333-354.
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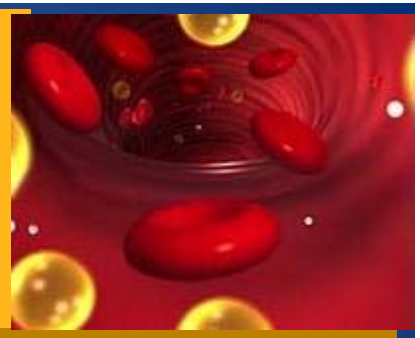
OBJECTIVES



- Review the underlying causes and mechanisms of dyslipidemia and dyslipidemia-induced cardiovascular disease.
- Discuss and apply advanced lipid testing (lipid particle number and size and HDL functionality and quality) for the diagnosis and treatment of dyslipidemia in clinical practice.
- Identify effective methods to promote vascular repair, reduce vascular damage and define the interrelationships of the cardiovascular system, gastrointestinal tract and microbiome.
- Specify nutrition and nutritional supplements to treat dyslipidemia.
- Review 45 new mechanisms involved in dyslipidemia-induced cardiovascular disease and review the integrative therapies.

Vascular Disease is a Balance

MC Houston. Vascular Biology in Clinical Practice. Hanley and Belfus 2000
MC Houston. Handbook of Hypertension Wiley Blackwell Oxford UK 2009

Vascular Injury

Nitric oxide vs angiotensin II endothelin and aldosterone

VS

Vascular Repair

Endothelial Progenitor Cells (EPC's)

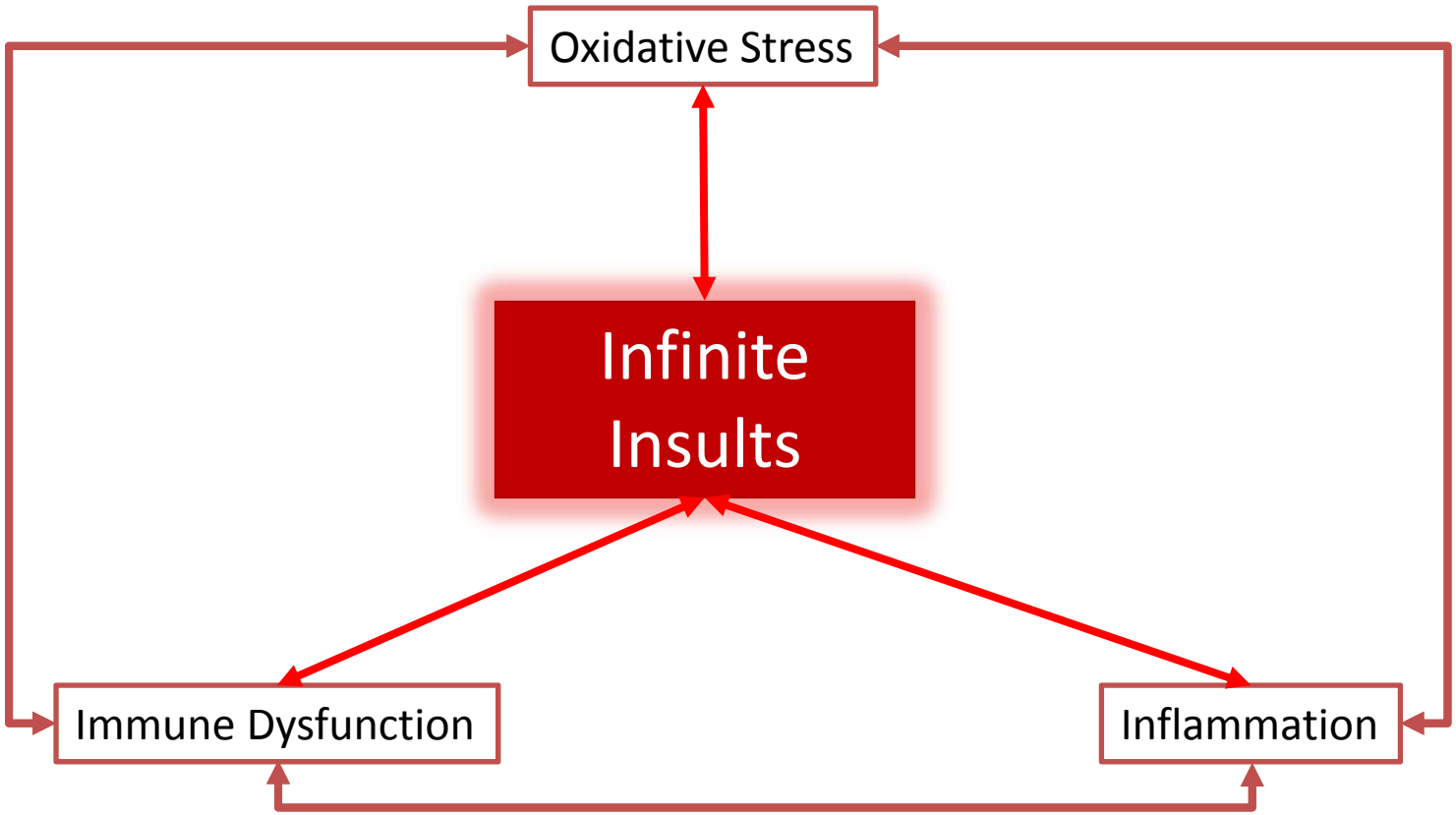
“The blood vessel has a finite number of responses to an infinite number of insults.”

The three finite responses are

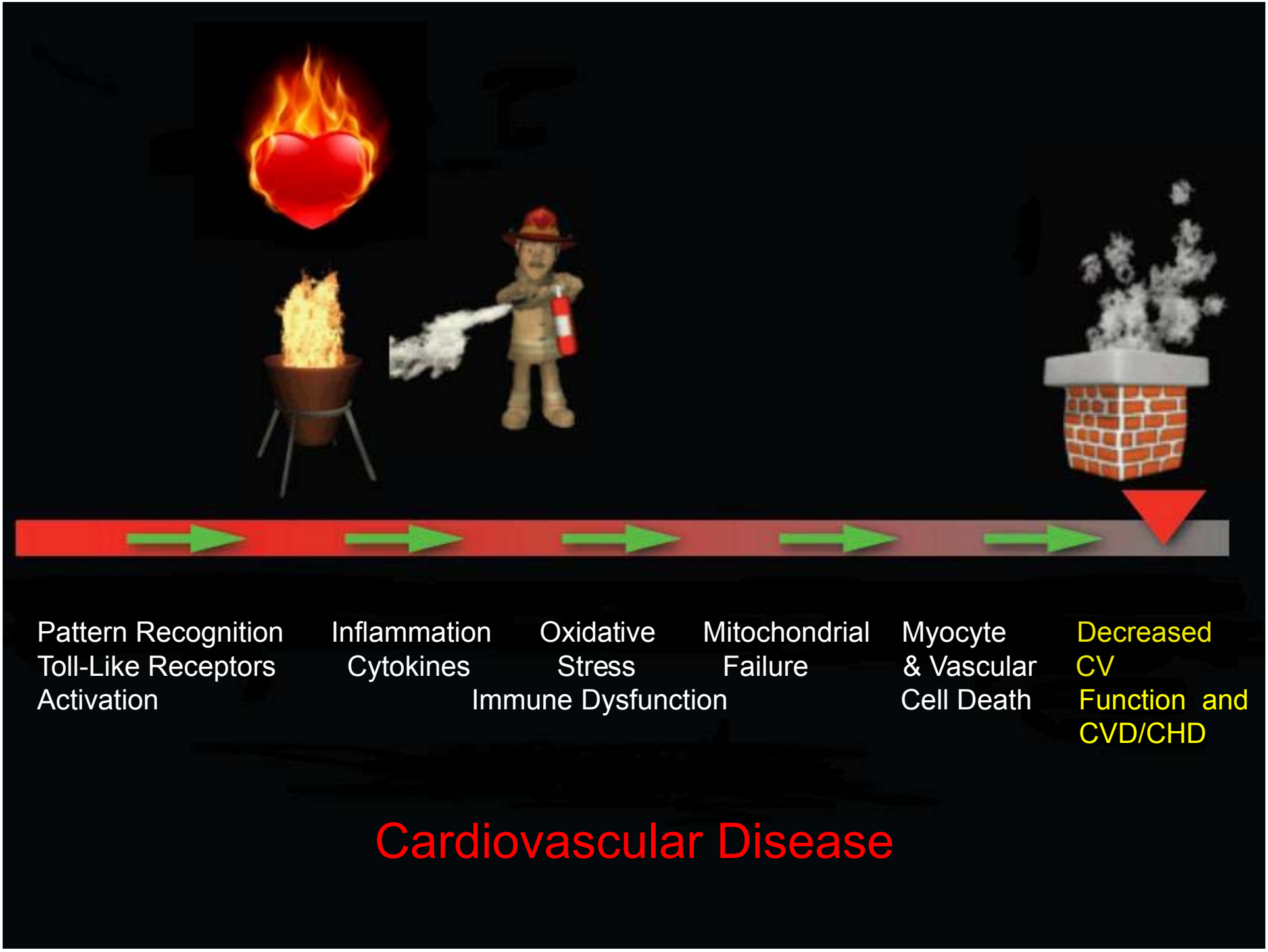
- Inflammation
- Oxidative stress
- Vascular immune dysfunction

Mark Houston MD,MS,MSc 2002
J Clinical Lipidology 2015;9:119-128

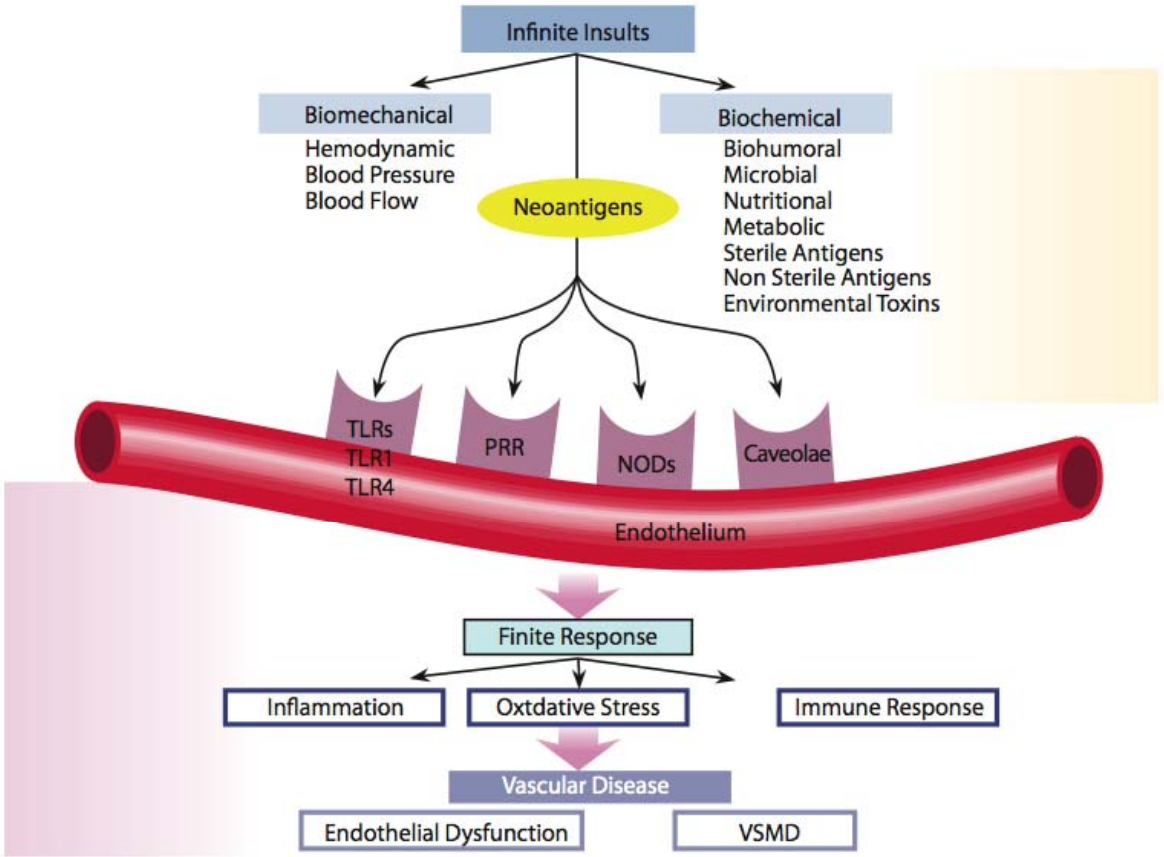
Mechanism Of Model



Finite Responses

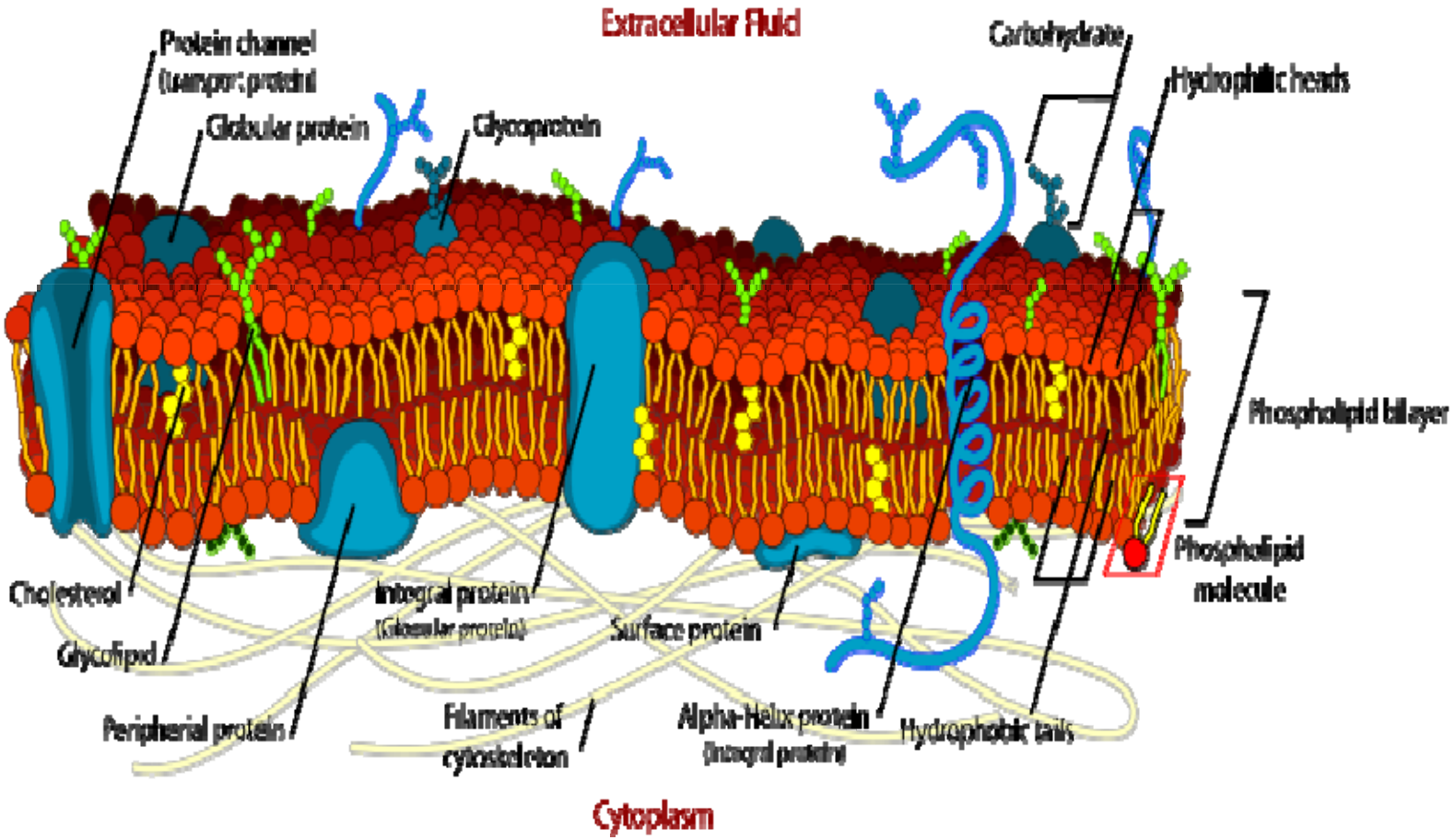

Pattern Recognition
Toll-Like Receptors
Activation
Inflammation
Cytokines
Oxidative
Stress
Mitochondrial
Failure
Immune Dysfunction
Myocyte
& Vascular
Cell Death
Decreased
CV
Function and
CVD/CHD
Cardiovascular Disease

Infinite Insults



Hypertension INSTITUTE

Cell Membrane Biochemistry and Physiology: Tsunami Effect



Caveoli, Lipid Rafts, Membrane Lipids and Nitric Oxide Bioactivity

J of Nutritional Biochemistry 2012;23:101-105

- **Calveolae** are invaginations in the membrane surface that become lipid enriched.
- **Endothelial caveloae** transfer molecules from the lumen of the blood vessels to the subendothelial space. Internalization and trafficking.
- **Calveolin-1** is the main component of the calveolae and it binds with eNOS, reducing access to cofactor calcium/calmodulin and reduces NO bioactivity.
- **Lipid rafts** of unesterified cholesterol create membrane microdomains and precipitate formation of extracellular cholesterol crystals, atherosclerosis, cell injury and death.

Caveoli and Lipid Rafts

J of Nutritional Biochemistry 2012;23:101-105

- Omega 3 fatty acids disrupt lipid rafts, especially DHA, improve membrane elasticity/fluidity, move cholesterol and caveolin-1 out of the cell membrane, which reduces inflammation, vascular damage and increases nitric oxide biovailability.

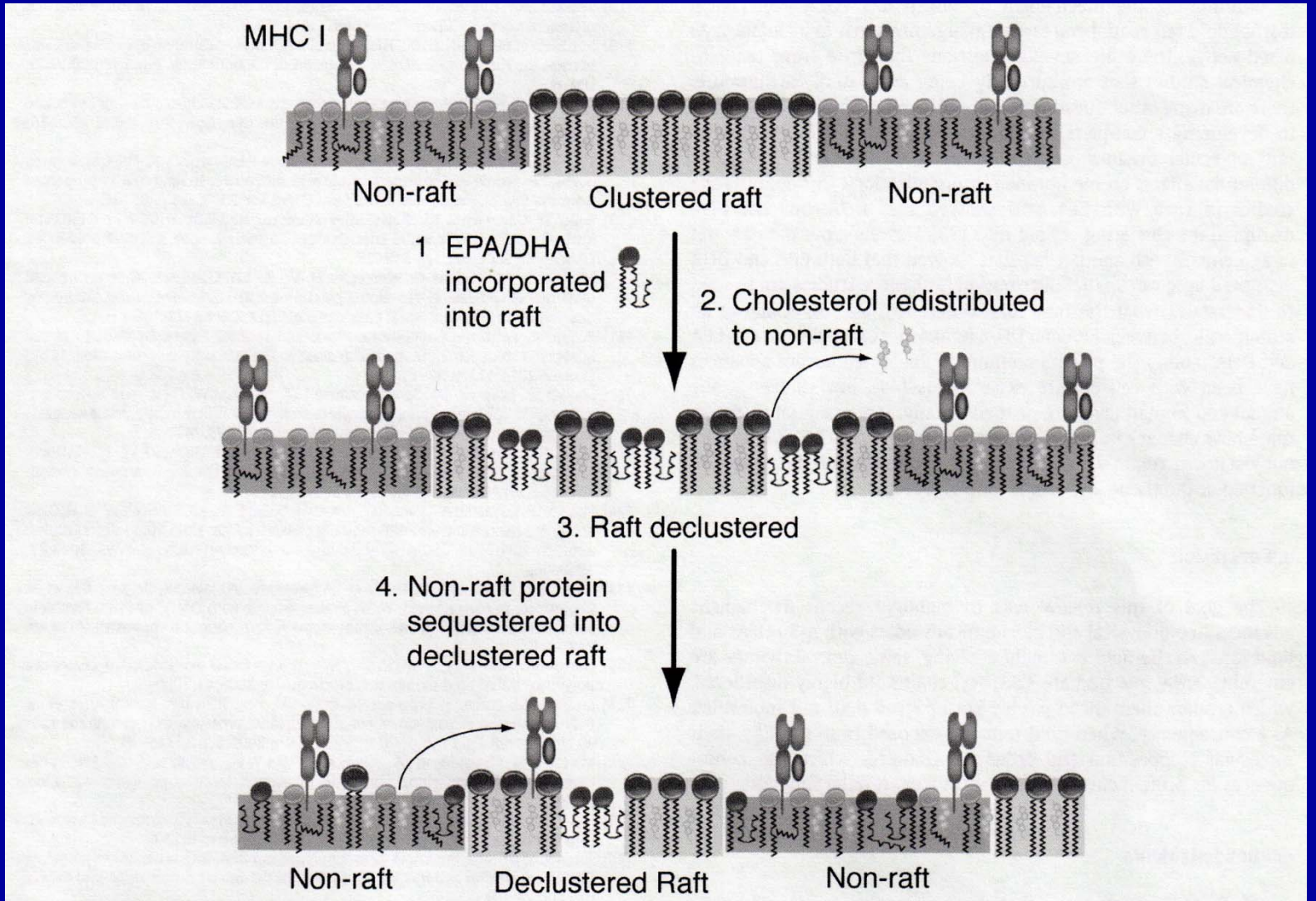


Fig. 2. Proposed model on how n-3 PUFA acyl chains disrupt the molecular organization of membrane lipid rafts and proteins. The model shows n-3 PUFAs declustering rafts by directly incorporating into the raft and then redistributing cholesterol toward nonrafts. As a consequence, a nonraft protein such as MHC class I is forced into the lipid raft. Similarly, raft proteins are likely declustered and forced into nonrafts. The order of events is shown for simplicity and may occur simultaneously.

Journal of Nutritional Biochemistry 23 (2012) 101-105

Pattern Recognition Receptors (PRR) and Inflammation
Innate Immune Response is the First Nonspecific Response to Injury from Infinite Insults.

Nutrition Reviews 2011;69:310; Current Opin Lipidology 2014:25: 339

PRR are extra- and intracellular on endothelium can be considered atypical immunologic cells/receptors that activate NfkB:

1. TLR: Toll like receptors (especially TLR 1,2,4 –vascular)
2. NODs, NLR and NLRP3: Nucleotide-binding oligomerization domain proteins, NOD like receptors and inflammasome.
3. CD 36 SR
4. RAGEs

These PRR detect invading pathogens by recognizing pathogen-associated molecular patterns (PAMPS) like LPS or DS-DNA, and activate the innate immune responses for host defense.

PRR can also be activated by various endogenous molecules of non-microbial origin, derived from tissue injuries, nutrients, nutrient metabolism and cell death which elicit sterile inflammation for wound healing These are damage-associated molecular patterns) (DAMPS) like ox LDL, disturbed blood flow, ATP, urate, calcium, cholesterol crystals.

PRR detect metabolic disturbances and bridge immune responses to metabolic homeostasis.

Functional diversity to recognize a wide variety of agonists that may lead to dysregulation and chronic inflammation.

Endothelial Innate Immunity, SREBP, NLR and Inflammasome: Response- to- Injury and Response- to- Intention

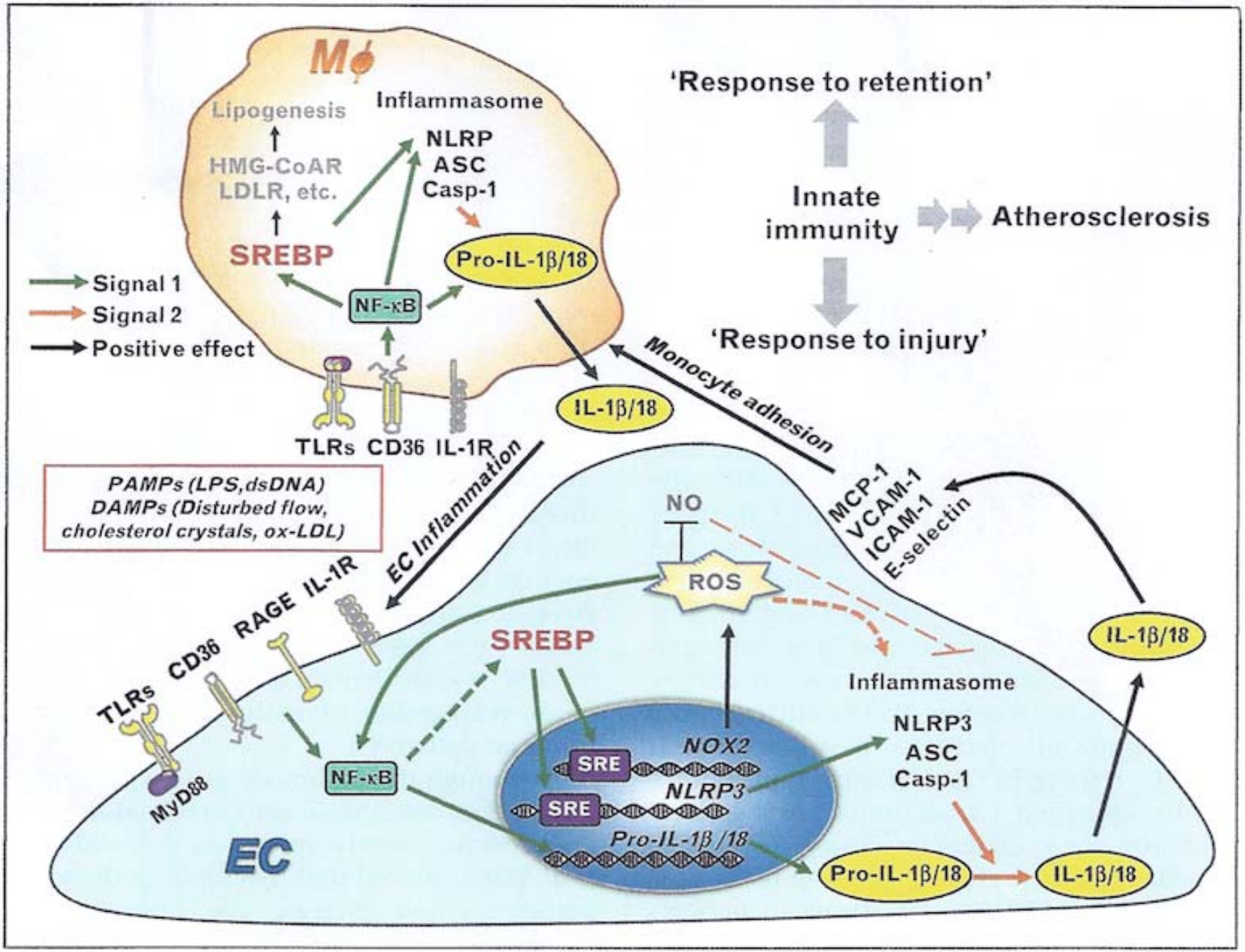
Current Opin Lipidology 2014:25: 339

Endothelial innate immunity mediated by **SREBP (sterol regulatory element binding protein) induced inflammasome** is a link between endothelial activation and monocyte recruitment and dyslipidemia, which forms a pro-inflammatory milieu disrupting vascular homeostasis and induces atherosclerosis.

SREBP plays primary role in cholesterol and fatty acid homeostasis via transcriptional regulation of genes involved in the biosynthesis of cholesterol (SREBP -1), TG (SREBP-2) and phospholipids, increases HMG-CoA and LDL-R. SREBP is induced by atherogenic factors such as disturbed flow and ox-PAPC.

Co- regulates with PCSK9 for transcription

Explains the response- to -injury and response- to -retention hypothesis. NLRs are cytoplasmic pathogen PRR that are activated by SFA, TFA, glucose, cholesterol crystals.


Mϕ
Lipogenesis
HMG-CoAR
LDLR, etc.
SREBP
Inflammasome
NLRP
ASC
Casp-1
Pro-IL-1β/18
NF-κB
Signal 1
Signal 2
Positive effect
TLRs
CD36
IL-1R
PAMPs (LPS,dsDNA)
DAMPs (Disturbed flow,
cholesterol crystals, ox-LDL)
IL-1β/18
EC Inflammation
'Response to retention'
Innate
immunity
Atherosclerosis
'Response to injury'
Monocyte adhesion
MCP-1
VCAM-1
ICAM-1
E-selectin
NO
ROS
SREBP
TLRs
CD36
RAGE
IL-1R
MyD88
NF-κB
SRE
NOX2
SRE
NLRP3
Pro-IL-1β /18
Inflammasome
NLRP3
ASC
Casp-1
Pro-IL-1β/18
IL-1β/18
IL-1β/18
EC

Neoantigens and Oxidation-Specific Epitopes (OSE) Antigenic Determinants) in Atherosclerosis

Curr Opin Lipidol 2013;24:426

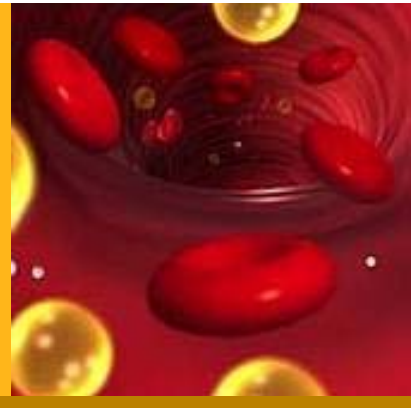
- **Atherogenesis and CHD are chronic, maladaptive inflammatory responses to OSE and related antigens.**
- **Lipid oxidation of LDL and cell membranes yields a large variety of OSE such as oxPL,** 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3 phosphocholine **(POPVC)(PGPC), oxLDL, malondialdehyde (MDA) epitopes.**
- **All OSEs are immunologic, pro-inflammatory, pro-atherogenic and plaque destabilizing. OxPL also induces apoptosis.**
- **All OSEs are DAMPs (damage-associated molecular patterns).**
- **DAMPS are recognized by innate immune system via PRR and scavenger receptors (SR) on macrophages, IgM natural antibodies and complement factor H.**
- **OxPL on APO B and Lp(a) predict CVD but oxPL on plasminogen improves fibrinolysis and decreases CHD.**
- **OSE antibodies reduce progression of atherosclerosis by neutralizing OSE and clearing and slowing foam cell formation.**

Neo-antigens and Oxidation-Specific Epitopes (OSE)(Antigenic Determinants) PAMPS and DAMPS in Atherosclerosis and CHD

Curr Opin Lipidol 2013;24:426

- OSEs, PAMPs and DAMPs are all recognized by the same PRR of innate immunity.
- PRR include cellular PRR on membranes, intracellular PRR, scavenger receptors on macrophages (SR like CD 36 and SR-B1), TLRs , soluble PRRs, pentraxins like hsCRP, complement factor H (CFH), and natural antibodies(Nabs) (immunoglobulin PRR).

New Definition of Dyslipidemia Metabolic and Infectious Endotoxemia (70% to 80% of causes)



Microbiol Immunol 2010;54(4):246
Circ Res 2010;107:56
Atherosclerosis 2010;208:396

The most common underlying reasons for dyslipidemia are:

1. Chronic inflammation
2. Immune dysfunction
3. Oxidative stress of the vascular system.

These are all correct protective/defense mechanisms.

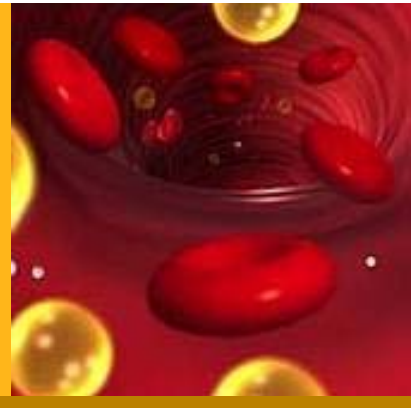
The most common reasons for these vascular responses:

1. Chronic inflammatory macro- and micro- nutrient intake.
2. Chronic infections (all types including bacteria, virus, fungi, TB and parasites).
3. Toxins, POPs (persistent organic pollutants) and heavy metals.

Metabolic, inflammatory, immune, toxic and infectious endotoxemia.

Plasma lipoproteins are important components of the immune system

Microbiol Immunol 2010;54(4):246
J Nutritional Biochemistry 2013;24:1183

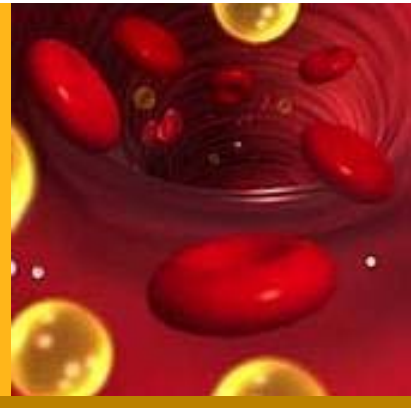


- Lipoproteins prevent infections, protect against toxins and inflammatory nutrition.
- They are a component of innate immunity.

However, as the lipids become modified they become vasculotoxic. The vascular system and heart become " innocent bystanders" that are injured during the acute, correct defensive/ protective responses which will induce atherosclerosis and CHD.

Plasma lipoproteins are important components of the immune system

Microbiol Immunol 2010;54(4):246
J Nutritional Biochemistry 2013;24:1183



Lipoproteins detoxify microbial LPS-lipopolysaccharide (gram negative bacteria) and LTA-lipoteichoic acid (gram positive bacteria).

Lipoproteins bind LPS to prevent LPS–induced activation of monocytes, macrophages and pro-inflammatory cytokines.

Infections, toxins, heavy metals and inflammatory nutrition induce and increase oxLDL, Apo B, LDL, LDL-P, small dense LDL , increase or decrease HDL and ApoA1, decrease HDL size and HDL-P and induce dysfunctional or proinflammatory/proatherogenic HDL.

All lipids and lipoproteins are anti-infective and protect against endotoxin and inflammation-induced vascular damage.

Apo A1 and HDL are the primary initial protective lipids against infections and pathogens. Elevated HDL may be functional or dysfunctional or even proinflammatory and protherogenic.

Apo B autoimmunity and atherosclerosis Disease mechanisms and therapy

Lipidology 2012;23:422

- Apo B/LDL are key antigens and vascular autoimmune agents.
- Both ox Apo B/ox LDL and non-modified Apo B are targeted by autoimmune responses.
- Regulatory T cells help prevent this autoimmune response and reduce atherosclerosis and CHD.
- Aggravation of plaque inflammation may occur as a result of a local loss of tolerance against LDL in the plaque from insufficient regulatory T cells.
- LysoPC formed by LpPLA2 and its metabolite, LPA mediate inflammatory effect of ox LDL.
- Immunization to Apo B is anti-atherogenic.

PCSK9(Serum proprotein convertase subtilisin/kexin 9) and HNF alpha (hepatocyte nuclear factor-1 alpha)
The inflammation- dyslipidemia CHD connection

NEJM 2012; 367:1891 NEJM 2012;366:1108-18
Curr Opin Lipidol 2012;23:511; JAMA 2012;308:2497
Curr Opin Lipidol 2013;24:251; Current Opin Lipidol 2013;24:307
Drug Design,Development and Therapy 2013;7: 1135.
Curr Opin Lipidol 2014:25:387

- **PCSK9** is a serine protease that binds to LDL receptors, increasing the degradation of LDLR receptors in hepatic lysosomes and reduces the rate that LDL cholesterol is removed from the circulation.
- **PCSK9** binds to APO B 100 on LDL, inhibits binding to LDL R.
- Hepatocyte nuclear factor-1 alpha (HNF-1alpha) is key transcriptional factor that cooperates with SREBP-2 to control PCSK9 expression.
- **HNF-1 alpha** is involved in acute phase responses with inflammatory pathways as well as lipid and bile acid metabolism.
- **LPS** induced inflammation from bacteria increases PCSK9 and dyslipidemia.
- **Link between inflammation, infection, metabolic pathways, dyslipidemia and CHD/CVD.**

Chronic Inflammatory Macronutrients and Micronutrients

Nutritional and Metabolic Endotoxemia alter serum lipid levels

Curr Opin Lipidol 2013;24:78
Am J Clin Nutr 2013;97:261
J Nutritional Biochemistry 2013;24:1183

- An inflammatory diet will increase circulating endotoxin levels. Positive correlation with increases in TC, LDL-C, TG and decreases in HDL-C and dysfunctional HDL.
- Also correlates with obesity, WC(waist circumference), WHR (waist/hip ratio), insulin levels, IR (insulin resistance), T2 DM, inflammatory. cytokines, NAFLD (non alcoholic fatty liver disease).
- SFA, TFA and refined carbohydrates intake doubles or triples the endotoxemia. Additive with high dietary NaCl. Role for OGTT (oral glucose tolerance test).

Metabolic Endotoxemia and Gut Microbiota Signatures (GMS)

Current Opin Lipidol 2013;24:78J of Nutritional Biochemistry 2011; 22:1105
Nutr Res 2012;32:727; J Nutr 2011;141:1961

Gut flora, gut microbiota signatures (GMS) act as an important determinant in the pathogenesis of inflammatory induced obesity, CHD, atherosclerosis and T2 DM

Endotoxin acts as the systemic insult, impacted by high fat intake and glucose in the presence of altered GMS

Leads to endothelial dysfunction (ED) and atherosclerosis

Metabolic Endotoxemia

Curr Opin Lipidol 2013;24:78

J Nutritional Biochemistry 2013;24:1183

- LPS (lipopolysaccharide) from gram negative bacteria is the endotoxin from the cell wall.
- LPS has high affinity for chylomicrons and cross enterocyte barrier coupled with lipoproteins.
- LPS stimulates innate immune system,TLR4 in adipocytes and vascular tissue, activates NFkB and increases inflammation, oxidative stress and immune dysfunction.

Metabolic Endotoxemia and CHD

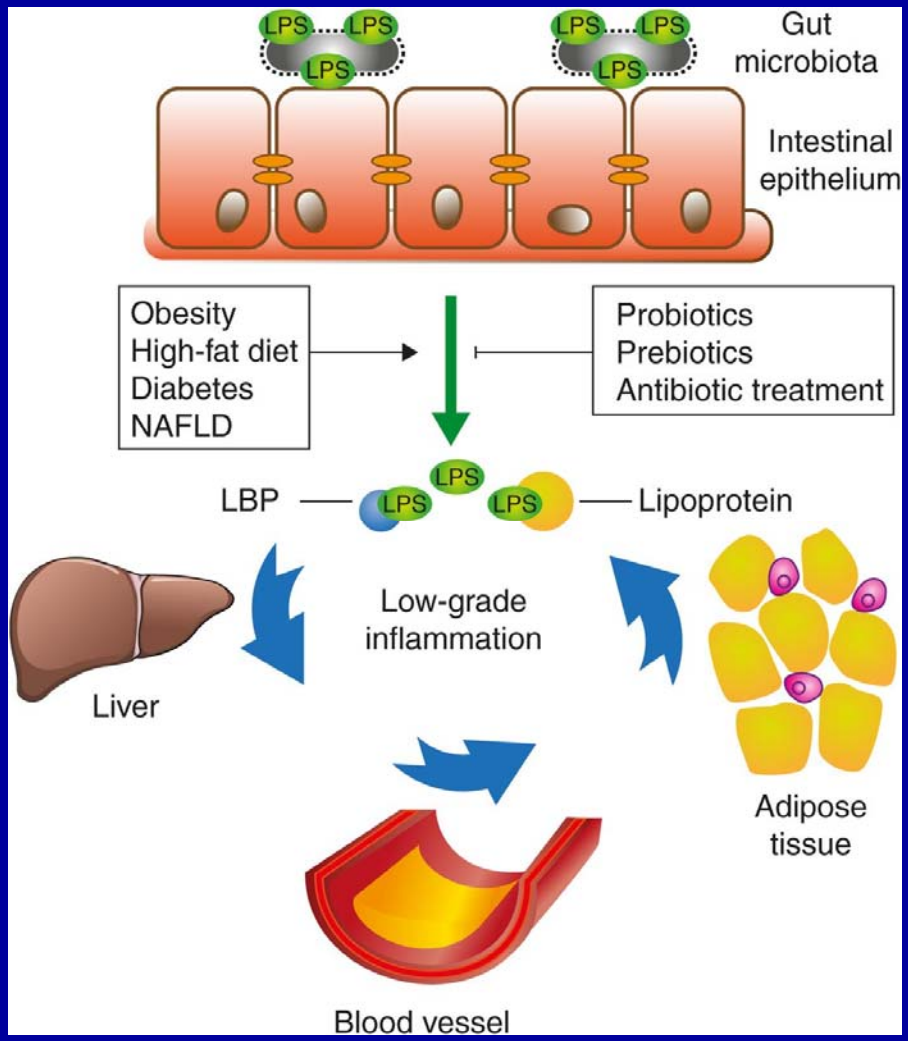
J of Molecular Endocrinology 2013;51:R51

Nutrition and Metabolism 2013;10:6

- Alterations in the intestinal barrier and enterocytes leads to increased intestinal permeability and decrease bifidobacteria levels. (SFA, TFA, high refined CHO, obesity, DM, MS, NAFLD). PUFA decreased LPS.
- LPS in gram negative bacteria is in gram concentration in gut, but only need picograms amounts in blood to induce endotoxemia.
- Transport of LPS is by para-cellular means in gap junctions, trans-cellular with endocytosis and TLR/CD 14/MD2 and also by lipid micro-domains rafts .
- SFA with refined CHO increase LPS concentration by 70%.
- SFA increase gram negative gut concentration.
- Fiber and probiotics decrease gram negative gut concentration.

The gut epithelium is an efficient barrier that prevents absorption of LPS derived from Gram-negative gut microbiota.

Neves A L et al.
J Mol Endocrinol 2013;51:R51-R64



Human Microbiome and CVD

Curr Opin Lipidology 2016;27:615

- Endotoxemia: LPS
- TMAO : from choline, phosphatidyl choline and carnitine
- SCFA : butyrate, propionate, acetate. Relates to conic health, IR, DM, lipids, gluconeogenesis, lipogenesis, intestinal epithelial health and gluconeogenesis, energy and glucose homeostasis, signaling molecules for GPR 41 and 43, GLP-1, PYY,
- Bile acid metabolism: primary to secondary bile acids. Metabolic switches for FXR, FPR TGR5, glucose metabolism, lipid metabolism, GLP-1, thermogenesis in BAT, role in obesity and alterations with antibiotics.
- Other microbiome products

- Relate to obesity, insulin resistance, DM, hypertension, dyslipidemia, CHD, MI, CHF.
- Treatment with diet (plant based), fiber, FMT (encapsulated), prebiotics, probiotics, EVOO, DMB (dimethylbutanol).

Microbiome in CVD

International J of Cardiology 2013;168:5118

- Increases in the abundance of the family Pseudomaoadaceae (Gammaproteobacteria of Proteobacteria) in CVD patients compared to healthy individuals.
- Firmicutes (Staphylococcaceae of Firmicutes) species are lower in CVD patients.
- CHD plaque also has higher ratio of Pseudomaoadaceae to Firmicutes bacteria and their respective DNA.

Direct Interactions between intestinal immune cells and diet

Cell Cycle 2012;11:3: 426

- Plants of the brassica family such as cabbages and broccoli contain high amounts of indole 3 carbinol (I3C) that oxidizes in upper GI tract to I3C carboxylic acid and condenses to diindolylmethane (DIM) in acidic environment.
- DIM activates aryl hydrocarbon receptor (AhR) in enterocyte to maintain intraepithelial lymphocytes (IELs) which line the intestinal tract, establish lymphoid structures, maintain intestinal integrity, decrease permeability, increase enterocyte repair and improve microbiome and reduce metabolic. endotoxemia. Also increase short chain fatty acids (SCFA), and production of vitamins and other compounds by enterocyte.

Metabolic Endotoxemia and CHD

J of Molecular Endocrinology 2013;51:R51
Nutrition and Metabolism 2013;10:6

- High fat diet decreases expression of genes involved in intestinal barrier function, namely zonula occludens I and occludin genes.
- Some SFA like myristic and lauric acids are part of the lipid-A component of LPS. (molecular mimicry/cross reactions. PUFA substitute for the LPS lipid A in SFA.
- PUFA, omega 3 FA, pre and probiotics reduce permeability and metabolic endotoxemia. PUFA reduce TLR4 signaling, lipid microdomain rafts and modulate LPS receptor.
- Translocation of microbiome-derived LPS occurs to the bloodstream especially after a high fat diet
- Triggers TLR 4- mediated inflammation and oxidative stress with increased CVD.

Metabolic Endotoxemia and CHD

J of Molecular Endocrinology 2013;51:R51
Nutrition and Metabolism 2013;10:6
Atherioscler, Thromb, Vasc Biol. 2004;24:2227

- LPS is transported by LBP (binding protein) and lipoproteins to hepatocytes for biliary excretion.
- All subclasses of lipoproteins can bind and neutralize the toxic effects of LPS which is dependent on the number of phospholipids on the lipoprotein surface.
- LDL is involved this anti-atherogenic effect but it is outweighed by is pro-atherogenic features.
- HDL has high capacity to bind to LPS. LPS increases endothelial lipase which lowers HDL and decreases HDL size.
- Increase NAFLD which further reduces zonula occludens 1.

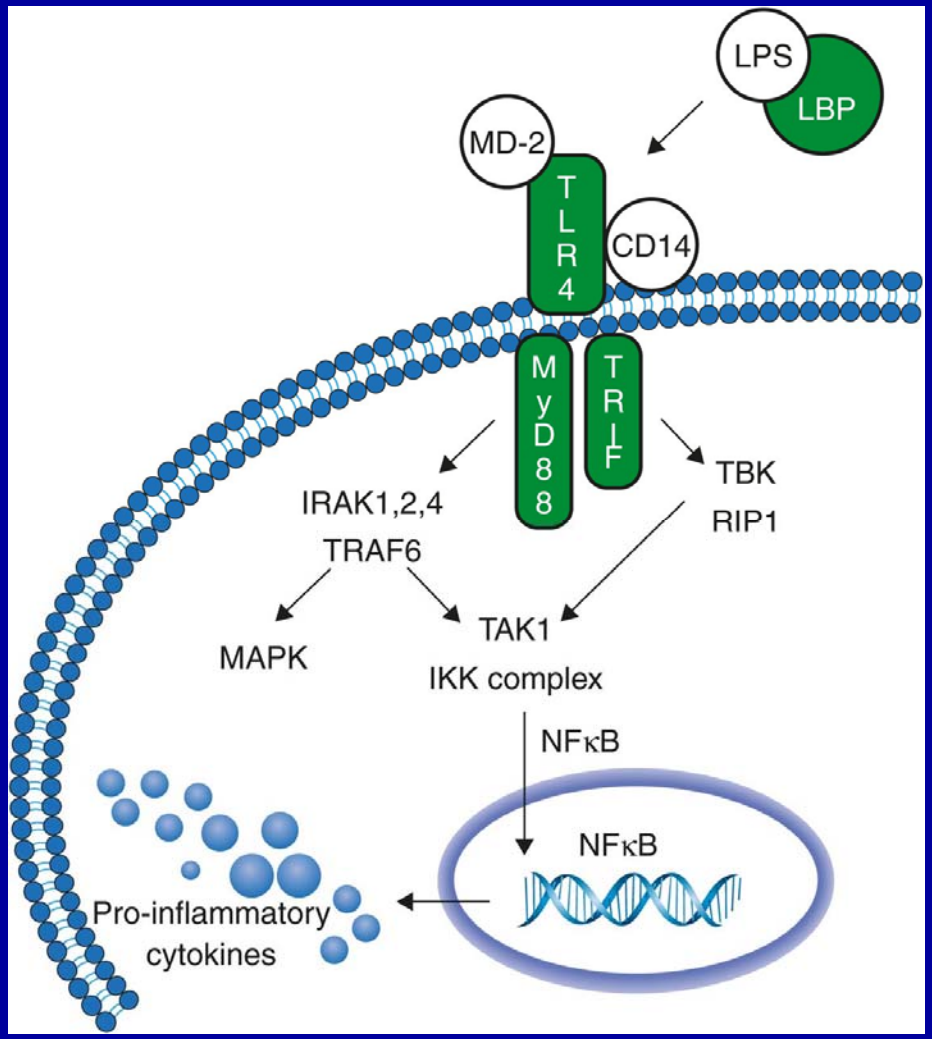
Metabolic Endotoxemia and CHD

J of Molecular Endocrinology 2013;51:R51

- PRR like TLRs recognize microbe-associated molecular patterns (MAMP) at the enterocyte such as gram negative outer membrane LPS and gram positive outer membrane LTA and peptidoglycan.
- LPS sensing is composed of LPS-BP, CD 14, MD 2 and TLR 4.
- Downstream mediators such as MyD88, TIR – DCAP, TRIF-RAM and TRIF –DCAI IFN gamma to activate NF K b to produce inflammatory cytokines.

LPS-induced TLR4 activation induces the transcription of pro-inflammatory mediators, via the recruitment of adaptor molecules such as MyD88 and TRIF. LPS is mainly sensed through the activation of TLR4 by the LBP–LPS trigger complex.

Neves A L et al. J Mol Endocrinol 2013;51:R51-R64



Atherosclerosis, postprandial vascular insults and "Metabolic Memory"

J of Nutritional Biochemistry 2012;23:39-50
Mediators Inflamm 2013; EPUB Jan 31

- Post prandial hyperglycemia, FFA ,TFA,SFA induce glucotoxicity and fat-toxicity with immediate endothelial dysfunction and macro- and micro-vascular complications.
- Increases in inflammatory cytokines, chemokines, ROS, NFkB, IKKB,TNF alpha, IL-6, activate immune mediators, TLRs (TLR4) and NLRs.
- **Metabolic Memory**: These responses may be perpetuated long after the original insult.

Atherosclerosis, postprandial vascular insults and "Metabolic Memory"

J of Nutritional Biochemistry 2012;23:39-50
J Nutrirional Biochemistry 2012;24:196
J Nutr Biochem 2012;23:22

- Chronic and oscillating glucose and SFA levels may activate adipose tissue TLR4/NFkB signaling pathway leading to downstream pro-inflammatory adipocytokines.
- While intracellularly the cell may aim to desensitize itself to the insult, in the innate immune pathway there is still a heightened continued inflammatory response.
- Gamma tocopherol blunts postprandial hypergylcemia and Methylglyoxal.

Dietary fatty acids, dietary patterns, and lipoprotein metabolism.

Curr Opin Lipidol.2015 Feb;26(1):42-7..

Dietary saturated fatty acids slow the clearance of LDL apolipoprotein (apo)B-100 and of apoA-I from the circulation, whereas possibly increasing also apoA-I production.

Dietary trans fats reduce the clearance of LDL apoB-100, whereas increasing the clearance of apoA-I.

n-3 polyunsaturated fatty acids (PUFAs) intake reduces the production of apoB-48-containing lipoproteins as well as of VLDL apoB-100 and increases their conversion into smaller lipoproteins.

Medium-chain triglycerides appear to have no significant effect on lipoprotein kinetics.

Mediterranean diet in the absence of weight loss reduces LDL cholesterol, primarily by enhancing its clearance from the circulation

Kinetic studies with tracers allow a better appreciation of the impact of specific dietary factors on plasma lipid risk factors. However, additional studies are required to better document the effect of monounsaturated fatty acids, n-6 PUFAs, and of whole diets on lipoprotein metabolism

Nutrition, Dyslipidemia and CHD

Curr Opin Lipidol 2016;27: 323

SFA relationship to CHD is complex and depends on many factors

- Chemical and metabolic heterogeneity of the SFA.
- Type of replacement nutrient
- Inter-individual variability in dietary response and genetics (PPAR)
- Food and or dietary pattern context in which the SFAs are consumed.
- Presence of insulin resistance
- Obesity, BMI, body fat
- An emphasis on foods and dietary patterns to achieve cardiovascular health supersedes a focus on individual macronutrients.
- Sugars, refined carbohydrates, fructose, HFCS starches and TFA confer more risk to dyslipidemia and CHD than SFA.
- Omega 3 FA, MUFA, fermented foods, fiber, F+V, dairy, TMD, DASH reduce CHD. Omega 6 FA consumption is now contested.

Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease

Am J Clin Nutr.2015 Dec;102(6):1563-73.

- Evaluate the association between total fat intake and fat subtypes with the risk of CVD (myocardial infarction, stroke, or death from cardiovascular causes) and cardiovascular and all-cause death. We also examined the hypothetical effect of the isocaloric substitution of one macronutrient for another.
- Prospectively studied 7038 participants at high CVD risk from the PREvención con DIeta MEDiterránea (PREDIMED) study. The trial was conducted from 2003 to 2010, but the present analysis was based on an expanded follow-up until 2012. At baseline and yearly thereafter, total and specific fat subtypes were repeatedly measured by using validated food-frequency questionnaires. Time-dependent Cox proportional hazards models were used.
- **RESULTS:** After 6 y of follow-up, we documented 336 CVD cases and 414 total deaths. HRs (95% CIs) for CVD for those in the highest quintile of total fat, monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA) intake compared with those in the lowest quintile were 0.58 (0.39, 0.86), 0.50 (0.31, 0.81), and 0.68 (0.48, 0.96), respectively. In the comparison between extreme quintiles, higher saturated fatty acid (SFA) and trans-fat intakes were associated with 81% (HR: 1.81; 95% CI: 1.05, 3.13) and 67% (HR: 1.67; 95% CI: 1.09, 2.57) higher risk of CVD. Inverse associations with all-cause death were also observed for PUFA and MUFA intakes. Isocaloric replacements of SFAs with MUFAs and PUFAs or trans fat with MUFAs were associated with a lower risk of CVD. SFAs from pastries and processed foods were associated with a higher risk of CVD.
- **CONCLUSIONS:** Intakes of MUFAs and PUFAs were associated with a lower risk of CVD and death, whereas SFA and trans-fat intakes were associated with a higher risk of CVD. The replacement of SFAs with MUFAs and PUFAs or of trans fat with MUFAs was inversely associated with CVD.

Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults.

Am J Clin Nutr. 2016 Nov;104(5):1209-1217.

- Evaluate the association between dairy fat and incident CVD in US adults.
- Followed 43,652 men in the Health Professionals Follow-Up Study (1986-2010), 87,907 women in the Nurses' Health Study (1980-2012), and 90,675 women in the Nurses' Health Study II (1991-2011). Dairy fat and other fat intakes were assessed every 4 y with the use of validated food-frequency questionnaires.
- During 5,158,337 person-years of follow-up, we documented 14,815 incident CVD cases including 8974 coronary heart disease cases (nonfatal myocardial infarction or fatal coronary disease) and 5841 stroke cases.
- In multivariate analyses, compared with an equivalent amount of energy from carbohydrates (excluding fruit and vegetables), dairy fat intake was not significantly related to risk of total CVD (for a 5% increase in energy from dairy fat, the RR was 1.02; 95% CI: 0.98, 1.05), coronary heart disease (RR: 1.03; 95% CI: 0.98, 1.09), or stroke (RR: 0.99; 95% CI: 0.93, 1.05) ($P > 0.05$ for all).
- In models in which we estimated the effects of exchanging different fat sources, the replacement of 5% of energy intake from dairy fat with equivalent energy intake from polyunsaturated fatty acid (PUFA) or vegetable fat was associated with 24% (RR: 0.76; 95% CI: 0.71, 0.81) and 10% (RR: 0.90; 95% CI: 0.87, 0.93) lower risk of CVD, respectively, whereas the 5% energy intake substitution of other animal fat with dairy fat was associated with 6% increased CVD risk (RR: 1.06; 95% CI: 1.02, 1.09).
- CONCLUSIONS: The replacement of animal fats, including dairy fat, with vegetable sources of fats and PUFAs may reduce risk of CVD.

SFA, PUFA, MUFA, Lipids and CHD: Summary

Lipids 2010:45:893-905;Progress in CVD 2016;58:464;Am J Clin Nutrition 2016;104:1209; J of Nutritional Biochemistry 2016;36:1-20

1. Dyslipidemia effects: increase LDL TC/HDL ratio
   - Increased LDL with lauric (12), myristic (14) and palmitic acid (16)
   - Decreased or neutral with stearic acid (18)
   - However the increase in LDL is large type A, not dense type B
2. Minimal to no association with CHD/CVD(2% increase)
   Mixed results with IR, DM, vascular function and stroke.
3. Replace SFA or dairy fat with PUFA reduces CHD/CVD 10%-24%
4. Replace dairy fat with other animal fat increases CHD/CVD risk 6%
5. Replace SFA with refined CHO, sugars, fructose, HFCS, or starches increase CVD/ CHD
6. Replace SFA or dairy fat with whole grains or non refined CHO reduce CHD/CVD by 28%
7. Replace SFA with MUFA lowers (1-2%) or minimal change in risk on CHD/CVD
8. Trans fat intake increased CHD 16%
9. Omega 6 FA increased CHD 1%

SFA, Lipids and CHD: Summary

Lipids 2010:45:893-905;Am J Clin Nutr 2016:103:356
Am J Clin Nutr 2010;91:535;BMJ 2015;351:h3978
AmJ Clin Nutr 2009:89:1425;Am J Clin Nutr 1999;70:1001
Am J Clin Nutr 2003;77:1146; Am J Clin Nutr 2012;96:397
Int J Epidemiol 2010;39:1170;Ann Intern Med 2014;160:398

Meta-analysis showed on association between SFA intake and CHD risk with RRR of 1.07 to 1.03 (NS).

However this depends on the following:

- **Macronutrients that replace the SFA in the diet**
- **Specific types of SFA that differ in carbon chain length. LCFA (C12-C18, lauric, myristic, palmitic and stearic) will have varied effects on both serum lipids and risk of CHD. LCFA increased risk of CHD but SCFA (C4-C10, butyric-capric) did not increase CHD risk.**
- **Different food sources and inherent nutrients in those food sources of SFA will alter lipids and CHD risk. In MESA, dairy SFA at 5 grams per day had 16% lower risk and meat at 5 grams per day had 29% higher risk of CHD.**

The relation of saturated fatty acids with low-grade inflammation and cardiovascular disease.

J Nutr Biochem.2016 Oct;36:1-20.

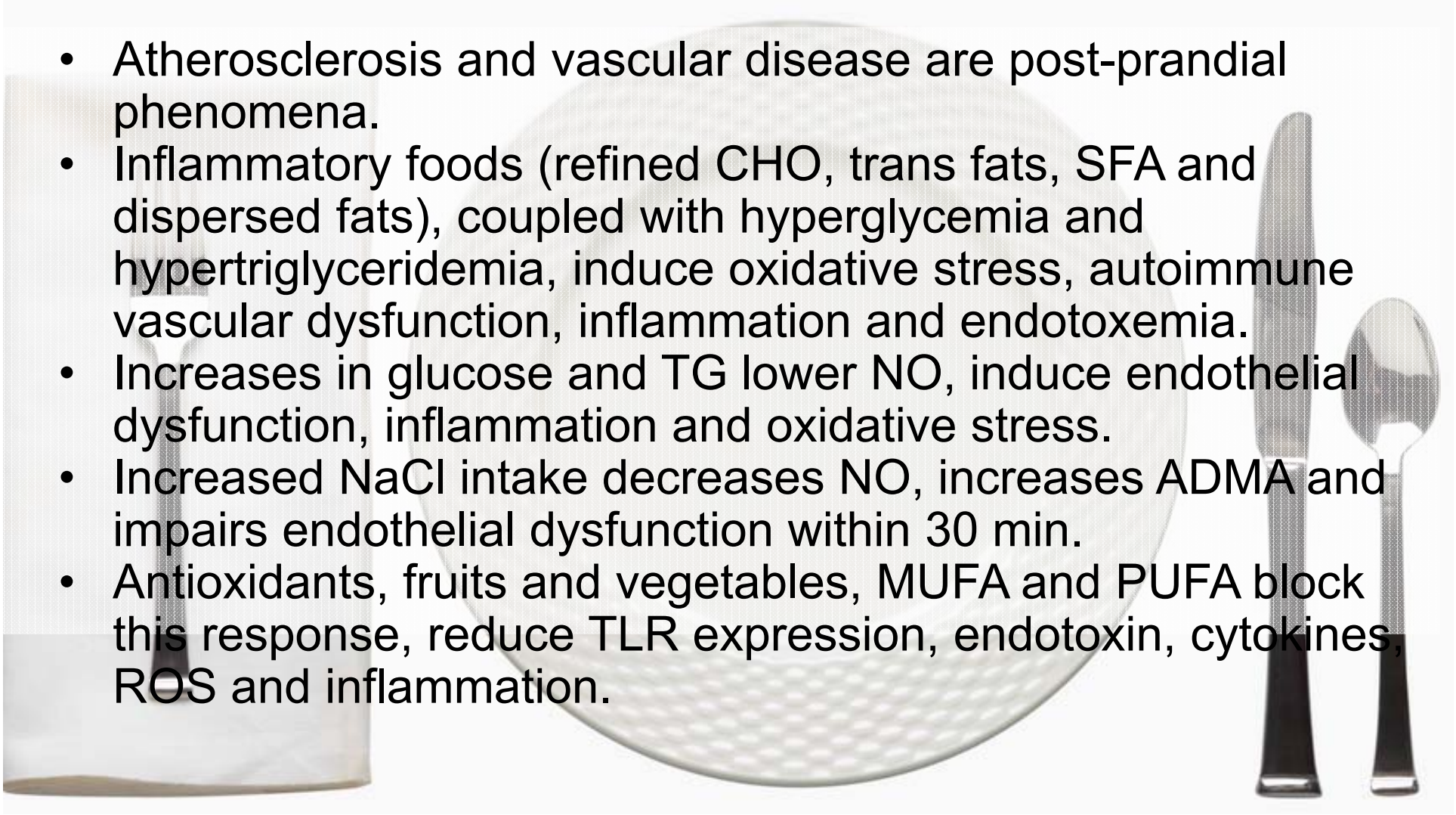
- The mantra that dietary (saturated) fat must be minimized to reduce cardiovascular disease (CVD) risk has dominated nutritional guidelines for decades.
- Parallel to decreasing intakes of fat and saturated fatty acids (SFA), there have been increases in carbohydrate and sugar intakes, overweight, obesity and type 2 diabetes mellitus.
- The "lipid hypothesis" coined the concept that fat, especially SFA, raises blood low-density lipoprotein-cholesterol and thereby CVD risk. In view of current controversies regarding their adequate intakes and effects.
- The intimate relationship between inflammation and metabolism, including glucose, fat and cholesterol metabolism, revealed that the dyslipidemia in Western societies, notably increased triglycerides, "small dense" low-density lipoprotein and "dysfunctional" high-density lipoprotein, is influenced by many unfavorable lifestyle factors. Dietary SFA is only one of these, not necessarily the most important, in healthy, insulin-sensitive people.
- The environment provides us not only with many other proinflammatory stimuli than SFA but also with many anti-inflammatory counterparts. Resolution of the conflict between our self-designed environment and ancient genome may rather rely on returning to the proinflammatory/ant-inflammatory balance of the Paleolithic era in consonance with the 21st century culture. Accordingly, dietary guidelines might reconsider recommendations for SFA replacement and investigate diet in a broader context, together with nondietary lifestyle factors.
- This should be a clear priority, opposed to the reductionist approach of studying the effects of single nutrients, such as SFA

Summary: Atherosclerosis, Vascular Disease and Meals

J of Nutritional Biochemistry 2011; 22:1105

Am J Clin Nutr 2010;91:940
J Clin Endocrinol Metab 2000;85:2970
Metabolism 2006;55:1177

Am J Clin Nutr 2004;79:682
J Nutr Biochem 2011;22:53
Am J Clin Nutr 2011;93:500 and 494



- Atherosclerosis and vascular disease are post-prandial phenomena.
- Inflammatory foods (refined CHO, trans fats, SFA and dispersed fats), coupled with hyperglycemia and hypertriglyceridemia, induce oxidative stress, autoimmune vascular dysfunction, inflammation and endotoxemia.
- Increases in glucose and TG lower NO, induce endothelial dysfunction, inflammation and oxidative stress.
- Increased NaCl intake decreases NO, increases ADMA and impairs endothelial dysfunction within 30 min.
- Antioxidants, fruits and vegetables, MUFA and PUFA block this response, reduce TLR expression, endotoxin, cytokines, ROS and inflammation.

Chronic Infections

Bacteria Role in Dyslipidemia, CHD and GI tract and Microbiome

Pathogen-------→Pathobiont

Disease---------→ CHD/CVD

Symbiont-----→Probiotics/Microbiome/GI

Balance-------→Health

Infections induce dyslipidemia, CHD and atherosclerosis by molecular mimicry

J Clin Immunol 2009;29(6):714

Am Heart J. 2014;114:1841

- Chronic infections allow formation of complexes of LPS (lipopolysaccharide) and beta 2 GPI (glycoprotein 1) with ox LDL to induce dyslipidemia, vascular inflammation, oxidative stress and immune dysfunction with CHD and atherosclerosis.
- CMI(cell mediated immunity) against H Pylori derived HSP (heat shock protein) 60 cross reacts with endogenous HSP 60 to induce dyslipidemia and CVD by MOLECULAR MIMICRY
- Other infectious pathogens will do this also.

Persistance of an atherogenic lipid profile after treatment of acute infection with Brucella and other Pathogens

J of Lipid Res 2009;50:2532 ;Cardiovasc Res 2011;92:476;Clin Res Hepatol Gastroenterol 2011;35(2): 111;J Periodontal Res 2011;46(4): 427 Dig Dis Sci 2011;56:109

- **Brucella** infection is associated with an atherogenic lipid profile not restored 4 months post treatment.
- Increased TC, HDL, LDL, Apo B, Apo A-1 / Apo CIII.
- Infectious pathogens induce chronic dyslipidemia, vascular inflammation, CHD and atherosclerosis.
- **Chlamydia Pneumonia** promotes mitogenic actions in vascular smooth muscle via oxLDL, ERK ½ (extracellular signal regulated kinase), MAPK (mitogen activated protein kinase) pathway, HSP 60, dyslipidemia and CHD.
- **Chronic hepatitis A,B,C, P gingivalis, H pylori, EBV,CMV,HSV** induce dyslipidemia, increase ox LDL, HS CRP and inflammation.

Interaction of Pathogens with Host Cholesterol Metabolism: Examples

Curr Opin Lipidol 2014;25:333
Am Heart Journal 2014;114:1841

- Pathogen attacks cell membrane receptors and lipid microdomains/rafts of glycosyl phosphatide inositol proteins.
- Allows entry point of pathogen to organize into assembly platforms with viral fusion, multimerization and virological synapses.
- Results in immune reaction, phaocytosis, raft disruption, cholesterol depletion and hidden pathogens.

Interaction of Pathogens with Host Cholesterol Metabolism

Curr Opin Lipidol 2014;25:333

- All pathogens have entry point and attack the cell membrane at the lipid rafts(microdomains) of glycosyl phosphatide inositol protein receptors.
- Develop organized entry, assembly platforms, viral fusion, multimerization, viral synapses, raft disruption, cholesterol raft duplication and fusion, cholesterol depletion, immune response, phagocytosis and “self protection and hiding” within the membrane.
- This allows the pathogen to salvage host cholesterol for survival but interferes with cellular cholesterol metabolism and thus CVD.

Interaction of Pathogens with Host Cholesterol Metabolism: Mechanisms

Curr Opin Lipidol 2014;25:333

- Alters host signaling
- Alters endocytic pathways
- Alters proteomics
- Upregulated oncogenic proteins
- Increase cholesterol uptake into phagosomes
- Increase abundance and size of lipid rafts
- Increase cholesterol synthesis
- Decrease RCT(reverses cholesterol transport) and CEC(cholesterol efflux capacity)
- Alter Nef-mediated delivery of cholesterol to rafts
- Reduces phagocytosis, endocytosis and T- cell stimulation.

Interaction of Pathogens with Host Cholesterol Metabolism: Examples

Curr Opin Lipidol 2014;25:333
Am Heart Journal 2014;114:1841

- Prion: PrPc ---→ PrPsc (mutated) results in cholesterol depletion of rafts, disrupts NO, reduces RCT via ABCA1. Cholesterol and sphingomyelin are needed for viral fusion and replication. The lipid rafts allow for fusion of the virus and cell membranes for survival.
- H Pylori: neutralizes immune defenses, disrupts rafts, extracts cholesterol from lipid rafts of epithelial cells and macrophages, prevents phagocytosis by APCs
- HCV: hijacks hepatocytes VLDL which enters blood and attaches to LDL-R, increases SREBP and induces steatosis. Increased CHD in HCV seropositive patients with highest incidence in those with detectable VCV RNA vs those with remote infection and only antibody positive.
- See similar mechanisms with HIV, influenza, enteroviruses, M TBC, EBV, Toxoplasmosis, malaria, entamoeba and some microbiotic pathogens (TMAO)

Interaction of Pathogens with Host Cholesterol Metabolism: Summary

Curr Opin Lipidol 2014;25:333
Am Heart Journal 2014;114:1841

- Pathogens by interfering with cellular cholesterol metabolism achieve several objectives.
- Impair host immune responses
- Procure cholesterol to organize entry, assembly and budding sites, protective membranes or as source of carbon
- Inflict changes on uninfected bystander cells and systemically to generate metabolic milieu advancing the spread of infection and causing metabolic complications such as dyslipidemia, CVD, CHD and atherosclerosis

Pathogenic Burden and CHD
The Microbial Connection

Pak J Pharm Sci 2012;25:89;In Vivo 2005;19:351
Circulation 2003;108:678; Circulation 2002;106:184

- The pathogenic burden of various microorganisms has a significant correlation with ED (endothelial dysfunction) with impaired responses to NO (nitric oxide) and AcH (acetyl choline) in coronary arteries and both the presence and severity of CHD defined by coronary calcification and coronary arteriograms (p =0.001).
- Individual micro-organisms also have significant correlations with dyslipidemia and CHD including HSV, CMV, H. Pylori, Chlamydia Pneumoniae, Hepatitis A, B, C , EBV and periodontal microbes as defined by IgG and IgM antibodies.
- HSV DNA is detected in CHD arteries and plaque at autopsy.

Summary: **Interaction of pathogens with host cholesterol metabolism.**

Curr Opin Lipidol.2014;25(5):333-8.

- Pathogens of different taxa of all types target cellular cholesterol metabolism to advance their own development and to impair host immune responses. They cause metabolic complications such as CHD, CVD and atherosclerosis.
- A common theme in interaction between pathogens and host cholesterol metabolism is pathogens targeting lipid rafts of the host plasma membrane. Many intracellular pathogens use rafts as an entry gate, taking advantage of the endocytic machinery and high abundance of outward-looking molecules that can be used as receptors.
- At the same time, disruption of the rafts' functional capacity, achieved by the pathogens through a number of various means, impairs the ability of the host to generate immune response, thus helping pathogen to thrive.
- Pathogens cannot synthesize cholesterol, and salvaging host cholesterol helps pathogens build advanced cholesterol-containing membranes and assembly platforms.
- Impact on cholesterol metabolism is not limited to the infected cells; proteins and microRNAs secreted by infected cells affect lipid metabolism systemically. Dyslipidemia and CVD result from this pathogen –host interaction.

Protective Role of LDL and HDL in Infections and Inflammation

J Nutritional Biochemistry 2013;24:1183
Handbook Exp Pharmacol 2015;224:483-508

During the "lipidemia of sepsis"

Total HDL level may increase or decrease relative to RCT, cargo unloading HDL production

Apo A-1 decreases

Phospholipids in HDL decrease

HDL-P decreases

HDL size decreases

HDL becomes dysfunctional /pro- inflammatory.

SAA increases in HDL which reduces RCT

sPLA 2 increases in HDL

LDL –P and LDL levels increase

LDL size decreases.

More LDL goes to tissues and more LDL stays intracellular as response to protection and repair.

VLDL and TG increase

Toxins

Heavy Metals and Dyslipidemia

Int J Occup Med Environ Health 2009;22: 135
Am J Ind Med 2013; 56:682
J Prve Med Public Health 2005;38:401
ISRN Hypertension 2013;ID 234034
Am Heart J 2014;168:812

- Mercury and other heavy metals will increase LDL, TG and decrease HDL, and induce dysfunctional HDL , especially mercury.
- Induces metabolic syndrome, especially cadmium.
- Increases CVD, CHD, hypertension, atherosclerosis.
- Reduces total antioxidant capacity.
- Mitochondrial toxins.

Persistent organic pollutants (POPs) distribution in lipoprotein fractions in relation to cardiovascular disease and cancer.

Environ Int. 2014 ;65:93-99

- POPs: lipophilic environmental toxins associated with CVD/ cancer.
- Lipoproteins from 28 individuals . Analyzed 20 different POPs and PON1(paroxnonase) with high resolution gas chromatography/high resolution mass spectrometry. Compared to 50 control subjects.
- Polychlorinated biphenyls (PCBs) and organochlorine pesticides were enriched in lipoproteins. Significantly higher concentrations of POPs in those with CVD or cancer compared to controls.

Persistent organic pollutants (POPs) distribution in lipoprotein fractions in relation to cardiovascular disease and cancer.

Environ Int. 2014 ;65:93-99

- **POP concentrations in HDL were associated with CVD.**
- **POP concentrations in LDL/VLDL were associated with cancer.**
- **PON1 activity was negatively correlated and CVD was positively correlated to increased PCB and decreased arylesterase-activity.**

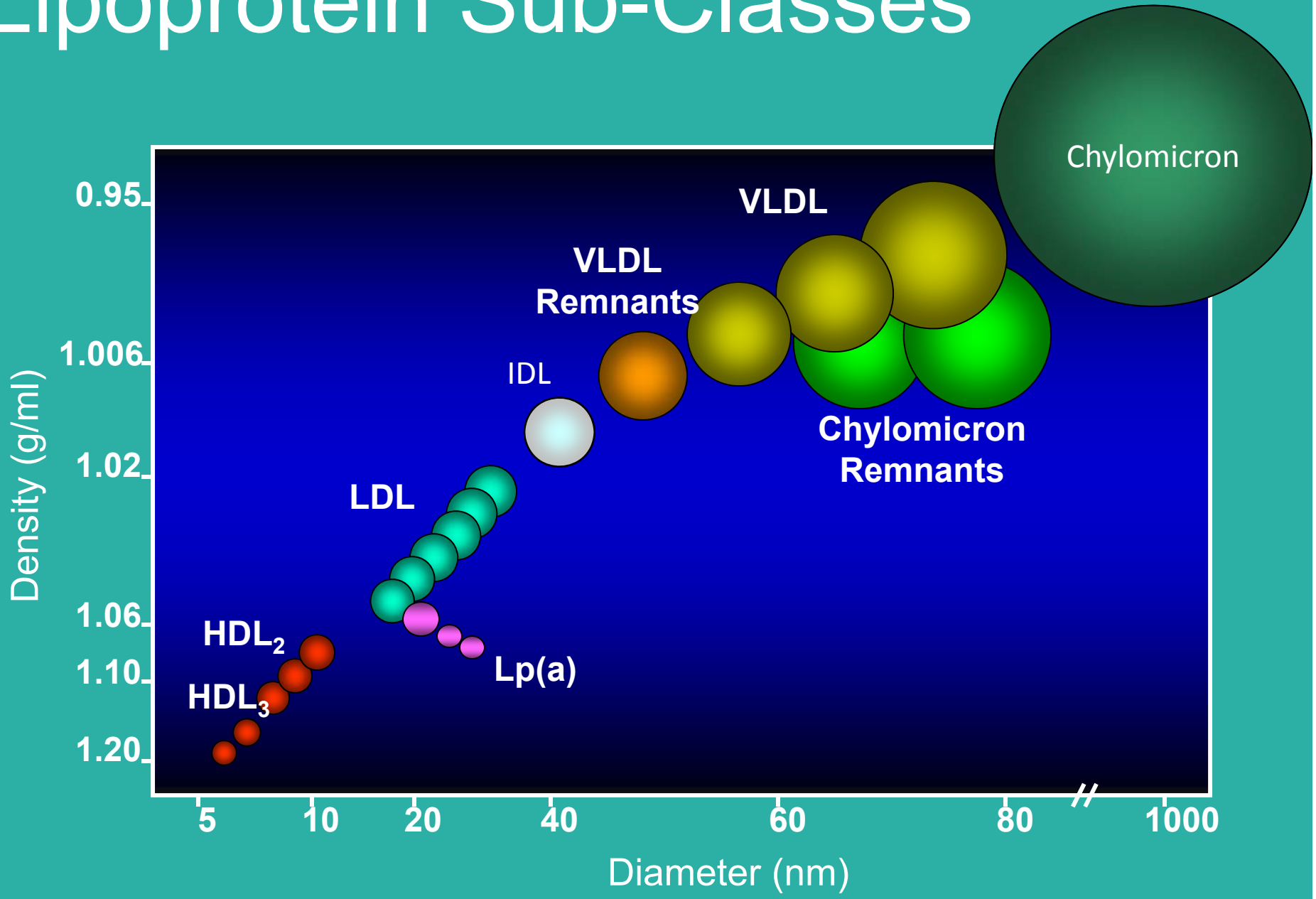
- **POPs are present in lipoproteins and were more abundant in individuals with CVD or cancer compared to healthy controls.**
- **PCB exposure is accompanied by reduced PON1 activity that could impair the HDL function.**

Emerging Roles of Qualitative Propertied of Lipoproteins and Atherosclerosis

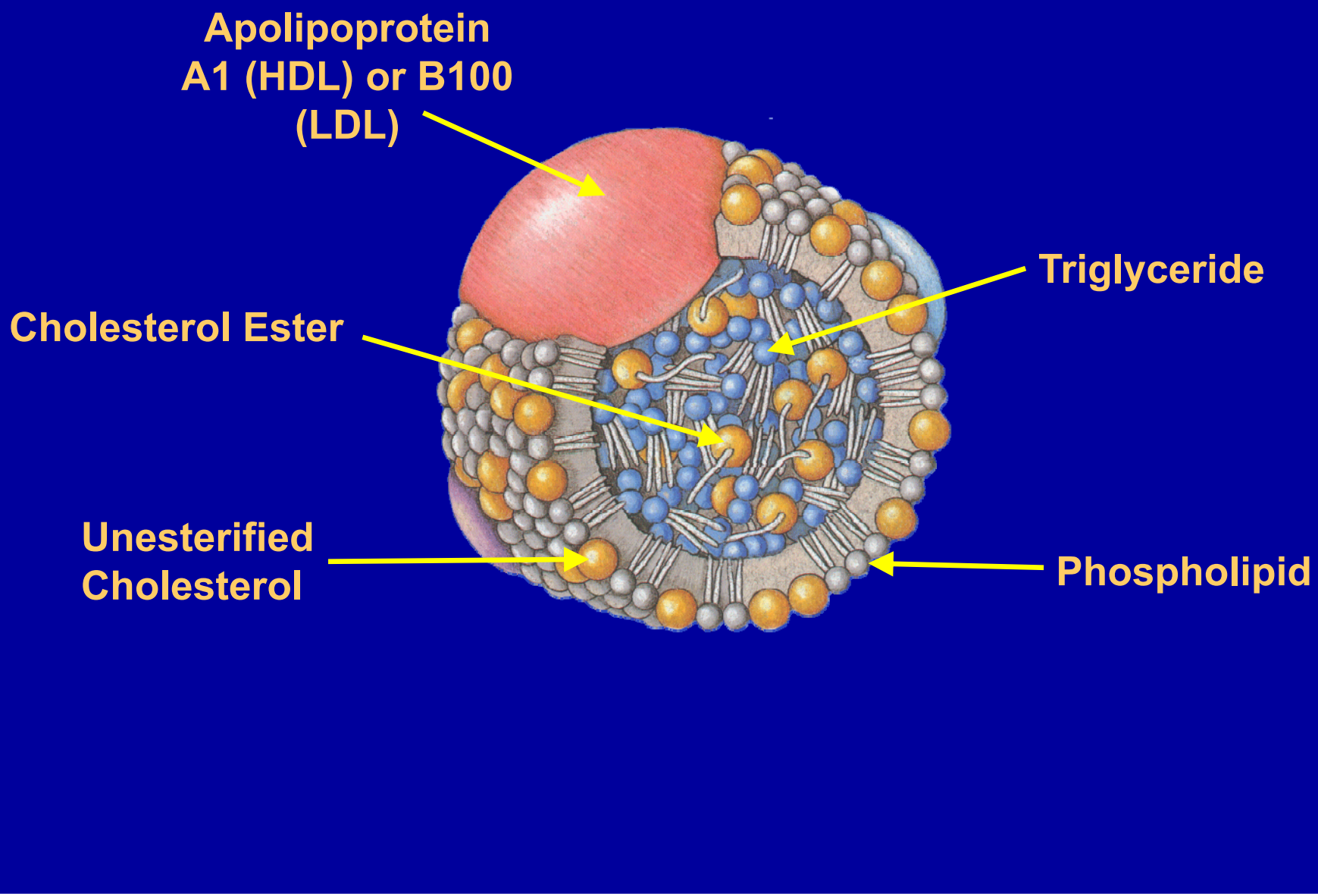
Curr Opin Lipidology 2014;25:406

- Important qualitative/ molecular differences exist among the lipoprotein species independent of their levels, which alter their anti- or pro-atherogenic activity.
- Oxidative modification of lipids (ROS, lipooxygenases, MPO, NADPH oxidase, xanthine oxidase).
- Covalent alteration of proteins (N- modified phospholipids increase PAF and thrombin activity). Schiff base adducts on apolipoproteins, aldehydes in DM, MS, CVD, CHF.
- Apo J (clusterin).
- SAA, MPO (nitration and chlorination) and hs CRP from inflammation (from any source such as RA, SLE, psoriasis etc.) Dysfunctional and inflammatory HDL and loss of RCT.
- microRNA especially in HDL.
- ApoB DS-1: proteolytic fragment Apo B-100 induces inflammatory response in innate immune cells and activates platelets.

Lipoprotein Sub-Classes



Lipoprotein Particles



Protective Role of Lipoproteins in Infections, Inflammation, Inflammatory micro – and macro nutrient intake and toxins

J Nutritional Biochemistry 2013;24:1183
Clin Biochem 2004;37(5): 377-81

- Circulating lipoproteins clear LPS(gram negative bacteria) for hepatic/biliary excretion. Limits inflammatory/ immune reaction.
- Ability of lipoproteins to bind to LPS is proportional to the cholesterol content, specifically the phospholipid/cholesterol ratio. (PL/Chol ratio). PL reacts to cell receptors and serum components to reduce inflammation and infection in arteries.
- The phospholipid surface is of special importance and is largest for HDL-C and enhances RCT(reverse cholesterol transport) and CEC(cholesterol efflux capacity).
- HDL : PL/Cholesterol ratio is 1.15 to 1.53.
- LDL : PL/Cholesterol ratio is 0.44-0.48.
- In chronically ill patients or those with severe inflammation, the LDL and VLDL become the primary lipoproteins to remove LPS.
- The HDL phospholipids are excellent predictors of the extent of CHD (0.001) . HDL-PL to LDL ratio helps predict CHD. HDL 2 has higher PL ratio than HDL 3. -Clin Biochem 2004;37(5): 377-81)

Protective Role of LDL and HDL in Infection and Inflammation

J Nutritional Biochemistry 2013;24:1183

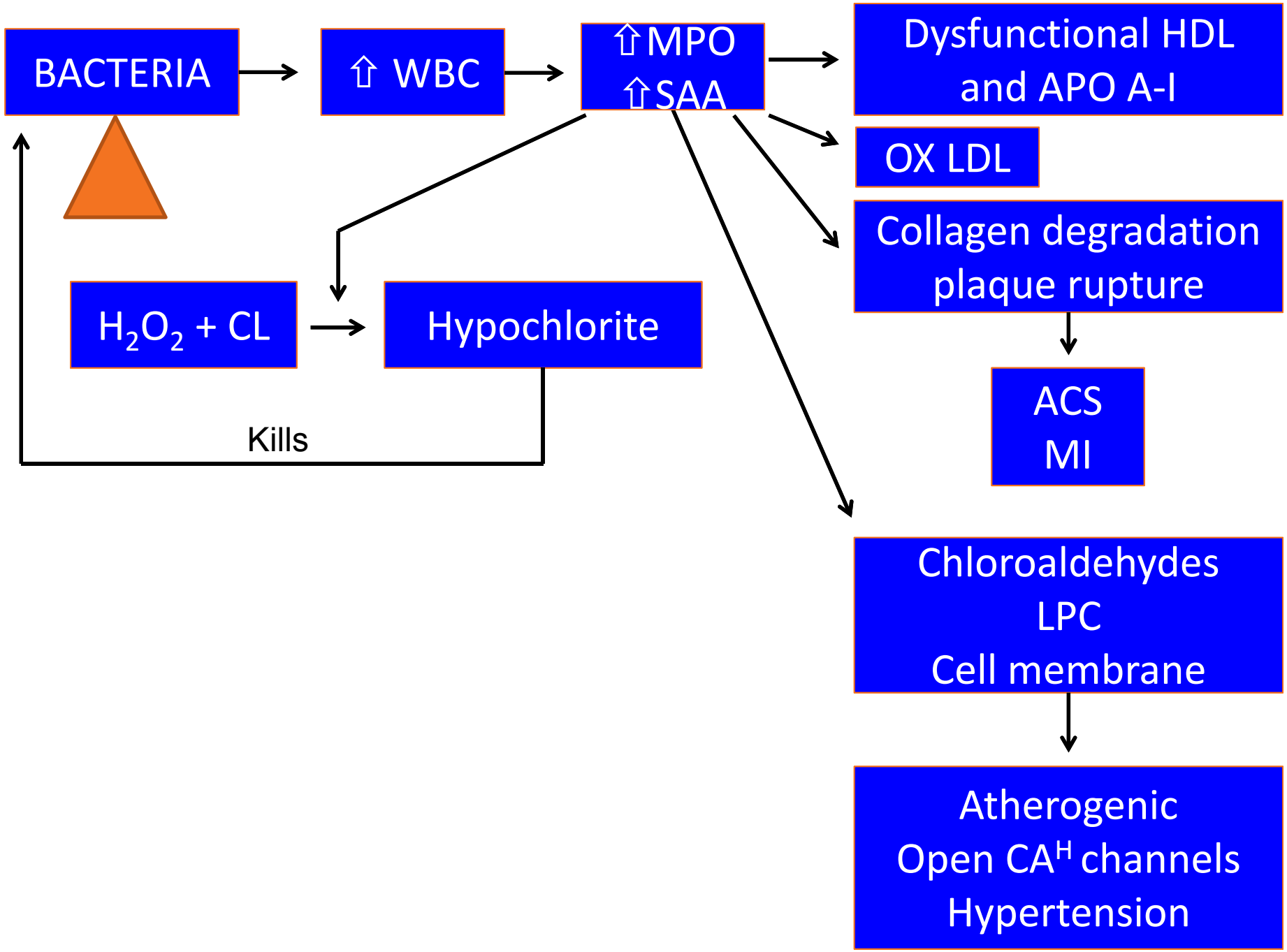
- HDL and LDL have protective roles in infection, inflammation, chronic nutritional endotoxemia and toxin exposure to defend the vascular system and improve survival.

- Both bind LPS to prevent LPS –induced activation of monocytes, macrophages and pro-inflammatory cytokines.

Protective Roles of HDL and LDL in Infections, Toxins, Nutritional Endotoxemia and Inflammation

J Nutritional Biochemistry 2013;24:1183

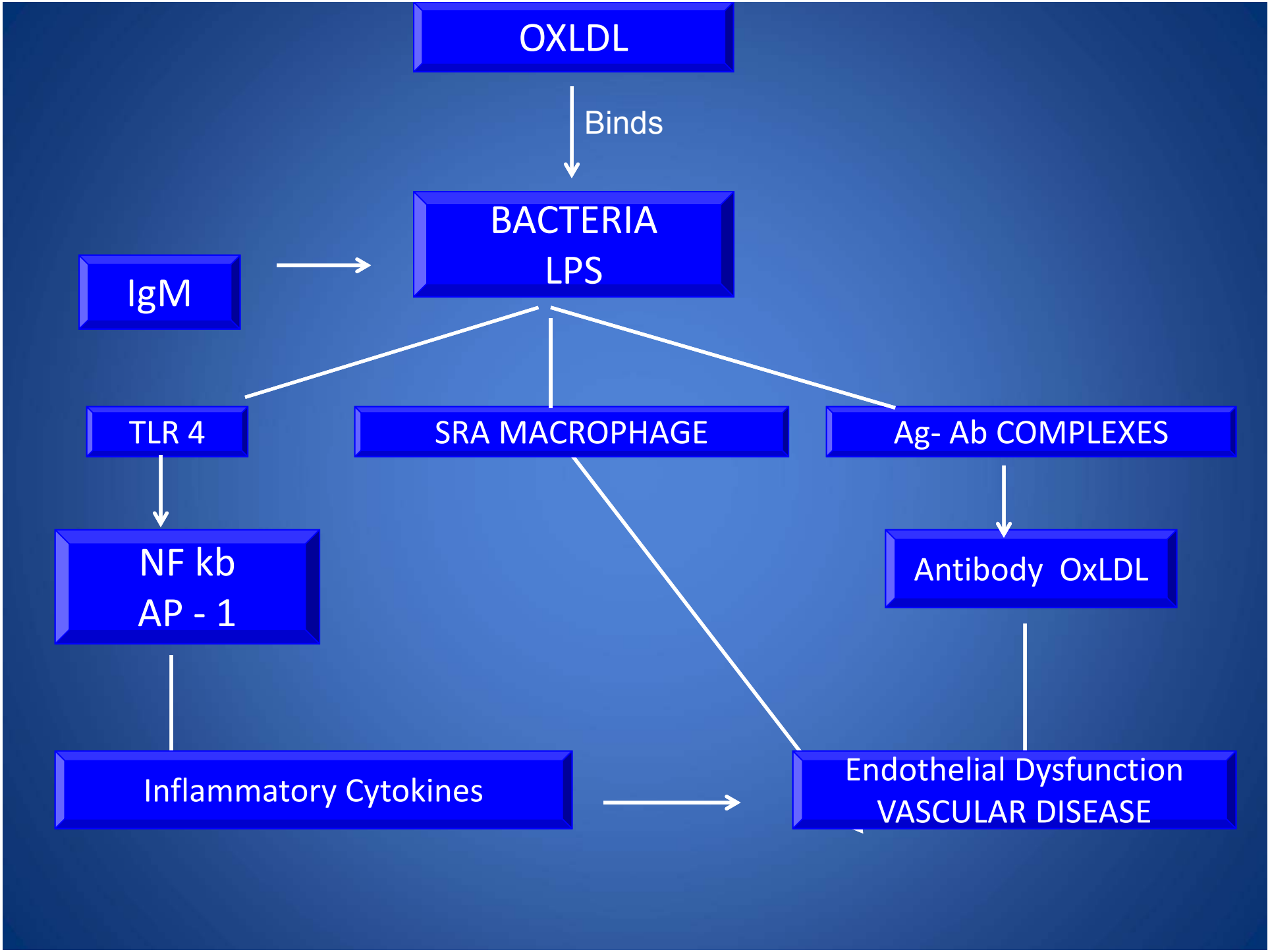
- During the "lipidemia of sepsis"
  - HDL-P decreases.
  - HDL size decreases.
  - HDL becomes dysfunctional, pro-inflammatory or proatherogenic.
  - Total HDL levels may increase or decrease relative to reverse cholesterol transport (RCT), cargo unloading or HDL production.
  - Reduce RCT and CEC (cholesterol efflux capacity)
  - LDL –P and LDL levels increase.
  - LDL size decreases.
- MPO (myeloperoxidase) and SAA (serum amyloid A) increase, inducing dysfunctional, modified, oxidized or pro-inflammatory and proatherogenic HDL which reduces RCT.
- LDL charge is altered, more LDL goes to tissues and clumps. More LDL stays intracellular as a response to protection and repair.


BACTERIA
⇧ WBC
⇧MPO
⇧SAA
Dysfunctional HDL
and APO A-I
OX LDL
Collagen degradation
plaque rupture
ACS
MI
H_2O_2 + CL
Hypochlorite
Kills
Chloroaldehydes
LPC
Cell membrane
Atherogenic
Open CA^H channels
Hypertension

Lipopolysaccharide (LPS) in oxLDL cooperatively activate macrophages via Nfkb and AP-1: Atherosclerosis due to subclinical endotoxemia

Circ Res 2010;107:56;Atherosclerosis 2010;208:396
J Nutritional Biochemistry 2013;24:1183

- Low grade chronic sub-clinical **immune metabolic/nutritional/toxic and infectious endotoxemia** induce atherosclerosis.
- oxLDL and LPS cooperatively activate TLR-4 on endothelium and macrophages (oxLDL binds to LPS membrane of infectious agent) to allow endocytosis by macrophage scavenger receptors (SR-A)
- Macrophages with pro-inflammatory cytokines, NFkb (nuclear factor kb) and AP-1(activated protein-1)
- Amount of LPS required is minimal. IGM-oxLDL/LPS complex binds to macrophages but this is not prevented by IgM's usual binding to oxLDL to neutralize its effect.
- Induces atherosclerotic lesions and CHD.

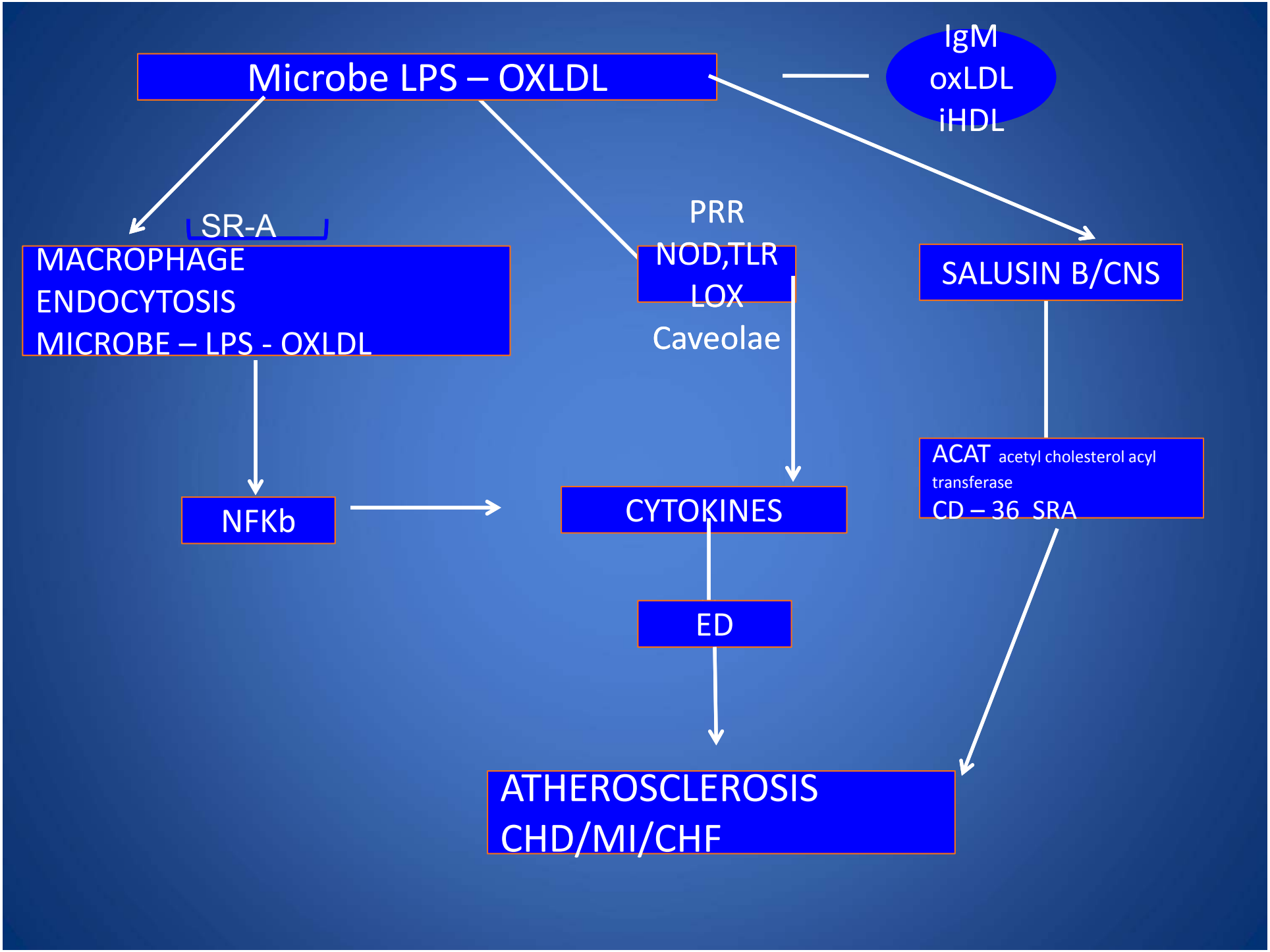

OXLDL
Binds
BACTERIA
LPS
IgM
TLR 4
SRA MACROPHAGE
Ag- Ab COMPLEXES
NF kb
AP - 1
Antibody OxLDL
Inflammatory Cytokines
Endothelial Dysfunction
VASCULAR DISEASE

Trained Innate Immunity and Atherosclerosis and CHD: 4 methods of Lipid Induced Vascular Disease

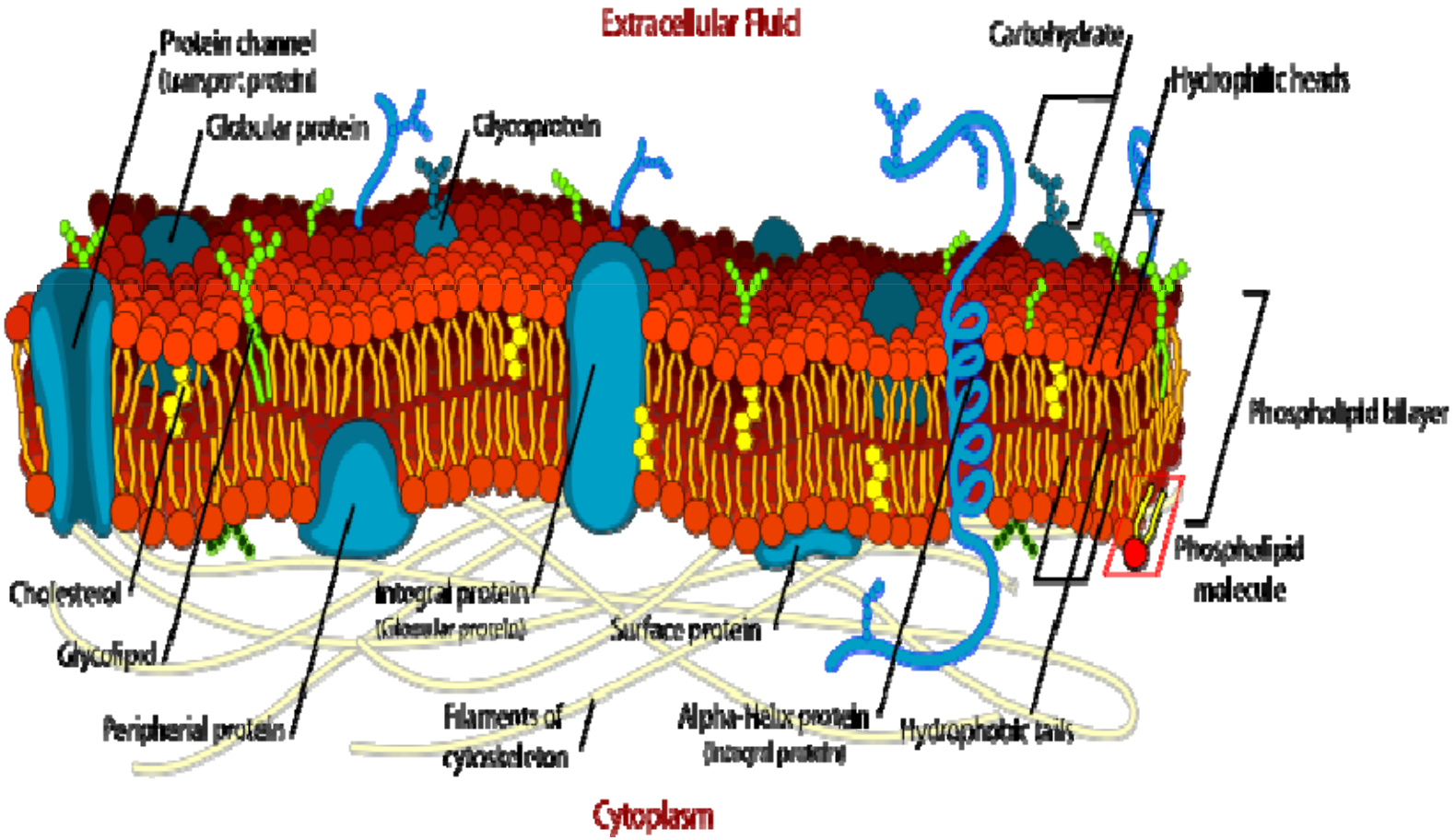
Curr Opin Lipidol 2013;24:487-92

Monocytes and macrophages increase long-term memory after microbial stimulation via epigenetic reprogramming. Leads to atherogenesis / CHD. Trained immunity is memory for cells of the innate immune system

1. Typical LDL transmigration to subendothelium with modification and macrophage scavenger uptake.
2. Membrane bound and intracellular PRR on macrophages and vascular cells. TLR 4/6 bind oxLDL stimulate MyD88 , Nfk-b, interleukins (IL-1b, IL 18) and beta cells.
3. Ox LDL stimulation of macrophage TLR 2 and TLR4.
4. Intracellular PRR are activated by minute cholesterol crystals via NLRP3(NOD receptor protein) inflammasone with IL-1 b and IL 18 activation.


Microbe LPS – OXLDL
IgM
oxLDL
iHDL
SR-A
MACROPHAGE
ENDOCYTOSIS
MICROBE – LPS - OXLDL
PRR
NOD,TLR
LOX
Caveolae
SALUSIN B/CNS
NFKb
CYTOKINES
ACAT acetyl cholesterol acyl transferase
CD – 36 SRA
ED
ATHEROSCLEROSIS
CHD/MI/CHF

Cell Membrane Biochemistry and Physiology: Tsunami Effect



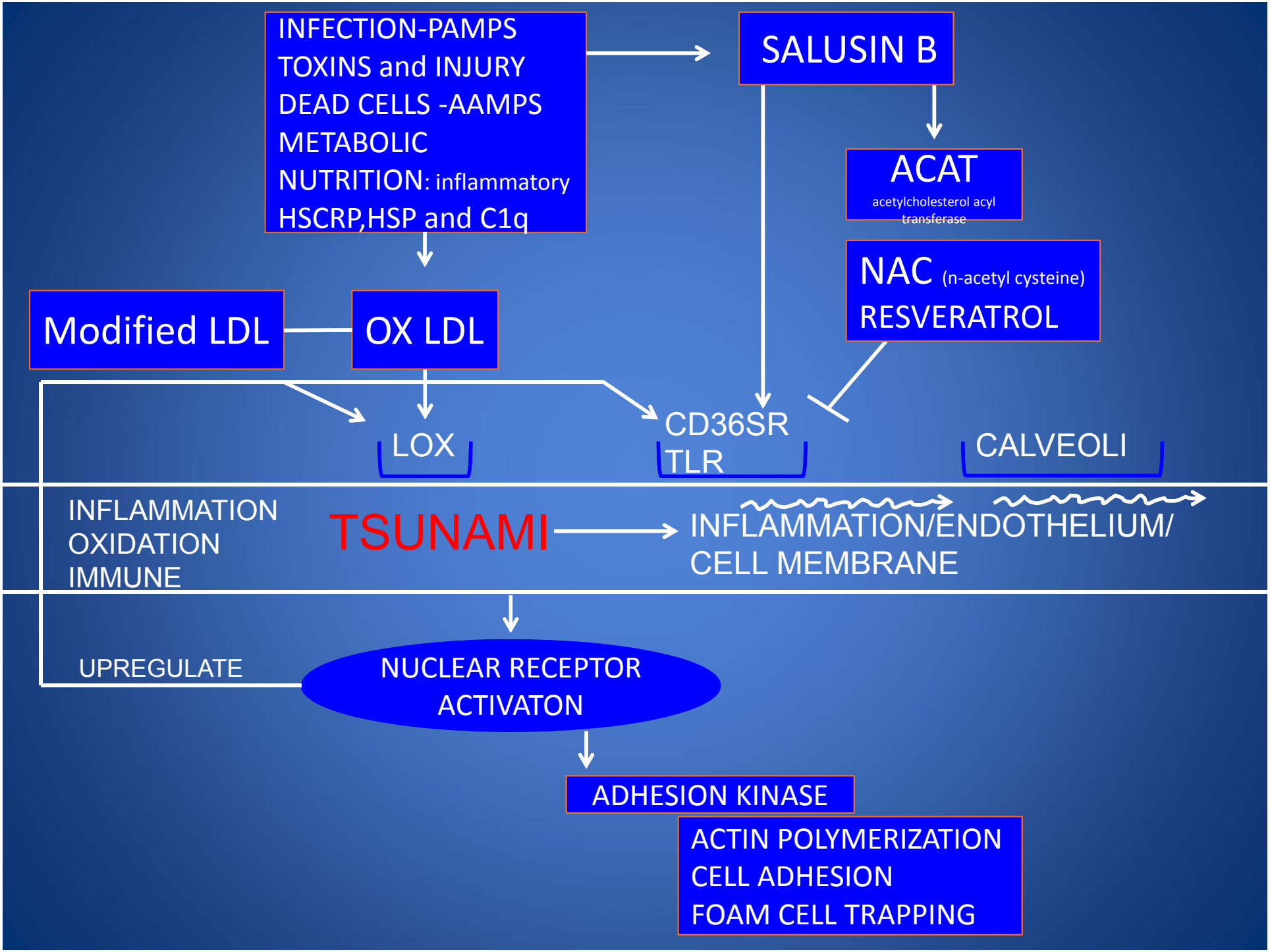
Atherosclerosis Develops as a Reaction-Diffusion Wave: Mathematical modeling as an inflammatory disease: TSUNAMI of Vascular System

Philos Transact A Math Phys Eng Sci 2009;367:4877

Cardiovasc Pathol 2011;20:369

Atherosclerosis develops as a result of a reaction diffusion wave (traveling waves)>>>>> Tsunami. Point of impact disruption vs diffuse disruption of membrane. Role of fluid membrane with integrity.

(PUFA) vs stiff membrane (TFA, SFA)


INFECTION-PAMPS
TOXINS and INJURY
DEAD CELLS -AAMPS
METABOLIC
NUTRITION: inflammatory
HSCRP,HSP and C1q
SALUSIN B
ACAT
acetylcholesterol acyl transferase
NAC (n-acetyl cysteine)
RESVERATROL
Modified LDL
OX LDL
LOX
CD36SR
TLR
CALVEOLI
INFLAMMATION
OXIDATION
IMMUNE
TSUNAMI
INFLAMMATION/ENDOTHELIUM/
CELL MEMBRANE
UPREGULATE
NUCLEAR RECEPTOR
ACTIVATON
ADHESION KINASE
ACTIN POLYMERIZATION
CELL ADHESION
FOAM CELL TRAPPING

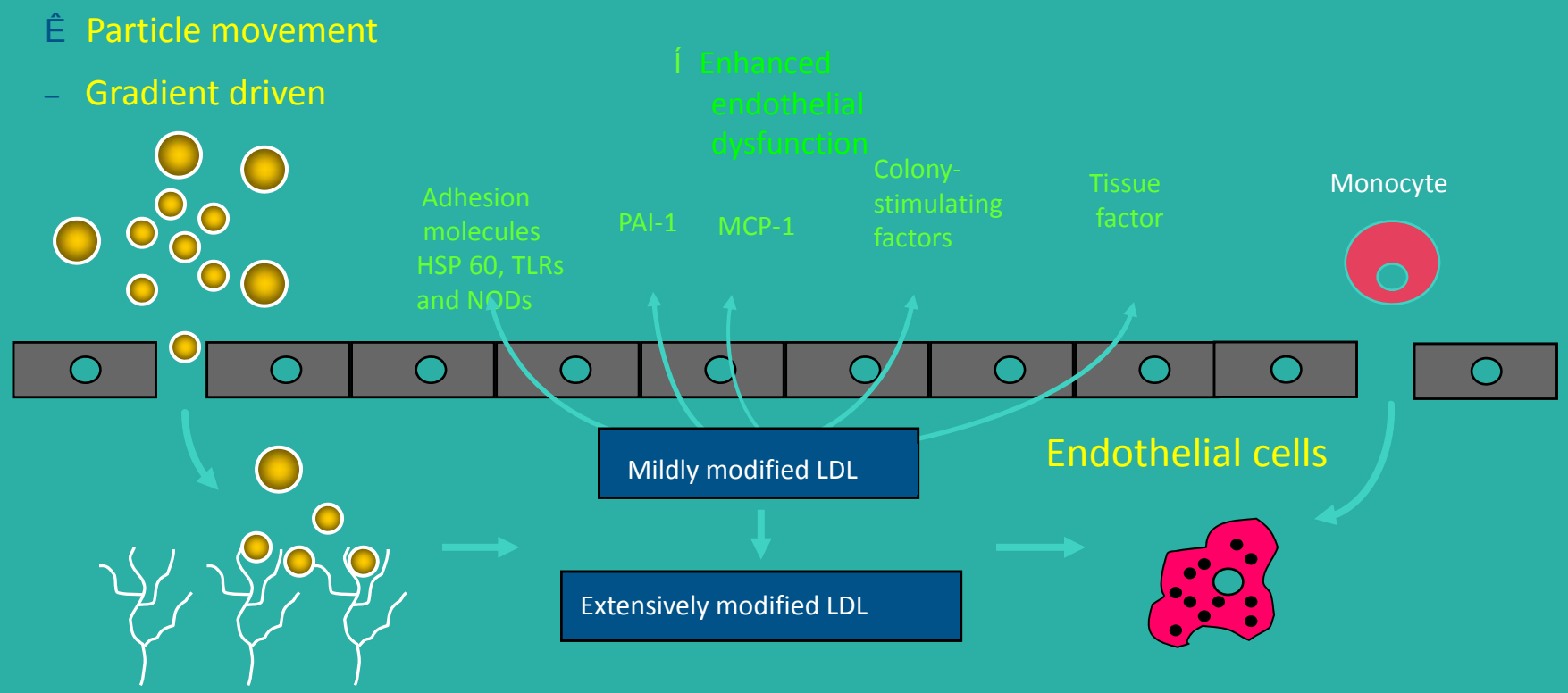
Dyslipidemia-induced CHD and Atherosclerosis is a Inflammatory and Immune Disease

Curr Opin Lipidol 2016;27:209

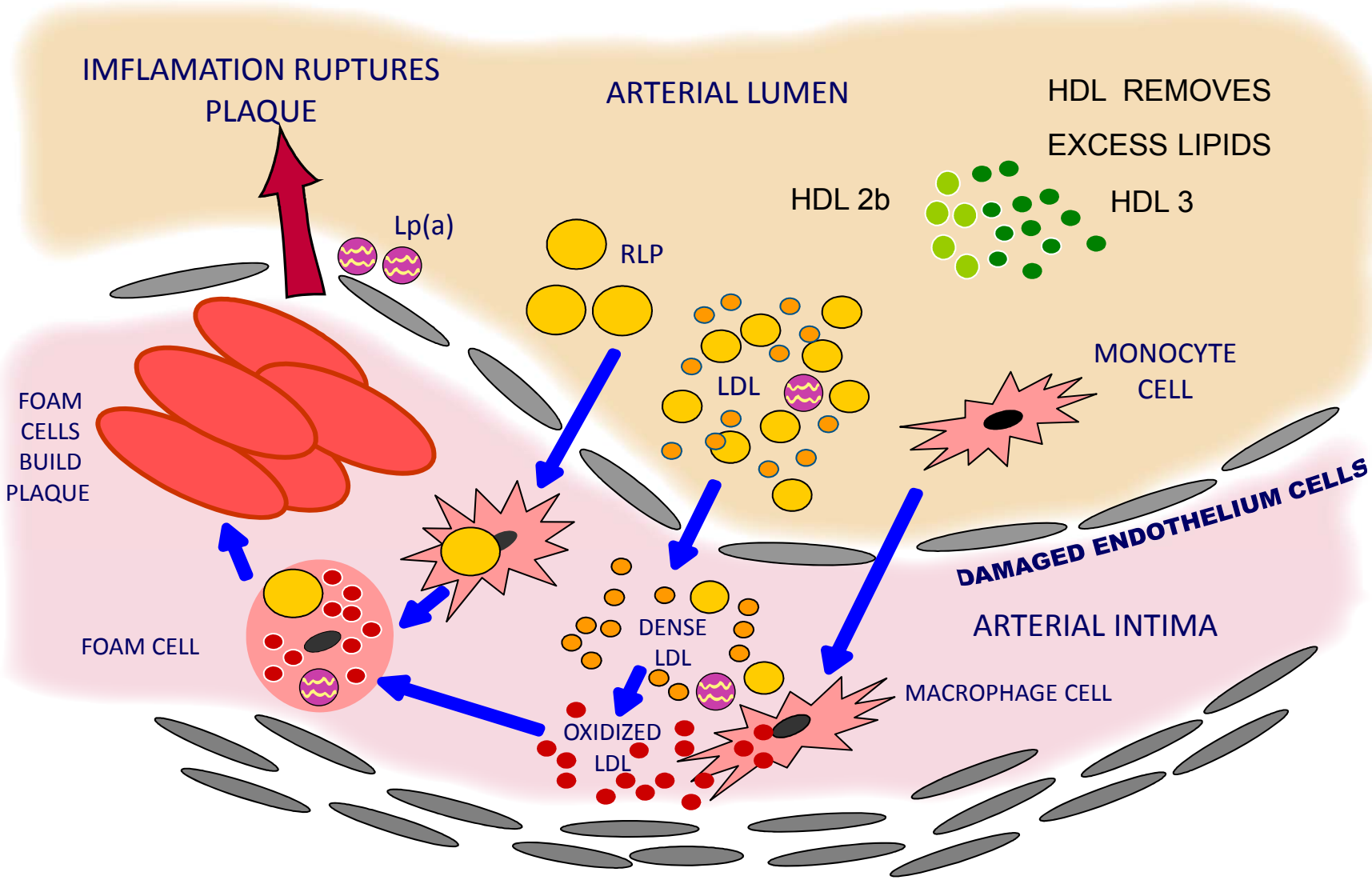
- Dyslipidemia affects the adaptive immune response
- T cells specific for modified lipoproteins aggravate atherosclerosis
- The adaptive immune response modulates lipoproteins metabolism
- Immune responses and lipid metabolism interact in a unique metabolic pathway underlying atherosclerosis
- HSPC's (hematopoietic stem and progenitor cells) are increased in the presence of dyslipidemia and produce leukocytes, lymphocytes, dendritic cells, erythrocytes, platelets and EPC's with a preference toward myeloid skewing which increases CHD risk
- ATP binding cassette transporters A1 and G1 and HDL involved in RCT will induce quiescence of HSPC's

Lipoproteins and Atherosclerosis

It Matters What You Have



Atherosclerotic Plaque Formation



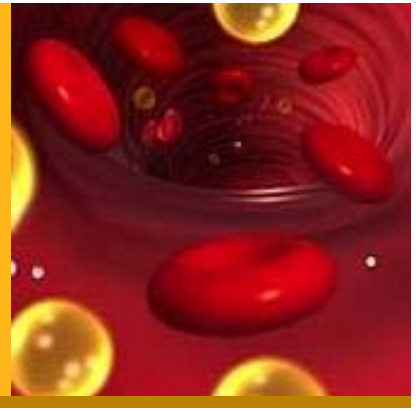
LDL and HDL

NEJM 2008;359:2195
Lancet 2009;373:1175

- Inflammation, oxidative stress and immune dysfunction are responses to intention. As you drive LDL down, the risk of all of these is decreased.
- If LDL is 55 mg/dl, then HDL has little influence on the risk of CHD (JUPITER TRIAL)
- HDL decreases the inflammation and number of cells in the plaque which reduces risk of rupture.
- The main problem is to resolve the INFLAMMATION!!
- It is the response to the modified LDL that induces the inflammation, oxidative stress and immune dysfunction which leads to ED, VSMC dysfunction and atherosclerosis.

Balance LDL-C levels

Mayo Clinic Proc. 2011;86:762; Circulation 1975;52:146
Lancet 2005;366:1267;



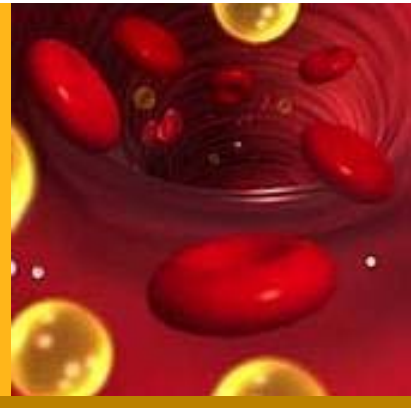
- Human infants, primates and South American Paleolithic tribes have LDL-C of 60 mg/dl.
- RCCT with statins demonstrate reductions in CHD, MI and ischemic CVA reductions to 60mg/dl.
- What level of LDL-C is too low for normal cellular function vs. the level that increases CV risk?
- Does an LDL < 60-70 mg/dl interfere with production of downstream steroidogenic path?
- **At an LDL of 60 mg/dl and above, there is progressive loss of nitric oxide and progressive endothelial dysfunction.**

Safety Profile of Subjects Treated to Very Low Low-Density Lipoprotein Cholesterol Levels (<30 mg/dl) With Rosuvastatin 20 mg Daily (from JUPITER).

Am J Cardiol.2014 Dec 1;114(11):1682-9.

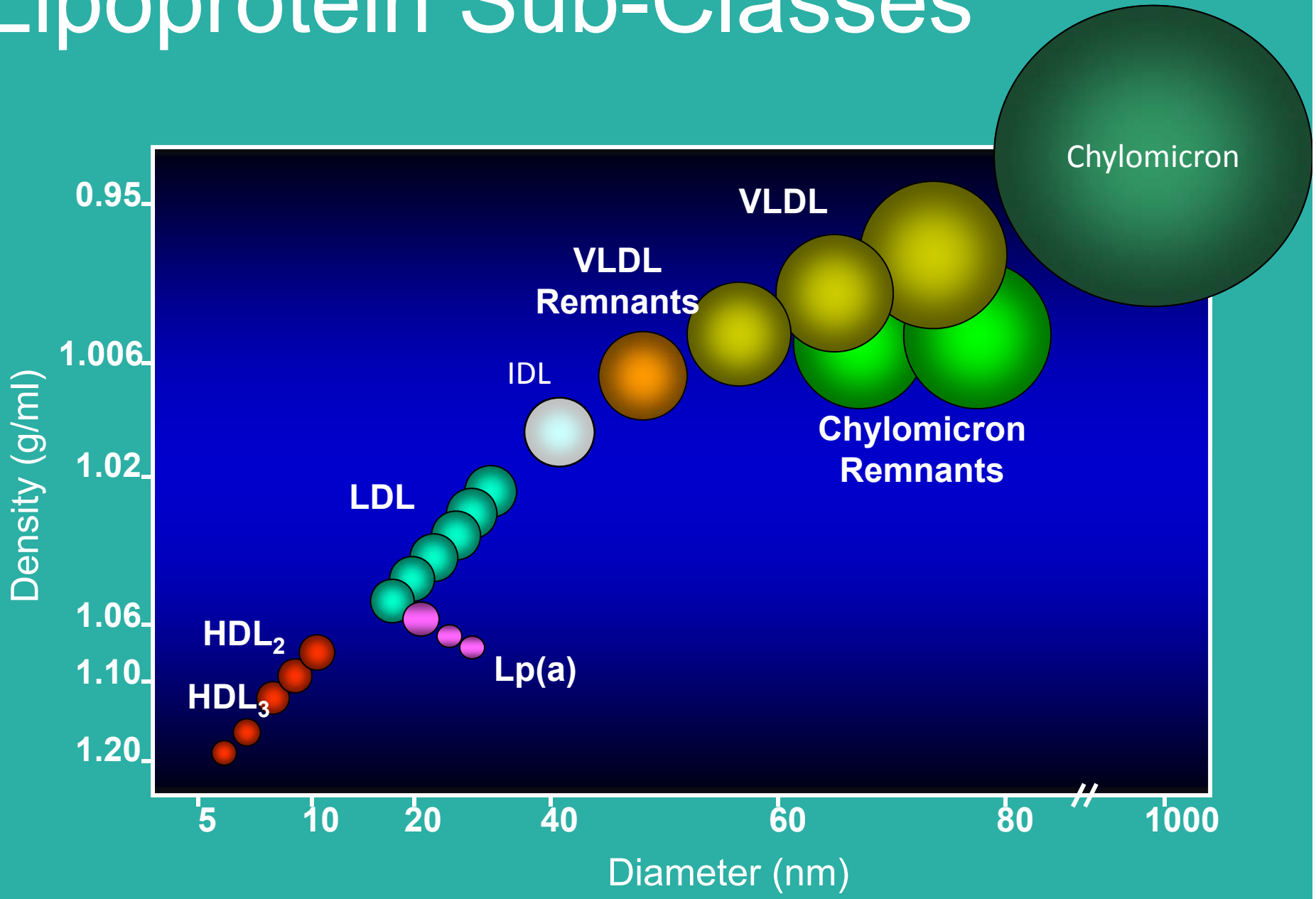
- An Intervention Trial Evaluating Rosuvastatin (JUPITER) with on-treatment LDL-C levels, we identified 767 who did and 7,387 who did not achieve LDL-C <30 mg/dl on rosuvastatin 20 mg daily and 718 participants who did and 7,436 who did not achieve LDL-C reductions of ≥70% on rosuvastatin, and 8,150 allocated to placebo.
- Participants with an LDL-C <30 mg/dl had an increase in the risk of 2 diabetes with an adjusted hazard ratio (95% confidence interval) of 1.56 (1.09 to 2.23, p = 0.01) and hematuria (hazard ratio 2.10 [1.39 to 3.19], p <0.001) compared with rosuvastatin-treated participants with LDL-C ≥30 mg/dl.
- There was also an increased risk of certain musculoskeletal, hepatobiliary, and psychiatric disorders. No difference in renal failure, cancer, memory impairment, or hemorrhagic stroke was observed, although there were few events in these categories
- In rosuvastatin-treated participants, achieving LDL-C reduction ≥70% versus <70% did not appear to be associated with increased risk of hepatobiliary, renal, or urinary disorders
- In conclusion, in this post hoc analysis in the JUPITER, achieving LDL-C levels <30 mg/dl with high-intensity statin therapy appeared to be generally well tolerated but associated with certain adverse events, including more physician-reported diabetes, hematuria, hepatobiliary disorders, and insomnia. These data may guide the monitoring of patients on intensive statin therapy and adverse events in trials of therapies that lead to very low LDL-C levels

Advanced Lipid Testing



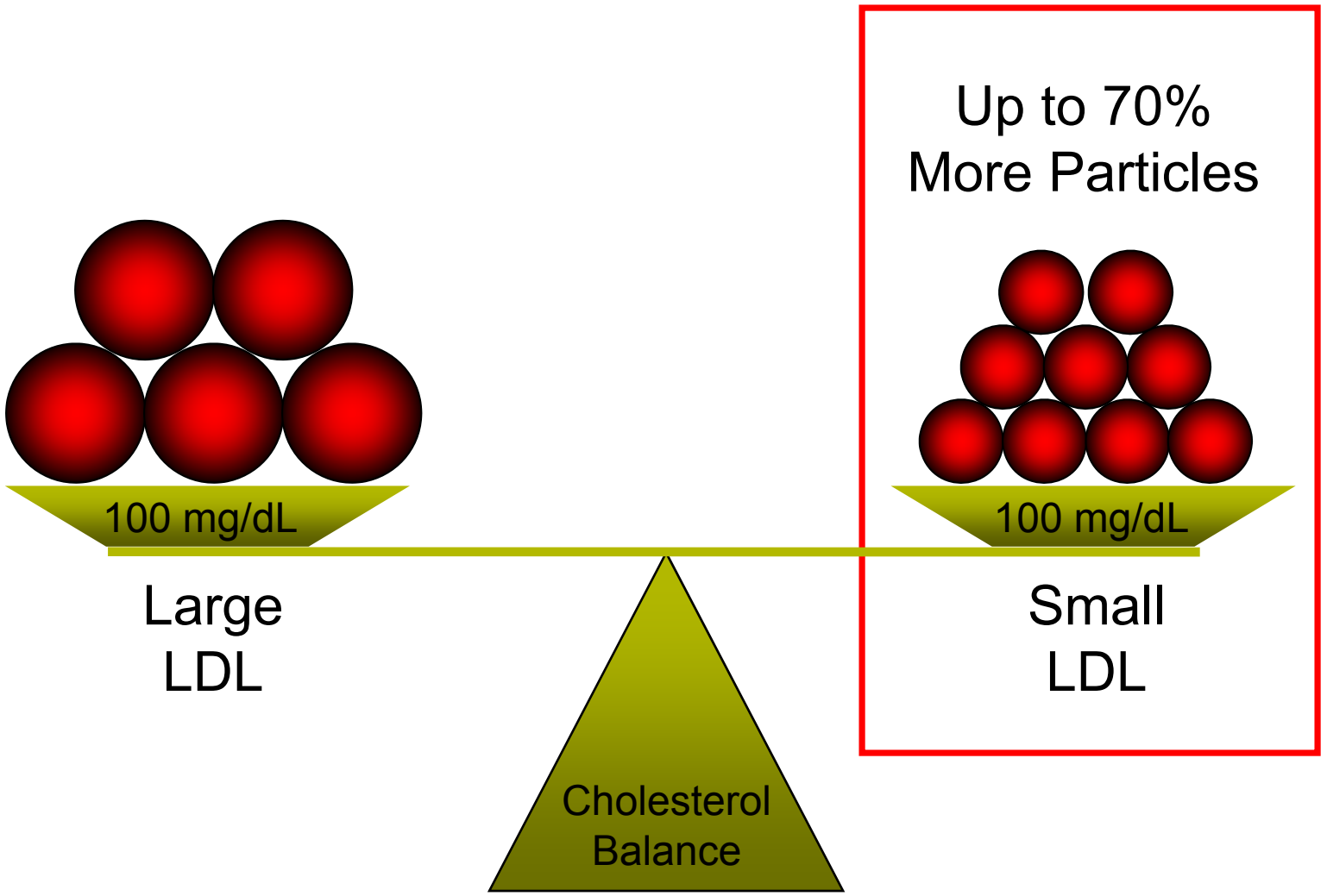
- Lipoprotein Particle Analysis (LPP): Spectracell
- NMR(Nuclear Magnetic Resonance): Liposcience (Lab Corp)
- Boston Heart Lab (BHL)
- Cleveland Heart Lab
- Berkley Heart Lab (BEHL) : Quest lab
- True Health

Lipoprotein Sub-Classes



Impact of LDL Size Differences

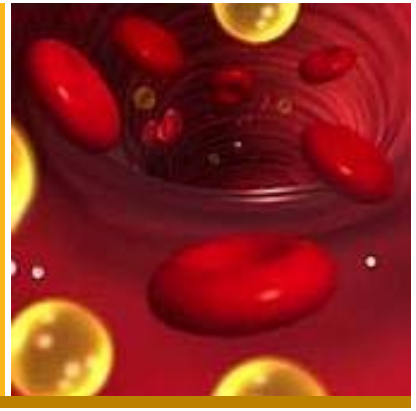
At the same LDL cholesterol



Residual CHD Risk and the Discordance of Total LDL and HDL vs LDL-P and HDL

J of Clinical Lipidology 2011;5:368
Circulation 2006;113:1556

J of Clinical Lipidology 2007;1:583
J of Clinical Lipidology 2011;5:105



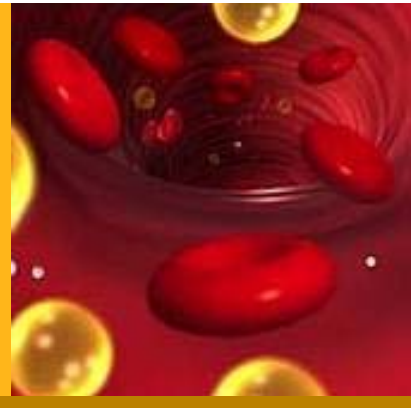
- Clinical outcome studies in CVD clearly demonstrate that in patients with discordance between total LDL and HDL levels and measures of LDL and HDL particle numbers (LDL-P and HDL-P), CVD risk tracks with the particle measurements of both. LDL-P direct. HDL-P inverse.

- Provides some data for the CHD gap issue and residual risk with LDL of 60-70 mg %

- Finally, most pharmacologic treatments for dyslipidemia are not very effective in altering the particle number of LDL (LDL-P) (statins, fibrates, niacin, omega 3 FA) and HDL-P (niacin and fibrates).

LDL Macrophage Uptake – Two Types

Current Opinion in Lipidology 2011;22:386

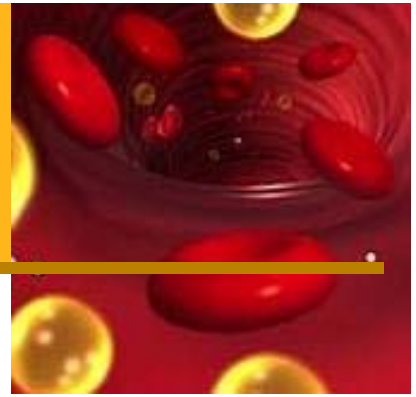


- Scavenger Receptor-Mediated Uptake: SR-CD36

- Receptor-independent with pinocytosis. Increased with inflammation and infections.

Intimal LDL vs Plasma LDL Levels

Current Opinion in Lipidology 2011;22:386



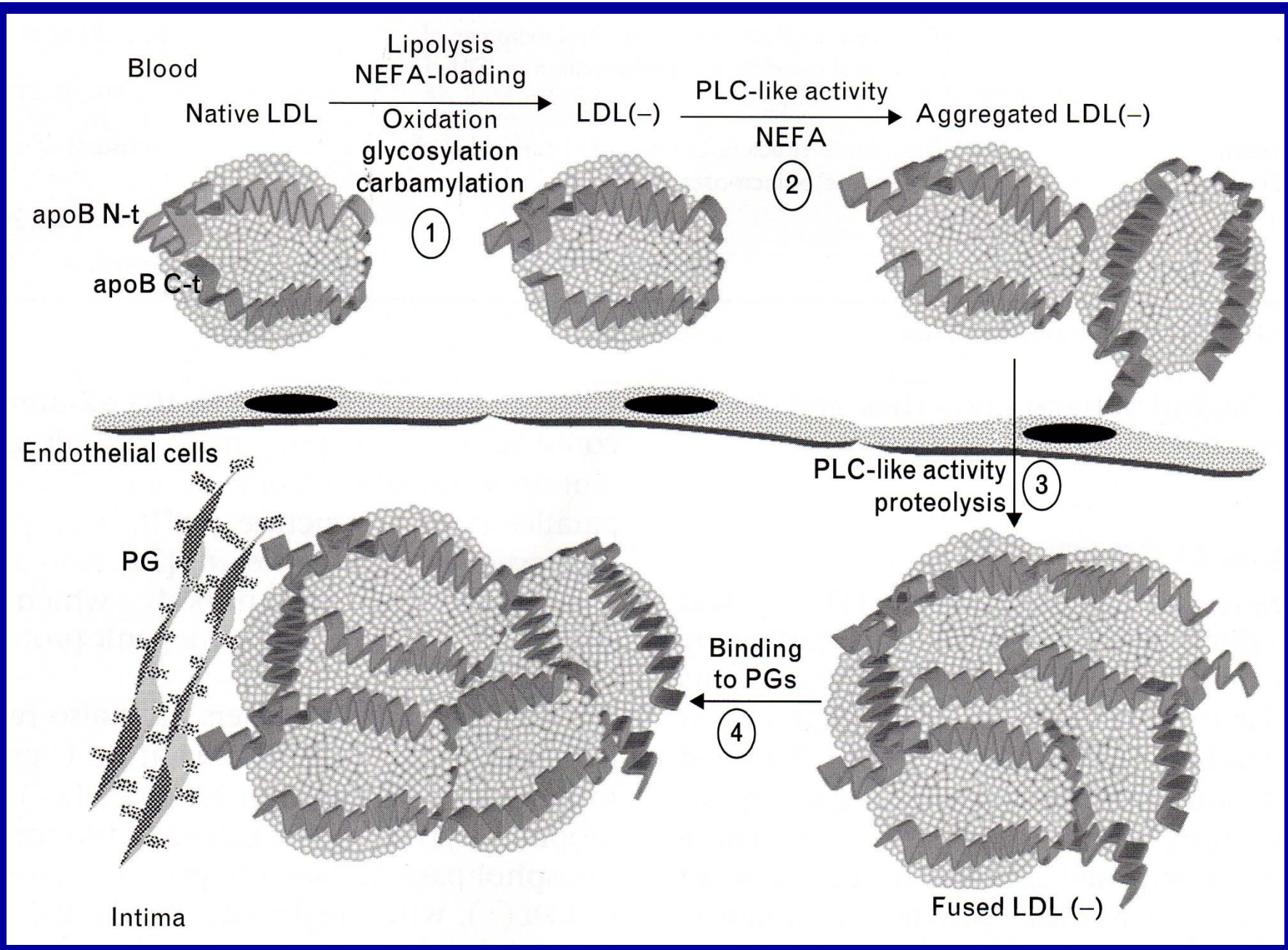
- Unbound native LDL concentrations in the intima are twice that of plasma LDL levels.
- Native LDL is not taken up by CD36 scavenger receptors on macrophages. Native LDL is not atherogenic…usually!
- However native LDL may be ingested by certain macrophages by pinocytosis via non receptor mediated uptake within both macro-pinosomes and micro-pinosomes to form foam cells.
- This uptake is linearly related to the concentration of LDL and does not show saturation of uptake
- This only occurs at higher levels of LDL
- Pinocytosis is triggered by viruses and bacteria
- Accounts for less than 29% of vascular LDL uptake by macrophages normally.

Electronegative LDL: Apo B misfolding, aggregation an proteoglycan binding. Subendothelial retention of LDL

Curr Opin Lipidol 2012;23:479

- A minor form of Apo B in LDL(-) (electronegative LDL)(lysine ionization) form has an abnormal misfolding conformation that contributes to LDL aggregation and subendothelial retention and binding by subendothelial proteoglycans (amyloidogenic character).

- Decreased binding affinity for LDLr.



Curr Opin Lipidol **2012, 23:479-486**

Gender disparity in LDL induced CVD related to electonegative LDL

Cardiovascular Diabetology 2014;13:64

- LDL 5 is the most electronegative LDL.
- LDL 5 is highest in metabolic syndrome and in men.
- Contains more Apo C III.
- Apo CIII on apo B and apo A-HDL is an independent risk factor for CVD and MI. Damages HDL and makes it dysfunctional ,induces vascular CAMs and inflammation (NfKb), and senescence, activates monocytes, induces DNA damage, antagonizes apoE and inhibits clearance of LDL, increases TG and small dense LDL.

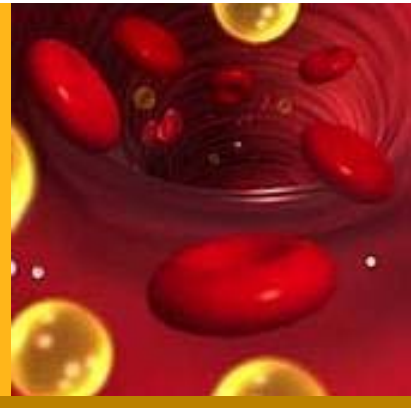
Role of Methylglyoxal and DM: Electronegative LDL: Apo B misfolding, aggregation and proteoglycan binding. Subendothelial retention of LDL

Curr Opin Lipidol 2012;23:479

- Modified LDL due to methylglyoxal in DM and IR share the same properties of LDL (-) with smaller particle size, more susceptibility to aggregation and binding to proteoglycans.
- Methylglyoxal modifies arginine residues in Apo B.
- Methylglyoxal has very high content in sodas.

ApoB and LDL Particle Number

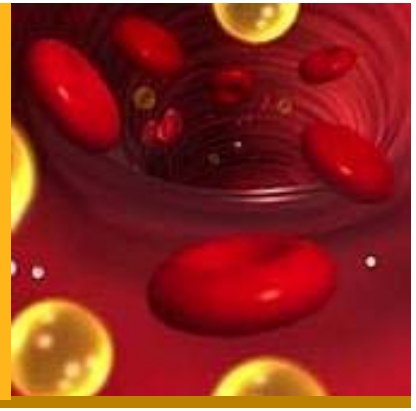
Lancet 2011;358:2026
, Current Opinion in Lipidology 2010;21:305
Current Opinion in Lipidology 2011;22:79 Mayo
Clin Proc 2011;86:762



- ApoB is the key structural component of all atherogenic lipoprotein particles.
- LDL-P drives CHD risk.
- Using the LPP advanced lipid testing an LDL-P below 700 and ApoB below 70 mg/dL is optimal.
- Large native LDL is not usually atherogenic except with pinocytosis.
- Small dense LDL-B(type 3 and 4) is more modifiable and atherogenic. Most common in dysglycemia,DM, MS, IR, obesity.
- As total LDL drops the LDL-P drops then small dense LDL has less correlation with CHD risk.

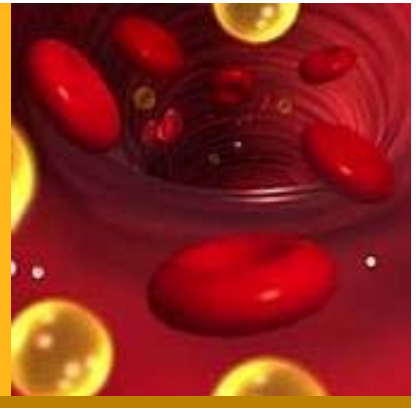
LDL Particle Number

Am Heart J 2006;151:975
Mayo Clin Proc 2010;85:440



- If HDL is less than 50 mg/dl then the LDL particle number increases faster that LDL. If the TG is over 125 mg/dl then the LDL particle number increases faster than the LDL.
- Statins are not very effective in reducing LDL particle number or ApoB and usually do not increase LDL size.
- Thus LDL decreases by a greater percent than LDL-P or APO B (CHD residual risk)
- Statin trials reduce CV risk the same degree independent of LDL.

Discordance Between LDL-C and LDL Particle Number



J of Clinical Lipidology 2011;5:105
MESA study of 6800 patients over 5.5 years. Atherosclerosis 2007 ;192:211,
Diabetes 2009;58:1887

- LDL particle number predicts CHD better than LDL. HR 1.32 vs 1.20
- In those with discordance of LDL-C and LDL particle number, only LDL-P predicts CHD. HR 1.45
- Intima-media thickness (IMT) tracks only with LDL-P
- LDL –P (LDL particle number) and small dense LDL are strongly and independently associated with the presence of CAC(coronary artery calcification), CHD, CVD, carotid atherosclerosis and increased carotid IMT (intimal medial thickness).

LDL and CVD: How and What Level

Curr Opin Lipidol 2016;27:207

- The lower the LDL the better at least to 40 mg/dL
- The earlier LDL is lower the better
- LDL reduction reduces atheroma volume and improves plaque stability
- Naturally randomized genetic evidence with loss of function PCSK-9 and others indicates LDL has a causal and cumulative effect on risk of CVD over the lifetime.
- LDL lowering rather than the mechanism of LDL reduction relates to the clinical benefit.

LDL Particle Number Effects of Common Lipoprotein Modifying Agents

Am Heart J 2006;151:975)

TREATMENT CONSIDERATIONS

Therapeutic lifestyle changes (diet/exercise) are the first objective.

Expected effects of drug monotherapy*

Drug Class	LDL-P	Small LDL-P
Statins	↓ 30%-50%	↓ 30%-50%
Niacin**	↓ 15%-25%	↓ 30%-50%
Fibrates**	↓ 3%-25%	↓ 30%-40%
Cholesterol Absorption Inhibitors**	↓ 20%	Trials in progress

* Combination therapy may give optimal LDL-P response, especially in patients with high triglycerides or low HDL-C.

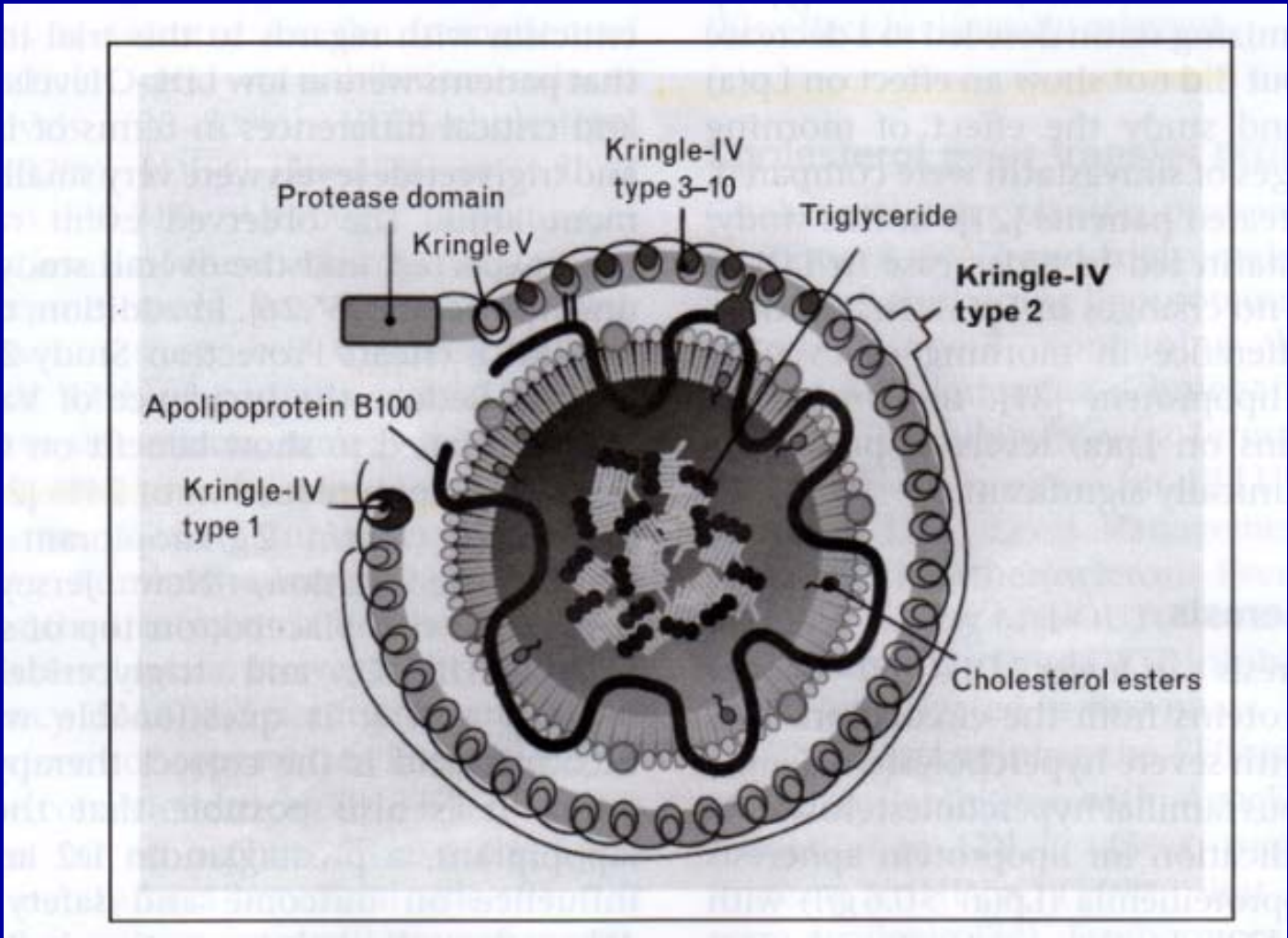
** Greater reductions are likely when used in combination with statin therapy.

APO CIII is potent risk factor for CHD

Curr Opin Lipidol 2014;25:35-39
J Clinical Lipidology 2015;9:498
J Clinical Lipidolog 2017;28:27

- Apo CIII on apo B and apo A-HDL is an independent risk factor for CVD and MI. Damages HDL and makes it dysfunctional.
- Ratio of HDL/Apo CIII or VLDL/Apo CIII is better CHD risk predictor than apo A or B
- Antagonizes apoE and inhibits clearance of TRL from circulation, increases TG and small dense LDL
- Role in hepatic assembly, formation and secretion of TRL and hepatic TG
- Inhibits lipoprotein lipase
- Inhibits clearance of LDL
- Promotes vascular inflammation, stimulates NfKb, increases CAMS, activates monocytes and endothelial cells
- High responder to endotoxin
- Role in pancreatic B cell function, survival and biology and type I DM
- Alters insulin sensitivity in T2 DM
- Genetic mutations exist

Lp(a) Particle



Curr Opin Lipidol 2014, 25:452-460

Lipoprotein (a)

Curr Opin in Lipidology 2012;23:133;Curr Opin in Lipidology 2012;23:560;Curr Opin in Lipidology 2014;25:189,Current Opin in Lipidology 2014;25: 289. Current Opinion in Lipidology 2014;25:423,452;

J of Clinical Lipidology 2014;8:550-553; J Clinical Lipidology 2015;9:557. J of Clinical Lipidology 2016;10:215
Am J Cardiol 2017;119;945; Curr Opin Lipidol 2017;28:170

- Lp(a) is a very heterogeneous *molecule*
- It is an LDL particle with one molecule of highly glycated apolipoprotein (a) that is covalently linked to apo B 100 of LDL and attached to apolipoprotein (a) by a single disulfide bond.

  Apo(a) is comprised of a protease domain and series of peptide kringles (4-2 repeats) in the KIV-2 domain. These plus the apo(a) gene locus determine Lp(a) plasma levels and thus the MASS of Lp(a).

- Lp(a) does not bind to LDL receptor, thus levels reflect synthesis rate not clearance.
- Clearance by renal megalin and hepatic SRB-1.
- Liver is better able to excrete the smaller apo (a) isoforms than the larger ones. Smaller low MW isoforms predominate in Caucasians (80%) and thus have higher Lp(a)-P (particle counts)
- Lp(a) –P with small low MW isoforms correlates with CHD risk more that Lp(a) mass. Lp(a) highly correlates with Lp(a) –C if TG are normal. CHD risk increased 1.5-3.0 fold.
- The fewer the number of KIV-2 repeats, he lower the MW and the higher the hepatic excretion rate.
- LP(a) (LPA) gene variants for CHD risk on chromosome 6q23 and 26-27 that codes for apo(a) near plasminogen gene.
- Autosomal dominant. Ischemic stroke risk = APLAb and Prot C def.
- Racial differences: B>W>A>H
- Levels remain stable throughout life except in postmenopausal women, it increases.

Lipoprotein (a)

Curr Opin in Lipidology 2012;23:133;Curr Opin in Lipidology 2012;23:560;Curr Opin in Lipidology 2014;25:189,Current Opin in Lipidology 2014;25: 289. Current Opinion in Lipidology 2014;25:423,452
J of Clinical Lipidology 2014;8:550-553; J Clinical Lipidology 2015;9:557. J of Clinical Lipidology 2016;10:215
Am J Cardiol 2017;119;945; Curry Opin Lipidol 2017;28:170

- Apo(a) has approximately 80% structural homology with plasminogen but does not contain the active site for fibrin cleavage. Lp(a) blocks plasmininogen by attaching to lysine and proline in damaged collagen in vascular wall. This binding during clot formation results in inhibition of fibrinolysis.
- Independent risk factor in CHD, MI, CVA, PAD and DVT. Linear relationship starting at 25 mg/dL. 40% of cryptogenic CVA, especially in young are due to Lp(a).
- It is the hidden lipid risk for CHD and the CHD/MI gap.
- Highly associated with both thrombosis and atherogenesis. Enters and leaves arterial wall with mechanisms similar to LDL but accumulates more at sites of vascular injury and enters atherosclerotic plaque.
- Increase in VSMH and plaque formation and instability.
- Most of apo B 100 associated oxidized phospholipid (oxPL)is associated with Lp(a), implicating it in proinflammatory (activates NfKb) oxidative stress, atherogenic and thrombogenic pathways (tissue factor)
- Lp(a)-P is associated with oxLDL.
- Major CHD risk factor proportional to serum level. 1.16 increase in CVD morbidity/ mortality / SD. (Jupiter , AIMHIGH). Predicts risk MACE in non-obstructive CHD
- Increase CVD by 37 % per SD of Lp(a). 10 x more than LDL. Each mg/dl Lp(a) increase graft closure 2% and stent re-stenosis
- Statins increase Lp(a) by 10-20%. Atorvastatin is worst. Dose related to initial level
- Trans fats increase Lp(a)
- Associated with calcific aortic stenosis, aortic calcification and retinal artery occlusion.
- Normal level < 30 mg/dl. 50% population is > 50 mg/dl.
- LP(a) (LPA) gene variants for CHD risk on chromosome 6q23 and 26-27 that codes for apo(a) near plasminogen gene. (rs10455772)
- Racial differences: B>W>A>H

Monocyte subset distribution in patients with stable atherosclerosis and elevated levels of lipoprotein(a).

J Clin Lipidol. 2015 Jul-Aug;9(4):533-41

- Lipoprotein(a) (Lp(a)) is a proatherogenic plasma lipoprotein currently established as an independent risk factor for the development of atherosclerotic disease and as a predictor for acute thrombotic complications. In addition, Lp(a) is the major carrier of proinflammatory oxidized phospholipids (OxPL). Atherosclerosis is considered to be an inflammatory disease of the vessel wall in which monocytes and monocyte-derived macrophages are crucially involved. Circulating monocytes can be divided according to their surface expression pattern of CD14 and CD16 into at least 3 subsets with distinct inflammatory and atherogenic potential.
- 90 patients with stable coronary artery disease. Lp(a) and OxPL/apoB were measured, and monocyte subsets were identified as classical monocytes (CMs; CD14++CD16-), intermediate monocytes (IMs; CD14++CD16+), and nonclassical monocytes (NCMs; CD14+CD16++) by flow cytometry.
- In patients with elevated levels of Lp(a) (>50 mg/dL), monocyte subset distribution was skewed toward an increase in the proportion of IM (7.0 ± 3.8% vs 5.2 ± 3.0%; P = .026), whereas CM (82.6 ± 6.5% vs 82.0 ± 6.8%; P = .73) and NCM (10.5 ± 5.3 vs 12.8 ± 6.0; P = .10) were not significantly different. This association was independent of clinical risk factors, choice of statin treatment regime, and inflammatory markers. In addition, OxPL/apoB was higher in patients with elevated Lp(a) and correlated with IM but not CM and NCM.
- **CONCLUSIONS:** There is a potential link between elevated levels of Lp(a) and a proatherogenic distribution of monocyte subtypes in patients with stable atherosclerotic disease

Impact of Lipoprotein(a) as Residual Risk on Long-Term Outcomes in Patients After Percutaneous Coronary Intervention.

Am J Cardiol.2015 Jan 15;115(2):157-60.

- Cardiovascular risk remains uncertain in patients with cardiovascular disease despite achieving target lipid levels.
- Serum levels of lipoprotein(a) [Lp(a)] can be risk factors for adverse events. The aim of this study was to determine the role of Lp(a) as a residual risk factor in patients who achieve target lipid levels by the time of treatment by percutaneous coronary intervention (PCI).
- A total of 3,508 patients were treated by PCI from 1997 to 2011 at our institution. Among them, we analyzed consecutive 569 patients who achieved target lipid levels of low-density lipoprotein cholesterol <100 mg/dl, high-density lipoprotein cholesterol ≥40 mg/dl, and triglycerides <150 mg/dl at PCI. A total of 411 eligible patients were assigned to groups according to Lp(a) levels of ≥30 mg/dl (high Lp(a); n = 119) or <30 mg/dl (low Lp(a); n = 292).
- The primary outcome was a composite of all-cause death and acute coronary syndrome. The median follow-up period was 4.7 years. Cumulative event-free survival was significantly worse for the group with high Lp(a) than with low Lp(a) group (p = 0.04). Multivariate analysis selected a high Lp(a) level as an independent predictor of primary outcomes (hazard ratio 1.68, 95% confidence interval 1.03 to 2.70, p = 0.04).
- In conclusion, a high Lp(a) value (≥30 mg/dl) could be associated with a poor prognosis after PCI even for patients who achieved target lipid levels

Lipoprotein (a)

Curry Opin in Lipidology 2012;23:133;Curr Opin in Lipidology 2012;23:560;Curr Opin in Lipidology 2014;2 5:189,Current Opin in Lipidology 2014;25: 289,423,452
J of Clinical Lipidology 2014;8:550-553; J of Clinical Lipidology 2016;10:215

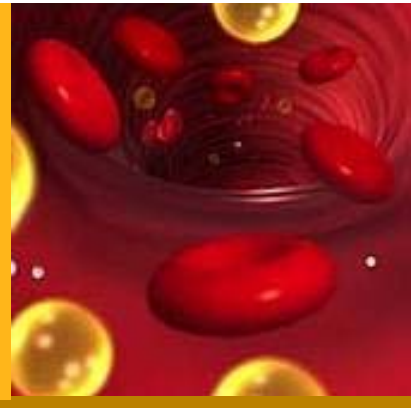
Treatment

There are no level 1 evidence trials which demonstrate that lowering Lp(a) will reduce cardiovascular events.

- Niacin dose related. 2 grams per day (21%-40% decrease)
- NAC 500-1000 mg bid
- Carnitine 2 grams (8-21%)
- Vitamin C 10 grams per day (27% decrease)
- Proline (500 mg) with Lysine (1000 mg) + Vitamin C 10,000 mg
- Inhibit PCSK9 (berberine) 500 mg bid
- Gamma delta tocotrienols 200 mg hs
- Arginine 5 grams per day
- Flax seed 0ne cup per day
- Co Q10 100 mg per day
- Omega 3 FA 5 grams per day
- Sex hormones: estrogen and testosterone. Postmenopausal women have 30 % increase Lp(a)
- Thyromimetics and thyroid hormone
- Apheresis in Russian study reduced coronary atheroma volume over 20 % compared to control
- ASA 81 mg (81% decrease), reduce IL -6 and inflammation.
- Even aggressive reduction of LDL to very low levels below 50 mg/dL in Jupiter trial with statins still left residual CHD risk due to Lp(a). Risk was 89% higher in those in 4th vs 1st quartile.

HDL

Current Opinion in Lipidology 2011;22:343;
Circulation 2002;106:1930
Lancet 2011:358:2026:
Journal of Clinical Lipidology 2011;5:105;
Mayo Clinic Proc 2010;85:440;
Mayo Clinic Proc 2011:86:762;
Journal of Clinical Lipiology 2008;2:36
Curr Opin Lipidology 2014;25:404-405



- There are five basic sizes/type of HDL on HDL mapping: alpha 1-4 and prebeta.
- Small HDL 3 is less protective for CHD than large HDL 2.
- Large HDL 2 is most protective.(HDL 2b)
- HDL particle number (HDL-P) is more protective.
- HDL levels predict Type 2 DM

ApoA-I (mg/dL) levels in HDL particles	Optimal	Borderline	High Risk
α-1	92.8		
Range	>20	14-20	<14 mg/dL
α-2	92.6		
Range	>55	45-55	<45 mg/dL
α-3	16.6		
Range	<25	25-30	>30 mg/dL
α-4	8.4		
Range	<15	15-18	>18 mg/dL
Preß-1		14.2	
Range	<10	10-15	>15 mg/dL

HDL Particles

Optimal Male HDL Map

Patient's HDL Map

Normalized Value (µmol x 100/mmol of Total Cholesterol)

		Optimal	Borderline	High
Production Markers				
Lathosterol	90	0	90	160
Desmosterol	63	0	90	120
Absorption Markers				
Beta-Sitosterol	147	0	100	180
Campesterol	213	0	150	260

BORDERLINE

BORDERLINE

Cholesterol Balance Score		Over Absorber		Over Producer
Production/Absorption	0.5	0.2	0.5	1.1

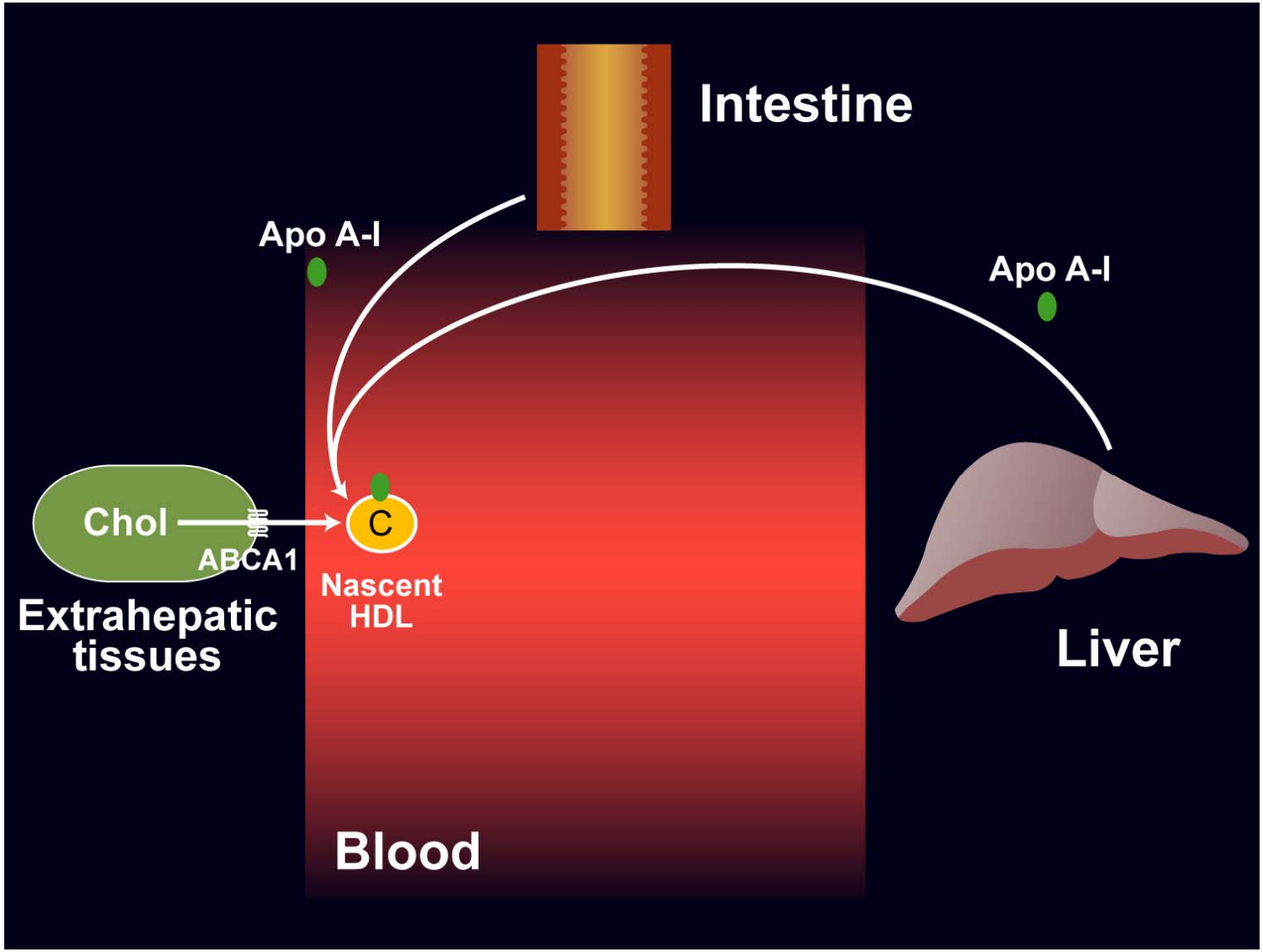
HDL has a complex structure, metabolism and dynamics

Current Opin Lipidol 2017;28:414

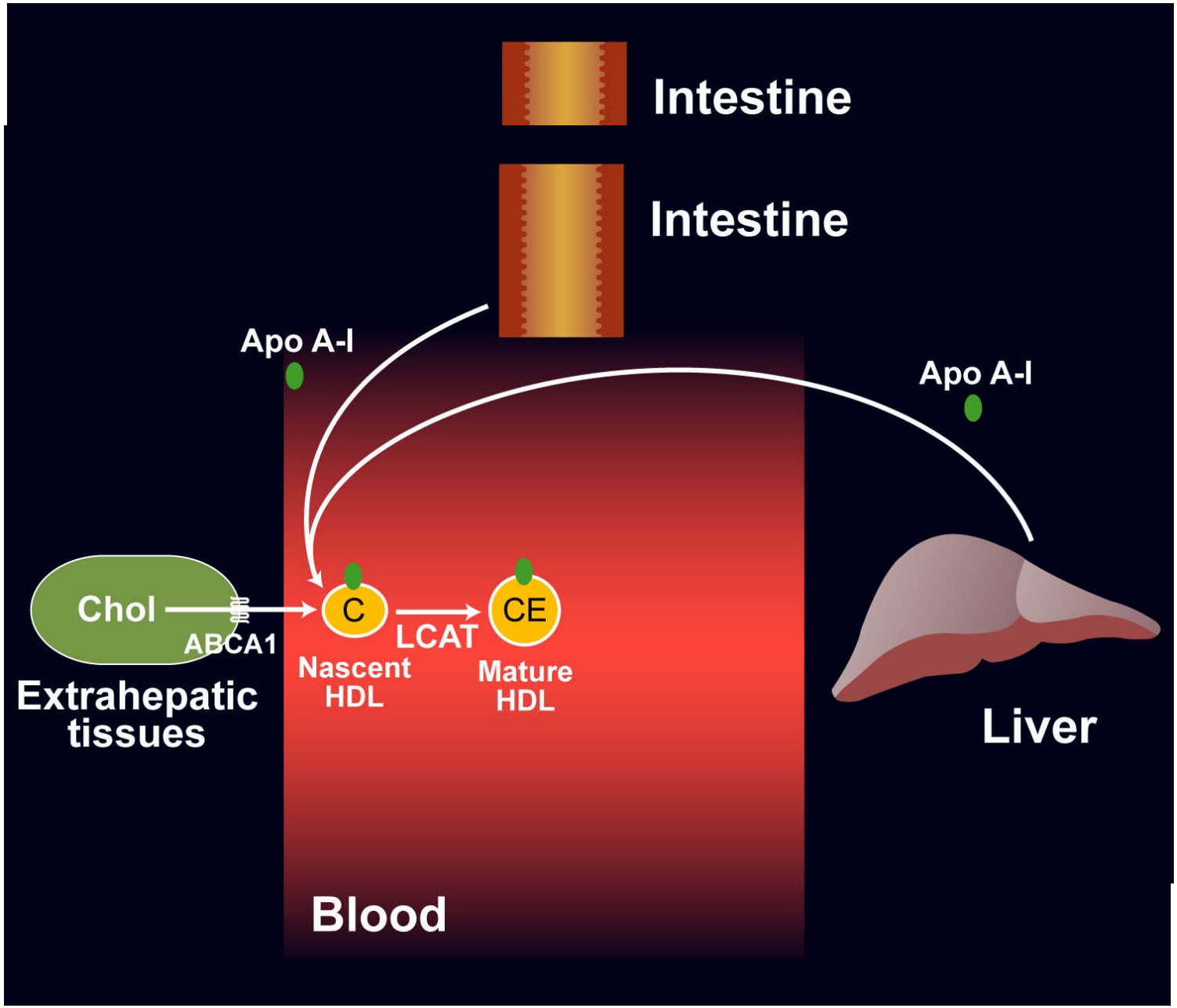
The first step in HDL maturation and removal of cholesterol from extrahepatic tissues

Apo A1 is HDL's major protein that binds to extrahepatic tissues and macrophages at the adenosine-triphosphate-binding cassette transporter AI (ABCA1) and acquires phospholipids and free cholesterol, giving rise to discoidal particles called pre-beta HDL which then mature to larger HDL

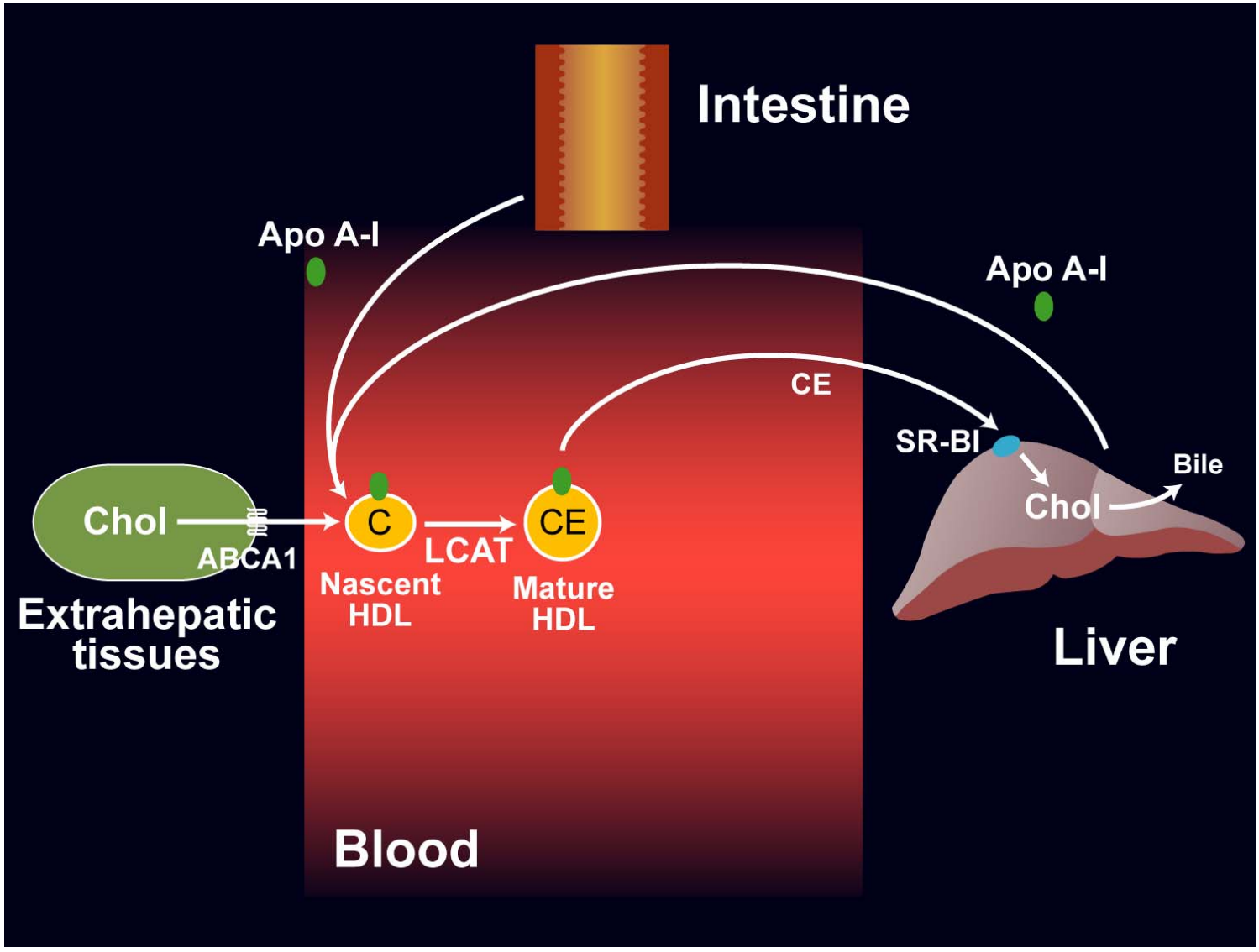
HDL and Reverse Cholesterol Transport



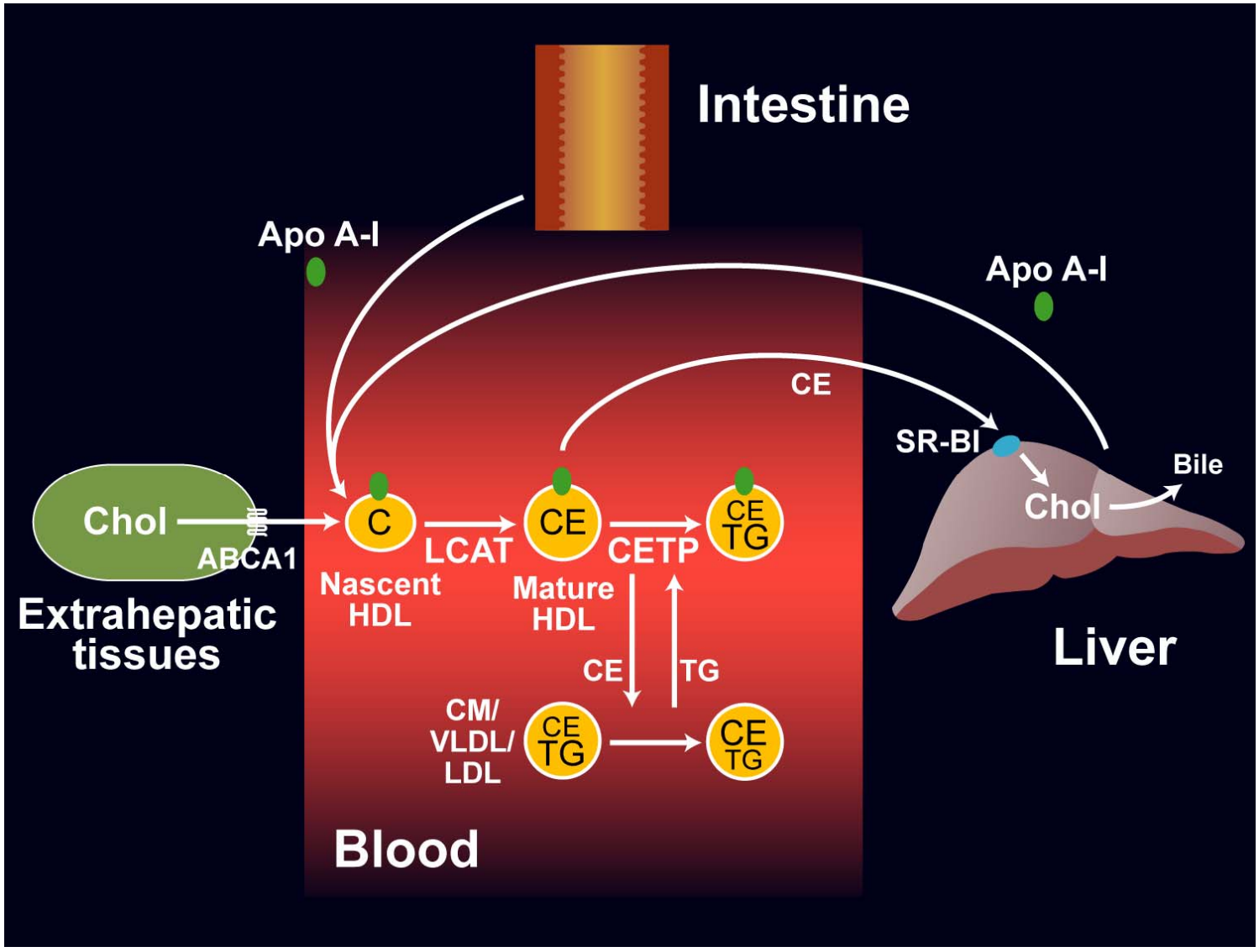
HDL and Reverse Cholesterol Transport



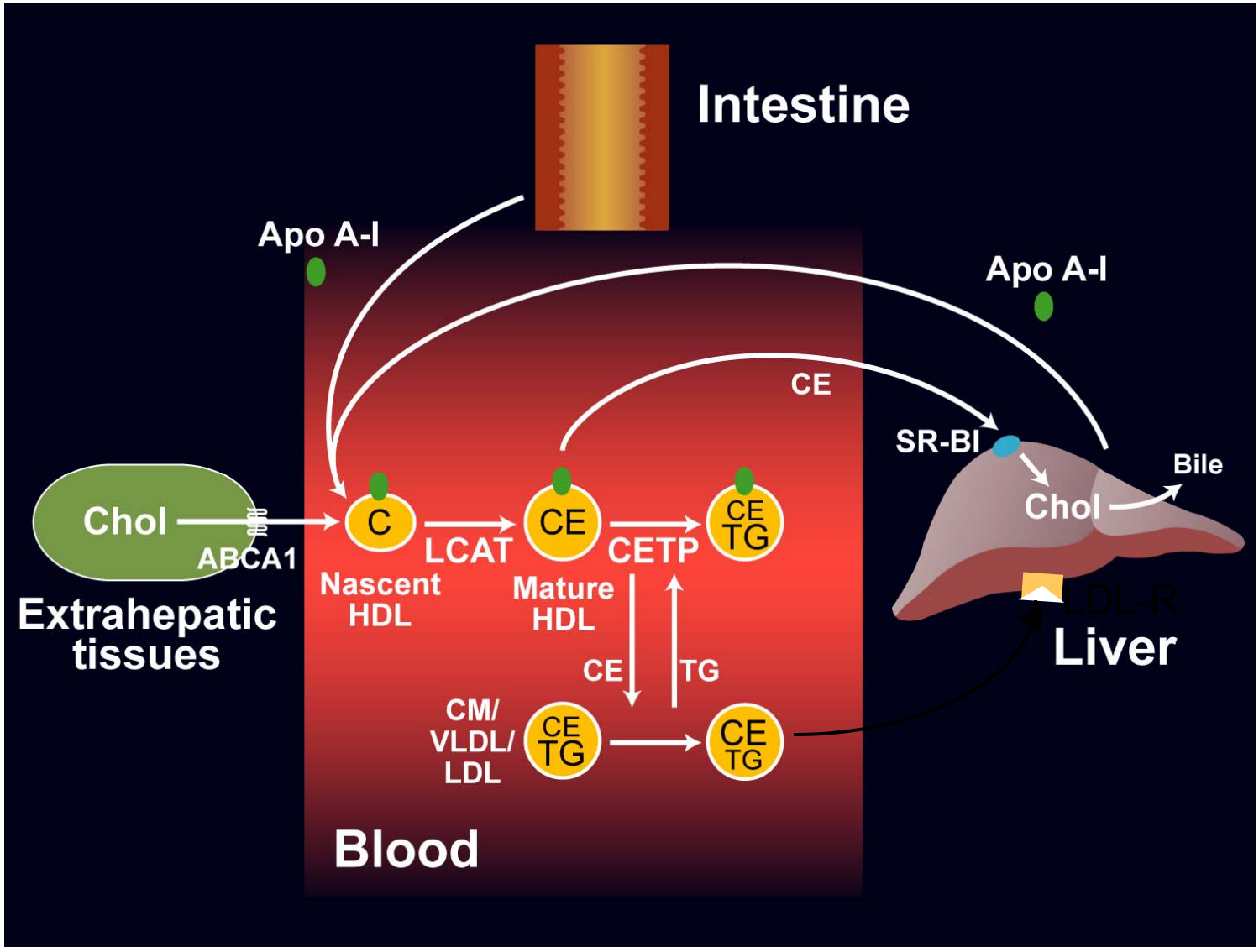
HDL and Reverse Cholesterol Transport



HDL and Reverse Cholesterol Transport



HDL and Reverse Cholesterol Transport



Four Pathways of HDL Reverse Cholesterol Transport or Cholesterol Efflux Capacity

Current Opin Lipidol 2017;28:414

- ABCA1 : Pre-beta HDL
- ABCG1 : Mature and larger HDL
  Improved by Niacin. Niacin also reduces HDL catabolism and increases HDL size and HDL levels.
- SR-B1
- Aqueous diffusion

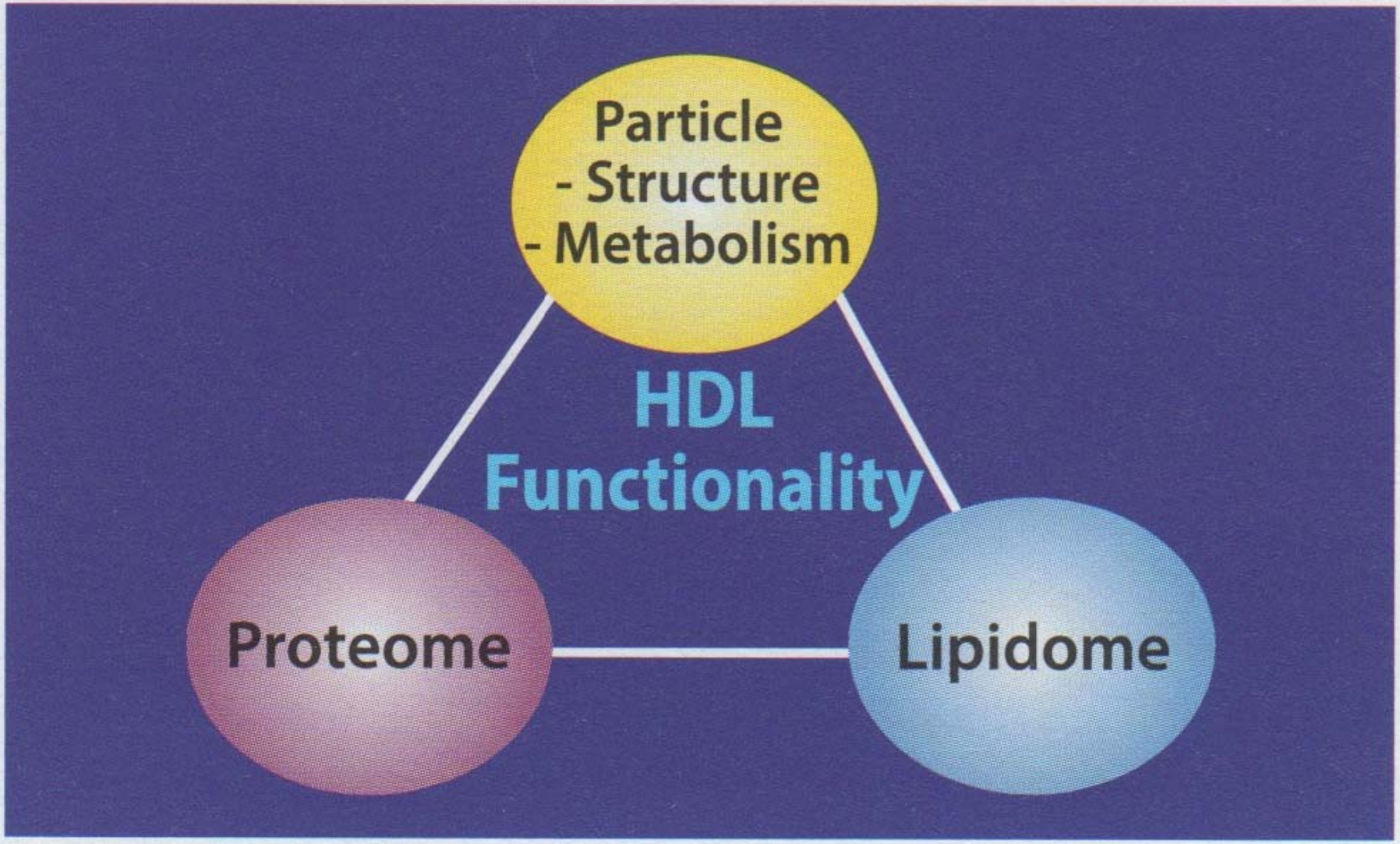


Figure 18 Schematic of HDL functionality as the integration of its proteome and lipidome. HDL, high-density lipoprotein.

Journal of Clinical Lipidology (2013) 7, 484-525

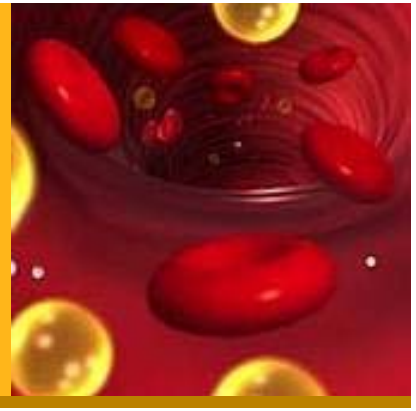
HDL Level is a Poor Marker for HDL Complexity

Current Opin Lipidol 2017;28:414

- Maturation of HDL results in diverse HDL particles that vary in size, density, lipid and protein composition.
- ApoA1 and ApoA2 account for 90 % of HDL protein content. This proteome varies in protein content among HDL size
- The remaining 10 % is composed of 100 other HDL proteins.
- The protein cargo determines the function of HDL such as inflammation, DM, autoimmune disease, protease inhibition, complement regulation, anti-oxidant effects and therapeutic response, etc.
- HDL measurement is only the cholesterol mass which is only 10-20% of the HDL particle and can vary up to 10-fold depending on the HDL particle size.

HDL Balance

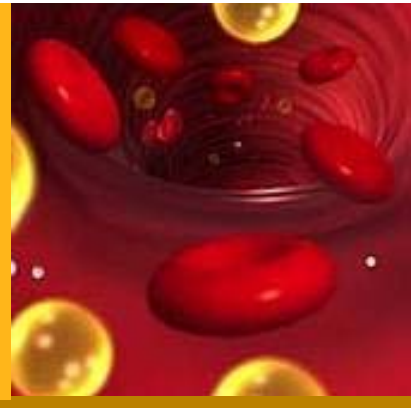
J Clinical Lipidology 2010;4:411



- Plasma HDL levels represent the balance between generation of mature HDL particles in the circulation and the loss of lipid cargo via both HDL receptor-mediated transfer to hepatocytes by SR-BI and CETP (cholesterol ester transfer protein) transfer to other lipoproteins.
- Loss of lipid cargo is desirable to unload cholesterol and oxidized phospholipids in the liver and to the rebirth of the HDL particle for a new round of cholesterol acquisition.

HDL Balance

J Clinical Lipidology 2010;4:411



- A functional HDL rather than higher plasma HDL is needed for a therapeutic effect on the vasculature.
- High HDL may mean enhanced production of mature HDL in the plasma which is good or a reduced loss of lipid cargo, which is not good.
- Low HDL may signal increased loss of lipid cargo (good) or reduced peripheral cholesterol collection (not good).
- Thus high HDL may not mean protection and a low HDL may not mean increased CHD risk.

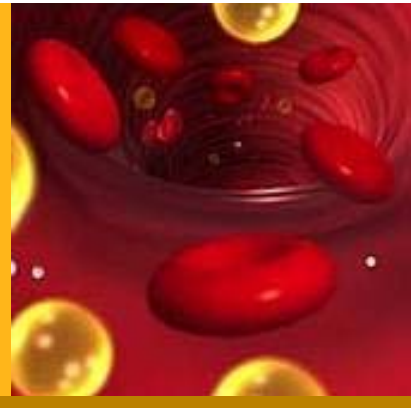
HDL and ApoA-1 clearance and catabolism

Current Opinion in Lipidology 2014;25:194

- Liver is the main site of HDL cholesterol clearance.
- Kidney is major site of HDL apoA-1 catabolism. Cubulin in proximal renal tubules mediates uptake of filtered ApoA-1 and albumin. Cubulin mediates and regulates primarily catabolism of very small HDL particles –HDL 3.

HDL Role in Atherogenesis

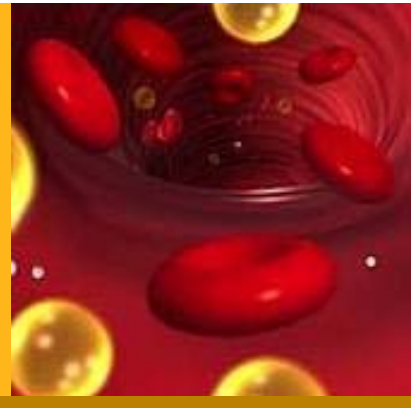
J of Clinical Lipidology 2010; 4: 411
J of Clinical Lipidology; 2010;4:359



- Reverse cholesterol transport from vascular tissue, ATP binding cassette transporters (ABCA-1 and ABCG -1), macrophages, and other tissues (plaque regression).
- Anti-atherosclerotic and lowers CAMS (cell adhesion molecules.
- Anti-oxidant (reduces plaque progression) ,reduces LDL oxidation, carries anti-oxidant enzymes like paraoxonase, PAF-AH (platelet activating factor),GPx (glutathione peroxidase) and methionine redox centers.
- Anti-inflammatory (plaque stabilization).
- Anti-thrombotic, fibrinolytic and reduces platelet activity.
- Anti-apoptotic.
- Innate immunity and decreases T cell activation.
- Increase eNOS (endothelial nitric oxide synthase and NO (nitric oxide).
- Endothelial repair.

HDL and HDL-P

J Clinical Lipidology 2011;5:368
JAMA 2009;302;1993
Mackey RH. AHA meeting March 2011
MESA study.
Circulation 2006;113:1556



- HDL after adjustment of LDL-P is less strongly related to CVD risk than HDL-P.
- Increasing HDL without increasing HDL-P may not have as much clinical benefit in decreasing CVD and CHD.
- HDL function is the most important.
- Subclass size parameters of LDL and HDL are not independently associated with CVD risk after accounting for LDL-P and HDL-P.
- Fibrates (gemfibrozil) increase HDL-P more than HDL and reduced CHD events (VA-HIT).
- Niacin increases HDL more than HDL-P, but increases HDL size (HDL 2 b), HDL-P and HDL functionality.

Functional vs Dysfunctional HDL

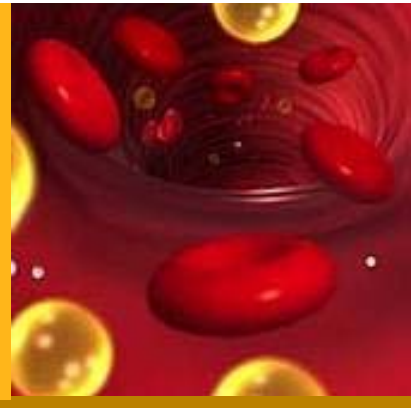
J of Clinical Lipidology 2010;4:411
Current Opinion in Lipidology 2011;22:394
Curr Opin Lipidol 2012;23:353

- HDL can undergo functional inactivation and become dysfunctional through enzymatic oxidation, lipolysis, proteolysis and nonenzymatic glycosylation.
- This compromises HDL cardioprotection.
- Neutral protease,chymase and tryptase in mast cells which are in high content in atherosclerotic plaque inactivate HDL and reverse cholesterol transport.
- Also SAA-HDL, MPO, haptoglobin 2 allele in DM, iron, metals , AGEs (advanced glycosylation end products) and glucose inactivate HDL.

Functional vs Dysfunctional HDL

Composition of Functional HDL

J of Clinical Lipidology 2010;4:411
Current Opinion in Lipidology 2011;22:394

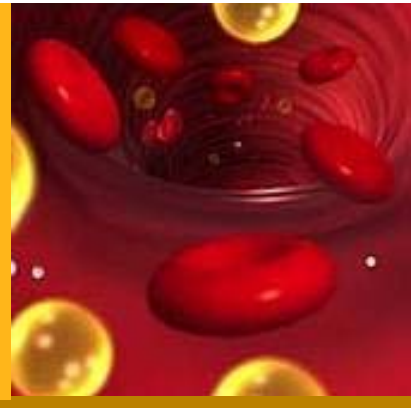


HDL dysfunction can be envisioned range of altered function:

- Lack of function: does not exert one or more of the expected effects.
- Opposite function of natural mandate and causes cholesterol deposition in the artery wall, induces oxidation,or activates inflammation.(pro-inflammatory ,pro-atherogenic).

Dysfunctional HDL

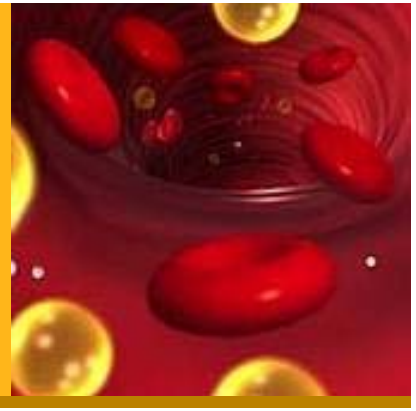
J of Clinical Lipidology 2010;4:411



- Under inflammatory conditions HDL can become dysfunctional, such as CHD, metabolic syndrome DM, infections, toxins and inflammatory diet.
- ai HDL (antioxidant and anti-inflammatory HDL) is the normal HDL with high levels of antioxidant proteins, enzymes and anti-inflammatory effects. Decreases risk for CHD.
- pi HDL(pro-inflammatory HDL) has high levels of pro-oxidant molecules which interfere with HDL removal of cellular waste(RCT and CEC) and HDL delivery of this metabolic waste for elimination. Increases CHD risk .

Levels of HDL – Correlation with CVD Risk

J of Clinical Lipidology 2010;4:411

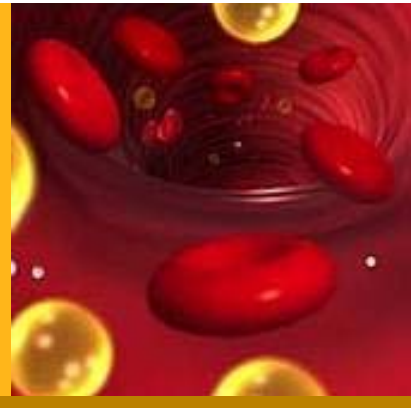


- Dysfunctional HDL is more likely associated with a high rather than low HDL because it may often reflect altered recycling of the mature plasma HDL. CHD risk may be increased.

- Cholesteryl ester transfer protein (CETP) and hepatic lipase polymorphisms have high HDL but increased risk of CHD.

Levels of HDL – Correlation with CVD Risk

J of Clinical Lipidology 2010;4:411 J Am Coll Cardiol 2008;51: 634
Circulation 2003; 108: 2751 Thromb Vasc Biol 2010;30:1642



- Patients with CHD and HDL >85 mg/dl carry mostly dysfunctional HDL. Statins, niacin, quercetin, pomegranate, EGCG, resveratrol and glutathione reduce dysfunctional/inflammatory HDL.
- IDEAL study: the classic inverse correlation of HDL and CHD risk is not sustained when evaluating subjects with HDL> 70 mg/dl and they also had larger HDL that was more lipid laden and pro-atherogenic.
- Dysfunctional HDL inhibits insulin exocytosis from pancreatic beta cells and may increase risk of diabetes in the absence of insulin resistance. (FINNS study).

Diabetes-Invoked High-Density Lipoprotein and Its Association With Coronary Artery Disease in Patients With Type 2 Diabetes Mellitus.

Am J Cardiol.2016 Dec 1;118(11):1674-1679

- Although high-density lipoprotein (HDL) can exhibit anti-inflammatory properties, these potent activities can become deficient and even transform into proinflammatory effects under various pathophysiological states.
- We investigated the effect of diabetic HDL on the inflammatory response in human monocytes and its relation to the existence of coronary artery disease (CAD) in patients with type 2 diabetes mellitus (DM). HDL was isolated from DM patients with (n = 61) or without (n = 31) CAD (diameter stenosis ≥50%) and healthy controls (n = 40).
- Human peripheral blood mononuclear cells were incubated with HDL and the proinflammatory ability of HDL was determined by tumor necrosis factor-α (TNF-α) secretion in peripheral blood mononuclear cells. Secretion of TNF-α in human monocytes in response to diabetic HDL was significantly increased compared with that of the control HDL.
- Of note, HDL from DM patients with CAD stimulated the release of TNF-α in monocytes to a greater extent than that of HDL from those without CAD.
- **Multiple linear regression analysis showed that the proinflammatory ability of HDL was independently associated with diabetes duration, hemoglobin A1c, serum levels of high-sensitivity C-reactive protein (hs-CRP) and reduced glomerular filtration rate (GFR).**
- **Proinflammatory ability of HDL was a significant predictor for the presence of CAD in patients with DM**

Cholesterol Efflux Capacity (CEC) and Reverse Cholesterol Transport (RCT)

Am Heart J 2016;180:54-63

- CEC and RCT are related to both the prevalence and incidence of CHD.
- HDL has numerous pathways to remove cholesterol from macrophages and other tissues which varies among different cell systems.

  Aqueous diffusion

  ABCA1 : ATP binding cassette transporter A1

  ABCG1 : ATP binding cassette transporter G1

  SR-B1: Scavenger receptor class B 1
- In CEC from the foam cell macrophages involved in atherosclerosis, the main pathways are diffusion, ABCA1(most important) and ABCG1
- CEC is most efficient with the small size HDL.
- CEC improves CHD risk stratification added to other CHD risk factors.
- Physiochemical changes in HDL such as inflammatory, oxidized and glycated proteins and lipids and loss of APOA1 impair CEC and induce HDL dysfunction.
- HDL-PL (phospholipids) correlates best with HDL function.

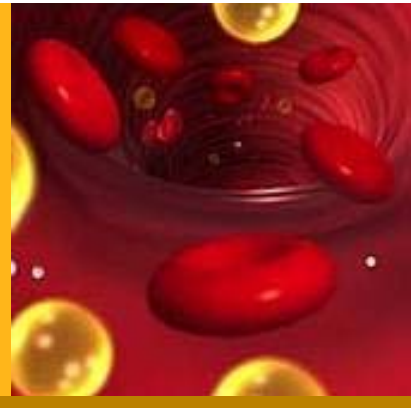
Cholesterol Efflux Capacity (CEC) and Reverse Cholesterol Transport (RCT)

Am Heart J 2016;180:54-63

- HDL dysfunction with loss of CEC common in SLE, RA, autoimmune disease, DM, psoriasis, oxidative stress, inflammation, immune dysfunction, obesity, sedentary life style, TFA and some SFA.
- CEC is improved by exercise, weight loss, PUFA, MUFA, EVOO and several nutraceutical supplements and some drugs with PPAR gamma and alpha agonism such as pioglitazone and fenofibrate and possibly alcohol. Notably, statins do not improve CEC.
- Supplements that improve CEC are lycopene, niacin, plant sterols, resveratrol, anthocyanidins, flavonoids and glutathione.

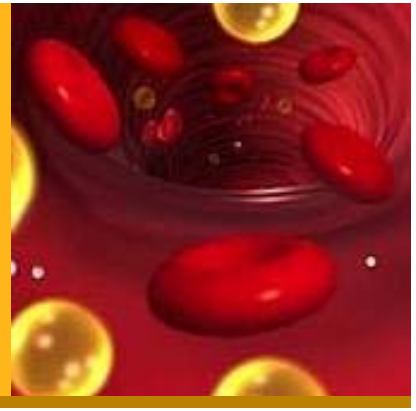
Cholesterol Efflux Capacity – HDL and Atherosclerosis

NEJM 2011;364:127



- Cholesterol efflux capacity from macrophages is a metric function of HDL function, both quality and quantity and is reflective of the role of HDL in atheroprotection.
- Strong inverse correlation with carotid IMT and CHD, independent of HDL level and Apolipoprotein A-1
- Efflux mediated by ABCA1, ABCG1, SRB1 and aqueous diffusion.
- Efflux is not changed with statins but is improved with pioglitazone, lycopene, niacin, plant sterols, resveratrol, anthocyanidins, flavonoids and glutathione.

Cholesterol Efflux Capacity



NEJM 2011;364:127

- Levels of HDL and apo-A1 account for only 40% of cholesterol efflux capacity (CEC).
- Each one SD decrease in CEC increases the risk of CHD by 30% even after adjustment for HDL and apoA1 levels.
- Nutritional supplements that improve CEC are lycopene, niacin, plant sterols, glutathione, resveratrol, anthocyanidins and flavonoids.

HDL Cholesterol Efflux Capacity (CE) and Incident Cardiovascular Events.

Rohatig A. et al. **NEJM 2014; November 18 Epub**

- HDL cholesterol level, HDL particle concentration, and cholesterol efflux capacity was measured in 2924 adults free from cardiovascular disease in the Dallas Heart Study.
- Primary end point: atherosclerotic cardiovascular disease, defined as a first nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization or death from cardiovascular causes. Median follow-up period was 9.4 years.
- Results: In contrast to HDL cholesterol level, which was associated with multiple traditional risk factors and metabolic variables, cholesterol efflux capacity had minimal association with these factors. Baseline HDL cholesterol level was not associated with cardiovascular events in an adjusted analysis (hazard ratio, 1.08; 95% confidence interval [CI], 0.59 to 1.99). In a fully adjusted model that included traditional risk factors, HDL cholesterol level, and HDL particle concentration, there was a 67% reduction in cardiovascular risk in the highest quartile of cholesterol efflux capacity versus the lowest quartile (hazard ratio, 0.33; 95% CI, 0.19 to 0.55). Adding cholesterol efflux capacity to traditional risk factors was associated with improvement in discrimination and reclassification indexes.
- Conclusions : Cholesterol efflux capacity, a key step in reverse cholesterol transport, was inversely associated with the incidence of cardiovascular events in a population-based cohort.

HDL Cholesterol Efflux Capacity (CEC) and Incident Cardiovascular Events.

Rohatig A. et al. **NEJM 2014; November 18 Epub**

1. HDL –P was inversely associated with primary end point. (HR .53 of first to 4th quartile).
2. Adding CEC to traditional risk factors improved all risk prediction indexes for primary end point (C-statistic from.827 to .841).
3. CEC is required for signaling by lipoprotein in endothelial cells, to activate eNOS and induce angiogenesis.
4. Increased CEC reduces platelet reactivity.
5. CEC is primarily mediated by ABCA-1 in humans.

Alcohol and RCT

Scientific Reports 2016; 6 : 33032 September 13

- Alcohol accelerates RCT in mouse model by regulating PPAR gamma dependent SR-B1 mediated RCT.
- SR-B1 mRNA increased 343 % in the alcohol high cholesterol group vs the control group.

HDL composition and function

Current Opinion in Lipidology 2014;25:194

- HDL-CKD (HDL in chronic kidney disease): promotes superoxide production, decreases NO, induces ED, increases BP, increases ADMA and inflammation.
- HDL in patients with CHD: reduced clusterin, increased apoC-III, decrease Bcl-2 and increased endothelial cell apoptosis.
- Increased MPO and decreased PON-1 and serum arylesterase (measures low anti-oxidant activity of PON-1) associated with HDL in CKD.
- MPO and PON-1 form complex on HDL with opposing actions.

Novel proteins associated with risk for coronary heart disease or stroke among postmenopausal women identified by in-depth plasma proteome profiling

Genome Med. 2010;2(7):48.

- Proteomics platform in the WHI from 800 women who developed CHD and 800 women who developed stroke during cohort follow-up, and from 1-1 matched controls. Identified proteins related to disease incidence, and the overlap with hormone therapy.
- Case versus control concentration differences in 37 proteins (l $P < 0.05$) for CHD, with three proteins, beta-2 microglobulin (B2M), alpha-1-acid glycoprotein 1 (ORM1), and insulin-like growth factor binding protein acid labile subunit (IGFALS) were best $P< 0.05$. Corresponding numbers for stroke were 47 proteins with $P < 0.05$, three of which, apo-lipoprotein A-II precursor (APOA2), peptidyl-prolyl isomerase A (PPIA), and insulin-like growth factor binding protein 4 (IGFBP4), were best $P < 0.05$. Other proteins involved in insulin-like growth factor signaling were also highly ranked. The associations of B2M with CHD ($P < 0.001$) and IGFBP4 with stroke ($P = 0.005$) were highest.
- **CONCLUSIONS:** In-depth proteomic discovery analysis of plasma samples identified B2M and IGFBP4 as risk markers for CHD and stroke respectively, and provided a number of candidate markers of disease risk and candidate mediators of hormone therapy effects on CHD and stroke.

Dyslipidemia

SCARB1 (rs4238001)

Rodriquez-OquendoPLOS ONE May 2015

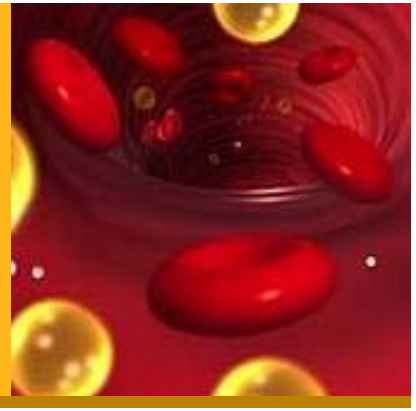
- Variant of SCARBI changes a hepatic receptor protein from glycine to serine
- Increased blood levels of HDL due to inability of HDL to attach to hepatic receptor for break down, disposal and recirculation. The HDL is not protective (dysfunctional)
- Increased risk of CHD by 49% in black males and 24% higher in white males.
- Frequency: 3 % Chinese, 8% in blacks and 12 % in Latinos and Whites.

Clinical Clues to Dysfunctional HDL

Metabolism 2011;60:499; Circulation 2013; 129:1256
Clin Rheumatolol. 2013;July Online

- Obesity with BMI over 30 kg/m2
- Insulin resistance, hyperglycemia, increased HBA1C, metabolic syndrome and diabetes mellitus
- CHD
- Elevated MPO
- Increased HS CRP
- Any markers for inflammation or oxidative stress
- HDL over 85 mg %
- Low adiponectin
- Increased mast cells
- Increase SAA
- Increased ADMA
- Chronic renal disease (increase ADMA, activates TLR -2
- Haptoglobin 2 allele in DM
- Heavy metals
- Hyperuricemia

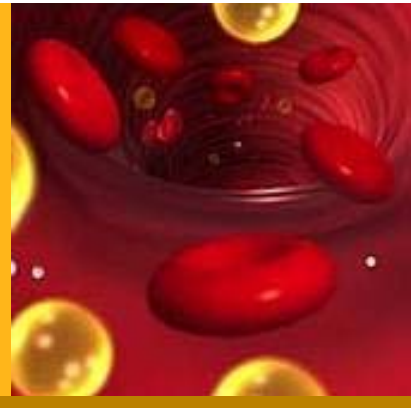
Myeloperoxidase (MPO) and HDL



Am Heart J 2010;160: 583.
Am Heart J 2011;162:893
Circulation 2007;50:159
Circulation 2003;108:1440
J Clinical Lipidology 2010;4:382

- Inflammatory and oxidative stress marker.
- Produced by PMN-WBC and macrophages. Catalyzes conversion of chloride and hydrogen peroxide to hypochlorite.
- MPO generated oxidation products are dityrosine, nitrotyrosine, chlorotyrosine, methionine sulphoxide or an MPO generated lipid peroxidation product.
- It has primarily anti-infective functions but cross reacts with and oxidizes apo A1 and HDL. HDL is dysfunctional which reduces reverse cholesterol transport.
- MPO also oxidizes LDL and promotes foam cells.
- Degrades collagen layer in plaque fibrous cap predisposing to rupture.
- Elevated levels of MPO increase the risk of CHD by 16-fold. High in ACS also.

Myeloperoxidase (MPO) and Atherosclerosis / CHD



Circulation 2003; 108:3128-3133

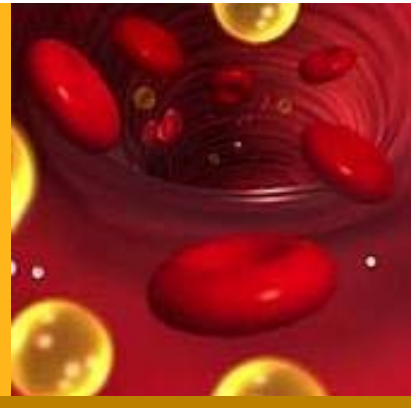
- MPO and MPO derived RCS (radical chloride species) catalyze oxidation of plasmalogens (the predominant membrane constituent in many CV cells) to 2 chloro fatty aldehyde species (2-ClHPA and 2-CLODA) and LPC (lysophosphatidyl choline).

- Plasmalogens are antioxidants that terminate propagation of free radical reactions, limit lipid peroxidation, protect vascular cells from ROS, and are anti-atherogenic.

- These aldehydes and LPC are pro-atherogenic. Aldehydes also open Ca^{++} channels inducing vasoconstriction and hypertension.

Dysfunctional HDL – Therapeutic implications

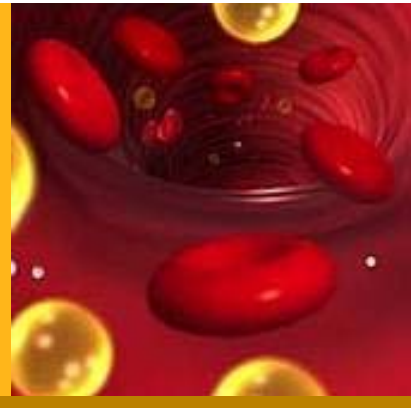
J of Clinical Lipidology 2010 4: 359
Curr Opinion in Lipidology 2010; 21: 305



Niacin and statins partially reverse the dysfunctional HDL by restoring its anti-inflammation and anti-oxidative properties.

Also improved with pomegranate, quercetin, EGCG, resveratrol and glutathione.

Modified LDL: primary DAMP. Activates TLR 2 TLR 4, NLR and LOX on vascular cells and macrophages with inflammation and immune response. Curr Opin Lipidol 2011;22:254 ,Mayo Clin Proc 2010;85:440 and 343.



- Oxidized LDL: 1 % of serum Apo B
- Glycated LDL: Most abundant form. 3-4% of serum Apo is glycataed in normal healthy patients. However 17 % of small dense LDL is glycated compared to only 1.8 % of large LDL.
- Glyco-oxidized LDL
- Acetylated LDL
- Lipolysis
- Proteolysis
- Carbamylated
- Methylglyoxal

OxLDL Is Associated with the Severity of Cardiovascular Disease

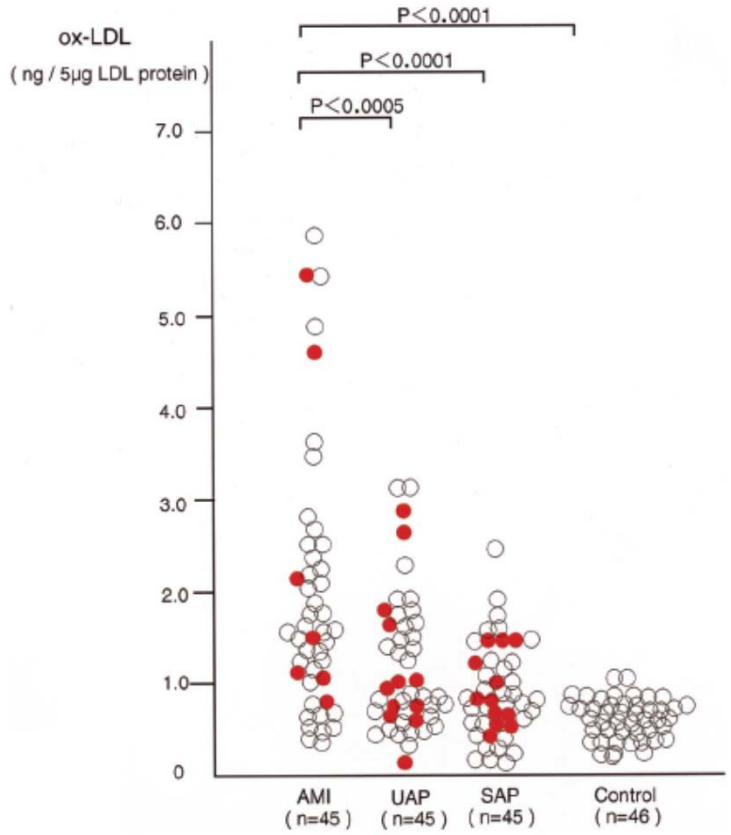


Figure 1. Graph showing ox-LDL levels in patients with AMI, UAP, and SAP. Solid circles indicate patients with hypercholesterolemia; open circles, patients without hypercholesterolemia; and n, number of patients and controls analyzed.

Ehara *et al*. Circulation 2001;103:1955-1960

Ox LDL and oxLDL ratios

Dis Markers 2008;24:341;Dis Markers 2012;:295
Life Sci 2013:EPUB; Clin Chem 2010;56:550
Thyroid 2012;Oct 16 ePUB
Lipids Health Dis 2012:11:85

- oxLDL, oxLDL/LDL,oxLDL/TC are better biomarkers fo CHD than TC, LDL, HDL.
- Higher the ratio the greater the risk as a continuum
- oxLDL/TC ratio over 0.175 has .925 sensitivity and specificity.
- Statins lower oxLDL independent of LDL.
- LOX index predicts CHD and CVA. LOXI = LOX x sLOX-1.
- OxLDL blunts non genomoic action T 3 on NO, cGMP in endothelial cells. T3 resistance. Increases SVR, BP, ED and CHD. Impairs T 3 mediated AKT phos.
- OxLDL toxic to stem cells and EPCs.

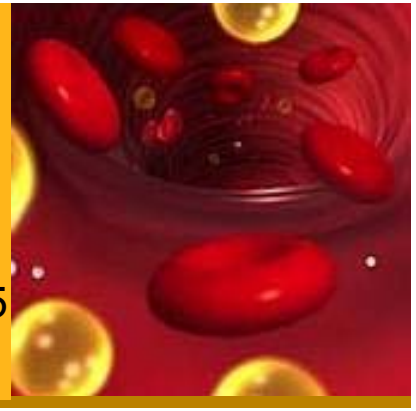
Usefulness of Antibodies to Oxidized Low-Density Lipoproteins as Predictors of Morbidity and Prognosis in Heart Failure Patients Aged ≥65 Years.

Am J Cardiol. 2015 ;116(9):1379-84.

- Elevated level of antibodies to oxidized low-density lipoproteins (OxLDL-Ab) reliably predict morbidity and mortality in patients with heart failure (HF).
- Two hundred and eleven patients aged ≥65 years treated at the Heart Failure Unit, Tel Aviv-Sourasky Medical Center in a retrospective study
- End points were time to the first hospitalization (morbidity), all-cause mortality, and a combination of the two (composite outcome). HF duration ranged from 8 to 10.5 years. Mean follow-up was 5.2 ± 1.9 years.
- Participants were divided according to OxLDL-Ab level. Group 1 had Ox LDL-Ab level <200 arbitrary U/ml. Group 2 had OxLDL-Ab level ≥200 arbitrary U/ml. The mean time to the first hospitalization was 25.8 ± 17.0 months. The mortality rate was 44.1%. Combined mortality and hospitalization rate was 58.8%. Adjusted hazard ratios of OxLDL-Ab for hospitalization were 3.16, p <0.001, 95% confidence interval 1.740 to 5.736 and for composite outcome 2.67, p <0.001, 95% confidence interval 1.580 to 4.518.
- OxLDL-Ab level was the best predictor for both hospitalization and composite outcome. Also predicts EF, CHD, extent of atherosclerosis and MI. Correlates with high oxidative stress. May be superior to NT-pro BNP.

Factors that Determine Susceptibility of LDL to Oxidation and/or Atherogenic Effects

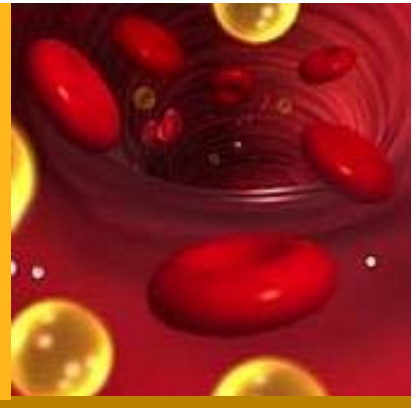
European Journal of Clinical Nutrition 2002; 56:114-120
American Journal of Clinical Nutrition 2002; 75:191-212 NEJM 2005;352:1685
Arterioscler Thromb Vasc Biol 2001;21:1876-95



1. MUFA / PUFA ratio
2. Oleic acid content
3. Antioxidant content
4. Phenolic compound content
5. Vitamin E content
6. Size of LDL particle
7. Number of LDL particles
8. Half life of LDL particle
9. Glycosylation ,oxidation and acetylation of apolipoprotein B

LDL Particles and CHD Risk Conclusions

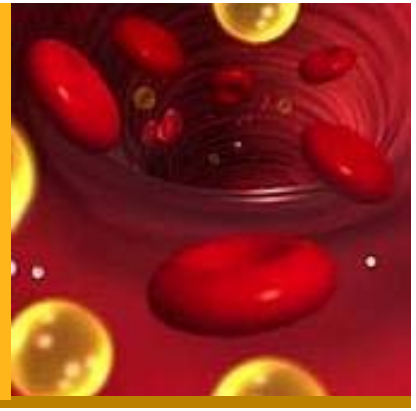
Cromwell WC and Otvos JD. Curr Athero Reports 2004;6:381-387



- Due to differences in core lipid particle composition, LDL cholesterol (LDL-C) measurements frequently do not accurately reflect a patient's LDL particle number (LDL-P) and associated risk of CHD;
- The relationship of small LDL size with CHD risk is intertwined with a complex physiologic syndrome that includes high triglycerides (TG), low HDL cholesterol (HDL-C) and increased LDL-P;
- Following multivariate analysis for these confounding risk factors (high TG, low HDL-C, increased LDL-P), LDL size is rarely a significant, independent predictor of CHD events unless LDL-P remains very high.

LDL Particles and CHD Risk Conclusions

Cromwell WC and Otvos JD. Curr Athero Reports 2004;6:381-387



- LDL-P is consistently a strong predictor of CHD events versus LDL-C, HDL-C, TG, non HDL-C, or LDL particle size and superior to APO B.
- CHD risk associated with increased LDL-P remains independently significant following adjustment for a wide variety of confounding factors including high TG, low HDL-C, small LDL particle size, and traditional risk factors (including hypertension and diabetes);
- Individuals most likely to manifest increased LDL-P at optimal LDL-C values included metabolic syndrome, insulin resistance, obesity and type 2 diabetic patients.

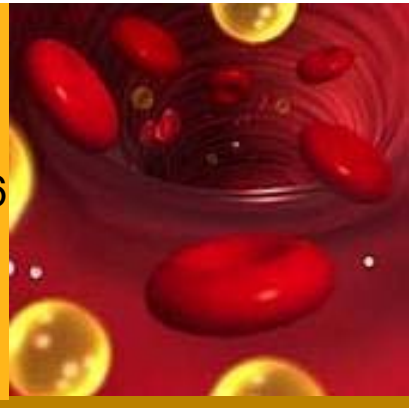
LDL and CVD: How and What Level

Curr Opin Lipidol 2016;27:207

- The lower the LDL the better at least to 40 mg/dL
- The earlier LDL is lower the better
- LDL reduction reduces atheroma volume and improves plaque stability
- Naturally randomized genetic evidence with loss of function PCSK-9 and others indicates LDL has a causal and cumulative effect on risk of CVD over the lifetime.
- LDL lowering rather than the mechanism of LDL reduction relates to the clinical benefit.

Atherogenic Lipid Particles

Current Opinion in Lipidology 2011;22:34
Circulation 2002;106:1930
Lancet 2011:358:2026
Journal of Clinical Lipidology 2011;5:105
Mayo Clinic Proc 2010;85:440
J of Clinical Lipidology 2014;8:550-553
Mayo Clinic Proc 2011:86:762
Journal of Clinical Lipiology 2008;2:36



- Increased LDL particle number (LDL- P)
- Small dense type B LDL (type 3 and 4)
- Modified LDL (oxidized, glycated and others.)
- Native LDL under chronic inflammatory conditions (pinocytosis)
- Lipoprotein (a) : Lp(a)
- Large VLDL is more atherogenic and thrombotic
- High TG decrease HDL. Low TG increase HDL
- ILDL(intermediate LDL) and RLP(remnant lipoproteins) are more atherogenic. ILDL is not recognized by LDL receptor due to APO C3. Increases circulation time and atherogenicity.
- If LDL is reduced to 60 mg/dl, then the effects of low HDL and high TG become less atherogenic.
- Dysfunctional HDL and Pro-inflammatory HDL (pi HDL)

Diabetic Dyslipidemia

Curr Opin Lipidol.2016 Aug;27(4):313-22

- Diabetic dyslipidemia can be gross with massive hypertriglyceridemia, or subtle with a lipid profile which would be regarded as normal in a nondiabetic patient, but which hides underlying increases in very atherogenic subfractions of LDL (e.g., increase LDL P, small dense LDL, increased large VLDL, glycated LDL, oxidized LDL) and remnant lipoproteins.
- Cardiovascular risk is frequently underestimated in DM especially young patients as insulin resistance precedes DM by decades with high CHD risk.
- Advanced lipid testing must be done to identify these lipid abnormalities which are missed on routine lipid panels.
- In type 2 diabetes, HDL cholesterol levels are often reduced.
- In type 1, insulin can raise HDL, but its anti-atherogenic properties are compromised.
- Dyslipidemia and hypertension predate the onset of glycaemia of diabetic proportions (metabolic syndrome). Obese people can thus die of diabetes before they develop it. Obesity, viseral fat and inflammatory adipokines should be prevented and treated.
- Statins decrease the risk of cardiovascular disease in primary and secondary prevention, in diabetes or metabolic syndrome regardless of whether glycaemia worsens.
- Omega 3 FA, niacin and red yeast rice address the increase LDL P, dense LDL, high TG and remnant particles also.

Methyl Donor and Phosphatidyl Choline Deficiency in Lipid Synthesis and Fatty Liver: SREBP-1

Cell 2011;147:840

- Low cellular availability of methyl group donors and choline stimulate an alternative lipid synthetic pathway that induces fatty liver (NASH), increased intracellular cholesterol and TG and decrease cell membrane fluidity.
- Activate SREBP-1 processing is the critical transcription factor.
- Deficiencies of 5-MTHF, B12, TMG, SAMe, phosphatidylcholine and phosphatidylethanolamine.

microRNA regulation of lipoprotein metabolism

Curr Opin Lipidology 2014;25:282

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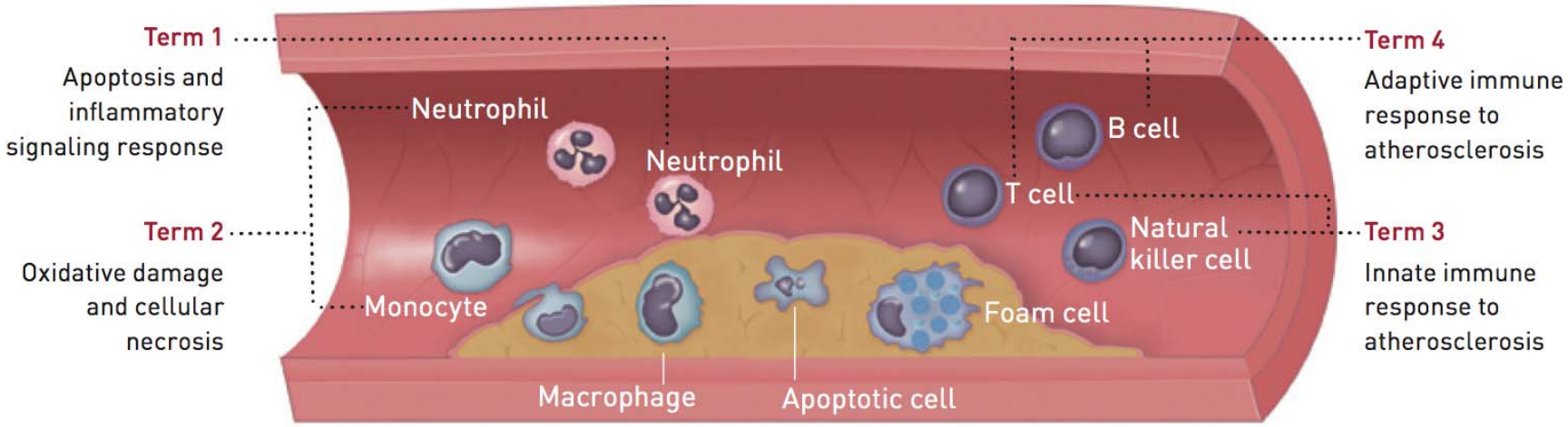
- microRNAs (miRNAs) in regulate lipoprotein metabolism and have importance in controlling plasma LDL-cholesterol (LDL-C) levels.
- A number of miRNAs that regulate plasma LDL-C levels, including miR-30c. Many miRNAs modulate LDL-C levels and lipoprotein secretion.
- Critical role of miRNAs in governing the many facets of HDL metabolism, such as the ATP transporters, ABCA1, and ABCG1, and the scavenger receptor, SRBI.
- The understanding of how these miRNAs modulate lipoprotein metabolism promises to reveal new therapeutic targets to treat dyslipidemias and related cardiovascular disorders.

Corus Gene Expression Testing (GET)

- Evaluates the gene expression of numerous biomarkers of vascular inflammation, oxidative stress and immune vascular dysfunction to predict obstructive coronary artery disease and risk for future myocardial infarction.
- Scoring system
  1. Below 15 is low risk
  2. 15 to 30 is moderate risk
  3. Over 30 is high risk. Maximum score is 40 and predicts 68% chance of multivessel CHD.

FIGURE 1: CORUS CAD GENE TERM SCHEMATIC



PATIENT REPORT

143501

CORUS CAD

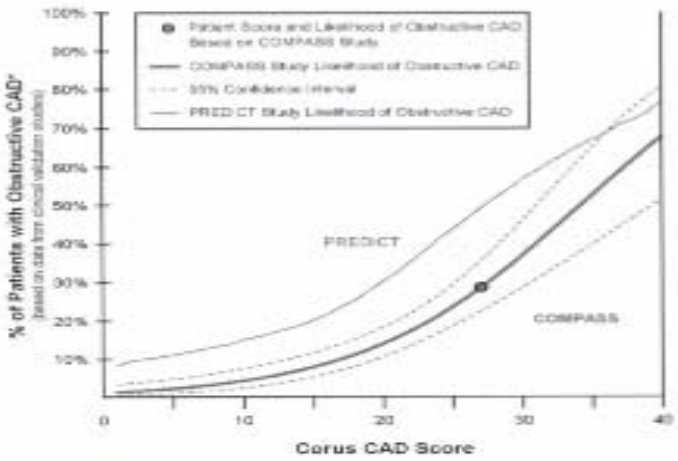
Gene Expression Test By CardioDx

Patient Name	Medical Record #	Blood Collection Date	Sample ID #
[redacted]	[redacted]	02-Apr-2014	TRF281234

Date of Birth: 09-Feb-1953
Sex: Male

Clinic Name: Hypertension Institute
Clinician: Mark Houston

Date Received: 03-Apr-2014
Date Reported: 05-Apr-2014



27
PATIENT SCORE

Likelihood of Obstructive CAD*†:
29%
95% Confidence Interval:
23-35%

TEST DESCRIPTION

The Corus CAD test has been validated in two clinical studies: PREDICT[1] (symptomatic and asymptomatic patients referred for cardiac catheterization, NCT00500617) and COMPASS[2] (symptomatic patients referred for myocardial perfusion imaging, NCT01117506).

The Corus CAD gene expression test measures the expression levels of 23 genes. An algorithm is applied to the gene expression results to calculate a score that indicates the likelihood of the presence of obstructive coronary artery disease (CAD) in a patient.[3,4] The score ranges from 1-40.

* Obstructive CAD is defined as at least one atherosclerotic plaque causing ≥50% luminal diameter stenosis in a major coronary artery (≥1.5 mm lumen diameter) as determined by invasive quantitative coronary angiography (QCA) or core-lab computed tomography angiography (CTA)(≥2.0mm lumen diameter).

† Likelihood function and corresponding 95% confidence interval derived by logistic regression on the COMPASS validation study data.

TEST RESULT INFORMATION

The Corus CAD gene expression test likelihood is based on [redacted] clinical validation study (COMPASS, NCT01117506). The study analyzed 431 non-diabetic patients who had no previously diagnosed myocardial infarction or revascularization, and who presented with typical or atypical symptoms suggestive of obstructive CAD. The prevalence of CAD in this study was 15%.[2] The sensitivity, specificity, and NPV were 89%, 52%, and 96% respectively at a pre-specified threshold of ≤15.[2] The result of the test should be used by clinicians in conjunction with other tests and clinical information in their assessment of CAD in their patients, and in developing patient-specific clinical management plans.

Comments:
No comments.

[redacted]

[redacted]

[1] Rosenberg S, et al. Ann Intern Med. 2010;153:425-434.
[2] Thomas GS, et al. Circ Cardiovasc Genet. 2013;6(2):154-162.
[3] Wingrove JA, et al. Circ Cardiovasc Genet. 2008;1:31-38.
[4] Elashoff MR, et al. BMC Med Genomics. 2011;4:26.

[redacted]

Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms.

Expert Rev Clin Pharmacol. 2015;8:189-199.

- In contrast to the current belief that cholesterol reduction with statins decreases atherosclerosis, statins may be causative in coronary artery calcification and can function as mitochondrial toxins that impair muscle function in the heart and blood vessels
- They deplete of coenzyme Q_{10} and 'heme A', and thereby ATP generation.
- Statins inhibit the synthesis of vitamin K_2, the cofactor for matrix Gla-protein activation, which in turn protects arteries from calcification.
- Statins inhibit the biosynthesis of selenium containing proteins, one of which is glutathione peroxidase serving to suppress peroxidative stress. An impairment of selenoprotein biosynthesis may be a factor in congestive heart failure, reminiscent of the dilated cardiomyopathies seen with selenium deficiency.
- Thus, the epidemic of heart failure and atherosclerosis that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs.

Statin treatment is associated with insulin sensitivity decrease in type 1 diabetes mellitus: A prospective, observational 56-month follow-up study.

J Clin Lipidol.2016 Jul-Aug;10(4):1004-10.

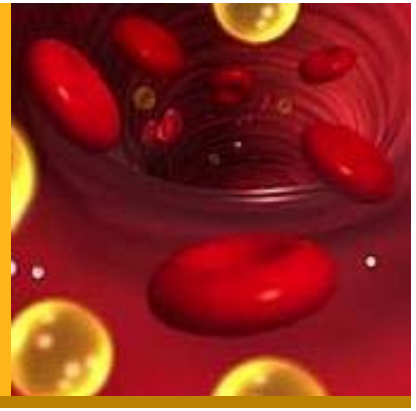
- The effect of statin therapy introduction on insulin sensitivity in patients with type 1 diabetes mellitus (T1DM).
- METHODS: This prospective observational 56-month long study included 832 randomly selected T1DM patients aged 25 to 61 years. Uncontrolled dyslipidemia and clinician-perceived need for treatment, rather than randomization, were basis for individuals being started on either atorvastatin or simvastatin (10-40 mg); N = 345, 41.47%. Patients on statin treatment were compared with those unexposed to statin. Insulin sensitivity was assessed using equation derived from euglycemic-hyperinsulinemic clamp studies-estimated glucose disposal rate.
- RESULTS: Patients who started statin therapy (N = 345, 59.42% atorvastatin and 40.58% simvastatin) experienced a greater decrease in insulin sensitivity (19.27% vs 12.82% P < .001) and metabolic control deterioration compared with statin-free group. The risk of decrease in insulin sensitivity attributable to statin use was 36.7% (hazard ratio 1.36; 95% confidence interval 1.31-1.43) after adjustment for age, gender, disease duration, smoking status, and the concomitant antihypertensive therapy.
- CONCLUSION: Although there is still a lack of a clear molecular explanation on the adverse effects of statin therapy on insulin sensitivity, we showed that it deteriorates insulin sensitivity in T1DM. The cardiovascular benefits of statin treatment might outweigh the risk of developing insulin resistance, but, the possible metabolic control worsening merits to be considered.

Nutrient depletions from Statins

Expert Reviews in Clinical Phamacology 2015;8:189-199

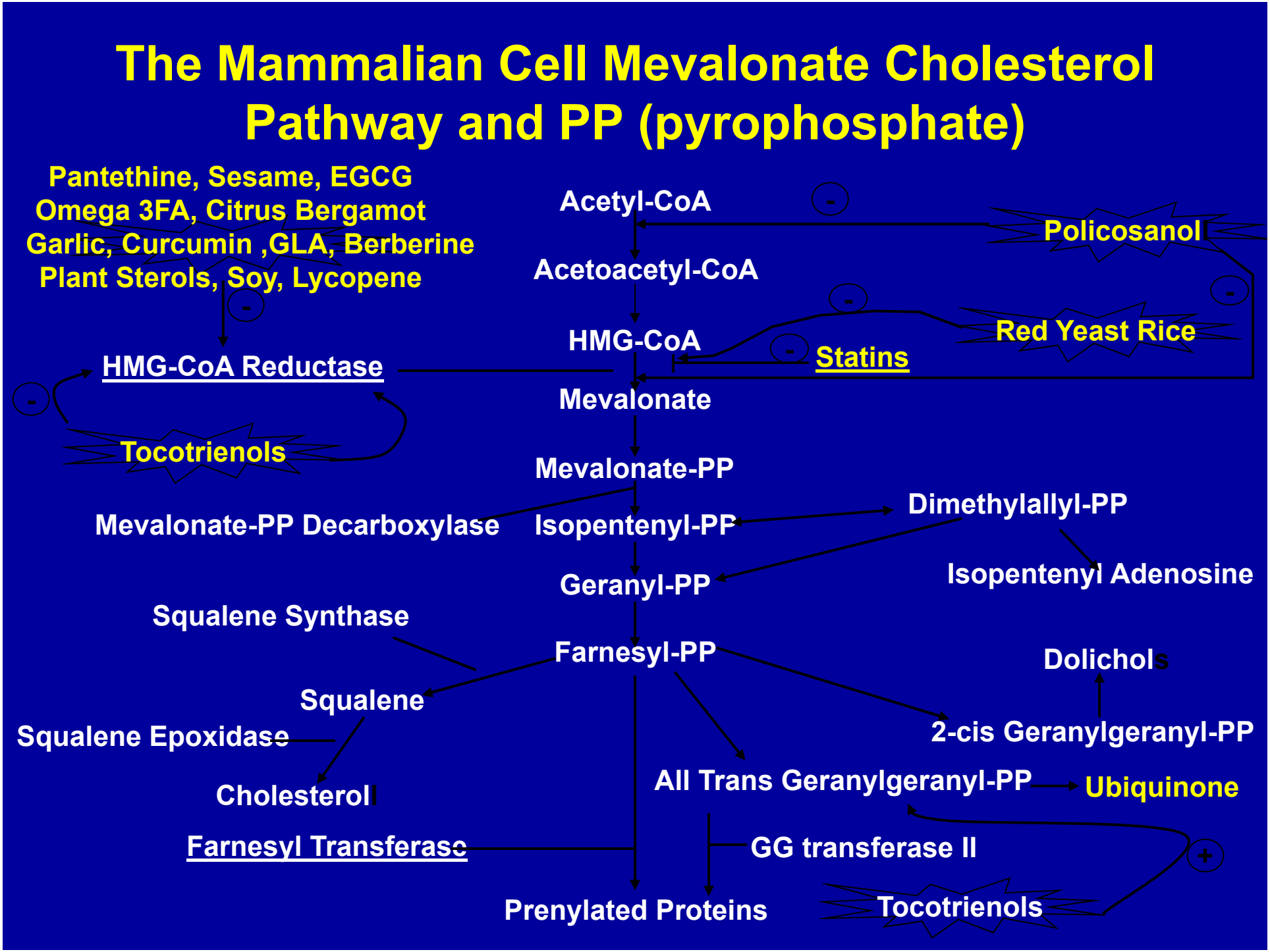
- Co Q 10
- Tocopherols and tocotrienols
- Omega 3 FA
- Vitamin D
- Vitamin K2
- Vitamin A
- Heme A
- Selenoproteins and selenium
- Carnitine
- Copper
- Zinc
- Creatine

Overview



- CV 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)
  - ALA-dietary. Mediterranean diet
  - Fiber

The Mammalian Cell Mevalonate Cholesterol Pathway and PP (pyrophosphate)



Niacin meta-analysis of lipid effects and CHD

J Am Coll Cardiol 2013:61(4):440Nutrition Reviews 2012;70:357; Curr Opin Lipidol 2013;24:475; American J of Medicine; 2017;130:173

- 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 outcomes.
- Niacin reduction in CVD events may occur through a mechanism not reflected by changes in HDL. (antioxidant, anti-inflammatory,anti-thrombotic, reduces MPO, increase adiponectin, reduce ED.
- Average changes in lipids in the dose range of 1 to 4 grams per day:

  TC: 20 – 25% decrease

  LDL and APO B: 10 – 25% decrease, decrease LDL-P and oxLDL, increase LDL size. Reduce Lp(a) 35%. Increase RCT and CEC.

  TG: 20 – 25% decrease and decrease VLDL size.

  HDL and APO A-1: 15 – 35% increase, increase HDL size, HDL-P and HDL function

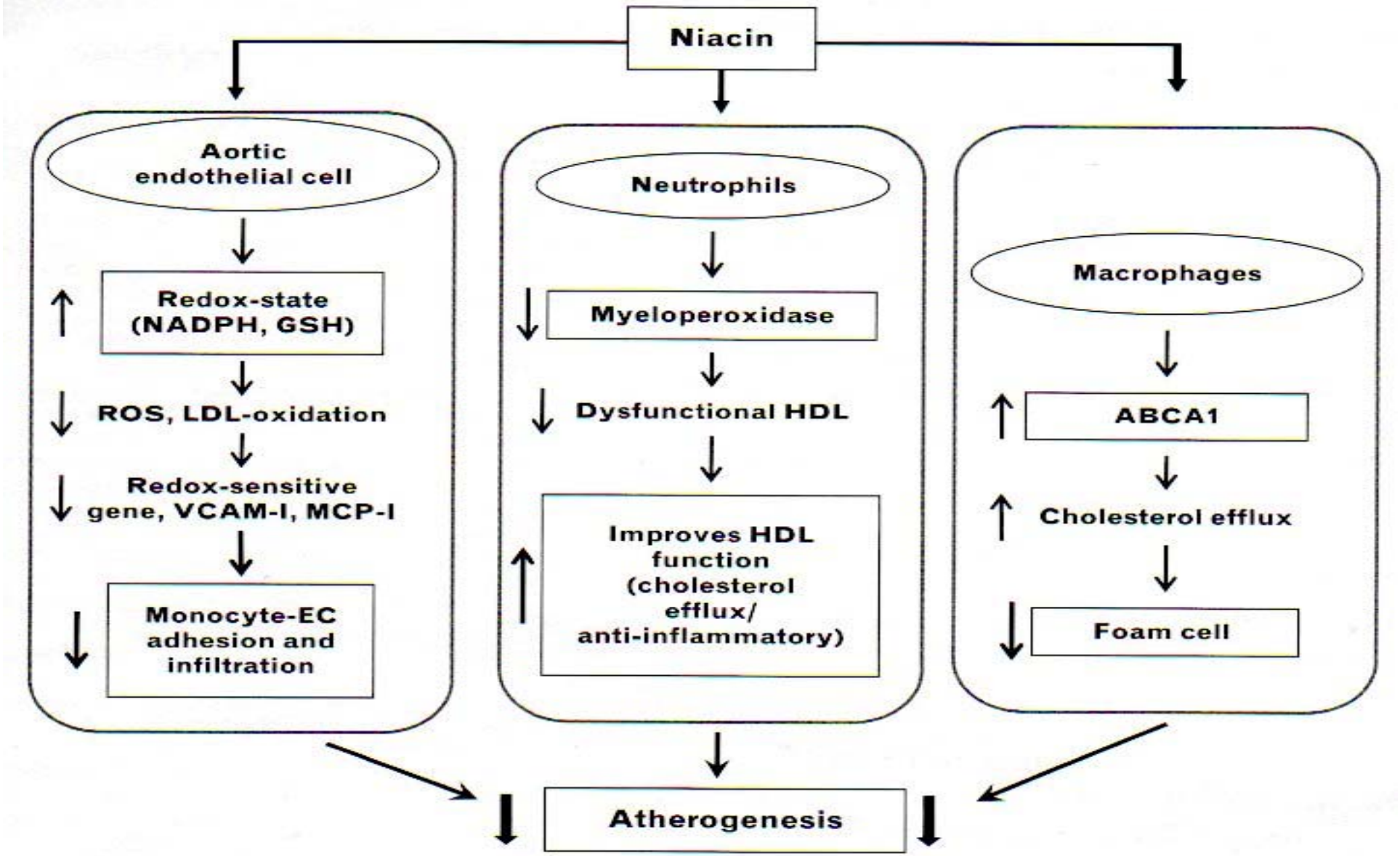
Meta-analysis 13 trials (AJM 2017) included AIM High and HPS which were flawed studies and due to their size the CV endpoints trended to significance.

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

Niacin and 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.



Curr Opin Lipidol 2013, 24:239-245

Prolonged Combination Lipid Therapy is Associated with Reduced Carotid intimal-media thickness: 20 years of FATS-OS Trial

J CInical Lipidolgy 2014;8:489-493

- Combination therapy with statin, colestipol and niacin had better lipid profiles ($p<0.001$) and lower CIMT ($P< 0.001$) than those patients on statins alone.
- Also reduction in carotid plaque and volume of lipid rich necrotic core.

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 statins (simvastatin) or bile acid resins (colestipol) with advanced lipid testing and coronary angiography.
- Improved angiography correlated with LDL-P, dense LDL, IDL and VLDL but not with HDL or HDL fractions or large LDL.
- Niacin combination therapy decreases LDL-P, dense LDL , IDL, VLDL and increases HDL which relates to CHD stenosis as measured by angiography and CHD event rate.

Niacin and its metabolites as master regulators of macrophage activation.

J Nutr Biochem.2017 Jan;39:40-47.

- Niacin is a broad-spectrum lipid-regulating drug used for clinical therapy of chronic high-grade inflammatory diseases.
- The mechanisms by which either niacin or the byproducts of its catabolism ameliorate these inflammatory diseases are now delineated.
- Niacin and its metabolites include:

  NAM: nicotinomide which is precursor to NAD and NADPH and NADH

  NUA : nicotinuric acid

  2-Pyr
- Improve oxidative stress, plasticity and inflammatory response and increases adiponectin
- Niacin, NAM and 2-Pyr significantly decreased ROS, NO and NOS2 expression in LPS-treated human mature macrophages.
- Niacin and NAM skewed macrophage polarization toward antiinflammatory M2 macrophage whereas a trend toward proinflammatory M1 macrophage was noted following treatment with NUA.
- Niacin and NAM also reduced the inflammatory competence of LPS-treated human mature macrophages and promoted bias toward antiinflammatory $CD14^{+}CD16^{++}$ nonclassical human primary monocytes.
- Niacin and its metabolites possess antioxidant, reprogramming and antiinflammatory properties on human primary monocytes and monocyte-derived macrophages.
- Niacin and its metabolites favor a continuous and gradual plasticity process in the human monocyte/macrophage system to reduce inflammation, ROS, CHD and MI.

NIACIN vs IHN (Inositol Hexanicotinate

J of Clinical Lipidology 2013;7:14

- Niacin: 500 to 4000 mg per day given twice per day. Various OTC and prescription forms available. ASA, food, quercetin and applesauce reduce flushing. Avoid alcohol

- IHN is not effective in dyslipidemia compared to placebo.

ISIFMC Position Paper July 30, 2014
Mark Houston MD, Mimi Guarneri MD and Joel Kahn MD

- 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 statins 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.

CHINESE RED YEAST RICE (MONASCUS PURPUREUS)

Am J Cardiol 2008;101:1689-93
Clin Med 2006;1:4 J Clin Lipidology 2010;119:374
J Altern Complement Med 2012;18:318
Nutrition Research 2013;33:622; Nutrition Research 2016;36:1162

- Monacolines are active ingredients, which inhibit cholesterol synthesis via HMG-CoA reductase (13 natural statins) Statin content evaluated by NMR. Even low doses of 3- 10 mg of monacolin K lowers LDL by 22-27%
- Sterols (B-sitosterol, campesterol, stimasterol, sapogenin)
- Isoflavones, isoflavone glycosides , flavonoids
- Monunstaruated fatty acids
- Over 30 pigments and unsaturated FA
- Ergosterol
- Amino acids
- Alkaloids and trace elements.

Red Yeast Rice

Am J Cardiol 2008;101:1689-93
Clin Med 2006;1:4
J Clin Lipidology 2010;119:374
J Altern Complement Med 2012;18:318

- 5000 Chinese patients with previous MI received Xuezhikang, an extract of RYR at 600 mg for 4.5 years vs placebo.
- Primary end point of MI and death.
- LDL decreased 17.6% with RYR ($p < 0.001$) and HDL 4.2% increase ($p<0.001$).
- 10.4 % frequency of primary end point in placebo vs. 5.7% in RYR ($p<0.001$), a RR reduction of 45% and absolute reduction of 4.7%.
- CV mortality decreased 30%. ($p<0.005$)
- Total mortality decreased 33%. ($p<0.0003$)
- No change in CVA.

RYR 22 clinical trials review

Complement Ther Med 2012;20:466
Shang Q et al. Evid Based Complement Alternat Med 2012; April EPUB;
Am J Health Syst Pharm 2012;69:291
Holist Nurs Pract 2012;26:173;Eur J Endocrinol 2005;153:679;Am J Clin Nutr 1999;69:231.
Fujimoto M et al. Evid Based Complement Alternat Med 2012; Dec 20 EPUB;
World J Cardiol 2012;4:77,J Ind Microbiol Biotechnol 2013; 40:169;
Forsch Komplementamed 2013;20:197Ann Intern Med 2009;150:830; Am J Cardiol 2010;105:198
Evid Based Complement Alternat Med 2013; epub

- Lipid Effects: "Statin like" (monocolin) and other effects : 2400 mg at night.
  - Reduce LDL ~ 22%
  - Reduce TC ~ 17%
  - Reduce TG ~ 12%
  - HDL - No change or increase
  - Lowers MMP 2 and 9, leptin, IR, hsCRP, TF (tissue factor), NADPH oxidase, thrombosis, caveolin-1, TNF(tissue necrosis factor) alpha and A-II(angiotension II)
  - Increase eNOS, FMD (flow mediated vasodilation), adiponectin
  - Decrease AAA (abdominal aortic aneurysm)
- Decreases nonfatal MI, total CHD events, revascularization and total deaths.
- No adverse effects or events. (liver, muscle etc).
- Alternative to statin –induced myalgias.

Effects of Xuezhikang in patients with dyslipidemia: A multicenter, randomized, placebo-controlled study in US and China.

Moriarty PM et al. J Clin Lipidol. 2014;8(6):568-75

- .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.

Berberine HCL

Metabolism 2008;57:1029;Nat Med 2004;10:1344
Lipids Health Dis 2012;11:123;Plant Med 2013;79:437; Expert Opin . Investig Drugs.2010;19:10; Curr Opin Lipidol 2017;28:282

- Alkaloid present in plant roots, rhizomes, stem barks.
- In 3 months at 500 mg bid TC decreases 29%, LDL 25% and TG 35 %.
- Meta-analysis of 11 trials in 874 subjects :significant reductions in TC (23 mg/dL), LDL(25 mg/dL), TG(44 mg/dL), increase in HDL (2mg/dL).
- Suppresses the PCSK9 expression.
- Increases hepatic LDL R (mRNA/ protein) 2.6 to 3.5 fold by inhibiting transactivation of PCSK9 mRNA expression by HNF1 alpha. Post-transcriptional mechanism depends on ERK, independent of SREBP.
- Reduces cholesterol absorption /increases biliary excretion of LDL.
- Inhibits HMG-CoA reductase.
- Stimulates AMPK, reduce IR via IRS RNA and protects beta cells, lowers glucose similar to Metformin, decrease FA synthesis, increase FA oxidation, delays adipocyte differentiation, weight loss, reduces CHO absorption , alters GI flora, LPS translocation blunted, increases EPCs (endothelial progenitor cells), increase eNOS and NO, lower BP, reduces ED, decreases CECs(circulating endothelial cells), decreases microparticles, lowers NFKb and Th1 cytokines, increase SOD(superoxide dismutase), lowers ROS (radical oxygen species) ACE (angiotensin converting enzyme), lowers NADPH oxidase.
- Additive reduction in LDL, TC and TG with ezetimibe, RYR and phytosterols and upregulation of LDL R with statins.
- Dose: 500 mg qd to bid of berberine HCL.

PCSK9 and Berberine

J of Translational Medicne 2014;12:103

- PCSK9 is composed of SREBP (sterol regulatory binding protein, HNF-1(hepatic nuclear factor 1 and SRE (sterol regulatory element
- HNF stimulates basal secretion of PCSK9 and decreases LDL R
- SREBP-2 increases with cholesterol depletion and increases LDL R.
- Berberine inhibits SREBP (this decreases LDL R) and blocks HNF 1(this increases LDL R)
- The balance of the effect of berberine is likely dose-dependent and relative in vivo effects on HNF-1 and SREBP 2 lower PCSK9 and thus increase LDL R and lower LDL C.
- This study in mice used on 20 mg per day of berberine (400 mg /kg/day in 50 gram rat). This is subtherapeutic dose.

PCSK9: Serum proprotein convertase subtilisin/kexin 9

NEJM 2012; 367:1891 NEJM 2012;366:1108-18
Curr Opin Lipidol 2012;23:511; JAMA 2012;308:2497
Curr Opin Lipidol 2013;24:251; Current Opin Lipidol 2013;24:307
Drug Design,Development and Therapy 2013;7: 1135.
Curr Opin Lipidol 2014:25:387; Mol Nutr Food Res 2014;58:2133.

- PCSK9 is a serine protease that binds to LDL receptors, increasing the degradation of LDLR receptors in hepatic lysosomes and reduces the rate that LDL cholesterol is removed from the circulation.
- PCSK9 binds to APO B 100 on LDL, inhibits binding to LDL R. Hepatocyte nuclear factor-1 alpha (HNF-1alpha) is key transcriptional factor that cooperates with SREBP-2 to controls PCSK9 expression.
- Statins induce gene expression of LDLR and PCSK9(dose related 28-43%) and ENaC (may alter renal sodium excretion and BP).
- Monoclonal antibodies to PCSK9 results in a greater reduction in LDL. Monoclonal antibody to PCSK9 (REGN 727, AMG 145) significantly reduced LDL by 61%-70% at 150 mg per day.
- Berberine downregulates PCSK9. Additive with statins in LDL reduction. More effective than ezetimibe in lowering LDL.
- Curcumin also downregulates PCSK9

PCSK9

NEJM 2012; 367:1891 NEJM 2012;366:1108-18
Curr Opin Lipidol 2012;23:511; JAMA 2012;308:2497
Curr Opin Lipidol 2013;24:251; Current Opin Lipidol 2013;24:307
Drug Design,Development and Therapy 2013;7: 1135
Curr Opin Lipidology 2014;25:387.

- **PCSK9 is a liver derived serine protease that binds to LDL receptors, increasing the degradation of LDLR receptors in hepatic lysosomes and reduces the rate that LDL cholesterol is removed from the circulation.**

- **Statins induce (and maybe red yeast rice) gene expression of LDLR and PCSK9(dose related 28-43%) and ENaC (may alter renal sodium excretion and BP).**

PCSK9

NEJM 2012; 367:1891 NEJM 2012;366:1108-18
Curr Opin Lipidol 2012;23:511; JAMA 2012;308:2497
Curr Opin Lipidol 2013;24:251; Current Opin Lipidol 2013;24:307
Drug Design,Development and Therapy 2013;7: 1135
Curr Opin Lipidology 2014;25:387.

1. PCSK9 also made in lower levels in intestine, kidney and brain.
2. Two mechanisms of LDL-R degradation
    a. Intracellular pathway. PCSK9 binds to LDLR and directs it from Golgi to lysosomes to degrade
    b. Binds at cell surface of LDL R and inhibits endocytic recycling of LDLR. Primary path in humans.
3. PCSK9 and LDL R expressions are co-regulated at the transcriptional level by SREBP-2. (regulates genes in cholesterol synthesis). SREBP -1 regulates genes in fatty acid synthesis.

PCSK9

NEJM 2012; 367:1891 NEJM 2012;366:1108-18
Curr Opin Lipidol 2012;23:511; JAMA 2012;308:2497
Curr Opin Lipidol 2013;24:251; Current Opin Lipidol 2013;24:307
Drug Design,Development and Therapy 2013;7: 1135
Curr Opin Lipidology 2014;25:387.

1. Secreted PCSK9 is subject to homeostatic regulatory mechanisms within the plasma compartment through binding to LDL-apoB 100 (30% PCSK9 bound to apoB).
2. HNF-1 alpha drives differential transcription of PCSK9 in hepatocytes and can alter the balance of PCSK9 and LDLR expression.
3. Through HNF1 alpha regulation, PCSK9 appears to respond to insulin signaling and acute inflammation. Insulin stimulates TOR which blocks HNF1 alpha and decreases PCSK9. Inflammation increase HNF1 alpha and increases PCSK9.
4. PCSK9 has diurnal variation and increased by feeding, insulin and inflammation and decreased by fasting.
5. Statin induces SREPB-2 activity and increase LDLR expression but PCSK9 degrades LDL R .
6. Hepatic LDLR also clears TG VLDL, remnant chylomicrons and apo B by binding to apo E.

PCSK9

NEJM 2012; 367:1891 NEJM 2012;366:1108-18
Curr Opin Lipidol 2012;23:511; JAMA 2012;308:2497
Curr Opin Lipidol 2013;24:251; Current Opin Lipidol 2013;24:307
Drug Design,Development and Therapy 2013;7: 1135
Curr Opin Lipidology 2014;25:387.

1. Berberine downregulates PCSK9 by inhibition of transactivation of PCSK9 mRNA expression by HNF1 alpha. Additive with statins in LDL reduction.

2. Monoclonal antibodies to PCSK9 results in a greater reduction in LDL. Monoclonal antibody to PCSK9 (REGN 727, AMG 145) significantly reduced LDL by 61%-70% at 150 mg per day.

PCSK9
Roles in Reverse Cholesterol Transport (RCT) and Innate Immunity

NEJM 2012; 367:1891 NEJM 2012;366:1108-18
Curr Opin Lipidol 2012;23:511; JAMA 2012;308:2497
Curr Opin Lipidol 2013;24:251; Current Opin Lipidol 2013;24:307
Drug Design,Development and Therapy 2013;7: 1135
Curr Opin Lipidology 2014;25:387.

1. Innate Immunity: Plasma lipoproteins participate in host defense against all pathogens such as bacterial infections through sequestration and clearance of LPS. LPS –BP is an acute phase protein that catalyzes the transfer of LPS into lipoproteins and is associated with VLDL and LDL. LPS increases PCSK9 and is inhibited by berberine.
2. RCT: down-regulated in the innate immune response. Increased cholesterol in cells and lipid rafts and improved TLR function and inflammation pathways.
3. Also inhibits non-biliary routes of cholesterol excretion in intestine (30-60%).

Red Yeast Rice (RYR) and Berberine

Alternative Therapies 2015;21(2): 40-45

- RYR 2400 mg with extracts of10 mg of monocolins/day

(especially monacolin K- like lovastatin) lowers LDL-C by 20% (28 mg/dl) and increased HDL 6 mg/dl, though its effects on HMG –CoA reductase and other mechanisms.

- RYR reduces CV morbidity and mortality and total mortality
- Rarely induces myopathy, hepatic dysfunction or diabetes
- Berberine 500 mg bid lowers LDL-C by 25% alone and with a statin added an additional 20% LDL-C reduction. Lowers TG 40%. Improves CHF and cardiomyopathy, EF and PVC's. Lowers MMP, VCAM, ICAM, MCP-1, hsCRP, IL-6.
- Mechanism of berberine is via PCSK-9 inhibition , increases hepatic expression of LDL receptors by extending the half-life of LDL receptor mRNA. Also activates AMPK. Lowers glucose,IR and improves NAFLD.
- Berberine also has a low incidence of adverse effects
- RYR and berberine are additive in lowering LDL-C by about 20%.

PLANT STEROLS

Nutrition Reviews 2011;69:371;J Nutr 2009;139:271
Nutrition 2013;29:96; Curr Opin Lipidol 2013;24:12; Nutrition Reviews 2017;75:134

- Plant Sterols: B-sitosterol, campesterol, stigmasterol, stanols Improve serum lipids:
- Marked variation in response due to individual polymorphisms and patient status as hyperabsorber or hyperproducer.
  TC decreased 8%-15%
  LDL decreased 10%-15%
  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. Remove cholesterol from hepatic lipid synthesis for recycling in GI tract.
- 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.
- Activate cellular stress responses and growth arrest.
- Reduction of Apo B 48 secretion of intestinal and hepatic cells.
- Suppress HMG COA reductase and suppress CYP7A1.
- Interfere with SREBP (steroid receptor binding protein).
- Promote reverse cholesterol transport (RCT).
- Decrease fat soluble vitamin absorption.
- Reduce atherosclerosis progression, IMT and improves plaque regression.
- Mixed data with CVD reduction.
- Can use with statins.

4S trial and PROCAM trial : increased risk of CV events in hyperabsorbers 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.

Lathosterol-to-cholesterol ratio in serum predicts cholesterol-lowering response to plant sterol consumption

Am J Clin Nutr.2015 ;101(3):432-9

- The goal was to test whether the lathosterol-to-cholesterol ratio (L:C ratio), a surrogate marker of endogenous cholesterol synthesis, serves as an a priori predictor of cholesterol lowering in response to PS consumption.
- Desmosterol and lathosterol are markers of endogenous cholesterol synthesis. Campesterol and sitosterol are markers of cholesterol absorption.

- Sixty-three mildly hypercholesterolemic adults who were preselected as possessing either high endogenous cholesterol synthesis [HS; n = 24; L:C = 2.03 ± 0.39 μmol/mmol (mean ± SD)] or low endogenous cholesterol synthesis (LS; n = 39; L:C = 0.99 ± 0.28 μmol/mmol) on the basis of baseline L:C consumed 2 g PS/d or a placebo for 28 d with the use of a dual-center, single-blind, randomized crossover design. Plasma lipid and noncholesterol sterol concentrations were measured at the end of each phase.

- PS consumption lowered total cholesterol (TC; -0.25 ± 0.05 mmol/L; P < 0.0001) and LDL cholesterol (-0.17 ± 0.04 mmol/L; P < 0.0001) overall.
- LS individuals responded to PS treatment with a reduction in TC (-0.40 ± 0.07 mmol/L; P < 0.0001) and LDL cholesterol (-0.29 ± 0.05 mmol/L; P = 0.0002), 11 mg / dL.
- HS individuals failed to show cholesterol lowering (TC: -0.09 ± 0.09 mmol/L; P = 0.2843; LDL cholesterol: -0.05 ± 0.07 mmol/L; P = 0.4917).
- The odds of LS participants responding to PS consumption with cholesterol lowering better than the mean cholesterol lowering in all participants were 4.25 (95% CI: 1.242, 14.556; P = 0.0211) for TC and 3.36 (95% CI: 1.112, 10.161; P = 0.0317) for LDL cholesterol, which was higher than for HS participants

- The L:C ratio predicts the extent of reduction in circulating TC and LDL cholesterol in response to PS consumption. Cholesterol synthesis assessment may thus have a use in identifying responders and nonresponders to PS therapy.

FIBER

Am J Clin Nutrition 1999;69:30-42; Arch Intern Med 2004;164:370-376;J Epidemiol Community Health 2009;63:582-8;J AM Diet Assoc 1994;94:425-36

- 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.

Effects of Omega 3 FA on Serum Lipids

Mori, Am J Clin Nutrition 2000;71:1085
Am J Card 2010;105:1409,J of Nutriton 2008;138:30
Am J Therapeutics 2009;16183,J of Clinical Lipidology 2012;6:5-18
Am J Clin Nutr 2012;95:1315, J of Clin Lipidol 2012;6:585

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 all LDL levels.
2. May have slight increase in LDL mostly in those with lowest LDL level less than 80 mg %,but decreased in those with higher LDL over 100 mg % but still beneficial (as above).
3. Increase conversion of dense small LDL B to larger LDL A.
4. Reduce TG (50%), VLDL, VLDL particles and VLDL size.
5. Lowers Apo CIII (inhibits lipoproprotein 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 decrease 7% (DHA), HDL 2b increase 29 % (DHA).
7. Decrease FA synthesis and increase in FA oxidation.
8. Improves insulin resistance, increases insulin levels 18%-27%, reduces or does not change fasting glucose or AIC even in high doses in normal patients.
9. Decreases lipoprotein associated phospholipase A2 levels (Lp-PLA 2), anti-inflammatory,anti-thrombotic,PPAR agonist, improve heart rate variability, lowers HR, increase eNOS / NO , improves ED ,reduces BP,decrease atrial fibrillation and arrhythmias, reduces growth of atherosclerotic plaque with more well-formed fibrous caps and fewer thin wall caps.
10. **RCCT: Reduce CVD events and death, CHD, primary and secondary prevention of MI, CVA, total mortality and sudden death. Reduce CHD progression, stent and CABG occlusion (DART: GISSI: Prevenzione Trial – Kuopio Heart Study in Finland).**

Optimal Dosing and Ratios of Omega 3 FA with GLA and gamma/delta tocopherols

Am J Clinical Nutrition 2003;77:77-43;J Lipid Res 1992;33:131;Essent Fatty Acids 1994;59:321;Atherosclerosis 1989;75:95; Prostaglandins Leukot Essent Fatty Acids 1990;40:9;Prostaglandins Leukot Essent Fatty Acids 1997;57:125;Lipids 1988;23:766;U Nutr 200:130

- 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 that 20% as alpha tocopherol.

Lowers TG (40%), LDL(12%) and BP. GLA with omega 3 FA is better in reducing LDL.

Decreases inflammation, lowers HSCRP and AA.

Estimated 43% reduction in 10 yr risk MI.

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

Lipid-modifying effects of krill oil in humans: systematic review and meta-analysis of randomized controlled trials.

Nutr Rev.2017 May 1;75(5):361-373.

- RCCTS impact of at least 2 weeks of supplementation with krill oil on plasma/serum concentrations
- Meta-analysis of data from 7 eligible trials with 662 participants
- Significant reduction in plasma concentrations of low-density lipoprotein cholesterol -15.52 mg/dL; 95%CI, -28.43 to -2.61; P = 0.018) and triglycerides -14.03 mg/dL; 95%CI, -21.38 to -6.67; P < 0.001)
- A significant elevation in plasma concentrations of high-density lipoprotein cholesterol was also observed (WMD, 6.65 mg/dL; 95%CI, 2.30 to 10.99; P = 0.003),
- Total cholesterol did not reach statistical significance , -7.50 mg/dL; 95%CI, -17.94 to 2.93; P = 0.159).
- Conclusion: Krill oil supplementation can reduce low-density lipoprotein cholesterol and triglycerides.

Japan EPA Lipid Intervention Study (JELIS trial)

Lancet 2007;369:1090
Atherosclerosis 2008; 200: 135
Stroke 2—8;39:2952

- 18,645 patients.
- Randomized to statin plus 1.8 grams of EPA vs statin alone.
- 19 % RRR in major coronary events and non fatal MI.

- 20% RRR in stroke.

Monounsaturated Fatty Acids Olive Oil

Current Atherosclerosis Reports 2007;9:494
Nutr Res Rev 2010;23:334 Pharmacol Res 2007;55:175
Atherosclerosis 2007;190:181 Am J Clin Nutr 2012;95:1238;J of Nutritional Biochem 2013;24:1334, Curr Opin Lipidol 2016;27;47.

- Reduce LDL (5-10%) and TG(10-15%)
- Decrease ox LDL
- Increase HDL(5%)
- Improve HDL function
- Increase CEC and RCT
- Increase HDL anti-oxidant and anti-inflammatory traits
- Upregulate genes involved in reverse cholesterol transport (RCT). ATPBC –A1, SRA B 1, PPAR, CD 36. Directly related to the polyphenol content.
- Reduces CD40L gene expression, MCP-1,, IL-23 R,ADR B2, IL-8 R, ICAM, VCAM, TNF a and INF gamma and OLR 1.
- Reduce CHD and MI (Mediterranean diet, EVOO, nuts. CHD reduced 30%)

Olive Oil and Proteomics

Am J Clinical Nutrition 2015;101: 44-54

European Comission. Commission regulation (EC) No 432/2013-Official Journa of the EuropeanUncion 2103: L 136/1.

- 6 week of olive oil at 20 ml/ 20 grams per day in healthy adults improved 133/238 proteomic. biomarkers of CHD, CKD, dyslipidemia and DM.
- Reduce oxLDL and increased HDL.
- Reduced glucose, AGEs and Hb A1C.
- Decrease ROS.
- Anti-inflammatory.
- Down-regulate CHD genes.
- Upregulate RCT and CEC.
- Reduced collagen peptides and other peptides related to CHD.

Monounsaturated Fatty Acids Olive Oil

Current Atherosclerosis Reports 2007;9:494
Nutr Res Rev 2010;23:334 Pharmacol Res 2007;55:175
Atherosclerosis 2007;190:181 Am J Clin Nutr 2012;95:1238; J of Nutritional Biochem 2013;24:1334;N Engl J Med. 2013;368(14):1279-90.
Nutrition 2015;31:834-840

- Reduce oxidation, inflammation and proatherogenic molecular mechanisms in CVD and CHD.
- Omega 3 with MUFA has synergistic effects on lipid metabolism and oxidative stress.
- Improve ED and reduce BP.
- Decrease thrombosis.
- Decrease CD 40L, IL 23a, ADRB2, oxLDL-R and IL-8.
- Related to polyphenol contents. Also to tyrosol and hydrotyroxsol in urine. Need 25 ml/d.

TOCOTRIENOLS

Current Pharm Des 2011;July 21 Epub
Nutrition Reviews 2012;70:483;*Nutr Biochem 1997; 8:290*

Inhibit cholesterol synthesis by post-transcriptionally suppressing **HMG-CoA reductase activity** by <u>two</u> post-transcriptional actions

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

<u>Lipid Reductions at</u> 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 at 50% of patients.
- Endogenous increase in GGPP (geronyl-geronyl 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.

Citrus Bergamot

Fitoterapia November 2011;82:309
J Agric Food Chem 2010;58:10768
J Agric Food Chem 2007;55:10671J Nat Prod 2009;72:1352Int N Cardiology 2013;170:140-145
Advances in Biological Chemistry 2014 EPUB

- 1000 mg per day lowers LDL 36%, TG 39% and increases HDL 40 % in 30 days. Increase LDL and HDL size, decrease remnant particles decrease NAFLD, reduce 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.

Bergamot Reduces Plasma Lipids, Atherogenic Small Dense LDL, and Subclinical Atherosclerosis in Subjects with Moderate Hypercholesterolemia: A 6 Months Prospective Study.

Toth PP. Front Pharmacol. 2016 Jan 6;6:299.

- Eighty subjects (42 men and 38 women, mean age: 55 ± 13 years) with moderate hypercholesterolemia [e.g., with plasma LDL-cholesterol concentrations between 160 and 190 mg/dl (between 4.1 and 4.9 mmol/l)] were included.
- A Bergamot-derived extract (Bergavit R(®)) was given at a fixed dose daily (150 mg of flavonoids, with 16% of neoeriocitrin, 47% of neohesperidin and 37% of naringin) for 6 months. Lipoprotein subfractions were assessed by gel electrophoresis. With this methodology low density lipoprotein (LDL) subclasses are distributed as seven bands (LDL-1 and -2 as large LDL, and LDL-3 to -7 as atherogenic small, dense LDL). Subclinical atherosclerosis was assessed by carotid intima-media thickness (cIMT) using B-mode ultrasound.
- After 6 months, Bergavit R(®) reduced total cholesterol (from 6.6 ± 0.4 to 5.8 ± 1.1 mmol/l, $p < 0.0001$), triglycerides (from 1.8 ± 0.6 to 1.5 ± 0.9 mmol/l, $p = 0.0020$), and LDL-cholesterol (from 4.6 ± 0.2 to 3.7 ± 1.0 mmol/l, $p < 0.0001$), while HDL- cholesterol increased (from 1.3 ± 0.2 to 1.4 ± 0.4 mmol/l, $p < 0.0007$). In addition, a significant increase in LDL-1 (from 41.2 ± 0.2 to 49.6 ± 0.2%, $p < 0.0001$) was accompanied by decreased small, dense LDL-3, -4, and 5 particles (from 14.5 ± 0.1 to 9.0 ± 0.1% $p < 0.0001$; 3.2 ± 0.1 to 1.5 ± 0.1% $p = 0.0053$; 0.3 ± 0.0% to 0.1 ± 0.0% $p = 0.0133$, respectively). cIMT also decreased from 1.2 ± 0.4 to 0.9 ± 0.1 mm ($p < 0.0001$).
- This is the first study investigating the effects of Bergamot flavonoids supplementation on cardio-metabolic risk in dyslipidemic subjects. Bergavit R(®) (Bergamot juice extract) supplementation significantly reduced plasma lipids and improved the lipoprotein profile. cIMT was also reduced significantly over a relatively short time frame of 6 months

Lycopene (Acyclic Carotenoid)

J of Nutritional Biochemistry 2011;22:971
J of Nutritional Biochemistry 2012;23:8-17
J of Nutrtional Biochemistry 2013;24:163
J Biol Regul Homeost Agents 2011;25:435;Lipids.1998 ;33(10):981-4.

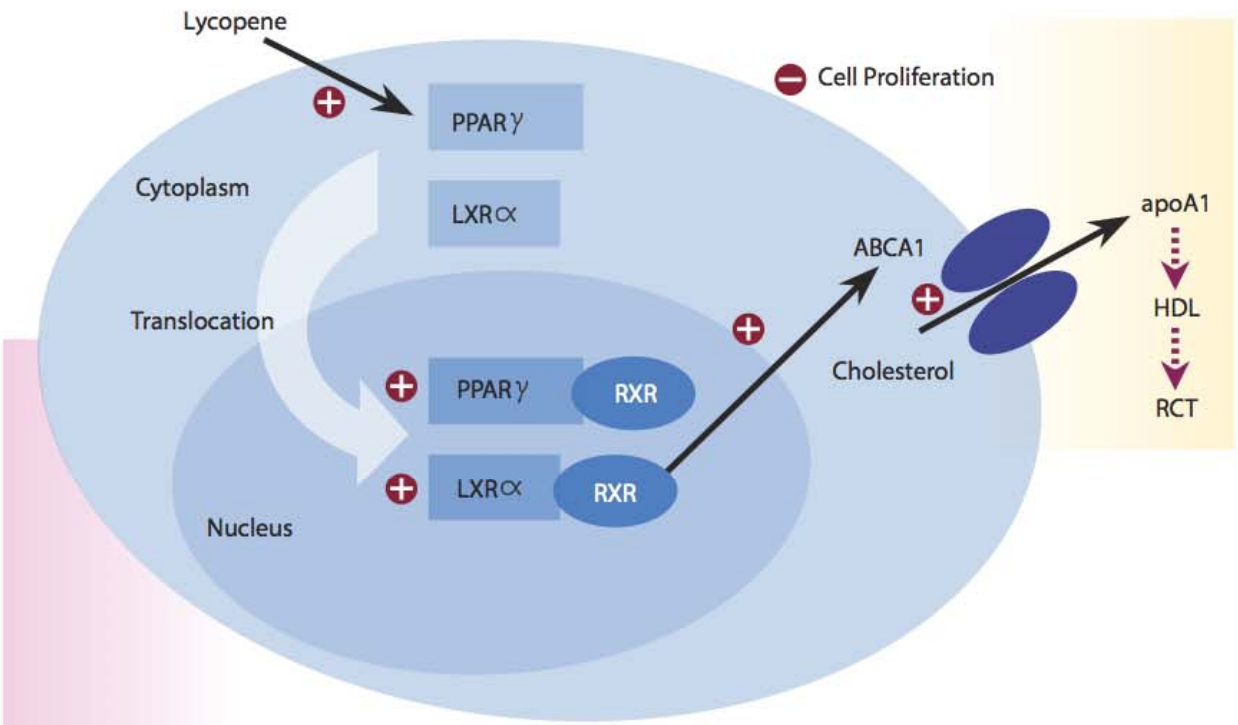
- Inhibits HMG CoA reductase.
- Inhibits RhoA.
- Increases PPAR gamma activities (nuclear hormone receptor superfamily that are ligand activated intracellular transcription factors.)
- Increases Liver X receptor alpha (LXR-a) activities. (nuclear receptors activated by oxysterols involved in lipid homeostasis).
- Forms heterodimer to stimulate RXR.
- Improves ED.
- Decreases NFkB signaling / decrease inflammation.
- Protective role in inhibiting carotid IMT and plaque.

Lycopene (Acyclic Carotenoid)

J of Nutritional Biochemistry 2011;22:971
J of Nutritional Biochemistry 2011;23:8-17
J of Nutrtional Biochemistry 2013;24:163 and 428
J of Hypertension 2012;31:521; Lipids.1998 ;33(10):981-4.

- Enhances ABCA1 expression, reverse cholesterol transport,apoA1 expression, reduces intracellular cholesterol and cholesterol in lipid domains ,alters membrane- induced cellular signal transduction.
- Enhances Caveolin-1 – expression.
- Two unconjugated double bonds reduce ROS.
- Increases HDL 2 and 3, improves HDL functionality.
- Upregulates Nrf2.
- Reduces SAA.
- Decreased CETP.
- Increase PON 1 and decrease oxLDL.
- Reduces inflammation. Immunomodulation.
- Dose 10-20 mg per day.

Lycopene Inhibits the Proliferation of LNCaP Cells



Hypertension INSTITUTE

Astaxanthin

Plant Foods Hum Nutr.2011 Nov;66(4):363-9
Atherosclerosis.2010;209(2):520-3

- Lowers LDL and Apo B
- Increases HDL
- Lowers TG
- Lowers MDA and isoprostanes
- Increases antioxidant capacity
- Increases adiponectin
- Dose 12-18 mg per day

PANTETHINE

Atherosclerosis 1984; 501:73) Atherosclerosis 1987; 68:41) (Biochem Biophys Acta 1988; 963:389) Nutrition Research 2005;25: 319 Ideggyogy 2009;62:220 Progress in Cardiovasc Nurs 2006;21:89 Nutrition Research 2011;31:608

- **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 FA synthesis and beta oxidation**
  - **Inhibits HMG-CoA reductase**

- **Additive to statins, niacin and fibrates.**
  Compared to fibrates: similar reductions in lipids.

Peak effect is at 4 months in most but may be up to 6-9 months.

Reduce lipid deposition/ fatty streaks in aorta and coronary arteries
Reduces intimal thickening in the aorta and coronary arteries.
Reduces peroxidation of LDL-C.

. Efficacy and tolerability of coenzyme A vs pantethine for the treatment of patients with hyperlipidemia: A randomized, double-blind, multicenter study.

J Clin Lipidol.2015;9(5):692-7

- 216 subjects (124 males and 92 females; age, 18-75 years) with moderate dyslipidemia (triglyceride [TG], 2.3-6.5 mmol/L) were randomly divided into 2 groups administered CoA 400 U/d (n = 111) or pantethine 600 U/d (n = 105 (4- and 8-week treatment.)
- TG reduction was 26.0% with CoA and 17.4% with pantethine after 4 weeks and 33.3% and 16.5% after 8 weeks ($P < .01$) in both groups. The difference between the 2 groups was significant at both 4 weeks ($P = .0413$) and 8 weeks ($P < .001$).
- Total cholesterol and non-high-density lipoprotein cholesterol (non-HDL-C) were reduced, whereas HDL-C was increased with CoA after 8 weeks (all $P < .05$). Compared with pantethine, total cholesterol ($P = .026$) and non-HDL-C ($P = .005$) were significantly reduced after 8 weeks of CoA treatment.
- There was no statistical difference in low-density lipoprotein cholesterol or HDL-C between the 2 groups ($P > .05$) and no difference in blood glucose, hepatic or renal function, myopathy, or gastrointestinal tract symptoms.
- CoA can improve TG and other lipoprotein parameters to a greater extent than pantethine in moderate dyslipidemia, with no obvious adverse effects

Garlic and Serum Lipids : Meta-analysis

Nutrition Reviews 2013;71:282

Ann Intern Med 2000; 133:420;J Royal College Phys 1994; 28:39

Arch Intern Med 2007; 167: 346-353;Life Sci2009;85:211 Prev Med 2009 ;49:101

J of Cardiovascular Disease Research 2012;3:185. ;Nutrition 2013;29:71-75

- 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 4 ml 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 (Kyolic) 600 mg bid (CV formulation).

Probiotics and Lipids

Dig Dis 2013;31:278; Mayo Clinic Pro 2014;89:107;Br J Nutrition 2012;017:1505;Eur J Clin Nutr 2012; 66:1234; J AM Coll Cardiol 2005;45:185

- 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%, Hs CRP and fibrinogen and increased vitamin D.
- Dose 100 mg per day.

Pomegranate juice/seeds

Current Opinion in Lipidology 2010;21:163-4
Nutrition 2010;26:359;J of Nutrition and Metabolism 2013;JUNE 22, epub;
J of Nutrition and Metabolism 2013;ID 708381 open access 1-7

- 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 and alkaloids.fiber, pectin.
- 1 cup of seeds per day or 6 oz of juice.

Effects of green tea catechin extract on serum lipids in postmenopausal women: a randomized, placebo-controlled clinical trial.

Am J Clin Nutr.2016 Dec;104(6):1671-1682.

-
- Efficacy and impact of green tea extract (GTE) supplementation high in epigallocatechin gallate (EGCG) on blood lipids in healthy postmenopausal women.
- This was an ancillary study of a double-blind, randomized, placebo-controlled, parallel-arm trial investigating the effects of a GTE supplement containing 1315 mg catechins (843 mg EGCG) on biomarkers of breast cancer risk. Participants were randomly assigned to receive GTE (n = 538) or placebo (n = 537) and were stratified by catechol-O-methyltransferase (COMT) genotype activity (high COMT compared with low or intermediate COMT genotype activity). They consumed either 4 GTE or identical placebo capsules daily for 12 mo. A total of 936 women completed this substudy. Circulating lipid panels including total cholesterol (TC), HDL cholesterol, and triglycerides were measured at baseline and at months 6 and 12.
- RESULTS: Compared with placebo, 1-y supplementation with GTE capsules resulted in a significant reduction in circulating TC (-2.1% compared with 0.7%; P = 0.0004), LDL cholesterol (-4.1% compared with 0.9%; P < 0.0001) and non-HDL cholesterol (-3.1% compared with 0.4%; P = 0.0032). There was no change in HDL-cholesterol concentration, but triglyceride concentrations increased by 3.6% in the GTE group, whereas they decreased by 2.5% in the placebo group (P = 0.046). A significant reduction in TC was observed only among women with high (i.e., ≥200 mg/dL) baseline TC concentrations (P-interaction = 0.01) who consumed GTE capsules. The effect of GTE on the increase in triglycerides was mainly observed among obese women and statin users (P-interaction = 0.06).
- CONCLUSION: Supplementation with GTE significantly reduced circulating TC and LDL-cholesterol concentrations, especially in those with elevated baseline TC concentrations

SESAME

Clin Chim Acta 2005;355:97
Nutriton Research 2005;25:559
J Nutr 2010 November epub
J Nutr 2006;136:1270
Crit Rev Food Sci Nutr 2007:47:651

- 40 Grams of dietary sesame reduces LDL-C by 9% decreases TG and increases HDL.
- Increases catalyse, 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.

PhosphatidylSerine in Atherosclerosis and CHD

Curr Opin Lipidol 2016;27:414

- Anti-inflammatory
- Anti-coagulation
- HDL functionality
- Apoptosis
- Cell membrane physiology
- RCT and CEC (LXR, ABCA1 transporter, PS membrane receptor with apoptotic cells,BSAI-1, Rac 1)
- Dose: 300-600 mg bid

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.
- Reduce HMG-COA reductase, SREBP, increase LDL receptors, and increases the antioxidant enzymatic activity of catalase and SOD.

N Engl J Med 1995; 333:276;Am J Clin Nutr 1998; 68:1385S;Am J Clin Nutr 2007; 85:1148Arch. Int Med 2007;167:1060;J of Clinical Lipidology 2010;4:248 Atherosclerosis 2008;200:13;Nutrition Research 2011;31:922

Purified palmitoleic acid for the reduction of high-sensitivity C-reactive protein and serum lipids: A double-blinded, randomized, placebo controlled study.

Bernstein AM J Clin Lipidol. 2014 ;8(6):612-7.

- Purified palmitoleic acid (16-1; omega-7) has shown lipid-lowering and anti-inflammatory benefits in open label, epidemiologic, and animal studies.
- This is the 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

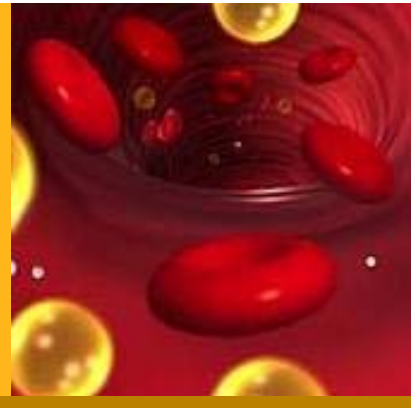
Usefulness of Nutraceuticals (Armolipid Plus) Versus Ezetimibe and Combination in Statin-Intolerant Patients With Dyslipidemia With Coronary Heart Disease.

Am J Cardiol.2015;116(12):1798-801.

- A single-blind, single-center, randomized, prospective, and parallel group trial comparing a combination of nutraceuticals (red yeast rice, policosanol, berberine, folic acid, coenzyme Q10 and astaxanthin), called Armolipid Plus, and ezetimibe for 3 months in terms of efficacy and tolerability.
- Patients who did not achieve their therapeutic target (low-density lipoprotein cholesterol <100 mg/dl) could add the alternative treatment on top of randomized treatment for another 12 months: 100 patients who are dyslipidemic with ischemic heart disease treated with percutaneous coronary intervention were enrolled (ezetimibe n = 50, nutraceutical n = 50).
- After 3 months, 14 patients in the nutraceutical group achieved their therapeutic target, whereas none of the patients in the ezetimibe group did. At 1-year follow-up, 58 patients (72.5%) of the combined therapy group (n = 86) and 14 (100%) of the nutraceutical group reached the therapeutic goal.
- No patients experienced important undesirable effects.
- Nutraceuticals alone or in combination with ezetimibe are well tolerated and improve the lipid profile in statin-intolerant patients with coronary heart disease.

Clinical Trial

Hypertension Institute Nashville, TN
Houston MC and Sparks W .Effect of Combination Pantethine, Plant Sterols, Green Tea Extract, Delta Tocotrienol, and Phytolens on Lipid Profiles in Patients with Hyperlipidemia. JANA: 2010;13(1):15-20



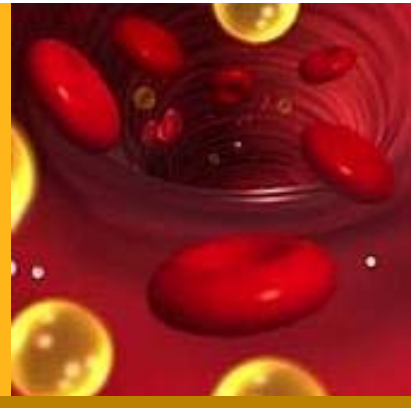
- 2 month open label study of 30 patients age 30 to 82 with dyslipidemia.

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

- LPP advanced lipid testing for all lipid parameters.

Clinical Trial

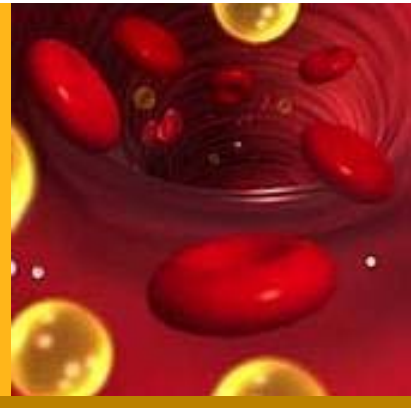
Hypertension Institute Nashville, TN
Houston MC and Sparks W .Effect of Combination Pantethine, Plant Sterols, Green Tea Extract, Delta Tocotrienol, and Phytolens on Lipid Profiles in Patients with Hyperlipidemia. JANA: 2010;13(1):15-20



- 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 Study Hypertension Institute Nashville, TN

Houston MC and Sparks W .Effect of Combination Pantethine, Plant Sterols, Green Tea Extract, Delta Tocotrienol, and Phytolens on Lipid Profiles in Patients with Hyperlipidemia. JANA: 2010;13(1):15-20



- 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).

Second Clinical Trial on Nutritional Supplements in the Treatment of Dyslipidemia

Houston M et al. Journal of Biological Regulations and Homeostasis.2016;30(4): 1-9

Table 1. Ingredient list Proprietary Supplement-LC

Double packet with daily dose

Ingredients	Dosage
Phytosterol esters	1600 mg
Aged Garlic Extract (bulb) (*Allium sativum*) (Kyolic®)	1200 mg
Red Yeast Rice (*Monascus purpureus*)	1000 mg
Curcumin Phytosome (*Curcuma longa* extract (root)/ Phosphatidylcholine complex)	500 mg
Green Tea Phytosome (*Camellia sinensis* extract (leaf) / Phosphatidylcholine complex)	500 mg
N-Acetyl-L-Cysteine	500 mg
Berberine HCL (from Indian Barberry extract (root) (*Berberis aristata*)	400 mg
Deglycyrrhizinated Licorice (DGL) extract (root)	200 mg
Trans-Reseveratrol	80 mg
Quercetin Phytosome (*Sophora japonica* concentrate	

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

	Proprietary Lipid Supplement(LC)			Placebo			
	Before	After	P Value[b]	Before	After	P Value[b]	P Value[a]
No. (Male/Female)		20 (8/12)			20 (10/10)		
Age (Yr)		62 + 6			58 + 7		
Body Weight (lb)	168.4 +26.5	165.3 +24.7	0.87	170.2 +31.5	171.4 +29.7	0.79	0.84
BMI	26.76 +2.41	26.49 +2.53	0.91	26.98 +3.05	27.01 +2.99	0.81	0.75
Systolic blood pressure (mm Hg)	135.7 + 4.92	130.9+3.62	0.098	136.6 + 4.57	135.1 +5.72	0.82	0.41
Diastolic blood pressure (mm Hg)	72.3 +2.09	69.4 +1.79	0.001	75.05 +2.01	74.78+ 2.14	0.79	0.04
Heart beat	66.5+2.24	63+1.99	0.001	67.5+3.1	70.8+2.4	0.38	0.009
HbA1C (%)	5.59 +0.41	5.63 +0.62	0.92	5.81 +0.57	5.77+0.48	0.65	0.69

Figure 2

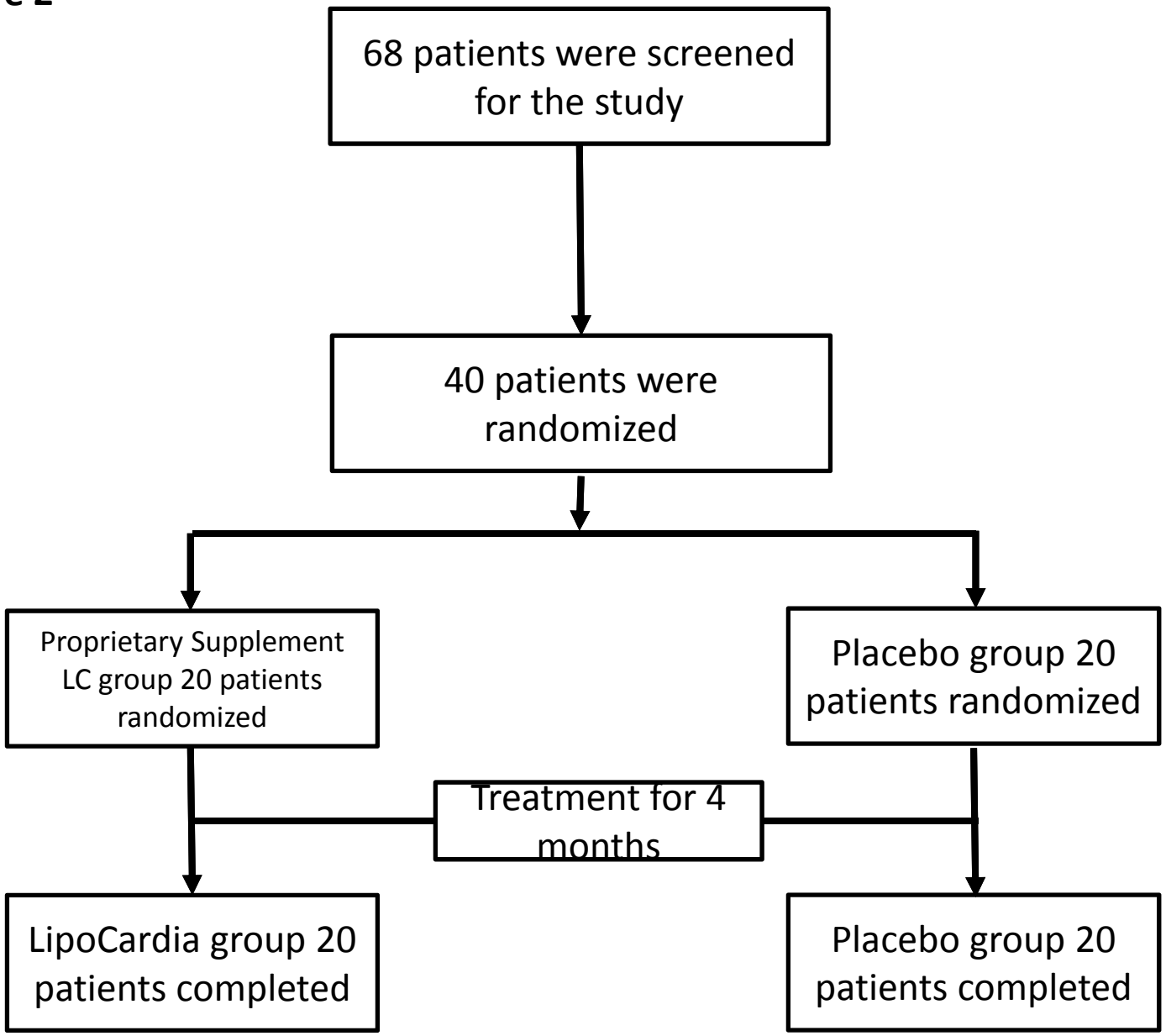
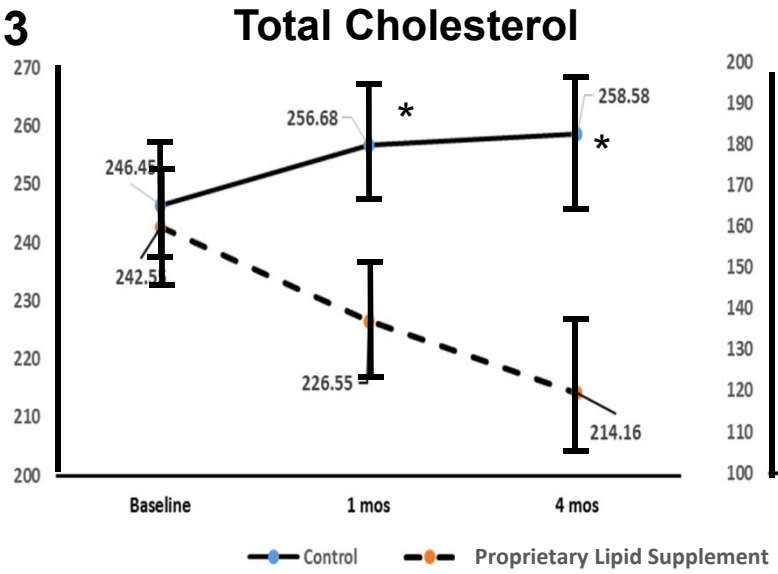
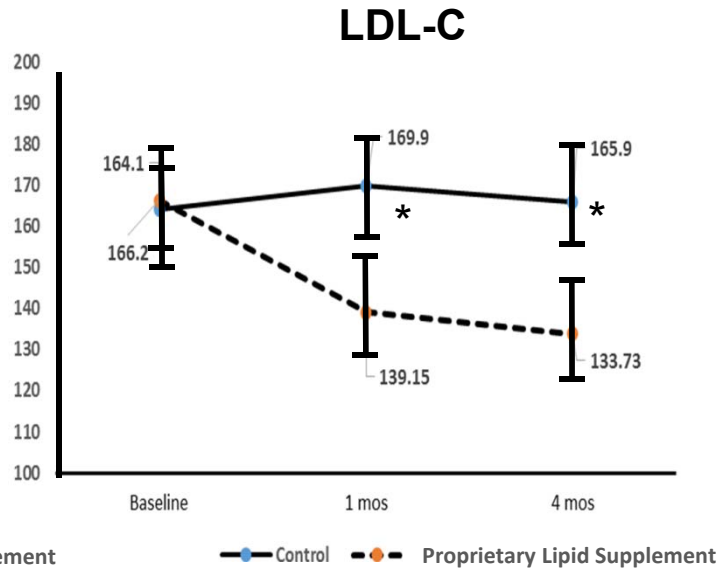

68 patients were screened for the study
40 patients were randomized
Proprietary Supplement LC group 20 patients randomized
Placebo group 20 patients randomized
Treatment for 4 months
LipoCardia group 20 patients completed
Placebo group 20 patients completed

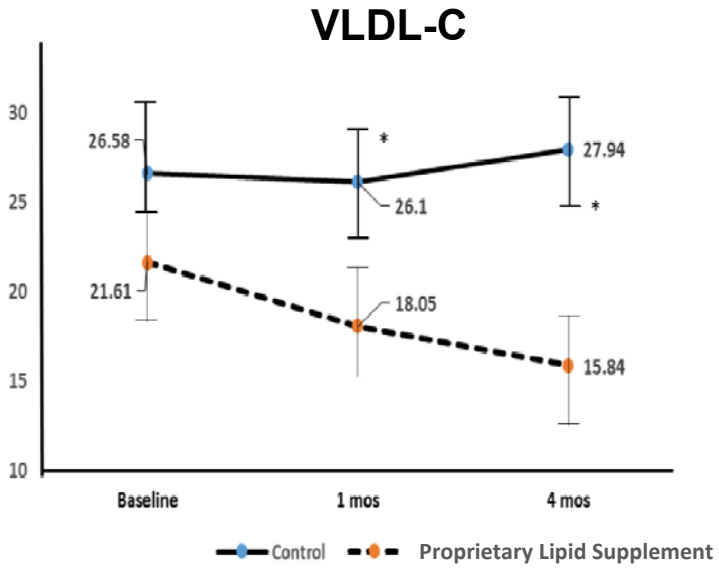
Figure 3


Total Cholesterol
270
260
250
240
230
220
210
200
256.68
258.58
246.45
242.51
226.55
214.16
*
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

A

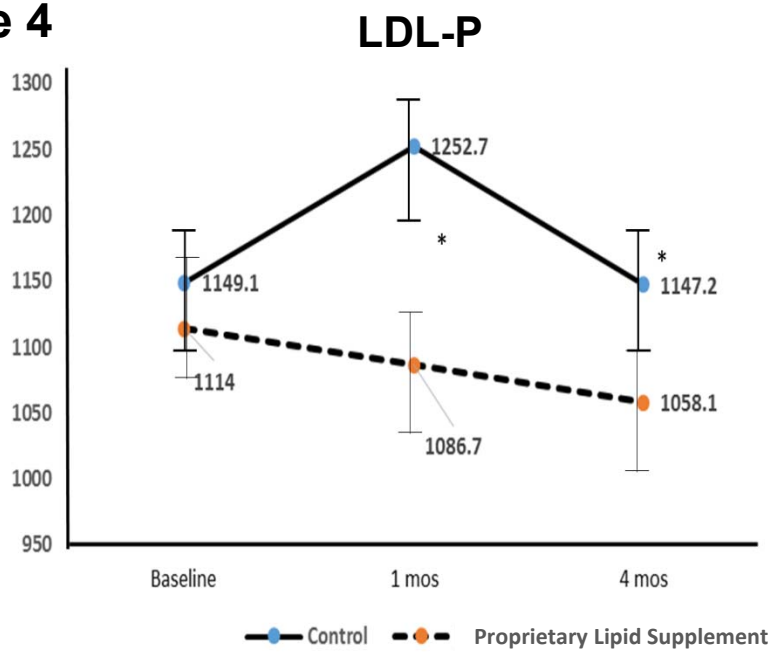

LDL-C
200
190
180
170
160
150
140
130
120
110
100
164.1
169.9
165.9
166.2
139.15
133.73
*
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

B

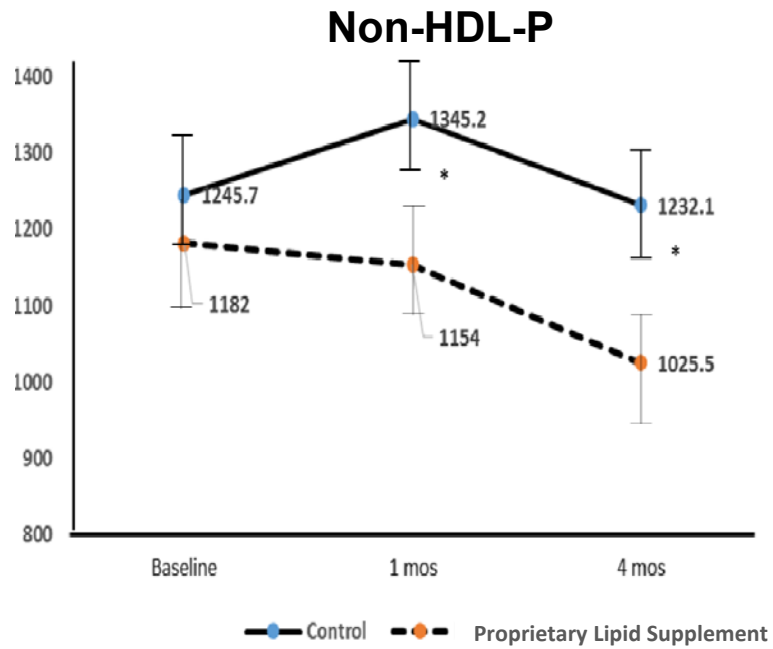

VLDL-C
30
25
20
15
10
26.58
27.94
26.1
21.61
18.05
15.84
*
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

C

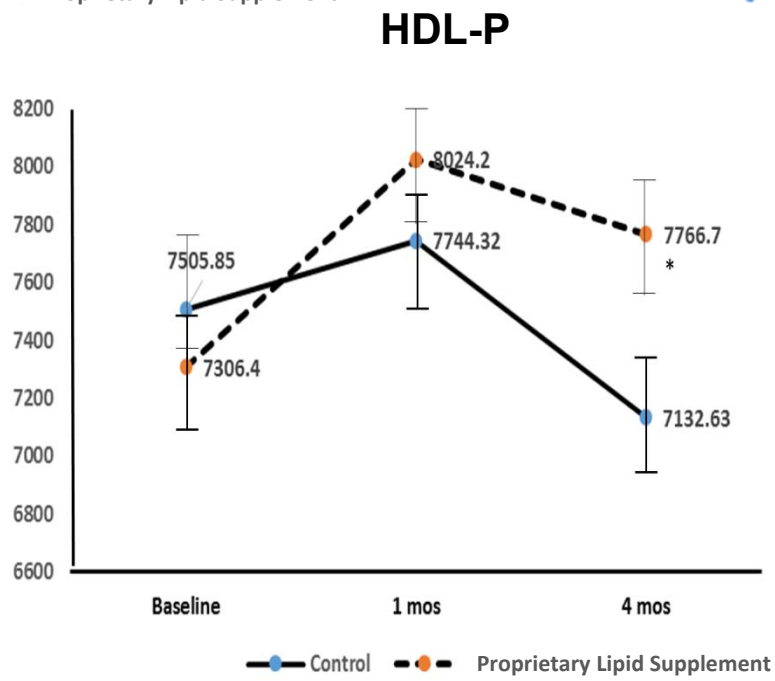
Figure 4


LDL-P
1300
1250
1200
1150
1100
1050
1000
950
1252.7
1149.1
1147.2
1114
1086.7
1058.1
*
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

A

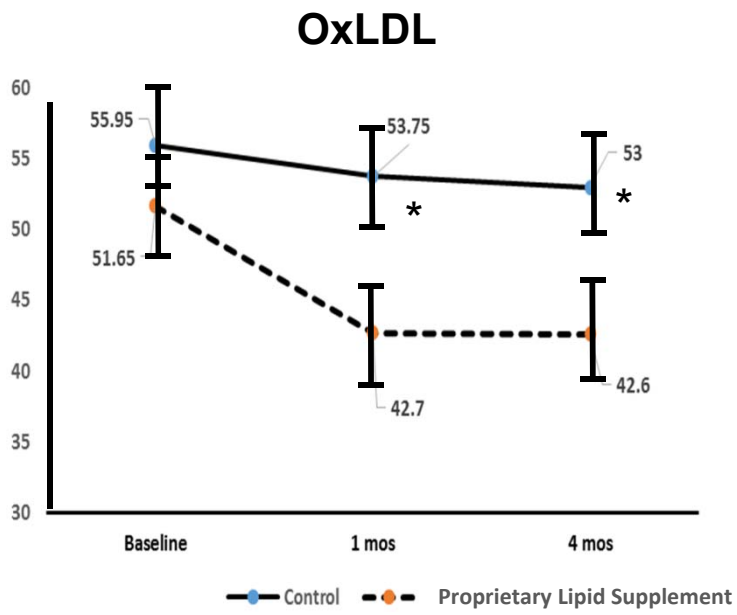

Non-HDL-P
1400
1300
1200
1100
1000
900
800
1345.2
1245.7
1232.1
1182
1154
1025.5
*
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

B

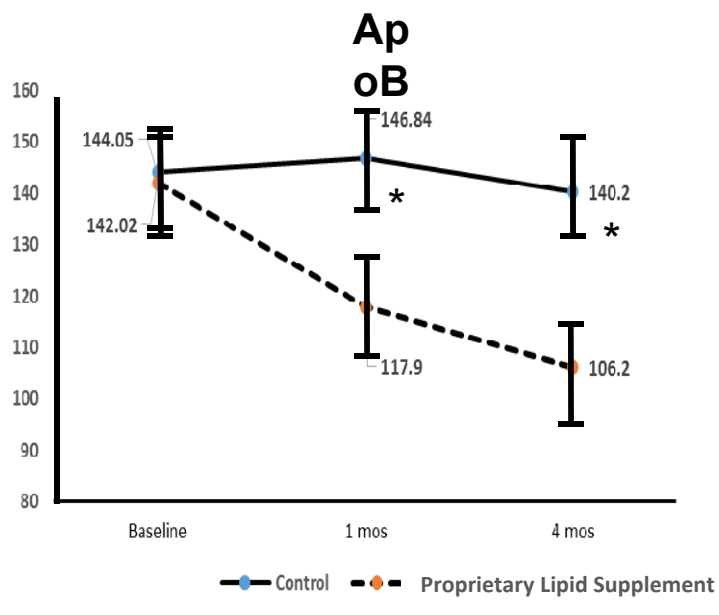

HDL-P
8200
8000
7800
7600
7400
7200
7000
6800
6600
8024.2
7744.32
7766.7
7505.85
7306.4
7132.63
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

C

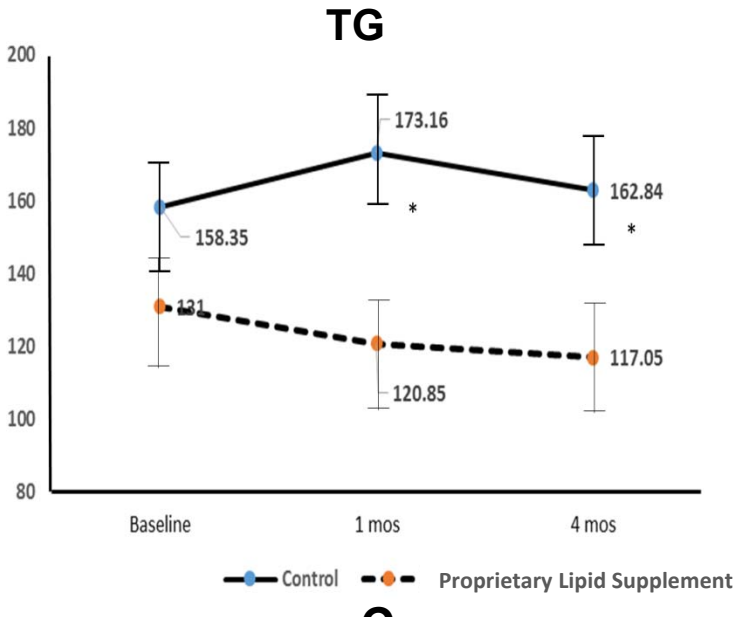
Figure 5


OxLDL
60
55
50
45
40
35
30
55.95
53.75
53
51.65
42.7
42.6
*
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

A


Ap
oB
160
150
140
130
120
110
100
90
80
144.05
146.84
140.2
142.02
117.9
106.2
*
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

B

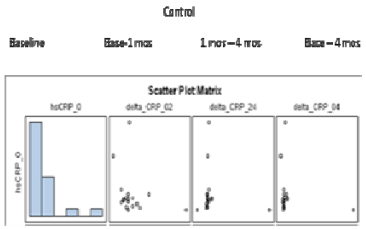

TG
200
180
160
140
120
100
80
173.16
162.84
158.35
131
117.05
120.85
*
*
Baseline
1 mos
4 mos
Control
Proprietary Lipid Supplement

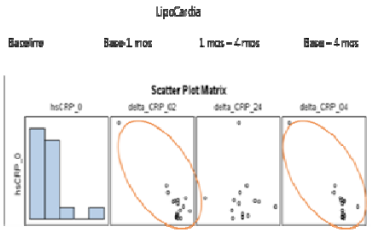
C

Figure 6

Placebo **Proprietary Lipid Supplement**

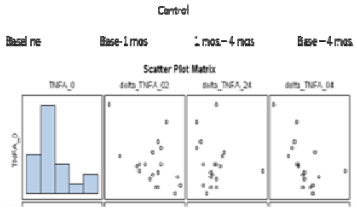
Pearson correlation			
		Baseline-4 mos	Baseline-4 mos
Baseline CRP	Coefficients	-0.0291	-0.9203
	P-values	0.9117	<0.0001

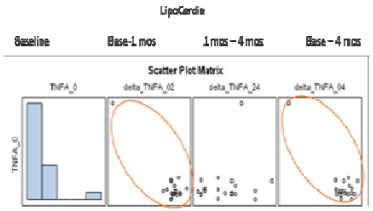




Placebo **Proprietary Lipid Supplement**

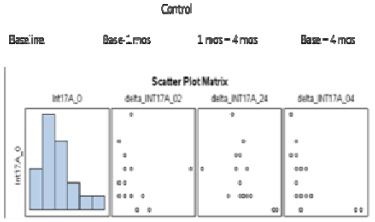
Pearson correlation							
		Baseline vs 1 mos	1 mos vs 4 mos	Baseline-4 mos	Baseline vs 1 mos	1 mos vs 4 mos	Baseline-4 mos
Baseline TNFA	Coefficients	-0.4837	-0.1315	-0.5861	-0.8946	0.1959	-0.8531
	P-values	0.0359	0.5917	0.0084	<0.0001	0.4216	<0.0001

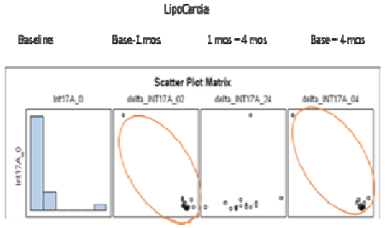




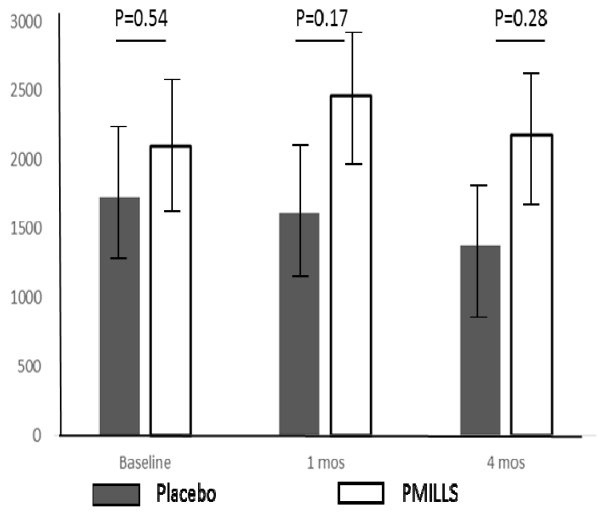
Placebo **Proprietary Lipid Supplement**

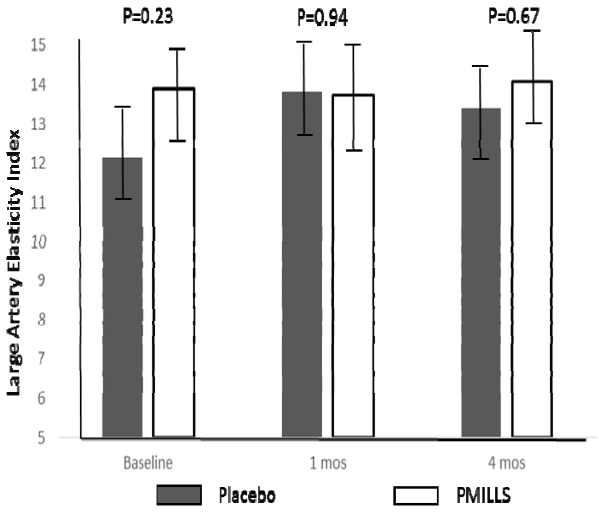
Pearson correlation							
		Baseline vs 1 mos	1 mos vs 4 mos	Baseline-4 mos	Baseline vs 1 mos	1 mos vs 4 mos	Baseline-4 mos
Baseline IL-6	Coefficients	0.0503	-0.3666	-0.3574	-0.9952	0.0728	-0.9915
	P-values	0.8381	0.1227	0.1331	<0.0001	0.7672	<0.0001

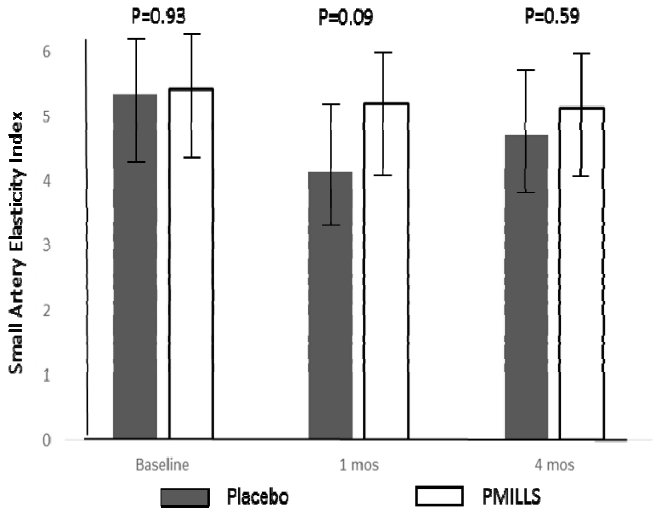




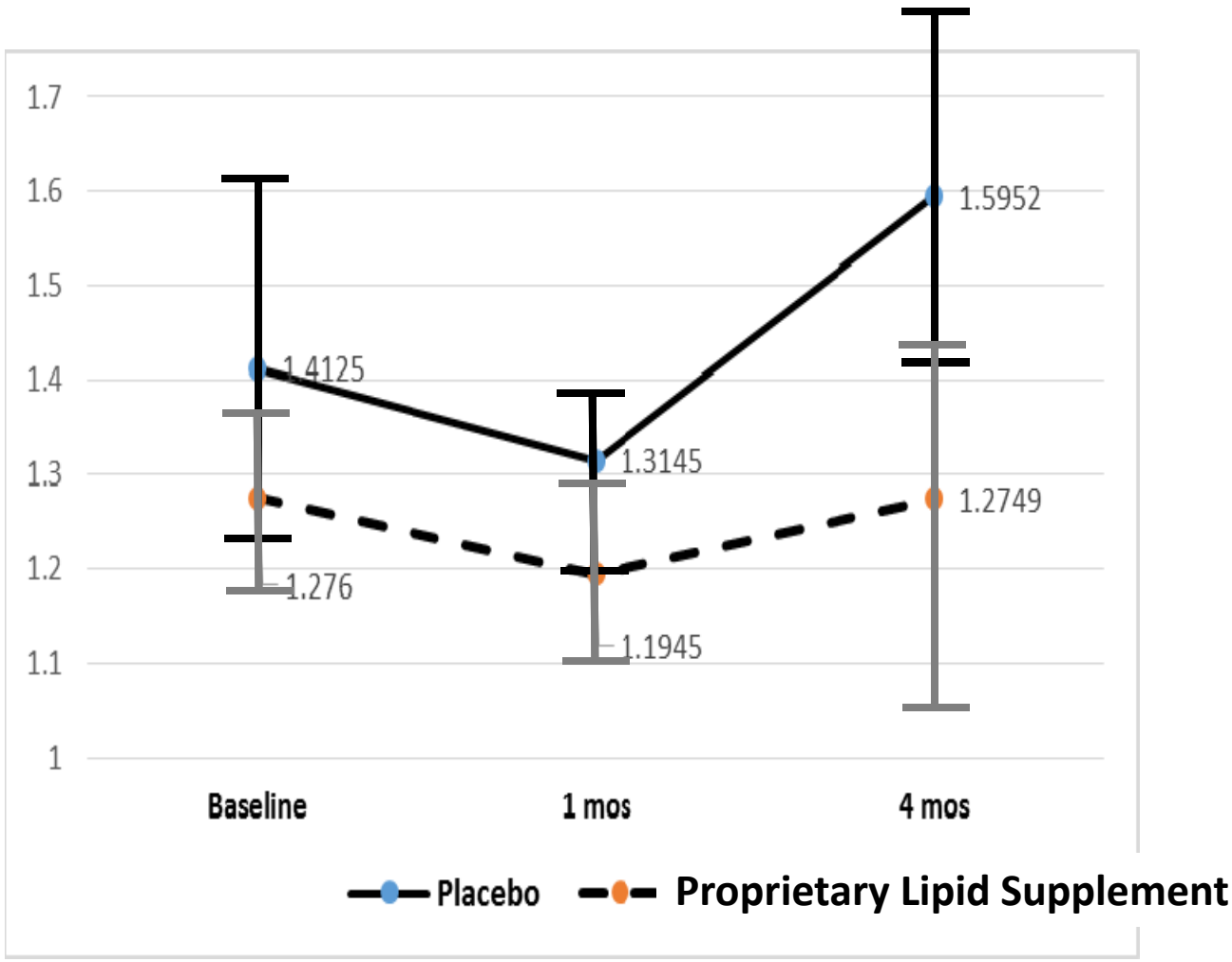
Supplement Fig1



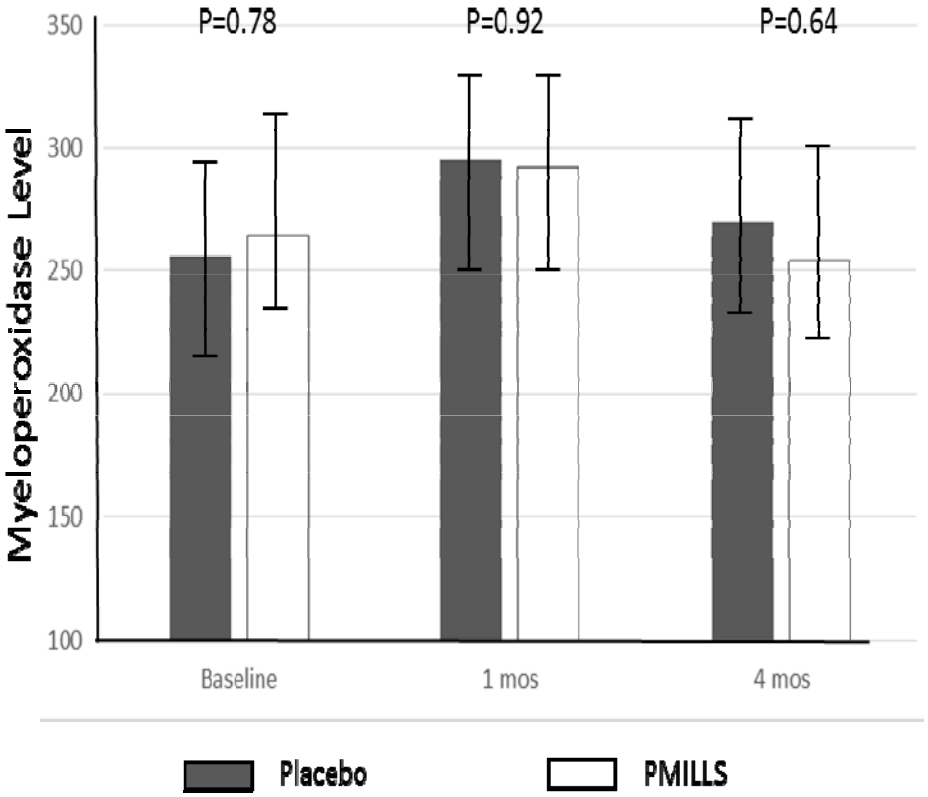




Supplement Fig 2



Supplement Fig 3



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

- Total cholesterol decreased from 242.55 mg/dl to 214.16 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 26.58 mg/dl to 27.94 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= 0.021), 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).

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

-
- LDL particles (LDL-P) were decreased from 1114 to 1058.1 /dl) (P= 0.0492) in 4 months with the treatment of LC while placebo has almost no effects (1149.1 vs. 1147.2/ dl).
- The total numbered of LDL-III plus LDL-IV, small dense LDL fell with LLC. Total LDL-III and IV particles number decreased to 392+44 nmol/L, significantly lower than 576+59 nmol/L in the placebo group (P=0.0027).
- Diastolic blood pressure decreased from 72.4 +9 to 68.1 +11 mm Hg in those treated with LC, exceeding the fall from 72.3 + 8 to 73.9 + 9 mm Hg with placebo (). (P = 0.047).
- Heart rate from 67.5 + 6 to 62.4 +7 (P=0.0093), significantly lower compared to the placebo treatment (Table 1).
- High sensitivity C-reactive protein (hs-CRP), tumor necrosis factor (TNF-a) and interleukin-6 (IL-6) were measured in the Pearson analysis was then conducted within each group All three inflammatory factors were reduced within the LC ($p < 0.001$. These effects were not observed in the placebo group.

Natural Treatment Rivals Drug Therapy For Dyslipidemia

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

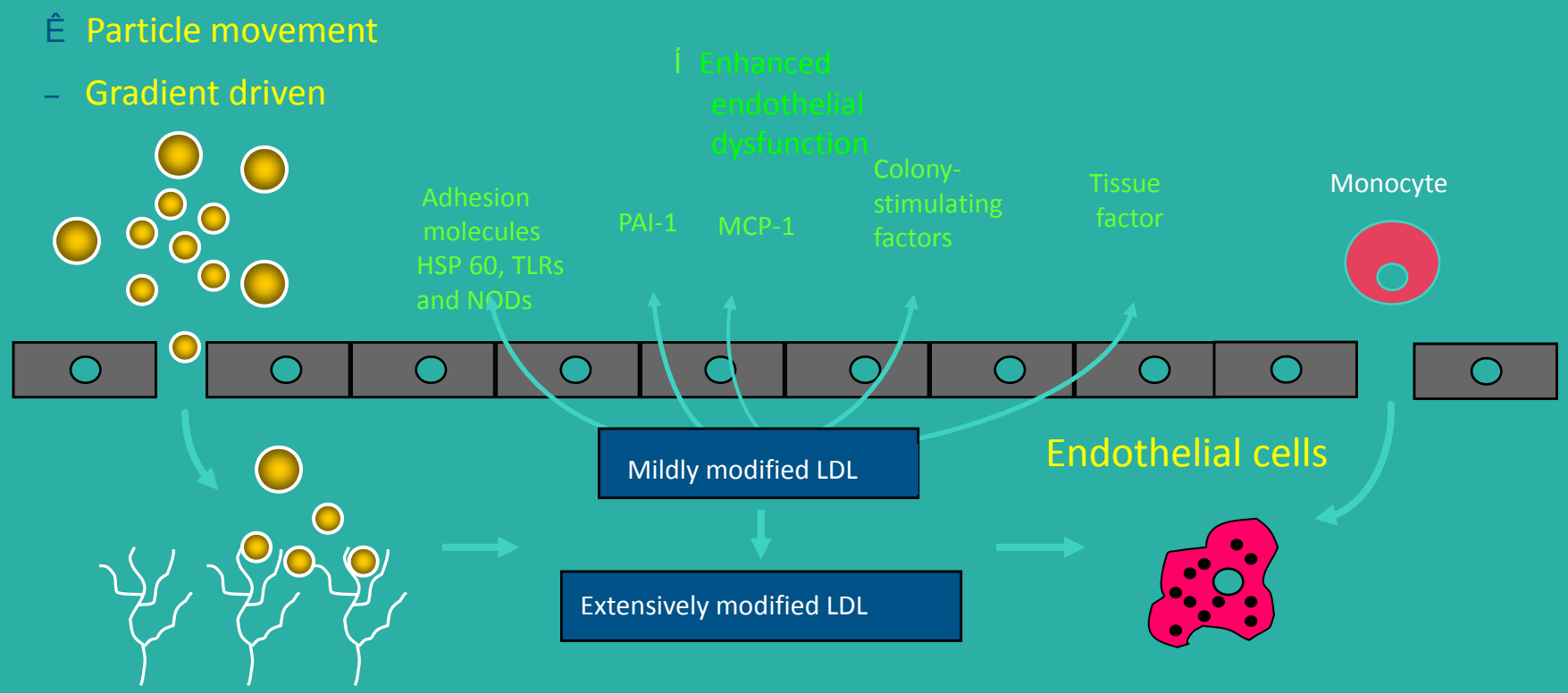
- TC and LDL reductions of 50% with reductions in VLDL, TG, ILDL, LDL-P, increase in LDL particle size, HDL, HDL size, HDL-P and HDL function.

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

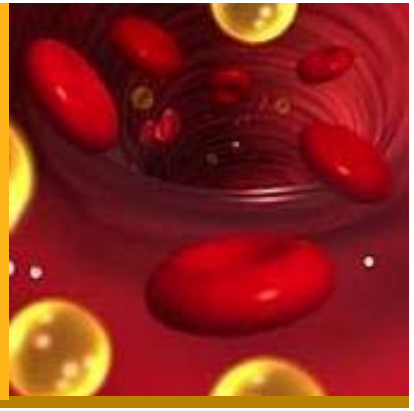
Lipoproteins and Atherosclerosis

It Matters What You Have



New Functional And Metabolic Medicine Approach To The Treatment Of Dyslipidemia

•Houston MC. The Role of Nutraceutical Supplements in the Treatment of Dyslipidemia. J Clin Hypertens 2012;14(2):121-32
•Houston MC et al. Nonpharmaolcolgic Treatment of Dyslipidemia. Prog Cardiovasc Dis. 2009;52(2):61-94
•Nijjar PS et al. Role of dietary supplements in lowering low-density lipoprotein cholesterol: A review. J of Clinical Lipidology 2010; 4:248-258.
•Mannarino MR et al. Nutraceuticals for the treatment of hypercholesterolemia. Eur J Intern Med.2014;25(7):592-9.
•Houston, Mark. The role of nutrition and nutritional supplements in the treatment of dyslipidemia. Clinical Lipidology 2014;9(3): 333-354.



Decrease endothelial permeability, gap junctions, endothelial dysfunction and improve endothelial repair.

Increase nitric oxide bioavailability and eNOS

Beets, dark green leafy vegetables, arginine/citrulline, vitamin D, vitamin C ,aged Kyolic 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, RYR, RLA, NAC, Taurine, Pyncogenol, GSE, POM,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

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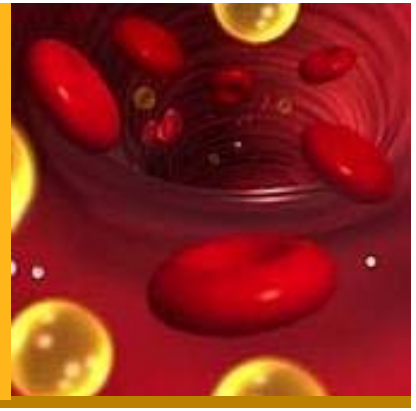

- Modify PRR activation -TLR (TLR 2 and 4) and NODs as well as MYD 88 from DAMP, which is primarily modified LDL.
- Niacin, lycopene,curcumin, quercetin, pomegranate, EGCG, pantethine, resveratrol, MUFA,, aged garlic, sesame, gamma/delta tocotrienols,, reduce saturated fatty acids like stearate and palmitic 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

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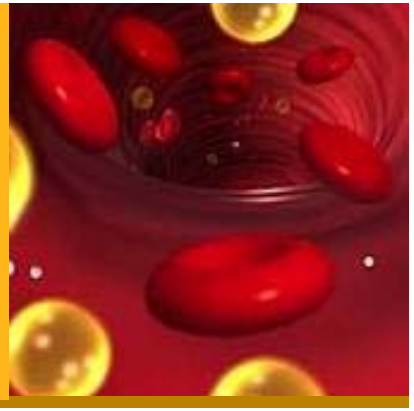

Decrease LDL burden to 55 mg/dl with inhibition of HMG CoA reductase and other mechanisms. This level of LDL decreases LDL particle number and Apo-B, reduces potential downstream inflammation.

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

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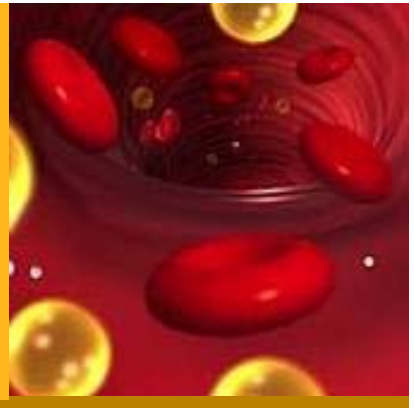

- Increase eNOS and nitric oxide.
- Arginine/citrulline, beets, beet juice and extract, dark green leafy vegetables, niacin, lycopene, berberine. omega 3 FA, EGCG, resveratrol, flax seed,, COQ 10, R lipoic acid, NAC, taurine, pycnogenol, grape seed extract, pomegranate, age garlic, Vitamin C and D, quercetin, leuteolin, cacao, MUFA, RYR.

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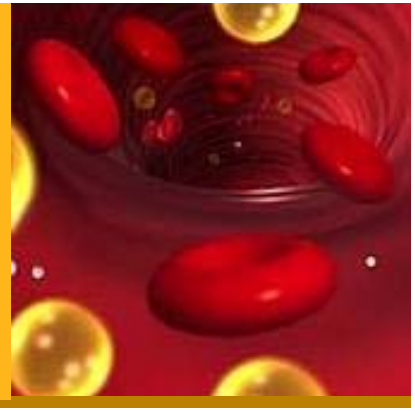

HMG CoA reductase inhibition.

- 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

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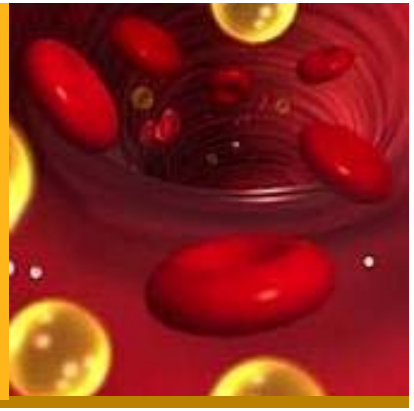

- Reduce cholesterol absorption.
- Plant sterols, berberine, soy (micelles), sesame, EGCG(micelles),flax seeds, garlic, fiber.

- Increase cholesterol bile excretion.
- Berberine, plant sterols, citrus bergamot, fiber, probiotics,, sesame, resveratrol.

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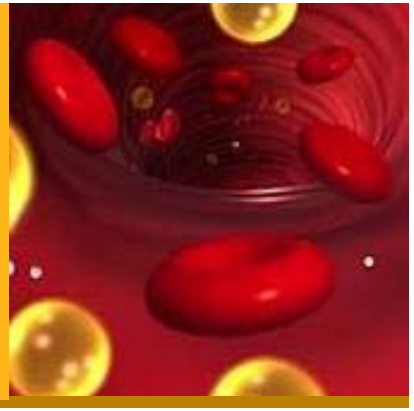

- Decrease ApoB.
- RYR, berberine, plant sterols, niacin, omega 3-FA, EGCG, astaxanthin.

- 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 and pycnogenol.

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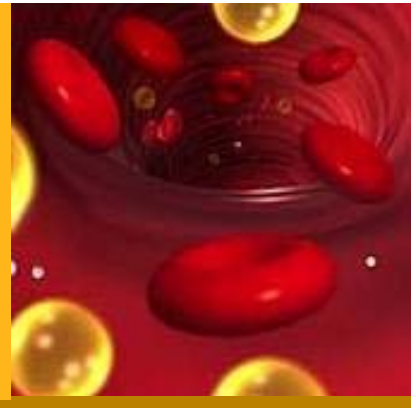

- Inhibit LDL glycation specifically.
- Carnosine, pomegranate, histidine, myricetin, kaempferol, rutin, morin, organosulfur compounds.

- 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.

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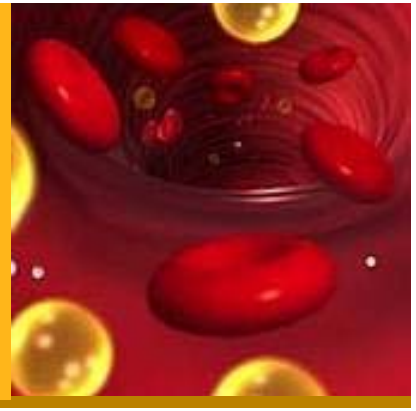

- Upregulate LDL receptor
- Berberine (PCSK9), niacin (PCSK9), plant sterols, EGCG, sesame, tocotrienols, curcumin (PCSK9), soy, fiber.

- 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).

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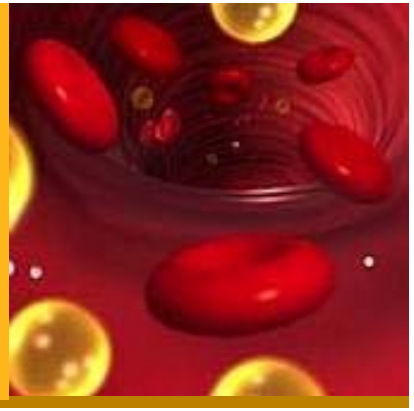

- Decrease modified LDL macrophage uptake via CD 36 SR- scavenger receptor and NADPH oxidase(70 % of vascular LDL foam cells).
- Resveratrol, NAC(n-acetyl cysteine), berberine, curcumin, quercetin, lycopene and luteolin.

- 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.

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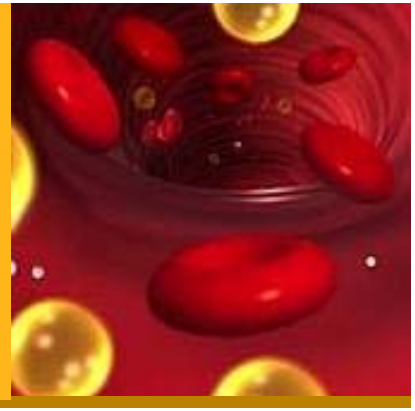

- Decrease macrophage recruitment and subendothelial migration.
- Reduce inflammation and immune responses.

- Alter macrophage phenotype from M1 to M2 anti-inflammatory
- Omega-3 FA and downstream resolvins and protectins, berberine, plant sterols, sterolins and glycosides – phytosterolins such as BSS(betasitosterols) and BSSG(betasitosterolins).

- Modify signaling pathways.
- Plant sterols and sterolins.

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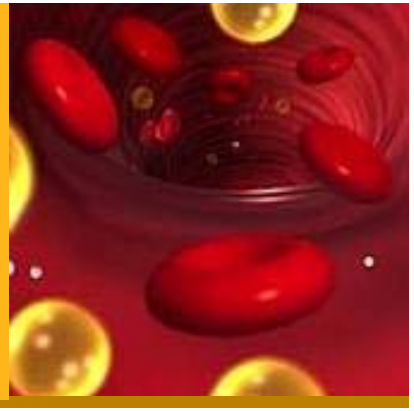

- Increase reverse cholesterol transport.
- Lycopene, niacin, plant sterols, curcumin, quercetin, glutathione, resveratrol, anthocyanadins, flavonoids, co enzyme Q 10, MUFA, phosphatidyl serine and alcohol

- 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, astaxanthin.

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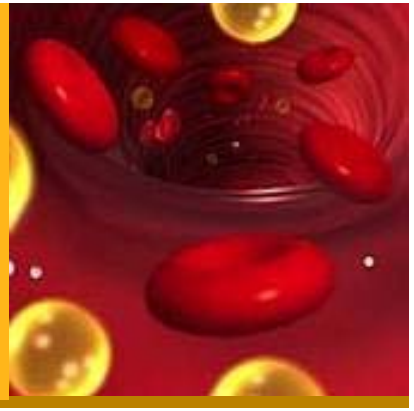

- Improve HDL function.
- Niacin, quercetin, pomegranate, EGCG, lycopene,resveratrol, glutathione, phosphatidyl serine. Reduce inflammation, oxidative stress and autoimmune dysfunction,

- Increase ApoA 1: Niacin, co enzyme Q 10

- Increase PON 1 and PON 2.
- Quercetin, pomegranate, EGCG, lycopene, resveratrol, glutathione.

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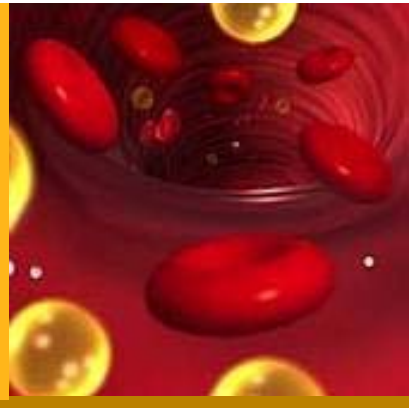

- Reduce inflammation.
- Omega-3 FA,curcumin, quercetin, niacin, flax seed, MUFA, plant sterols, resveratrol, glutathione, lower hs CRP.

- 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, astaxanthin, berberine.

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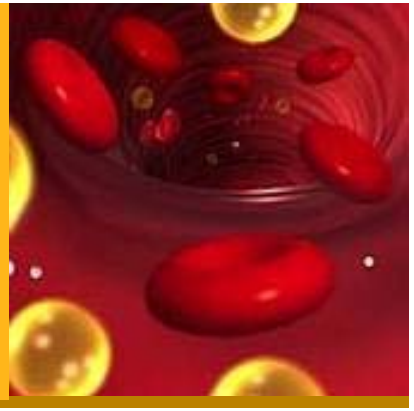

- Reduce foam cell and fatty streak formation.
- Resveratrol, NAC, reduce inflammation and oxidative stress, modulate Th 1/Th 2 balance with phytosterolins BSS and BSSG.

- 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.

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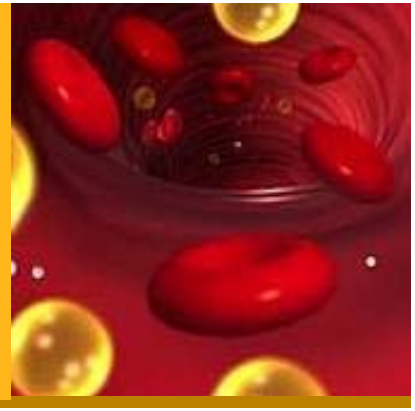

Lipoprotein (a) Lp(a)

- 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.

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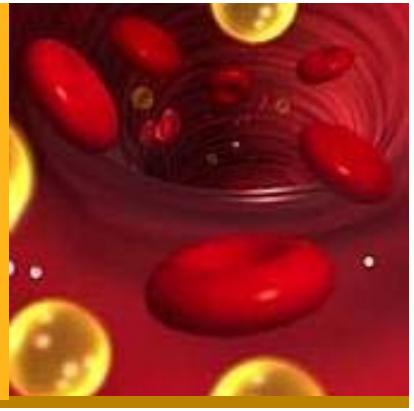

- Stabilize plaque, reduce lipid core, and reduce plaque burden with lack of progression or reversal. (CHD, carotid)
- Omega-3 FA, vitamin K2 MK7, aged garlic, curcumin, quercetin, niacin, plant sterols, lycopene, pomegranate, MUFA, RYR
- Reduce LpPLA-2.

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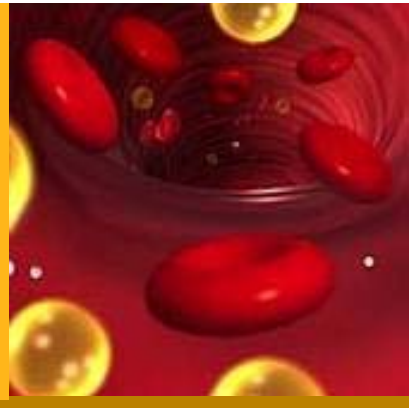

Reduce Fibrinogen

RYR

Plant Sterols

L Reuteri

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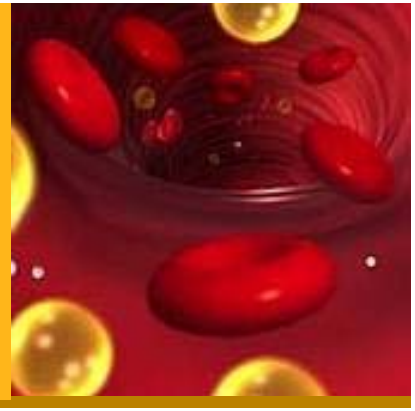

Reduce TNF Alpha

MUFA

RYR

Plant Sterols

Omega 3 FA

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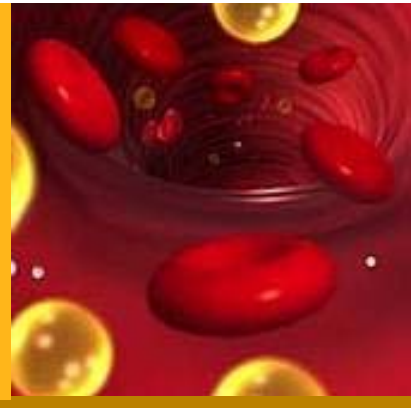

Reduce CAMs

Niacin

MUFA

Lycopene

Resveratrol

Curcumin

Luteolin

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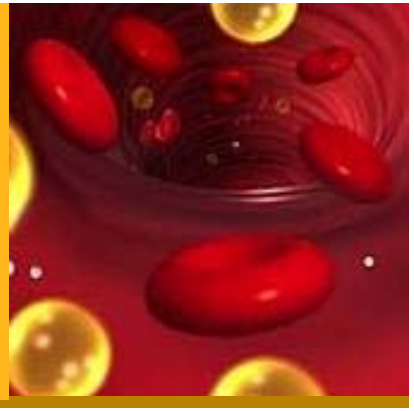
Houston, Mark. The role of nutrition and nutritional supplements in the treatment of dyslipidemia. Clinical Lipidology 2014;9(3): 333-354.



Reduce NADPH oxidase

Niacin

RYR

Resveratrol

NAC

Berberine

New Functional And Metabolic Medicine Approach To The Treatment Of Dyslipidemia

•Houston MC. The Role of Nutraceutical Supplements in the Treatment of Dyslipidemia. J Clin Hypertens 2012;14(2):121-32
•Houston MC et al. Nonpharmaolcolgic Treatment of Dyslipidemia. Prog Cardiovasc Dis. 2009;52(2):61-94
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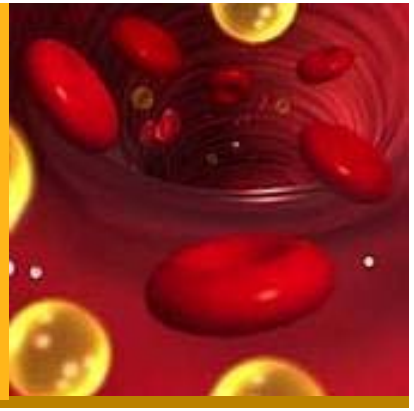

Reduce Myeloperoxidase (MPO)

Niacin

Pomegranate

Curcumin

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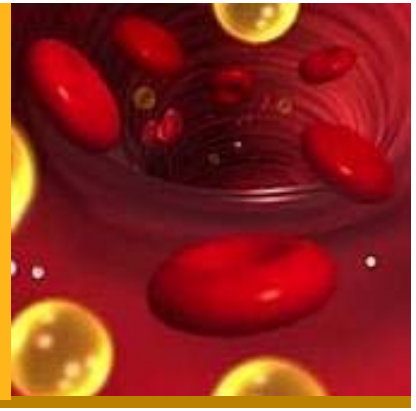
Nutrition 2016;32:1116



Increase Adiponectin and lower Leptin

RYR

Niacin

Omega 3 FA (PPAR)

Curcumin

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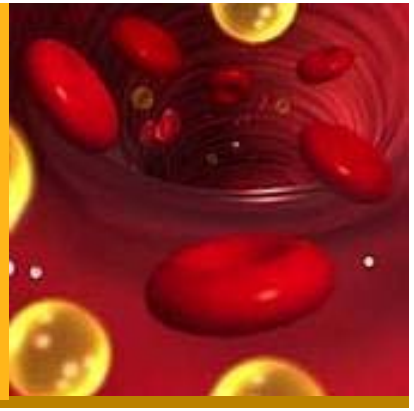

Improve Insulin Sensitivity

RYR

Omega 3 FA (PPAR)

Berberine

Lycopene (PPAR)

EGCG

Quercetin (PPAR)

Curcumin

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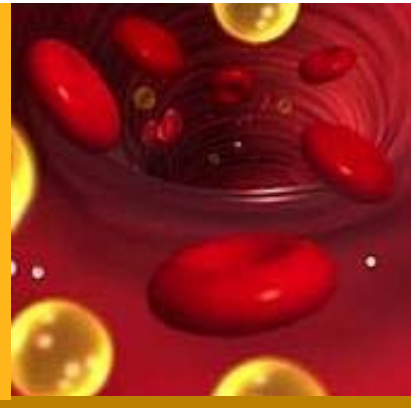


Reduce MMP

RYR

Leuteolin

Endogenous and exogenous anti-oxidants and macrophage atherogenicity and CHD

Curr Opin Lipidol 2016;27:204

- Macrophage foam cell formation involves increased scavenger receptor uptake of oxLDL, increase cholesterol biosynthesis and attenuated HDL- mediated cholesterol efflux from macrophages.
- HDL PON 1 is has anti-oxidant properties and specific for macrophages.
- HDL and HDL 3 specifically stimulates PON 1 activities
- HDL-PON anti-athergenic effects are increased by Quercetin, Pomegranate, NAC, catalase, SOD, GSH
- GSH + Quercetin is most potent and Pomegranate with statin is synergistic

Other agents to consider with less clinical human data

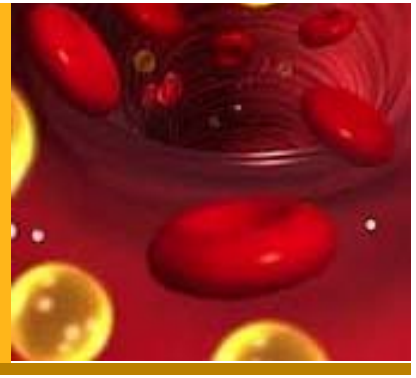
- Chia seeds
- Flax seeds
- Artichoke leaf
- Gamma oryzanol (rice bran phytosterol)
- Co-enzyme Q 10
- Vitamin C
- Palmitoleic acid

Agents that are not supported in clinical trials in humans

JAMA 2006;259: 2262;J Clinical Lipidology 2010;4:248;Br J Nutr 2006;95:968; Metabolism 2004;53:1309; Am J Clin Nutrition 2001;84:1543; J of Clinical Lipidology 2013;7:14 *;Pharmacol Res 1990; 22:37;J Assoc Physicians India 1989; 37:323;Cardiovasc Drugs There 1994; 8:659 JAMA 2003; 290:765;Annual Rev Nutr 2003; 23:303;Complement Ther Med 2005;13:279 Complement Ther Med 2009;17:16*

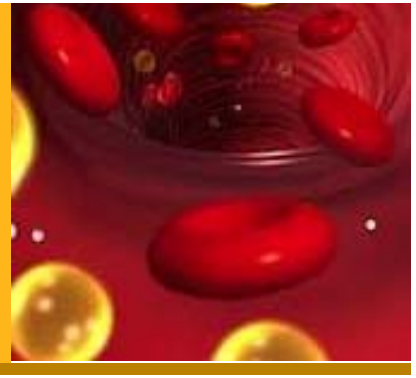
- Policosanol
- Guggulipid
- Inositol hexanicotinate

Dyslipidemia
Conclusions , Summary and Take Home Points 1



- Identify underlying causes of dyslipidemia, remove and treat them (nutritional, toxins and infections) and other secondary causes such as hypothyroidism etc.
- Evaluate global CV risk with risk scoring systems (COSHEC, Rasmussen)
- Measure non invasive cardiovascular testing to identify CHD risk
- Routine lipid testing will not identify dyslipidemia and CHD risk accurately
- Advanced lipid testing should now be routine in all patients
- RCT, CEC, large HDL and HDL-P drives reduction in CHD risk
- HDL is often dysfunctional with inflammation, infections and oxidative stress
- HDL levels over 85 mg/dL are often dysfunctional
- Low HDL , small HDL and low HDL-P is best treated with niacin, pantethine, omega 3 FA and pomegranate seeds or juice.
- Measuring MPO, SAA and HSCRP help define dysfunctional HDL
- LDL-P drives the risk for CHD and MI > APO B> Non HDL C> LDL C
- LDL P is best treated with omega 3 fatty acids, niacin, berberine and red yeast rice. Statins are only 30-50% effective
- Small LDL is the primary driver of CHD and MI until the LDL P is normal , then small LDL is not an important factor.
- Small LDL is best treated with omega 3 fatty acids and niacin

Dyslipidemia
Conclusions , Summary and Take Home Points 2



- Lp(a) is missed on routine lipid testing and is the HIDDEN RISK related to lipids for CHD, MI and thrombosis. " The CHD GAP"
- Lp(a) is best reduced with niacin and NAC
- Lp(a) attachment to the vascular wall is achieved with the Linus Pauling protocol with vitamin C, proline and lysine.
- High TG and large VLDL induce thrombosis and CHD and are best treated with omega 3 FA, niacin, weight loss and low refined CHO diet
- Remnant particles and large VLDL increase CHD risk.
- The most common lipid profile with insulin resistance is high TG with large VLDL, low HDL, high LDL-P with small dense LDL
- Use scientifically proven nutraceuticals with the 45 different mechanisms of action to reduce dyslipidemia-induced vascular disease. Think/treat beyond just numbers. Look at mechanisms!
- Use logical combinations of lipid lowering drugs with nutrition and nutraceutical supplement and lifestyle therapies.
- Statin use is clearly indicated in patients post MI , post stent, post CABG, those with known CHD or CVD and in patients with DM.
- The multiple nutrient deficiencies with statins must be measured and repleted.

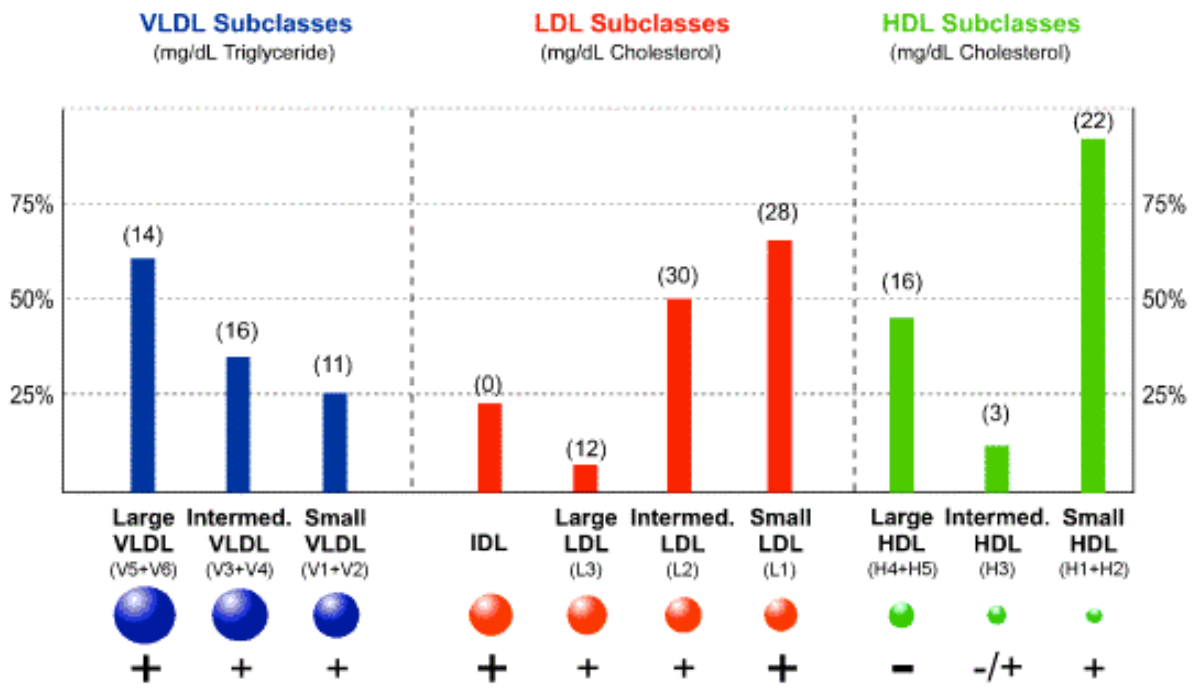
Case Presentations

CASE 1

- 38 yo black male in for physical exam
- Family history is positive for CHD early in life
- Normal weight, non smoker, excellent diet and exercise program
- History and PE are normal
- All labs are normal including a routine lipid profile
- Expanded lipid profile done

SUBCLASS LEVELS

Lipoprotein subclass levels (mg/dL) are given in parentheses above each bar.
The height of the bar gives the percent of the population with equal or lower levels.*



NMR-DERIVED LIPID VALUES

	mg/dL	Current NCEP Risk Categories
Total Cholesterol	**124**	Desirable: less than 200 | Borderline-High: 200 - 239 | High: 240 or greater
LDL Cholesterol	**70**	Optimal*: under 100 | Near optimal: 100 - 129 | Borderline-high: 130 - 159 | High: 160 - 190 | Very high: over 190
HDL Cholesterol	**41**	Negative Risk Factor: 60 or greater | Intermediate: 59 - 40 | Positive Risk Factor: less than 40
Triglycerides	**70**	Normal: less than 150 | Borderline-high: 150 - 199 | High: 200 - 500 | Very high: over 500

** Goal for patients with CHD or CHD risk equivalents*

LIPOPROTEIN PANEL

Coronary Heart Disease (CHD) Risk Categories

		Optimal*	Near optimal	Borderline-high	High	Very high
LDL Particle Number	nmol/L **999**	under 1100	1100 - 1399	1400 - 1799	1800 - 2100	over 2100

** Goal for patients with CHD or CHD risk equivalents*

		Pattern A (large LDL)	Pattern B (small LDL)
LDL Particle Size	nm **20.3**	22.0 - 20.6 Lower-Risk	20.5 - 19.0 Higher-Risk

		Negative Risk Factor	Intermediate	Positive Risk Factor
Large HDL (cholesterol)	mg/dL **16**	greater than 30	30 - 11	less than 11

		Lower-Risk	Intermediate	Higher-Risk
Large VLDL (triglyceride)	mg/dL **14**	less than 7	7 - 27	greater than 27

RISK ASSESSMENT PANEL

Elevated LDL particle number and the lipoprotein traits of the metabolic syndrome affect CHD risk interactively. Risk is highest when both are present.

Elevated LDL Particle Number >1400 nmol/L ☐

Lipoprotein Traits of the Metabolic Syndrome* ≥2 traits ☐

Lipoprotein Traits of the Metabolic Syndrome*

Small LDL Pattern B (≤ 20.5 nm)	Reduced Large HDL (<11 mg/dL)	Elevated Large VLDL (>27 mg/dL)
✓	☐	☐

** Other identifiers of the metabolic syndrome include abdominal obesity, elevated blood pressure, and fasting glucose ≥ 110 mg/dL.*

CASE 1

- Lp(a) is 120 (normal is < 30)
- hsCRP is 1.5 (borderline)

Audience Response Questions CASE 1

1. This patient needs no treatment and is at low risk for cardiovascular disease

2. This patient should be treated immediately with high dose statin

3. This patient should be treated with appropriate non drug treatment such as niacin and omega 3 fatty acids.

4. This patient should be treated with a combination of fibrates and statins

CASE 1: Treatment and Results
Results at 2 months

- Niacin B3 1000 mg BID
- NAC 1000 mg bid
- Omega 3 FA 4 grams per day
- Vitamin C buffered 5000 mg per day
- Lysine 1000 mg per day
- Proline 500 mg per day

- LDL: 70 to 60 mg%
- LDL(p): 999 to 870
- LDL size: 20.3 to 22
- HDL: 41 to 40 mg%
- HDL 2 b: 16 to 24 mg%
- TG: 70 to 55 mg%
- Lp(a) from 120 to 70

CASE 2

- 52 yo wm with cc of “high cholesterol”
- Cannot take statins or fibrates due to myalgias. Refuses drugs
- Has no clinical symptoms and PE is normal. BMI is 24 with normal weight. Non smoker, minimal exercise, poor diet.
- Fasting lipids by LPP: TC – 290 mg/dl, LDL – 175 mg/dl, small dense LDL type III and IV with 1600 particles and LDL size of 19.6 (normal 20.2), HDL – 42 mg/dl with mostly small HDL 3, abnormal HDL map, low HDL -P , TG – 160 mg/dl with large VLDL.
- LDL oxidized: 82 mU/L increased (nl < 72)
- All other labs are normal

Audience Response Questions CASE 2

This patient's primary cardiovascular risk is due to:

1. The low HDL
2. The high TG
3. The dense LDL and increased LDL particle number
4. The oxidized LDL
5. None of the above

CASE 2: Treatment & Results
3 month results

- Portfolio Diet
- Lipid modifying supplement 4 caps BID
- Red Yeast Rice: 4800 mg HS
- Niacin B3: 1000 mg BID
- Sesame at 40 grams per day
- NAC at 500 mg BID
- Resveratrol at 250 mg per day…one capsule
- EFA 4 caps BID

- TC to 188 mg/dl
- LDL to 96 mg /dl
- LDL(p) to 1100 particles
- LDL size to 23
- HDL to 48 mg /dl
- TG to 96 mg /dl
- LDL ox to 72 mU/L

CASE 3

- 41 yo Hispanic female with cc of obesity, "high fats in her blood" and mild hypertension
- Clinical history and PE are normal except for weight of 190 lbs at 5 ft 3 inches, BMI of 30 and WC of 42 inches. BP is 142/88 mm Hg
- Lipid profile: TC – 200 mg/dl,
  TG – 430 mg/dl, HDL – 38 mg/dl,
  LDL – 120 mg/dl, small dense LDL type III and IV with 1200 particles and size of 20.1
- All other lab is except FBS of 112 mg/dl and LDL ox of 90 mU/L (normal ELISA assay is 72 mU/L)

Audience Response Questions CASE 3

1. The diagnosis is metabolic syndrome and insulin resistance. The treatment is weight loss, exercise, proper diet and selected nutraceuticals
2. The diagnosis cannot be determined from this data and the best treatment is weight loss with a low carbohydrate diet.
3. The diagnosis is type 2 diabetes and the best treatment is metformin and low dose nocturnal insulin
4. The diagnosis is insulin resistance. The best treatment is with a TZD and low glycemic index diet.

Treatment and Results Case 3
All Results at 3 months

- Dash 2 (Dietary Approaches to Stop Hypertension) modified diet.
- ABCT exercise program.
- Niacin B3 at 500 mg BID.
- Lipid-modifying supplement at 4 capsules BID.
- EFA at 6 caps BID.
- Resveratrol at 250 mg per day (one capsule).
- Extra virgin olive oil at 4 tablespoons per day.
- Fresh nuts at one cup BID.

Treatment and Results Case 3
All Results at 3 months

- Weight to 166 lbs
- BMI to 28 and WC to 38 inches

- TC to 177 and LDL to to 98 mg /dl
- TG to 170 mg/dl
- HDL to 46 mg/dl
- LDL III and IV to normal size at 24
- LDL(p) to 990 particles
- FBS to 94 mg /dl
- LDL ox to 70 mU/L

CASE 4

- 40 yo BM in for work physical with no complaints
- History and PE are normal. Normal weight, BMI and WC. Not exercising
- Fast food, minimal fruits and vegetables and low protein intake. Smokes 1ppd
- Family History positive for early MI in Father
- Lipid profile: TC – 160 mg/dl,
  LDL – 100 mg/dl, LDL type A with 800 particles, HDL – 25 mg/dl, HDL 3 predominant (75%), TG – 140 mg/dl
- All other lab is normal

Audience Response Questions CASE 4

1. The major risk is the LDL and LDL lowering is the best treatment
2. The major risk is the low HDL and it is due to genetics and smoking
3. The best treatment is to stop smoking, exercise and take niacin, pantethine and omega-3 fatty acids
4. The patient is at low risk due to the HDL/LDL ratio and needs no treatment
5. None of the above
6. Number 2 and 3 are correct.

CASE 4: Treatment and Results
4 month evaluation

- Exercise regimen ABCT program
- Stopped smoking
- Mediterranean diet
- No trans fats. Increased coconut oil but reduced SFA.
- Niacin 1000 mg BID
- Pantethine 450 mg BID
- EFA 3 caps BID

CASE 4 Results at 4 months

- TC 160 mg/dl to 150 mg/dl
- LDL 100 mg/dl to 90 mg/dl
- LDL(p) 800 to 760
- HDL 25 to 34 with HDL 3 at 45% and HDL 2b at 55%
- TG 140 mg/dl to 96 mg/dl

CASE 5

- 38 yo WF with family history of premature CHD. No complaints. Not overweight, nonsmoker. No exercise. Terrible diet
- Previous regular lipid profile: TC – 280 mg/dl, LDL – 150 mg/dl, HDL – 100 mg/dl, TG – 90 mg/dl
- CAPWA: C2 AC is 2.0 (normal is 10)
- EBT: CACS: 35 (95^{th} percentile for CHD)
- Lipid profile: TC – 290 mg/dl, LDL –
  160 mg/dl, type B with 1500 particles, LDL size 18.1
  HDL – 96 mg/dl with 90/dl HDL 3 small dense, TG – 98 mg/dl.
  Lp(a) increased at 60 mg/dL (normal < 30)
- All other labs normal
- DISCUSSION PLEASE

CASE 5: Treatment and Results
6 month Results

- Portfolio Diet
- ABCT exercise program
- Lipid-modifying supplement 4 capsules BID
- RYR 4800 mg at night
- Niacin 1500 mg BID
- NAC 1000 mg BID
- Sesame 40 gms per day
- Resveratrol 250 mg per day (one)
- 50 grams mixed fiber
- Extra virgin olive oil 4 tablespoons per day and mixed nuts 2 cups per day
- EFA 6 caps BID
- Buffered Vitamin C 1.5 grams BID
- Carnitine tartrate: 1.5 grams BID
- Baby aspirin per day

CASE 5: RESULTS AT 6 MONTHS

- TC to 185 mg /dl
- LDL to 74 mg /dl
- LDL III and IV decreased . Size to 20.5
- LDL p to 1050
- HDL to 102 mg/dl
- HDL 3 to 50% and HDL 2 b to 50%
- TG to 73 mg /dl
- Lp(a) to 42 mg/dl
- CAPWA to 6.0 (normal is over 9)
- EBT: no change

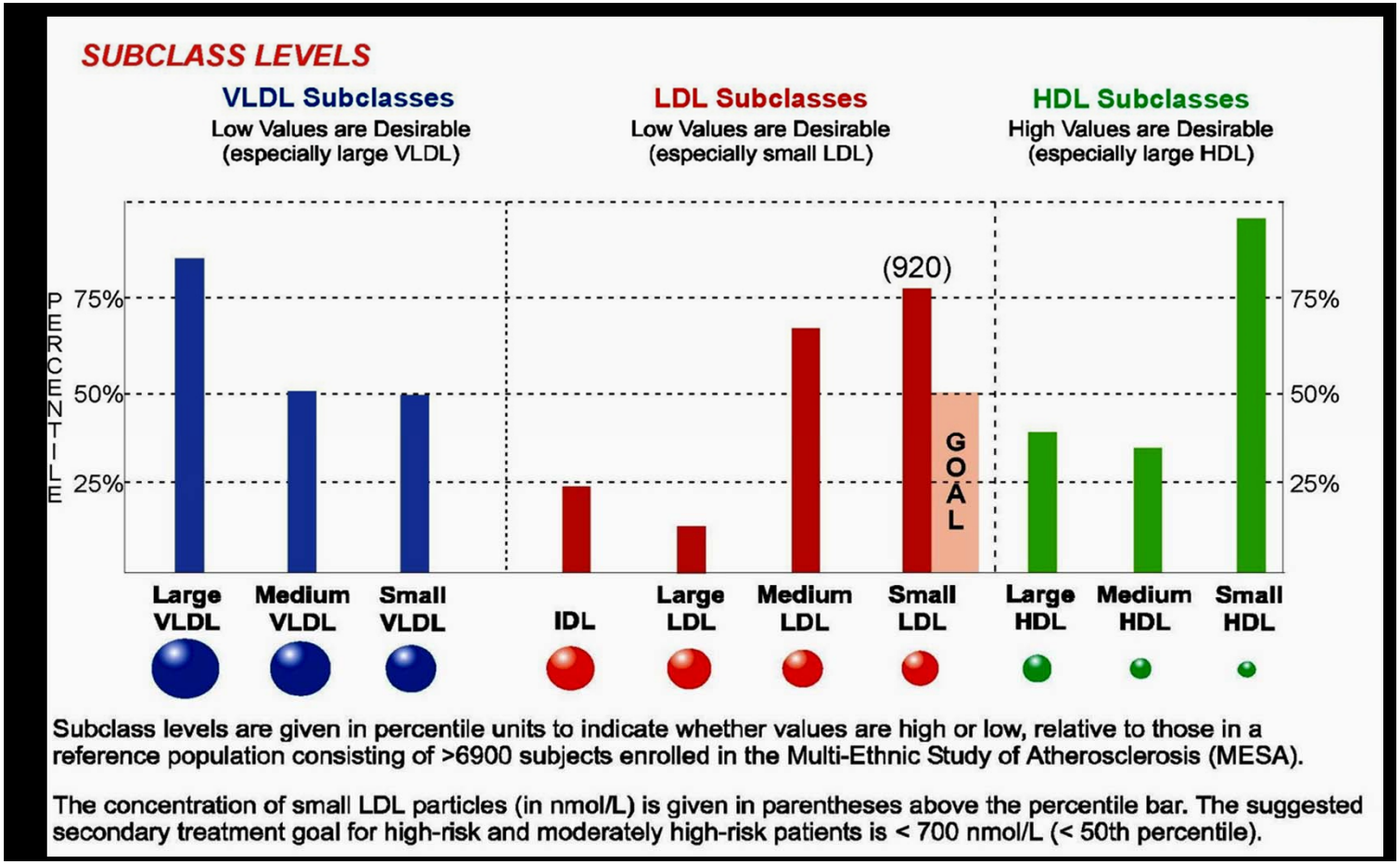
CASE 6

- Strict Vegetarian Diet (10% calories from fat).
- Aerobic Exercise Program
- Simvastatin 40 mg q day

Post CABG Lipids

Total-C	154 mg/dL
LDL-C	94 mg/dL
HDL-C	39 mg/dL
TG	105 mg/dL

CASE 6


SUBCLASS LEVELS
VLDL Subclasses
Low Values are Desirable
(especially large VLDL)
LDL Subclasses
Low Values are Desirable
(especially small LDL)
HDL Subclasses
High Values are Desirable
(especially large HDL)
PERCENTILE
75%
50%
25%
(920)
GOAL
Large VLDL
Medium VLDL
Small VLDL
IDL
Large LDL
Medium LDL
Small LDL
Large HDL
Medium HDL
Small HDL
Subclass levels are given in percentile units to indicate whether values are high or low, relative to those in a reference population consisting of >6900 subjects enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA).
The concentration of small LDL particles (in nmol/L) is given in parentheses above the percentile bar. The suggested secondary treatment goal for high-risk and moderately high-risk patients is < 700 nmol/L (< 50th percentile).

CASE 6

LIPOPROFILE PANEL

Coronary Heart Disease (CHD) Risk Categories

		Goal for High-Risk Patient	Goal for Moderately High-Risk Patient	Borderline High Risk	High Risk	Very High Risk
LDL Particle Number (LDL-P™)	nmol/L	under 1000	under 1300	**1300-1599**	1600-2000	over 2000
	1482					

For High-Risk Patients with CHD or CHD Risk Equivalents:
- primary goal: LDL-C < 100 mg/dL and LDL-P < 1000 nmol/L
- secondary goal: Small LDL particle number < 700 nmol/L
  (< 50th percentile; see subclass levels graph on page 2)

For Moderately High-Risk Patients (10-20% 10-year risk):
- primary goal: LDL-C < 130 mg/dL and LDL-P < 1300 nmol/L
- secondary goal: Small LDL particle number < 700 nmol/L
  (< 50th percentile; see subclass levels graph on page 2)

		Pattern A (large LDL)	Pattern B (small LDL)
LDL Size	nm	23.0 - 20.6	**20.5 - 18.0**
	20.4	Lower-Risk	Higher-Risk

		Lower Risk	Intermediate	Higher Risk
Large HDL (cholesterol)	mg/dL	greater than 30	**30 - 11**	less than 11
	12			

		Lower-Risk	Intermediate	Higher-Risk
Large VLDL (triglyceride)	mg/dL	less than 7	7 - 27	**greater than 27**
	28			

LDL Particle Size (small), Large HDL (low levels), and Large VLDL (high levels) contribute to CHD risk and are important markers of the Metabolic Syndrome and risk of developing Type 2 Diabetes Mellitus.

PRIMARY PREVENTION PANEL

Elevated numbers of LDL particles and the lipoprotein traits of the metabolic syndrome affect CHD risk interactively. Risk is highest when both are present.

Elevated LDL Particle Number	>1300 nmol/L	✓
Lipoprotein Traits of the Metabolic Syndrome*	≥ 2 traits	✓

Lipoprotein Traits of the Metabolic Syndrome*

Small LDL Pattern B (≤ 20.5 nm)	Reduced Large HDL (< 11 mg/dL)	Elevated Large VLDL (> 27 mg/dL)
✓		✓

**Other identifiers of the metabolic syndrome include abdominal obesity, elevated blood pressure, and fasting glucose ≥ 110 mg/dL.*

CASE 6

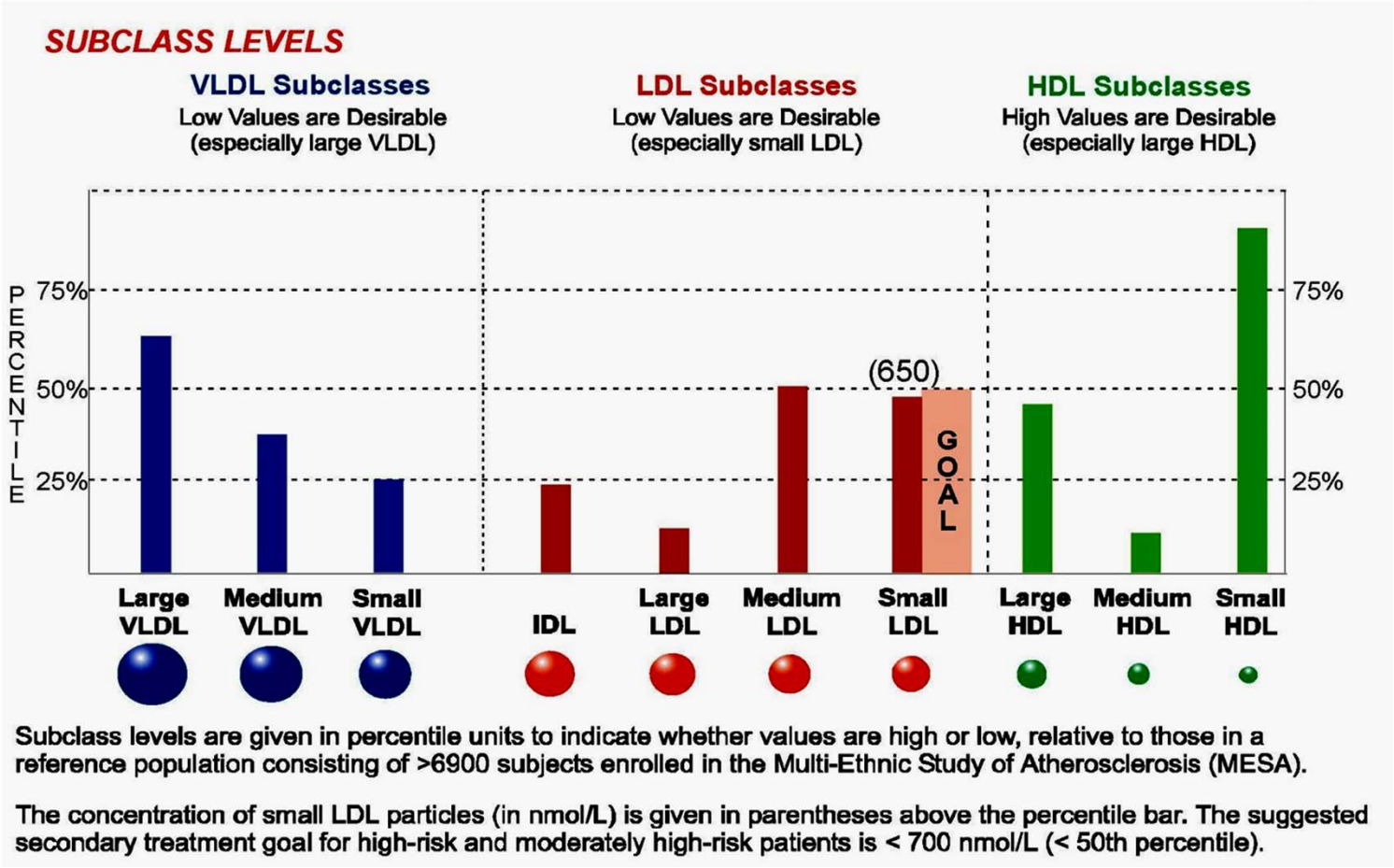
Mediterranean Diet
(30 Percent Calories from Fat)

Simvastatin 40 mg qhs

Omega 3FA 5 grams per day

Total-C	124 mg/dL
LDL-C	74 mg/dL
HDL-C	41 mg/dL
TG	70 mg/dL

CASE 6



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CASE 6

LIPOPROFILE PANEL

Coronary Heart Disease (CHD) Risk Categories

		Goal for High-Risk Patient	Goal for Moderately High-Risk Patient	Borderline High Risk	High Risk	Very High Risk
LDL Particle Number (LDL-P™)	nmol/L					
999		under 1000	under 1300	1300-1599	1600-2000	over 2000

For High-Risk Patients with CHD or CHD Risk Equivalents:
- primary goal: LDL-C < 100 mg/dL and LDL-P < 1000 nmol/L
- secondary goal: Small LDL particle number < 700 nmol/L
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For Moderately High-Risk Patients (10-20% 10-year risk):
- primary goal: LDL-C < 130 mg/dL and LDL-P < 1300 nmol/L
- secondary goal: Small LDL particle number < 700 nmol/L
  (< 50th percentile; see subclass levels graph on page 2)

		Pattern A (large LDL)	Pattern B (small LDL)
LDL Size	nm		
20.3		23.0 - 20.6 Lower-Risk	20.5 - 18.0 Higher-Risk

		Lower Risk	Intermediate	Higher Risk
Large HDL (cholesterol)	mg/dL			
16		greater than 30	30 - 11	less than 11

		Lower-Risk	Intermediate	Higher-Risk
Large VLDL (triglyceride)	mg/dL			
14		less than 7	7 - 27	greater than 27

LDL Particle Size (small), Large HDL (low levels), and Large VLDL (high levels) contribute to CHD risk and are important markers of the Metabolic Syndrome and risk of developing Type 2 Diabetes Mellitus.

PRIMARY PREVENTION PANEL

Elevated numbers of LDL particles and the lipoprotein traits of the metabolic syndrome affect CHD risk interactively. Risk is highest when both are present.

Elevated LDL Particle Number	>1300 nmol/L	☐
Lipoprotein Traits of the Metabolic Syndrome*	≥ 2 traits	☐

Lipoprotein Traits of the Metabolic Syndrome*

Small LDL Pattern B (≤ 20.5 nm)	Reduced Large HDL (< 11 mg/dL)	Elevated Large VLDL (> 27 mg/dL)
✓	☐	☐

**Other identifiers of the metabolic syndrome include abdominal obesity, elevated blood pressure, and fasting glucose ≥ 110 mg/dL.*

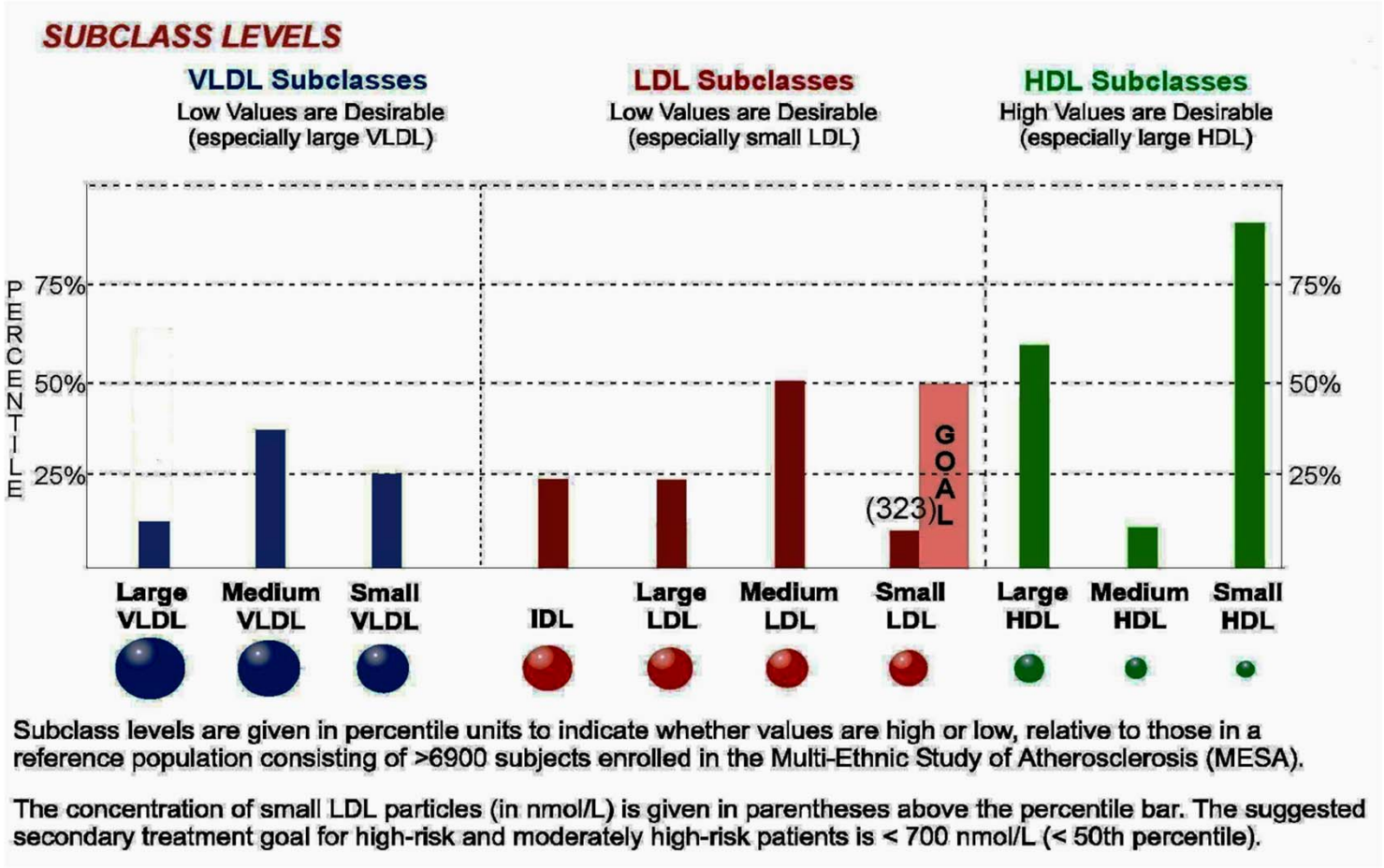
CASE 6

Mediterranean Diet
(30 Percent Calories from Fat)

Simvastatin 40 mg qhs
Omega 3 FA 5 grams q day
Niacin 1000 mg q day

Total-C	134 mg/dL
LDL-C	74 mg/dL
HDL-C	48 mg/dL
TG	60

CASE 6



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CASE 6

LIPOPROFILE PANEL

Coronary Heart Disease (CHD) Risk Categories

		Goal for High-Risk Patient	Goal for Moderately High-Risk Patient	Borderline High Risk	High Risk	Very High Risk
LDL Particle Number (LDL-P™)	nmol/L					
	721	under 1000	under 1300	1300-1599	1600-2000	over 2000

For High-Risk Patients with CHD or CHD Risk Equivalents:
- primary goal: LDL-C < 100 mg/dL and LDL-P < 1000 nmol/L
- secondary goal: Small LDL particle number < 700 nmol/L
  (< 50th percentile; see subclass levels graph on page 2)

For Moderately High-Risk Patients (10-20% 10-year risk):
- primary goal: LDL-C < 130 mg/dL and LDL-P < 1300 nmol/L
- secondary goal: Small LDL particle number < 700 nmol/L
  (< 50th percentile; see subclass levels graph on page 2)

		Pattern A (large LDL)	Pattern B (small LDL)
LDL Size	nm		
	21.2	23.0 - 20.6	20.5 - 18.0
		Lower-Risk	Higher-Risk

		Lower Risk	Intermediate	Higher Risk
Large HDL (cholesterol)	mg/dL			
	21	greater than 30	30 - 11	less than 11

		Lower-Risk	Intermediate	Higher-Risk
Large VLDL (triglyceride)	mg/dL			
	2	less than 7	7 - 27	greater than 27

LDL Particle Size (small), Large HDL (low levels), and Large VLDL (high levels) contribute to CHD risk and are important markers of the Metabolic Syndrome and risk of developing Type 2 Diabetes Mellitus.

PRIMARY PREVENTION PANEL

Elevated numbers of LDL particles and the lipoprotein traits of the metabolic syndrome affect CHD risk interactively. Risk is highest when both are present.

Elevated LDL Particle Number >1300 nmol/L ☐

Lipoprotein Traits of the Metabolic Syndrome* ≥2 traits ☐

Lipoprotein Traits of the Metabolic Syndrome*

Small LDL Pattern B (≤ 20.5 nm)	Reduced Large HDL (< 11 mg/dL)	Elevated Large VLDL (> 27 mg/dL)
☐	☐	☐

**Other identifiers of the metabolic syndrome include abdominal obesity, elevated blood pressure, and fasting glucose ≥ 110 mg/dL.*

CASE 7

- 32 year old WM presents to the ER with an ischemic CVA with right hemiparesis.
- At age 26 he had a retinal artery occlusion of unknown etiology
- At age 30 he had an anterior MI
- No history of hypertension, dyslipidemia, DM. Not obese. Does not smoke
- FH is positive for CHD, MI and CVA at early ages in both parents
- Exam shows BP of 132/82 mm Hg, HR 88. Right hemiparesis. Rest of PE is normal
- Labs normal. FBS 82 mg/dL, LDL 88 mg/dL, TG 90, HDL 48. All other labs are normal

- What is your diagnosis?
- What labs do you order?

Case 7

- Advanced lipid testing shows Lp(a) at 150 mg/dL.
- Explain this case ?
- What is the treatment?

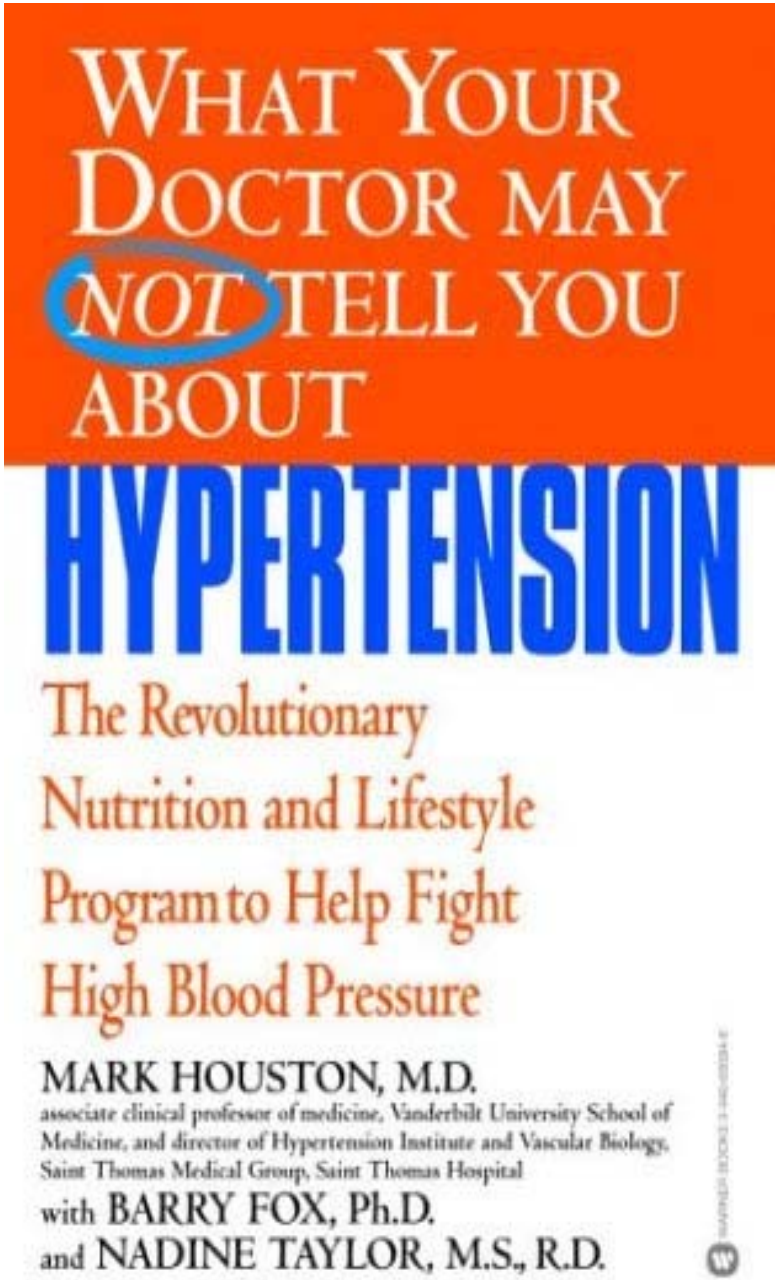
Case 7

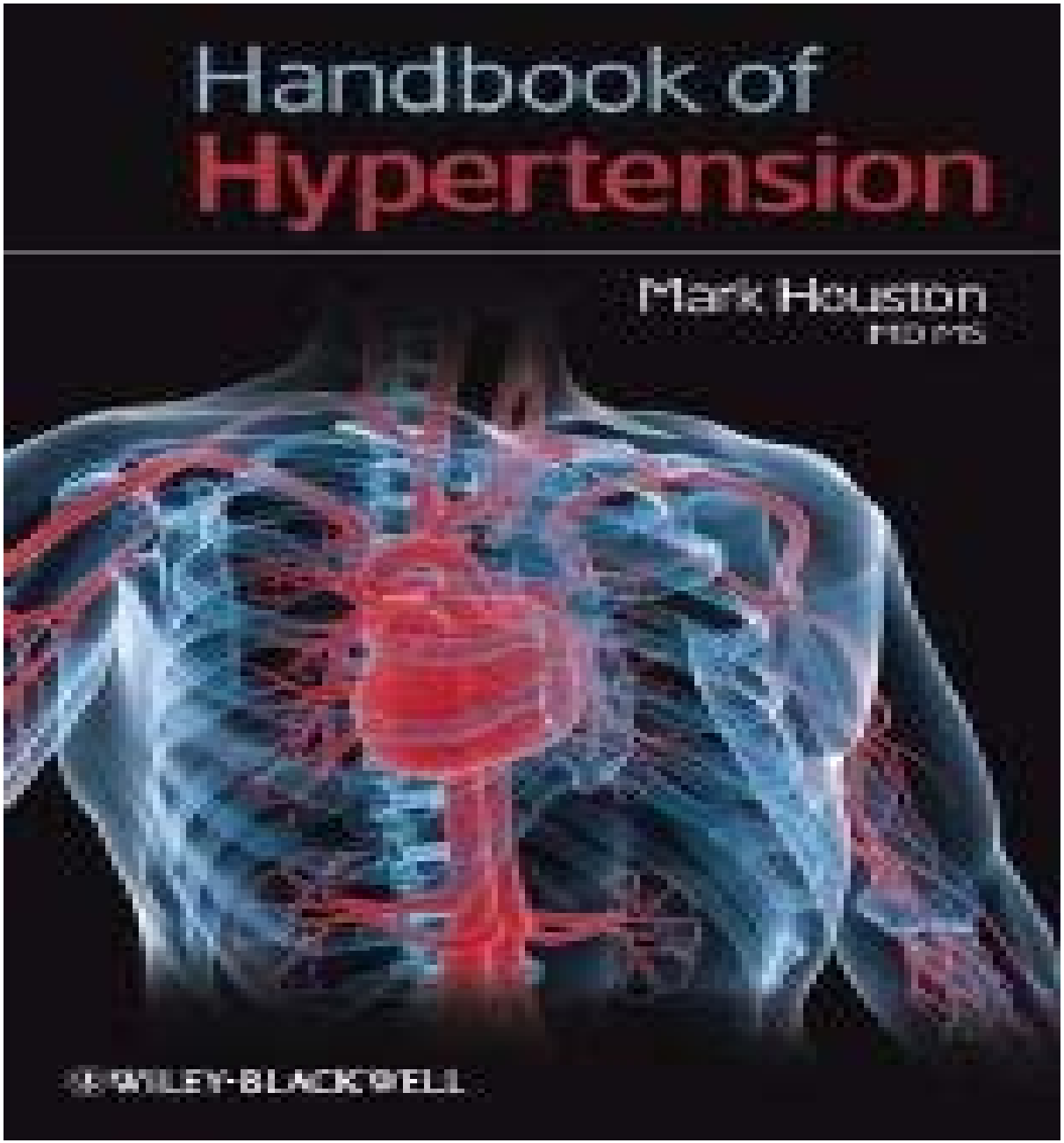
- Treatment after 4 months Lp(a) is 64 mg/dL

- Niacin dose related. 4 grams per day
- NAC 1000 mg bid
- Carnitine 2 grams per day
- Proline (500 mg) with Lysine (1000 mg) + Vitamin C 10,000 mg
- Inhibit PCSK9 (berberine) 500 mg bid
- Gamma delta tocotrienols 200 mg hs
- Arginine 5 grams per day
- Flax seed one cup per day
- Co Q10 100 mg per day
- Omega 3 FA 5 grams per day
- ASA baby 81 mg per day

Suggested Reading

- What Your Doctor May Not Tell You About Hypertension by Mark Houston MD
- Handbook of Hypertension by Mark Houston MD
- What Your Doctor May Not Tell You About Heart Disease by Mark Houston MD
- Vascular Biology for the Clinician by Mark Houston MD
- Nutrition and Integrative Strategies in Cardiovascular Medicine. Sinatra and Houston, Editors.


WHAT YOUR DOCTOR MAY NOT TELL YOU ABOUT
HYPERTENSION
The Revolutionary Nutrition and Lifestyle Program to Help Fight High Blood Pressure
MARK HOUSTON, M.D.
associate clinical professor of medicine, Vanderbilt University School of Medicine, and director of Hypertension Institute and Vascular Biology, Saint Thomas Medical Group, Saint Thomas Hospital
with BARRY FOX, Ph.D.
and NADINE TAYLOR, M.S., R.D.


Handbook of
Hypertension
Mark Houston
MD FACP
WILEY-BLACKWELL

WHAT YOUR DOCTOR MAY *NOT* TELL YOU ABOUT™

HEART DISEASE

The Revolutionary Book that Reveals the Truth Behind Coronary Illnesses—and How You Can Fight Them

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associate clinical professor of medicine, Vanderbilt University School of Medicine, and director of Hypertension Institute and Vascular Biology, Saint Thomas Medical Group, Saint Thomas Hospital

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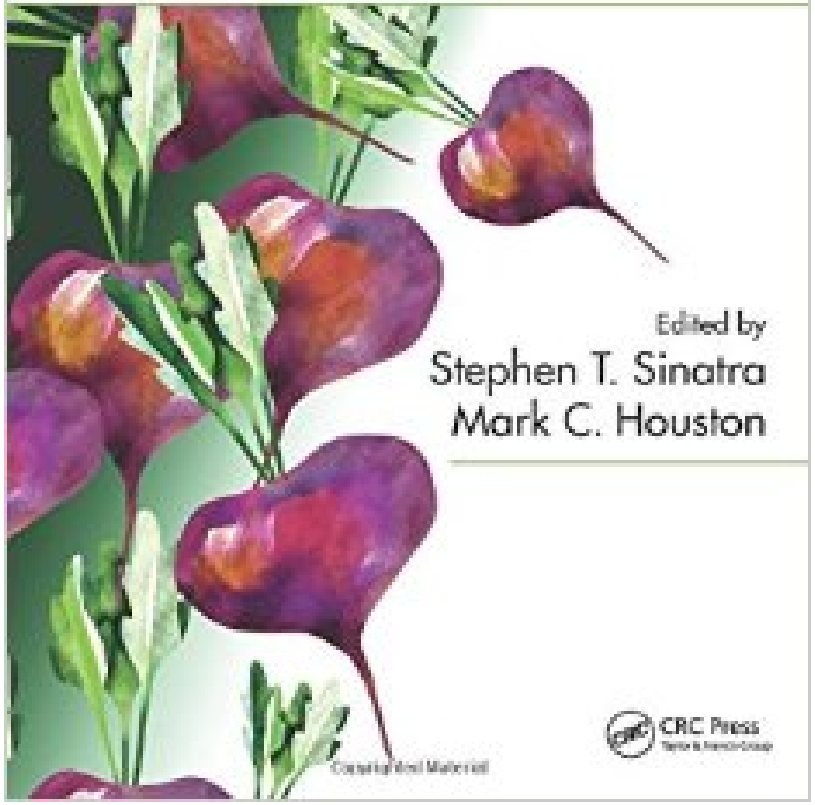

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