Chad Oler, ND

Correcting Cardiovascular Disease: Using Advanced Assessments to Address Blood Lipid Imbalances

1

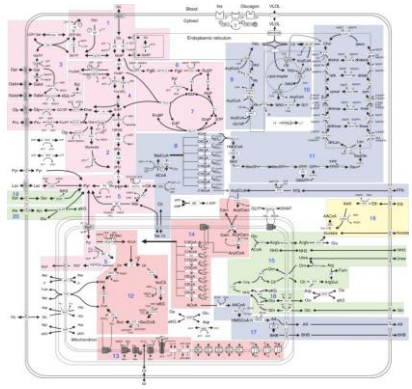
Clinical Takeaways

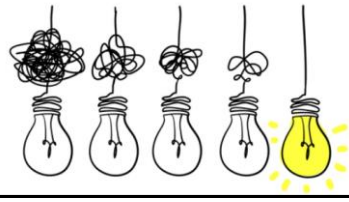
- How CVD develops and the scope of the problem
- The role that dyslipidemia plays in the development of atherosclerosis and CVD
- Identifying and addressing dyslipidemia to improve CV health
  - Functional testing, diet, supplemental support & lifestyle therapies
- Implementing these strategies with you patients

2

Biochemistry: Focus on Concepts

- Mechanisms are important
  - Practitioners need to know they are known
  - Not important to know them thoroughly
- You should understand basic concepts
  - Communication with practitioners/patients
  - Protocol modification for specific cases





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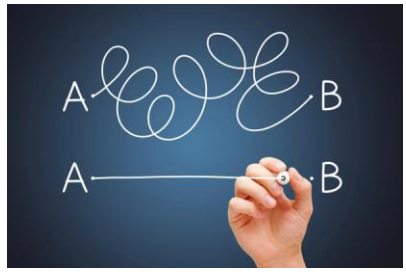
Facilitate Action

- Avoid jargon
  - We want them to act – NOW!

- Be a translator/facilitator:
  - Decipher mechanisms into concepts and descriptions your practitioners can use to understand and implement these strategies



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Cardiovascular Disease (CVD)

- Leading cause of death in US & globally
- In US, over 941,000 deaths/year (2022)
  - 1 of every 3 deaths in US
  - 2500 people die of CVD *every day*
  - Average of *1 death every 33 seconds*
- CVD kills more people than all cancers & accidental deaths combined (#2 & #3 causes of death)
- Most common conversation patients have with clinicians
- Focus on managing glucose, blood pressure, LDL-C, HDL-C and total cholesterol with Rx
  - Not working

Woolf SH, Aron L. US health in international perspective: Shorter lives, poorer health: National Academies Press; 2013.
Estruch R, et al. Primary prevention of cardiovascular disease with a Mediterranean die. New Eng J Med. 2013;368:1279-1290.
Burke LE, et al. Compliance with cardiovascular disease prevention strategies: a review of the research. Annals of Behav Med. 1997;19:239-263.
https://www.heart.org/en/about-us/heart-and-stroke-association-statistics?uid=1740

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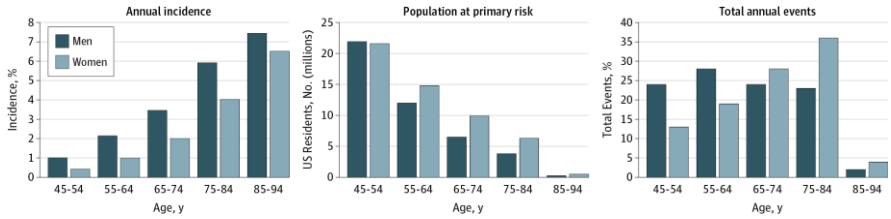
CVD: Incidence and Risk

- 48.6% of US adults have CVD
- By 2050, 61%% of the US adult population is projected to have some form of CVD
- Risk increases with age, however:
  - 13% of 20-40 yo have CVD
  - 40% of 40-60 yo have CVD
  - 70% of 60-80 yo have CVD
  - 85% of people over 80 yo have CVD

Benjamin EJ, et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association; Circulation Volume 139, Number 10
National Center for Health Statistics and National Heart, Lung, and Blood Institute.
Benjamin EJ, Blaha MJ, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146-e603.
Go AS, Mozaffarian D, et al. Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. Circulation. 2013;127(1):e6-e245.

6

Incidence of Cardiac Events



- 50% of men who are going to have a cardiac event will have it BEFORE age 65
- 1/3 of women will have their 1st cardiac event before age 65
- Almost 25% of cardiac events in men <54 years old!
- ➢ Early prevention is the key

JAMA Cardiol. 2016;1(4):492-494. doi:10.1001/jamacardio.2016.0991

7

Sudden Death and CVD

- ~40% of people that have a heart attack die
- Initial presentation in ~35% of cases of CVD is sudden death

Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: the Framingham study. Am J Cardiol. 1979 Jul;44(1):53-9.
Tsao CW, et al. Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. Circulation, Volume 145, Number 8
Brunzell JD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2008;51:1512–24.
Thaulow E, et al. Initial clinical presentation of cardiac disease in asymptomatic men with silent myocardial ischemia and angiographically documented coronary artery disease (the Oslo Ischemia Study). Am J Cardiol. 1993 Sep 15;72(9):629-33.

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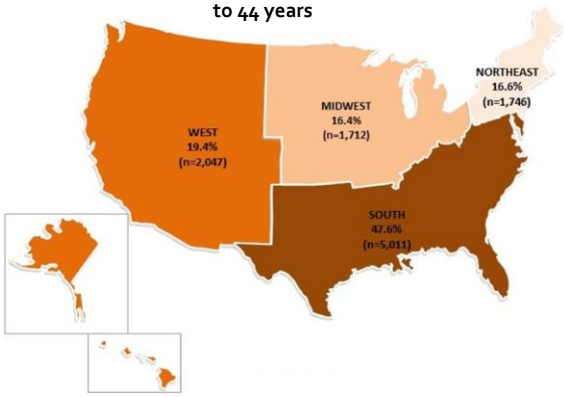
Death due to CVD is Increasing in Young Adults

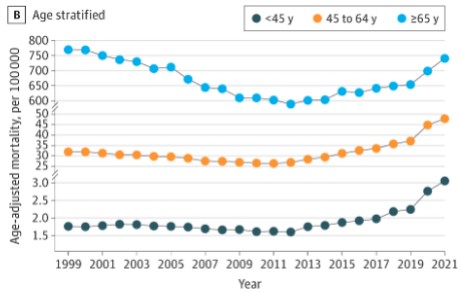
SUDDEN DEATH MORTALITY RATE HAS INCREASED ~28% FROM 1999-2020 FOR ADULTS AGED 25-40

Distribution of sudden cardiac death among early adults, aged 25 to 44 years



SINCE 2012, HEART FAILURE MORTALITY RATES HAVE INCREASED:

- **906% FOR THOSE < 45 YEARS OLD**
- **385% FOR THOSE AGED 45-64**



Peter P. Toth,Maciej Banach,No second chances: Cardiovascular death is the most frequent incident event among patients with coronary artery calcium, Progress in Cardiovascular Diseases, (2025).
Ryan Quinn,James Sawalla Guseh,From Stadiums to Streets: Preventing Sudden Cardiac Death in Young Adults, Journal of the American Heart Association, 14, 1, (2024).
Zuin M, et al. Trends in Sudden Cardiac Death Among Adults Aged 25 to 44 Years in the United States: An Analysis of 2 Large US Databases. Journal of the American Heart Association; Volume 14, Number 1
Saved A, Abramov D, Fonarow GC, et al. Reversals in the Decline of Heart Failure Mortality in the US, 1999 to 2021. JAMA Cardiol. 2024;9(6):585–589.

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We Need to Act - NOW

- Based on recent data, 50% of your patients, as well as 50% of your (adult) friends and family currently have some form of CVD – most of them just don't know it yet.
- CVD isn't just a disease of aging; in fact, 50% of men and 1/3 of women who have a cardiac event - like a heart attack or stroke – have it BEFORE age 65.
- We have to catch this early because many people don't get a 2nd chance – for 35% of people, the very first symptom they have is sudden death.
- 40% of people that have a heart attack die.
- Based on the latest statistics, people should have testing done beginning in their 20s, 30s and 40s.

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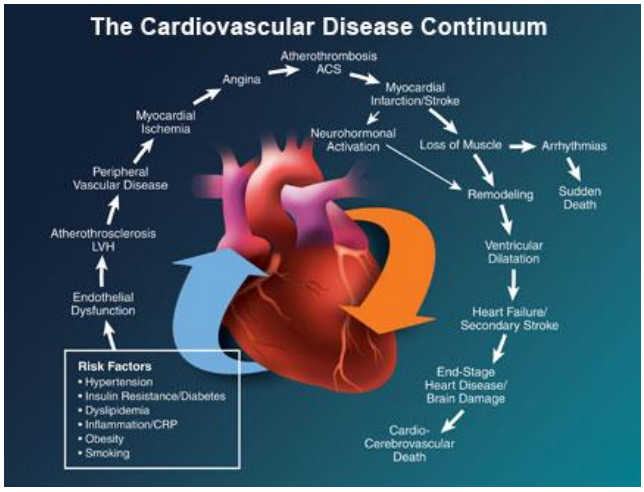
Cardiovascular Disease Continuum



Shanthi Mendis; Pekka Puska; Bo Norrving; World Health Organization (2011). Global Atlas on Cardiovascular Disease Prevention and Control (PDF). World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. pp. 3–18.

Figure adapted from: http://www.awaremed.com/tag/diabetes-and-heart-disease/page/4/

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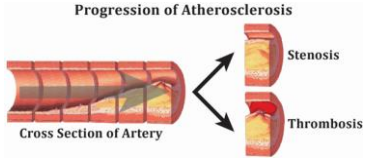
CVD is Preventable & Reversible

- 90% of CVD is preventable/reversible
  - You just need the right keys
- Coronary artery disease and strokes account for 75-80% of CVD deaths
  - Need to target atherosclerosis



McGill HC, McMahan CA, Gidding SS (March 2008). "Preventing heart disease in the 21st century: implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study". Circulation. 117 (9): 1216–27.
McNeal, Catherine J.; Dajani, Tala; Wilson, Don; et al. "Hypercholesterolemia in youth: opportunities and obstacles to prevent premature atherosclerotic cardiovascular disease". Current Atherosclerosis Reports. 12 (1): 20–28.
Flying arrows picture from www.johnlund.com

12

Key Event in Development of Atherosclerosis

- Key event is damage to the endothelium caused by:
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - Toxins (i.e., components of cigarette smoke)
  - ➢ All lead to Nitric Oxide Dysregulation

Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2008;51:1512–24.
Thaulow E, Erikssen J, Sandvik L, et al. Initial clinical presentation of cardiac disease in asymptomatic men with silent myocardial ischemia and angiographically documented coronary artery disease (the Oslo Ischemia Study). Am J Cardiol. 1993 Sep 15;72(9):629-33.
Kádár A, Glasz T. Development of atherosclerosis and plaque biology. Cardiovasc Surg. 2001 Apr;9(2):109-21.
Gimbrone MA, García-Cardeña G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. Circulation research. 2016;118(4):620-636.
Davignon J, Ganz P. Role of Endothelial Dysfunction in Atherosclerosis. Circulation. 2004;109:III-27-III-32.

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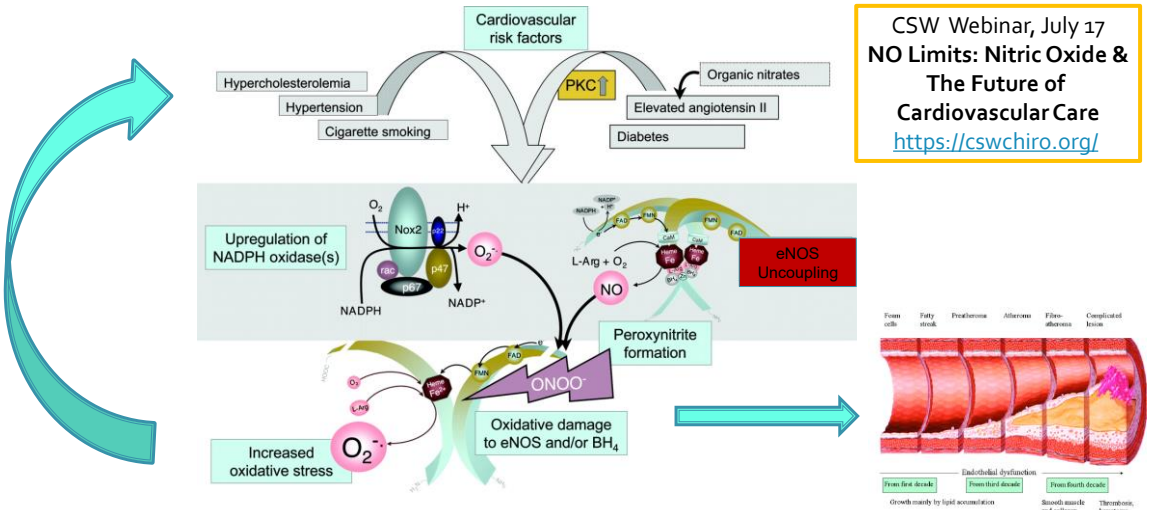
Nitric Oxide Dysregulation: Fundamental Cause of Endothelial Dysfunction



CSW Webinar, July 17
NO Limits: Nitric Oxide & The Future of Cardiovascular Care
https://cswchiro.org/

Förstermann U, Münzel T, Endothelial Nitric Oxide Synthase in Vascular Disease: From Marvel to Menace. Circulation, Volume 113, Number 13.

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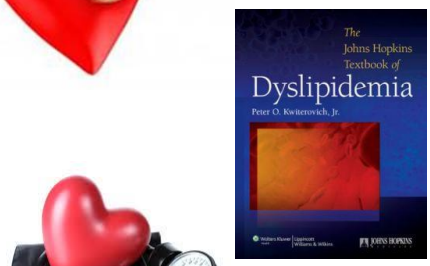
Addressing the Causes of CVD

- Nutritional Imbalances
- Dyslipidemia
- High blood pressure
- Nitric Oxide Dysfunction
- Blood sugar/insulin resistance
- Chronic Inflammation/Infection
- Mitochondrial Dysfunction
- Hormone Imbalances
- Visceral obesity



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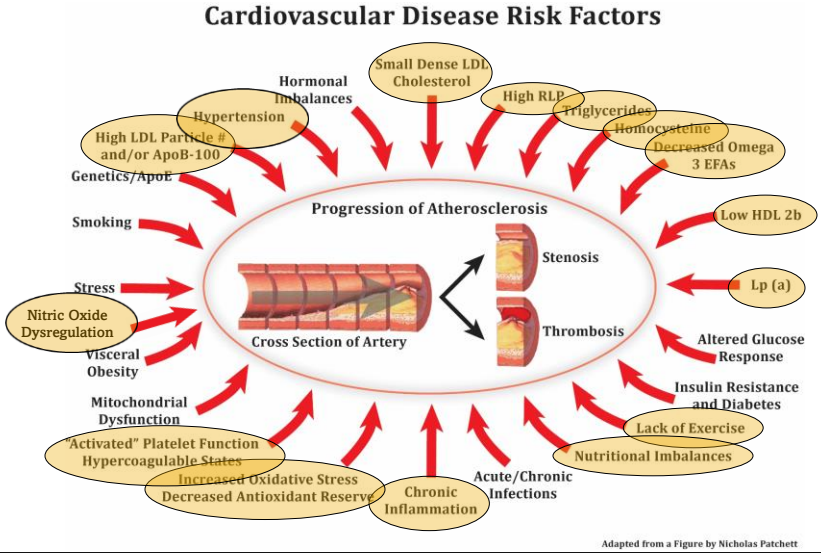
Cardiovascular Disease Risk Factors



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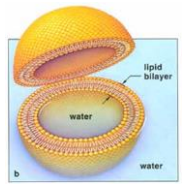
Cholesterol Is Essential for Life

- Cholesterol is a lipid (fat) that is vital to life
- Every cell in the body makes cholesterol
  - Essential component of cell membranes
  - Provides fluidity and structure
  - Responsible for membrane permeability
    - Enables nutrients, hormones & wastes into move in/out
- No cholesterol, no life



Luc G, Douste-Blazy P, Fruchart JC. Le cholestérol: d'où vient-il, comment circule-t-il, où va-t-il? [Cholesterol: from where does it come, how does it circulate, where does it go?]. Rev Prat. 1989 Apr 20;39(12):1011-7.
Huff T, Boyd B, Jialal I. Physiology, Cholesterol. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan.
Craig M, Yarrarapu SNS, Dimri M. Biochemistry, Cholesterol. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan.

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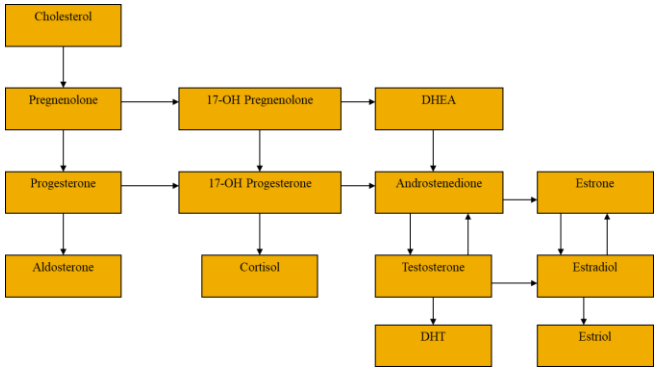
What Cholesterol Is and Does

- Cholesterol is a precursor of:
  - Steroid hormones (Estrogens, progesterone, testosterone, cortisol, DHEA)

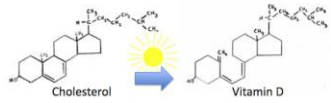


Feingold KR, Grunfeld C. Lipids: a key player in the battle between the host and microorganisms. Journal of Lipid Research. 2012;53(12):2487-2489.

18

What Cholesterol Is and Does

- Cholesterol is a precursor of:
  - Steroid hormones (Estrogens, progesterone, testosterone, cortisol, DHEA)
  - Bile acids (fat digestion)
  - Vitamin D



- Important for the metabolism/use of Vit A, D, E & K
- Cholesterol is used to build/maintain myelin sheath
- Cholesterol helps the body repair and modulate the inflammatory process
- Cholesterol plays a important role in immune function and the toxic effects of microorganisms
- Cholesterol is vital for brain health

Feingold KR, Grunfeld C. Lipids: a key player in the battle between the host and microorganisms. Journal of Lipid Research. 2012;53(12):2487-2489.

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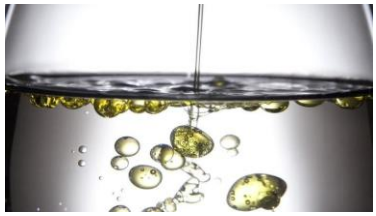
Cholesterol Transport

- Some cells/tissues need more cholesterol than they can make
- Some cells (liver/gut) are net exporters of cholesterol
- Body needs to be able to traffic cholesterol
  - Does so through circulatory system



Huff T, Boyd B, Jialal I. Physiology, Cholesterol. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan.

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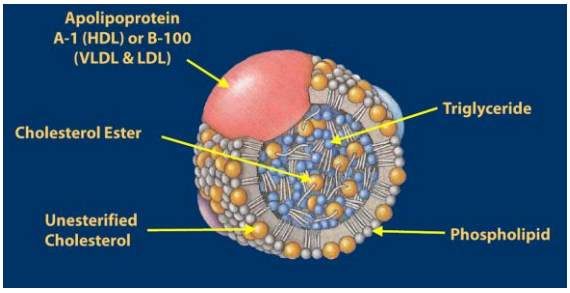
Lipoprotein Particles



- Transport cholesterol & triglycerides through circulatory system
  - To tissues that need them
  - To liver for removal/recycling
- Contain Apolipoproteins
  - Determine functionality of lipoprotein particle

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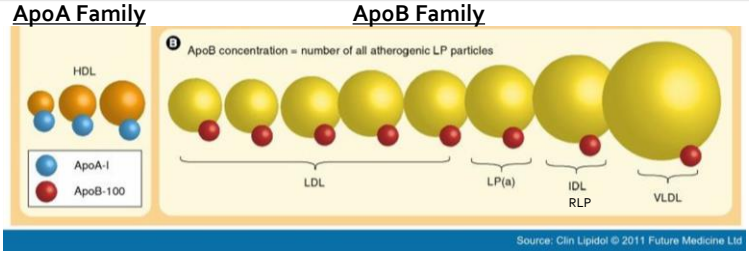
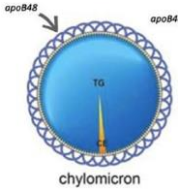
Lipoprotein Families





- ApoB Family: VLDL-P, LDL-P, IDL-P, RLP-P, Lp(a)
  - Potentially atherogenic
- ApoA Family: HDL-P
  - Potentially antiatherogenic
- The cholesterol in all of these particles is the same

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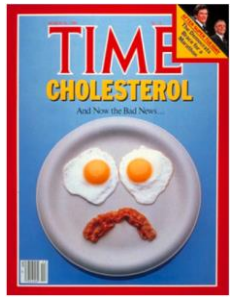
How Did We Get Here?

- Cholesterol deposits found in atherosclerotic plaques in humans in 1910
  - Beginning of the "lipid hypothesis"
    - That cholesterol plays a major *causative* role in atherosclerotic/CV disease



Leibowitz, JO. The history of coronary heart disease. University of California Press; Berkeley and Los Angeles: 1970. p. 227.
Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins - An integrated approach to mechanisms and disorders. N. Engl. J. Med. 1967; 276:32–44. 94–l03.
Gofman JW, Delalla O, Glazier F, et al. The serum lipoprotein transport system in health, metabolic disorders, atherosclerosis and coronary heart disease. Plasma. 1954a; 2:413–484.

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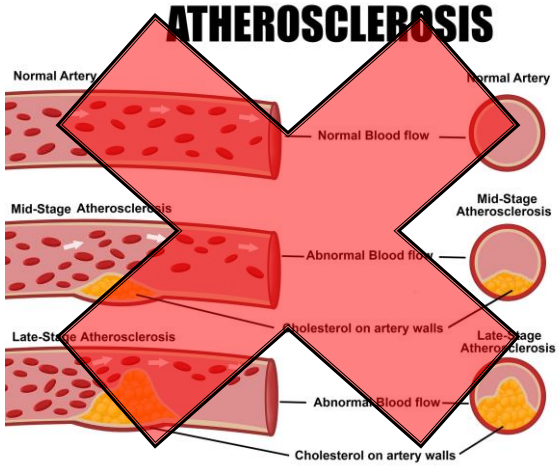
Lipid Hypothesis



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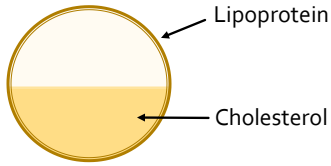
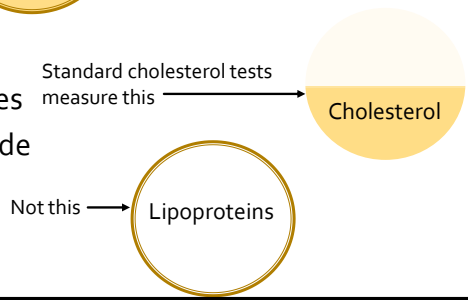
Lipoproteins vs. Cholesterol

- There is a disconnect between cholesterol and lipoproteins



- Standard cholesterol tests
  - Dissociate lipoprotein particles
  - Measures the cholesterol inside
    - Total cholesterol
    - HDL-C



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Standard Cholesterol Testing Misleading

- 50% of people that have a heart attack have "normal" LDL-cholesterol (LDL-C<100 mg/dL)
  - Framingham Heart Study (started in 1948, ongoing)
  - Multiple Risk Factor Intervention Trial (over 350,000 people)
- Standard cholesterol tests do NOT identify thousands of people that are high risk of heart attack or cardiovascular events

What are standard cholesterol tests missing?

Sachdeva et al. *Am Heart J* 2009;157:111-117.e2.
Kannel et al. *Am Heart J* 1992;124:768-774.
Wilson et al. *Circulation* 1998;97:1837-1847.

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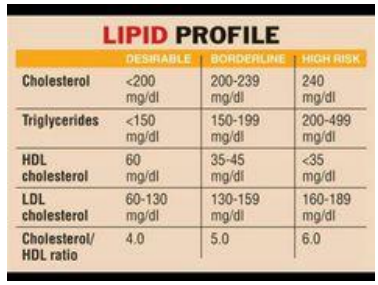
Fasting Lipid Panel

Component	Your result	Standard range	Units
CHOLESTEROL	126	<200	mg/dL
TRIGLYCERIDE	79	<150	mg/dL
HDL	43	>/=40	mg/dL
LDL CALCULATED	67	<100	mg/dL
CHOLESTEROL/HDL	2.9	<5.0	



LIPID PROFILE

	DESIRABLE	BORDERLINE	HIGH RISK
Cholesterol	<200 mg/dl	200-239 mg/dl	240 mg/dl
Triglycerides	<150 mg/dl	150-199 mg/dl	200-499 mg/dl
HDL cholesterol	60 mg/dl	35-45 mg/dl	<35 mg/dl
LDL cholesterol	60-130 mg/dl	130-159 mg/dl	160-189 mg/dl
Cholesterol/ HDL ratio	4.0	5.0	6.0

- TC = VLDL-C + LDL-C + HDL-C
- Friedewald Equation: VLDL-C = TG/5
- Calculated LDL-C = TC – (HDL-C + TG/5)

Martin SS, Blaha MJ, Elshazly MB, et al. Friedewald-Estimated Versus Directly Measured Low-Density Lipoprotein Cholesterol and Treatment Implications. *J Am Coll Cardiol.* 2013;62(8):732-739. doi:10.1016/j.jacc.2013.01.079.
Otvos JD. Measurement of triglyceride-rich lipoproteins by nuclear magnetic resonance spectroscopy. Clin Cardiol 1999;22(6 Suppl):II21–7.
Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun;18(6):499-502.

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Issues with the Friedewald equation

- Estimates VLDL triglycerides/cholesterol ≈"5"
  - In reality, it varies between 2-12
  - Especially important when TG high (>150 mg/dL)
    - Metabolic syndrome, insulin resistance, diabetes
      - ~225 MILLION people in the US
  - ➢ Inaccurate
    - ➢ Underestimates LDL-C ("normal" Calc LDL-C)
  - ➢ Underestimates CVD risk, especially as TG ↑

McNamara JR, Cohn JS, Wilson PWF, Schaefer EJ. Calculated values for low-density lipoprotein cholesterol in the assessment of lipid abnormalities and coronary disease risk. Clin Chem 1990;36:36-42.
Warnick R, Knopp RH, Fitzpatrick V, Branson L. Estimating low-density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. Clin Chem 1990;36:15-19.
Martin SS, Blaha MJ, Elshazly MB, et al. Friedewald-Estimated Versus Directly Measured Low-Density Lipoprotein Cholesterol and Treatment Implications. *J Am Coll Cardiol.* 2013;62(8):732-739. Otvos JD. Measurement of triglyceride-rich lipoproteins by nuclear magnetic resonance spectroscopy. Clin Cardiol 1999;22(6 Suppl):II21–7.

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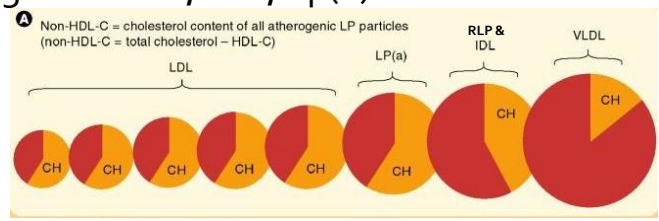
Why Cholesterol Panels are Misleading

- TC = VLDL-C + LDL-C + HDL-C
- Calculated LDL-C = TC – (HDL-C + TG/5)
- Lumps together: IDL, RLP, Lp(a) & various LDL



  - All have different atherogenic properties
  - Does not provide accurate information about the actual number of potentially atherosclerotic particles present

Contois JH, McConnell JP, Sethi AA, et al. Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. Clinical Chemistry Mar 2009, 55 (3) 407-419.
Martin SS, Blaha MJ, Elshazly MB, et al. Friedewald-Estimated Versus Directly Measured Low-Density Lipoprotein Cholesterol and Treatment Implications. *J Am Coll Cardiol.* 2013;62(8):732-739. Otvos JD. Measurement of triglyceride-rich lipoproteins by nuclear magnetic resonance spectroscopy. Clin Cardiol 1999;22(6 Suppl):II21–7.

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Why Cholesterol Panels are Misleading

- Lipoproteins vs. Cholesterol
  - Atherogenic lipoproteins, not the cholesterol they contain, are the actual cause of atherosclerosis
  - Cholesterol is a surrogate marker
    - Provides a crude estimate for atherogenic lipoproteins in ~50% of population
    - Correlation vs. causation
  - LDL-C Calc does NOT accurately reflect atherogenic lipoproteins for ~50% of the population
    - Inaccurate
    - Greatly underestimate CVD risk
  - # and size of LDL, VLDL, RLP, Lp(a) and HDL particles are important

Otvos J. Why Cholesterol Measurements May be Misleading about Lipoprotein Levels and Cardiovascular Risk. Technical Summary: J Lab Med 2002;26(11/12): 544-550.

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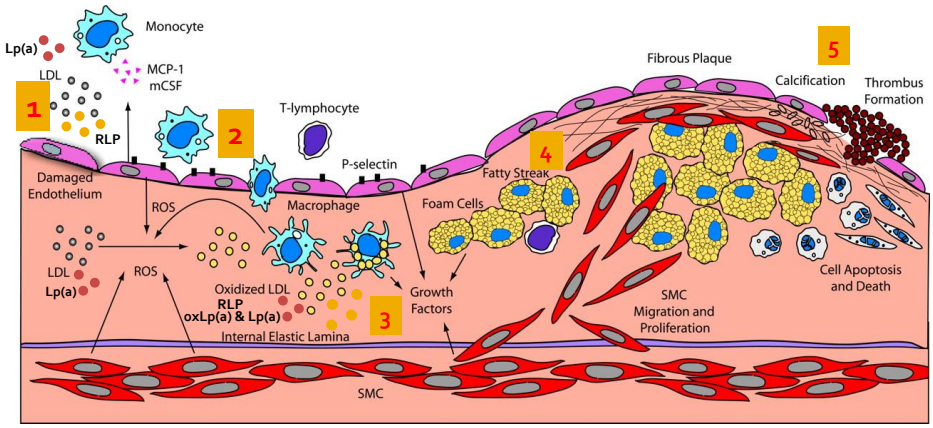
Standard Lipid Panels are Insufficient

- Standard lipid panels do not provide the information you need to make clinical decisions
  - 50% of people that have a heart attack have "normal" LDL-cholesterol (LDL-C<100 mg/dL)
  - LDL-C Calc does NOT accurately reflect atherogenic lipoproteins for ~50% of the population
    - Inaccurate
    - Greatly *underestimate* CVD risk for a large portion of the population
      - Especially those with metabolic syndrome, insulin resistance, pre-diabetes, T2D
  - Atherogenic lipoproteins, not the cholesterol they contain, are the actual cause of atherosclerosis
    - We need to identify the # and size of LDL, VLDL, RLP, Lp(a) and HDL particles

31

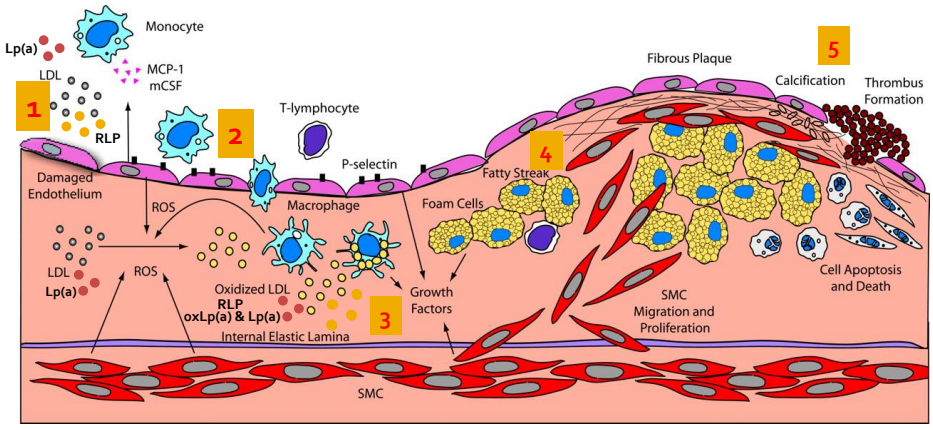
Atherosclerosis Development



Madamanchi NR, Vendrov A, Runge MS. Oxidative Stress and Vascular Disease. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25:29-38.

32

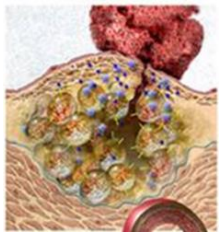
Lipoprotein Particles Determine Atherosclerosis Progression

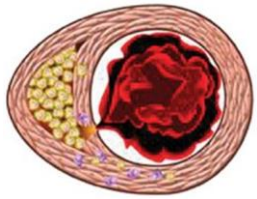


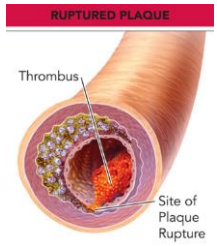
Madamanchi NR, Vendrov A, Runge MS. Oxidative Stress and Vascular Disease. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25:29-38.

33

Cardiovascular Disease



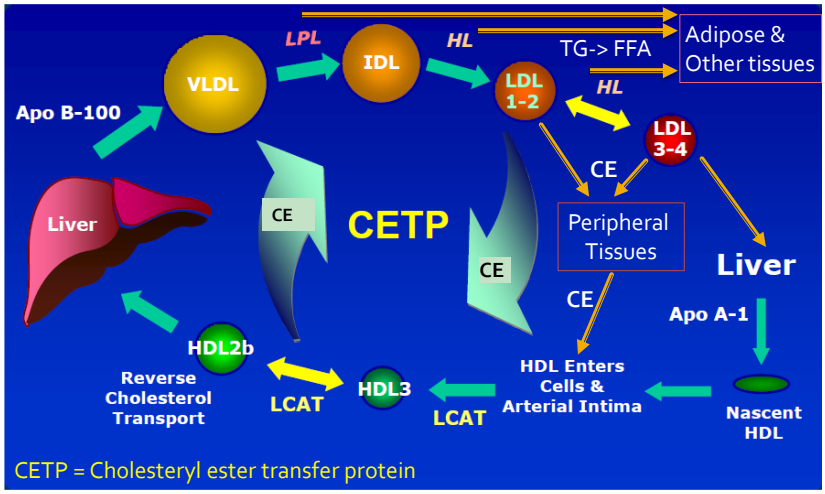




- Many factors lead to this eruption
- We have control over most of them

34

Lipoprotein Metabolism



Brewer HB Jr, Santamarina-Fojo S. Clinical significance of high-density lipoproteins and the development of atherosclerosis: focus on the role of the adenosine triphosphate-binding cassette protein A1 transporter. Am J Cardiol. 2003 Aug 21;92(4B):10K-16K.
Rajman I, Eacho PI, Chowienczyk PJ, Ritter JM. LDL particle size: an important drug target? British Journal of Clinical Pharmacology. 1999;48(2):125-133.
Mabuchi H, Nohara A, Inazu A. Cholesteryl ester transfer protein (CETP) deficiency and CETP inhibitors. Molecules and cells. 2014 Nov;37(11):777-84.

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Lipoprotein Metabolism

- "The body has a lot of different ways to move and metabolize cholesterol. We can take advantage of this fact to alter cholesterol metabolism if and as necessary to overcome almost any imbalance in this process so that we can prevent & reverse CVD."

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Outdated Paradigm

- Old: Patients having a heart attack have increased LDL-cholesterol
- New: Half the patients having a heart attack have normal LDL-cholesterol

➢ What other risk factors should we be addressing?

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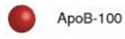
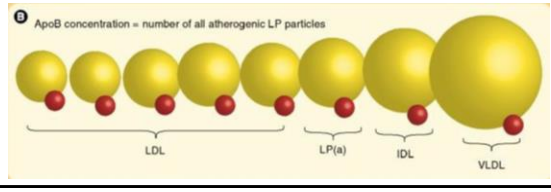
Apolipoprotein B-100 (ApoB-100)

- ApoB-100 is synthesized in the liver
- Major structural component of VLDL, IDL, LDL and Lp(a) particles
- Plays major role in how LDL is delivered to cells
- **One Apo-B per VLDL, IDL, LDL, Lp(a) particle**

➢ Very accurate measure of all atherogenic lipoprotein particles





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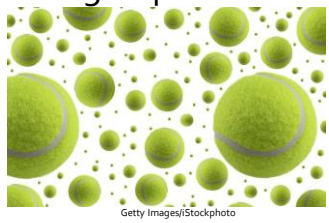
Why high ApoB-100 (or LDL-P#) Is Harmful

Low ApoB-100

Getty Images/iStockphoto

VS

High ApoB-100



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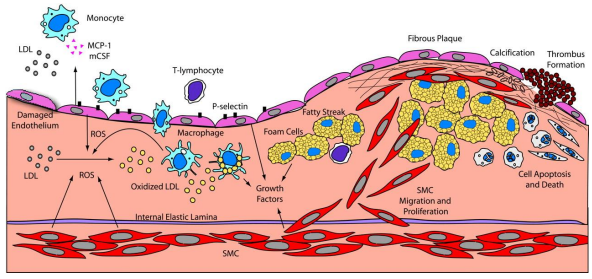

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ApoB and Risk Assessment

- Greatly improves evaluation of CVD risk assessment and of therapeutic action
- Especially important for:
  - Males, those over 65 yo, smokers
  - People with metabolic syndrome, high HDL-C, high triglycerides, larger waist circumference and/or low total cholesterol
  - People taking statin medications
    - Statins reduce LDL-C to a much greater extent than LDL-P, ApoB or other atherogenic lipoproteins

Kim BJ, Hwang ST, Sung KC, et al. Comparison of the relationships between serum apolipoprotein B and serum lipid distributions. Clin Chem. 2005 De;51(12):2257-63.
Rizzo M, Berneis K. The clinical relevance of low-density-lipoproteins size modulation by statins. Cardiovasc Drugs Ther. 2006;20:205–217.
Despres JP, Lemieux I, Salomon H, Delaval D. Effects of micronized fenofibrate versus atorvastatin in the treatment of dyslipidaemic patients with low plasma HDL-cholesterol levels: a 12-week randomized trial. J Intern Med. 2002;251:490 – 499.

40

ApoB-100/LDL Particle Number

- "…measurement of LDL-cholesterol may not accurately reflect the true burden of atherogenic particles, especially in those with the typical lipoprotein abnormalities of cardiometabolic risk (CMR): increased triglycerides, low HDL-cholesterol and increased numbers of small LDL particles"
  - ACC/ADA consensus statement 2008

CMR – cardiometabolic risk

Brunzell, John D. et al. "Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation." Journal of the American College of Cardiology 51 15 (2008): 1512-24.

41

ApoB-100/LDL Particle Number

- "Many cross-sectional and prospective studies show that ApoB-100 and/or LDL particle number is a better discriminator of risk than is LDL-cholesterol"
  - ACC/ADA consensus statement, 2008
- "There is now advanced testing available that can provide more accurate information on CVD risk."
  - Cardiologists' hands are tied & they don't have the right tools for the job

Brunzell, John D. et al. "Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation." Journal of the American College of Cardiology 51 15 (2008): 1512-24.

42

Consensus Statements

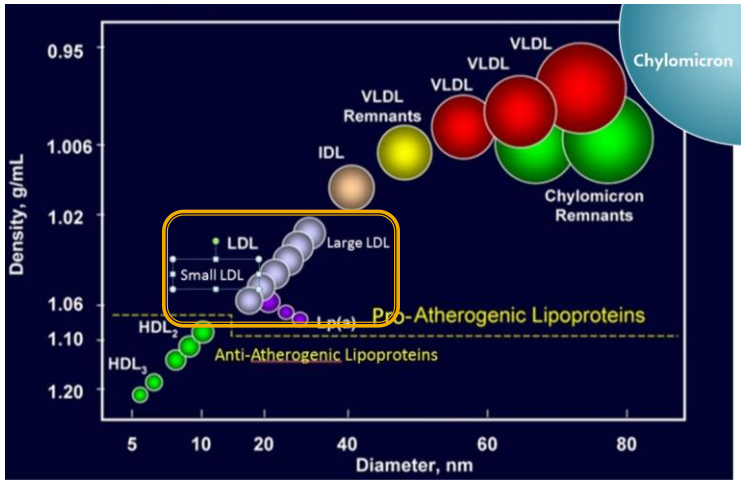
- ApoB -100 or LDL particle # Predict CVD risk Better than Cholesterol:
  - American Diabetes Association (2008)
  - American Heart Associations(2008)
  - American Diabetes Association (2008)
  - American College of Cardiology (2008)
  - Canadian Cardiovascular Society (2009)
  - National Lipid Association (2011)
  - European Atherosclerosis Society (2011)
  - American Association of Clinical Endocrinologists (2012)
  - Centers for Disease Control (2014)

- ApoB is a good starting point; Lipoprotein particle # by size/density is better

Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol 2009;25:567-79.
Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013;19:327-36.
Davidson MH, Ballantyne CM, Jacobson TA, et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists. J Clin Lipidol 2011;5:338-67.
Stone NJ, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013.
Catapano AL, Reiner Z, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011;217:3-46.
Center for Disease Control and Prevention's Lipid Standardization Program. 2014

43

LDL Particle Size & Density



Segrest et al. Atlas of Atherosclerosis. 2nd Edition; Philadelphia.

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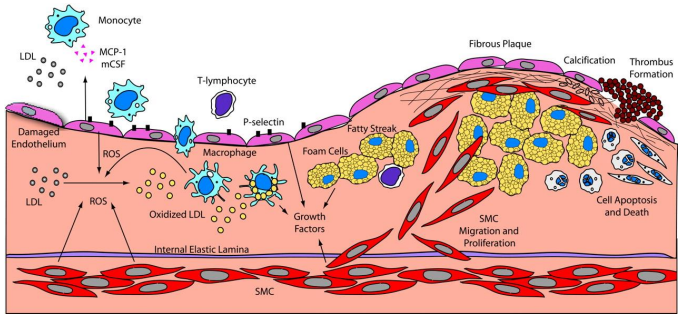
LDL Particle Size & Density

- Smaller LDL particles are more atherogenic than larger LDL particles
  - Penetrate the arterial wall more easily
  - Oxidize more readily
  - Cause calcification of arteries



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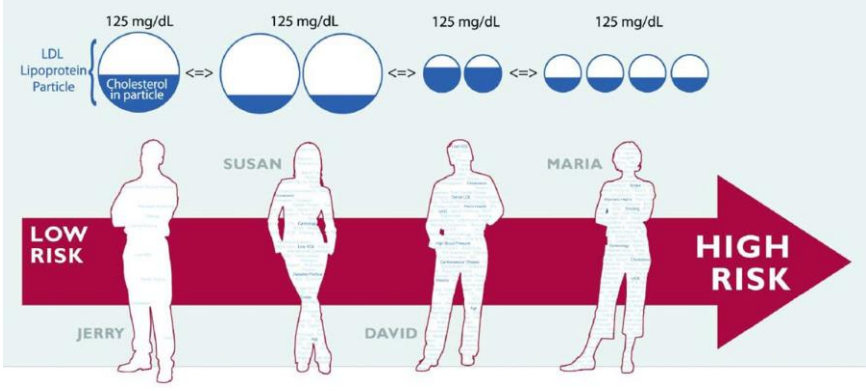
LDL Particle size and density matters – A LOT



- People with small, dense LDL-P have a 300% increased risk of coronary heart disease

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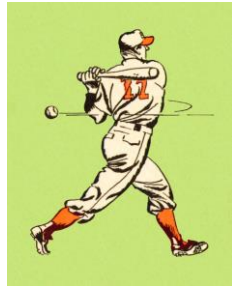
LDL particle size/density and CVD risk

- Small, dense LDL particles confer <u>at least a 3-fold higher risk of CVD compared with large LDL particles</u>
- Small, dense LDL particles do *not* correlate with LDL-C levels
  - Completely missed with standard cholesterol tests



Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM: Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA 1998;260:1917-1921.
Lamarche B, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: Prospective results from the Québec Cardiovascular Study. *Circulation* 1997;**95**: 69–75.
Zambon S, et al. Pravastatin treatment in combined hyperlipidemia: effect on plasma lipoprotein and size. Eur J Clin Pharmacol. 1994;46:221–224.
Franceschini G, et al. Pravastatin effectively lowers LDL cholesterol in familial combined hyperlipidemia without changing LDL subclass pattern. Arterioscler Thromb. 1994;14:1569–1575.
Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. Circulation 2004;109:III2–III7.
Nicholls S, Lundman P. The emerging role of lipoproteins in atherogenesis: beyond LDL cholesterol. Semin Vasc Med. 2004;4:187–195.
Liu ML, Yltalo K, Nuotio I, Salonen R, Salonen JT, Taskinen MR. Association between carotid intima-media thickness and low-density lipoprotein size and susceptibility of low-density lipoprotein to oxidation in asymptomatic members of familial combined hyperlipidemia families. Stroke 2002;33:1255– 60.

47

LDL Particle size/density References

- Nordestgaard BG, Nielsen LB. Atherosclerosis and arterial influx of lipoproteins, Curr Opin Lipidol. 1994;4:252–257.
- Steinberg D, Parsatharathy S, Carew T, Khoo J, Witztum J. Beyond cholesterol: Modifications of low-density lipoprotein that increase its atherogenecity. N Engl J Med. 1989;320:915–924.
- Dejager S, Bruckert E, Chapman MJ. Dense LDL subspecies with diminished oxidative resistance predominate in combined hyperlipidaemia. J Lipid Res. 1993;34:295–308.
- ribble DL. Lipoprotein oxidation in dyslipidaemia: insights into general mechanisms affecting lipoprotein oxidative behaviour. Curr Opin Lipidol. 1995;6:196–208.
- Madamanchi NR, Vendrov A, Runge MS. Oxidative Stress and Vascular Disease. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25:29-38.
- Parhami F, et al. Lipid oxidation products have opposite effects on calcifying vascular cell and bone cell differentiation. A possible explanation for the paradox of arterial calcification in osteoporotic patients. Arterioscler Thromb Vasc Biol. 1997;17:680 – 687.
- Tintut Y, et alL. Monocyte/macrophage regulation of vascular calcification in vitro. Circulation. 2002;105:650 – 655.

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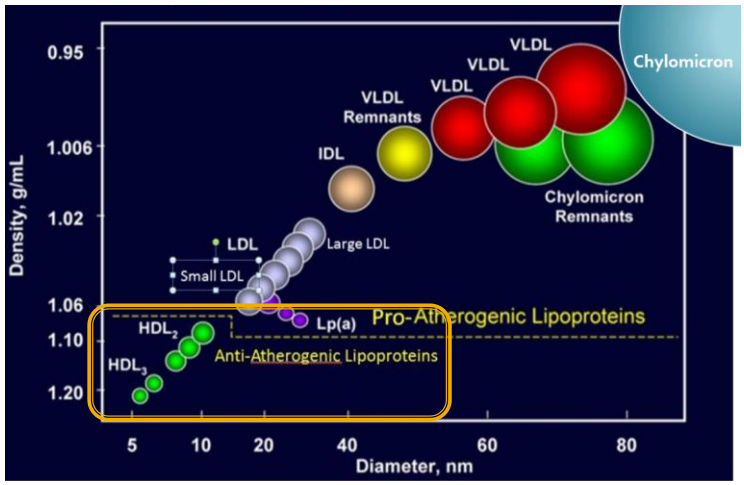
HDL Particle Size/Density



Segrest et al. Atlas of Atherosclerosis. 2nd Edition; Philadelphia.

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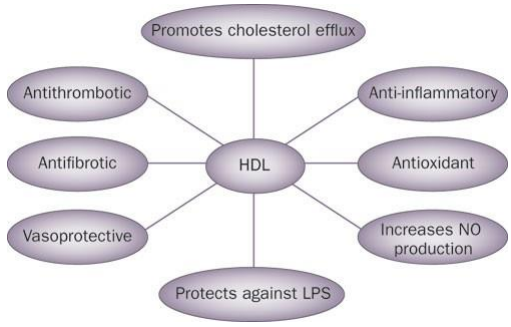
HDL Particles (HDL-P)

- Diverse group of particles
- Many anti-atherogenic properties
  - Cholesterol removal from cells & plaques (Reverse Cholesterol Transport)
  - Inhibit LDL-P oxidation
  - Promote endothelial repair
  - Improve endothelial dysfunction
  - Anti-thrombotic (prevent blood clots)
  - Anti-inflammatory
  - Inhibit monocyte binding to endothelium
  - Increase nitric oxide production
  - Prevent atherosclerotic lesion progression
  - Promote atherosclerotic lesion regression



50

HDL Particles (HDL-P) References

- Navab, M., Reddy, S., Van Lenten, B. et al. HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. Nat Rev Cardiol 8, 222–232 (2011).
- Rye KA, Bursill CA, Lambert G, Tabet F, Barter PJ. The metabolism and anti-atherogenic properties of HDL. J Lipid Res. 2009 Apr;50 Suppl(Suppl):S195-200.
- Lewis G. F., and D. J. Rader. 2005. New insights into the regulation of HDL metabolism and reverse cholesterol transport. Circ. Res. 96 1221–1232.
- Negre-Salvayre A., N. Dousset, G. Ferretti, T. Bacchetti, G. Curatola, and R. Salvayre. 2006. Antioxidant and cytoprotective properties of high-density lipoproteins in vascular cells. Free Radic. Biol. Med. 41 1031–1040.
- Tso C., G. Martinic, W. H. Fan, C. Rogers, K. A. Rye, and P. J. Barter. 2006. High-density lipoproteins enhance progenitor-mediated endothelium repair in mice. Arterioscler. Thromb. Vasc. Biol. 26 1144–1149.
- Mineo C., H. Deguchi, J. H. Griffin, and P. W. Shaul. 2006. Endothelial and antithrombotic actions of HDL. Circ. Res. 98 1352–1364.
- Cockerill G. W., K. A. Rye, J. R. Gamble, M. A. Vadas, and P. J. Barter. 1995. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler. Thromb. Vasc. Biol. 15 1987–1994.
- Murphy, A. J., K. J. Woollard, A. Hoang, N. Mukhamedova, R. A. Stirzaker, S. P. McCormick, A. T. Remaley, D. Sviridov, and J. Chin-Dusting. 2008. High-Density Lipoprotein Reduces the Human Monocyte Inflammatory Response. Arterioscler Thromb Vasc Biol.
- Tangirala R. K., K. Tsukamoto, S. H. Chun, D. Usher, E. Pure, and D. J. Rader. 1999. Regression of atherosclerosis induced by liver-directed gene transfer of apolipoprotein A-I in mice. Circulation. 100 1816–1822.
- Badimon J. J., L. Badimon, and V. Fuster. 1990. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. J. Clin. Invest. 85 1234–1241.

51

HDL-P are VERY GOOD

- "HDL *particles* play a number of important roles in preventing and REVERSING CVD, but – just like LDL-P – we need to focus on a specific type of HDL-P"

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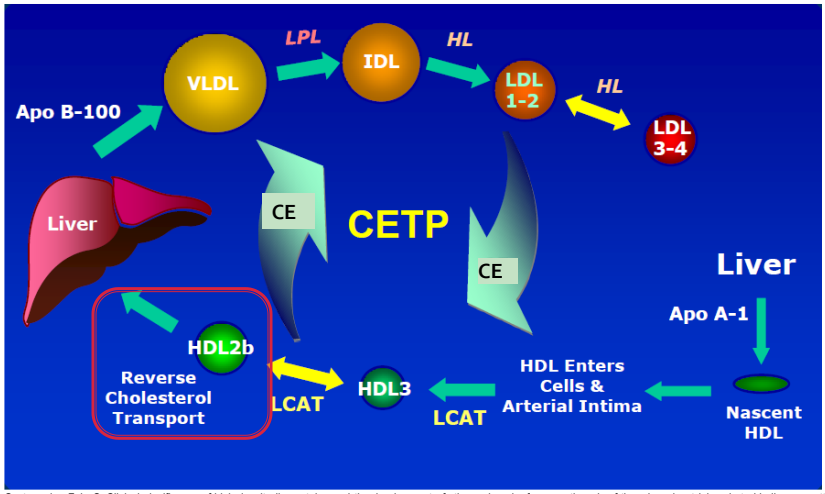
HDL Particles (HDL-P)

- HDL-P are a better predictor of CVD risk than HDL-C
  - HDL-C no longer predictive of CVD after adjusting for HDL-P
- HDL2b particles are an indicator of rate of reverse cholesterol transport
  - Indicates how well lipids are removed from cells/macrophages/plaques
  - High HDL2b = ↓ CVD risk
  - Low HDL2b = ↑ CVD risk

Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. Circulation 2013;128:1189-97.
Mackey RH, Greenland P, Goff DC, Jr., et al. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2012;60:508-16.
Morgan J, et al.High-density lipoprotein subfractions and risk of coronary artery disease. Current Atherosclerosis Reports. 2004. 6: pages 359-365.
Alterations of high-density lipoprotein subclasses in hypercholesterolemia and combined hyperlipidemia. Int J Cardiol. 2007. 120(3): pages 331-337.

53

Reverse Cholesterol Transport (RCT)



Brewer HB Jr, Santamarina-Fojo S. Clinical significance of high-density lipoproteins and the development of atherosclerosis: focus on the role of the adenosine triphosphate-binding cassette protein A1 transporter. Am J Cardiol. 2003 Aug 21;92(4B):10K-16K.
Rajman I, Eacho PI, Chowienczyk PJ, Ritter JM. LDL particle size: an important drug target? British Journal of Clinical Pharmacology. 1999;48(2):125-133.

54

No "Good" vs. "Bad" Cholesterol

- Cholesterol isn't "good" or "bad", it's just carried by different lipoprotein particles
- *It's the different lipoprotein particles that carry the cholesterol that confer risk or protection from atherosclerosis & CVD*
- *So, we need to measure the particles & NOT cholesterol*

55

Triglycerides (TG):HDL-C

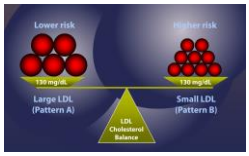
- Ratio of TG:HDL-C correlates strongly with incidence and extent of CVD (ratio > 4)
  - Best CVD predictor that can be derived from standard lipid testing
  - Marker of insulin resistance/metabolic syndrome (TG/HDL-C >3)
  - Can be useful to predict LDL particle size and to some extent particle number

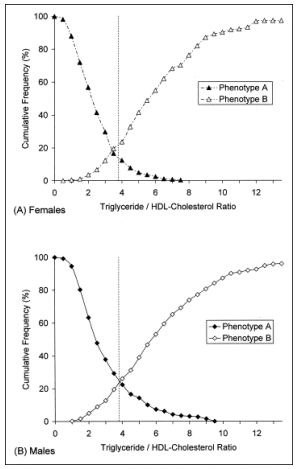
Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk. 1996; 3: 213–219.
Assmann G, Schulte H, von Eckardstein A. Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. Am J Cardiol. 1996; 77: 1179–1184.
Yarnell JW, Patterson CC, Sweetnam PM, et al. Do total and high density lipoprotein cholesterol and triglycerides act independently in the prediction of ischemic heart disease? Ten-year follow-up of Caerphilly and Speedwell Cohorts. Arterioscler Thromb Vasc Biol. 2001; 21: 1340–1345.
McLaughlin T, et al. Use of Metabolic Markers To Identify Overweight Individuals Who Are Insulin Resistant. Ann Intern Med. 2003;139:802–809.
da Luz PL, et al. Comparison of serum lipid values in patients with coronary artery disease at <50, 50 to 59, 60 to 69, and >70 years of age. Am J Cardiol. 2005 Dec 15;96(12):1640-3. Epub 2005 Oct 21.

56

TG:HDL-C and LDL Particle size

- TG:HDL-C ratio can predict particle size
  - 79% of people with ratio > 3.8 had increased small, dense LDL particles
  - 81% of those with ratio < 3.8 had increased large, buoyant LDL particles

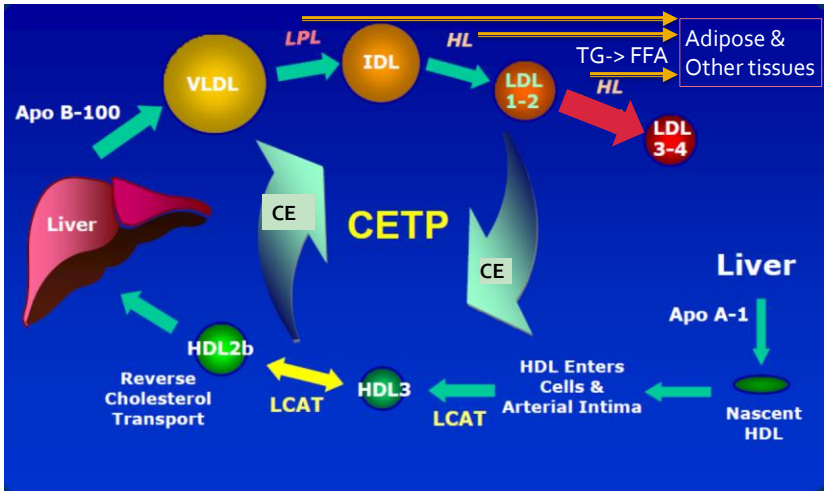




Hanak V, et al. Accuracy of the triglyceride to high-density lipoprotein cholesterol ratio for prediction of the low-density lipoprotein phenotype B. Am J of Cardio; 94(2); 219-222.
Miller BD, et al. Predominance of Dense Low-Density Lipoprotein Particles Predicts Angiographic Benefit of Therapy in the Stanford Coronary Risk Intervention Project. Circulation. 1996;94:2146-2153, originally published November 1, 1996.

57

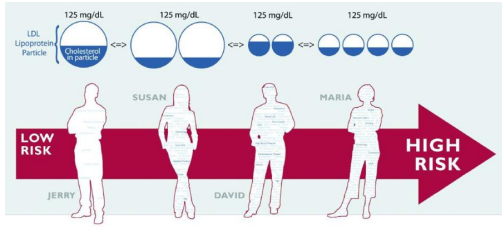
Endogenous/RCT Pathways



Fielding CJ, Fielding PE. Molecular physiology of reverse cholesterol transport. J Lipid Res. 1995;36:211–28.
Xu Y, Fu M. Alterations of HDL subclasses in hyperlipidemia. Clin Chim Acta. 2003;332:95–102.

58

TG:HDL-C and Particle Number



- Explain the difference between LDL-C and the LDL-P that carry that cholesterol
- A high TG:HDL-C ratio indicates that they likely have a higher number of small, dense LDL-P, which dramatically increases their risk of CVD
  - People with small, dense LDL-P have a 300% increased risk of coronary heart disease
- This can be verified with advanced testing for ~$200
  - Provides the information needed to identify and address issues with blood lipid metabolism

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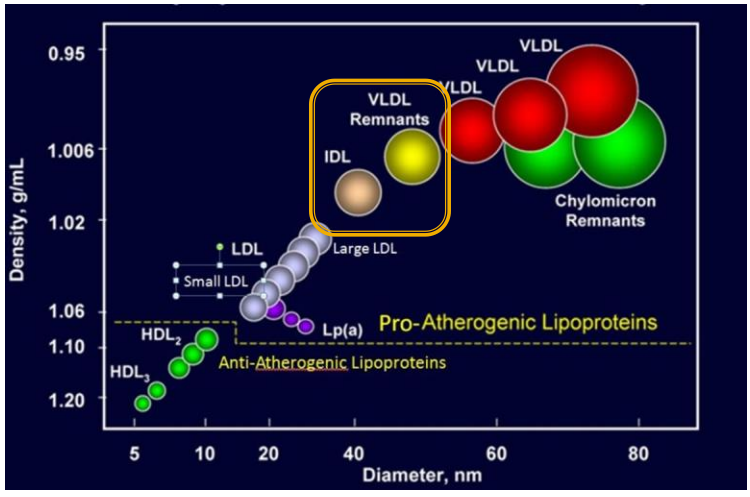
Remnant Lipoproteins (RLP-P)



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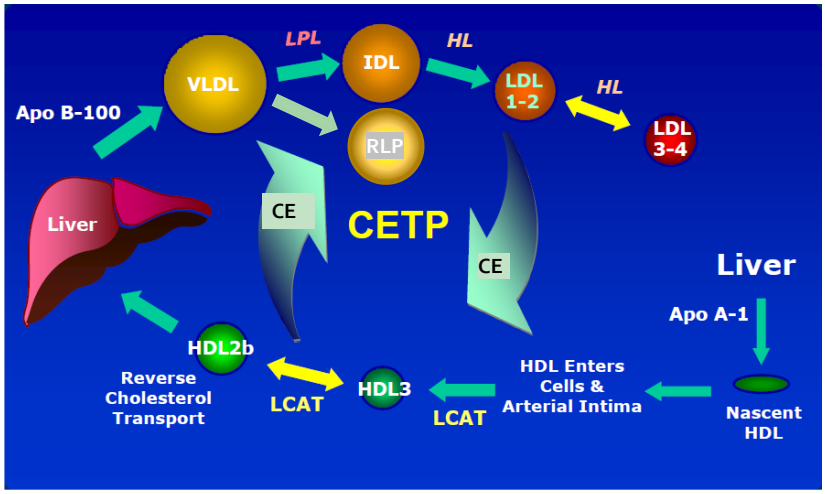
Remnant Lipoprotein (RLP-P)



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Rajman I, Eacho PI, Chowienczyk PJ, Ritter JM. LDL particle size: an important drug target? British Journal of Clinical Pharmacology. 1999;48(2):125-133.

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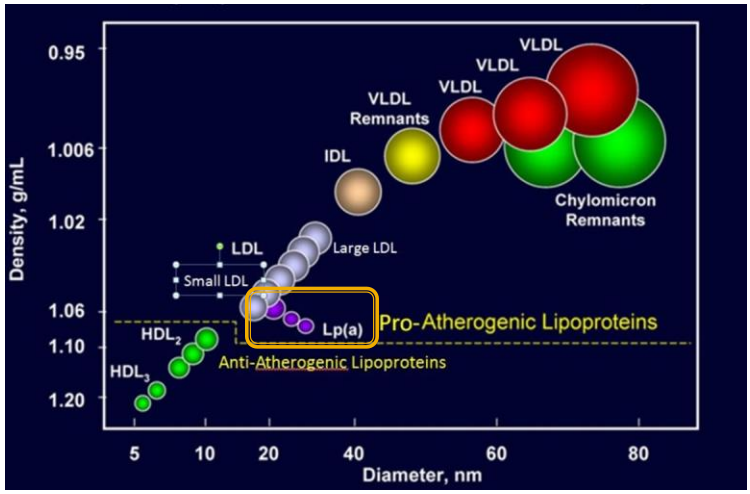
Remnant Lipoprotein Particles (RLP-P)

- One of the most atherogenic lipoproteins
  - Initiate and propagate that atherosclerotic process
  - Can be taken up by macrophages and form foam cells with or *without* being oxidized
    - Dramatically increases the rate of foam cell/atherosclerotic plaque formation
  - RLPs also induce thrombin generation, which increases the risk of blood clots
- RLP-P # does NOT correlate with LDL-C
  - Often, people with high RLP particles have normal or low LDL-C
    - NOT accounted for in standard lipid testing
- High in 25% of the population
- Common in people with metabolic syndrome
  - ~1 in 3 US Adults = 93 million people
- ↑ RLP-P often leads to high blood pressure

Kim, J.-Y., Park, J.-H., et al (2011). High Levels of Remnant Lipoprotein Cholesterol Is a Risk Factor for Large Artery Atherosclerotic Stroke. Journal of Clinical Neurology, 7(4), 203–209.
Fujioka Y, Ishikawa Y. Remnant lipoproteins as strong key particles to atherogenesis. J Atheroscler Thromb. 2009;16:145–154.
Nakajima K, et al. The oxidative modification hypothesis of atherosclerosis: The comparison of atherogenic effects on oxidized LDL and remnant lipoproteins in plasma. Clin Chim Acta. 2006 May;367(1-2):36-47. Epub 2006 Jan 30.
Sane T., Nikkila E. A.. 1988. Very low density lipoprotein triglyceride metabolism in relatives of hypertriglyceridemic probands. Arteriosclerosis. 8: 217–226.
Grundy S. M., Mok H. Y. I., Zech L., Steinberg D., Berman M.. 1979. Transport of very low density lipoprotein triglycerides in varying degrees of obesity and hypertriglyceridemia. J. Clin. Invest. 63: 1274–1283.
Whitman SC, et al. Oxidized type IV hypertriglyceridemic VLDL-remnants cause greater macrophage cholesteryl ester accumulation than oxidized LDL. J Lipid Res. 1998 May;39(5):1008-20.

62

Lipoprotein (a)



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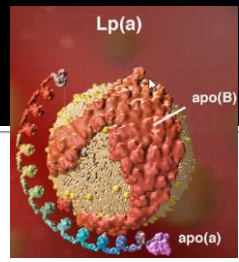
Lipoprotein (a)



- Genetic component of CVD
- High in 20-25% of the population
- Small particle that is easily oxidized to cause plaque
- Very strong independent risk factor for CVD
- Particularly detrimental with ↑ LDL-C, ↓ HDL-C, diabetes, hypertension, ↑ homocysteine or ↑ hs-CRP/inflammation
  - Most detrimental if/when other CVD risk factors are present
    - ➢ Address all other known risk factors and lower Lp(a) AMAP

Solfrizzi V, et al. Relation of lipoprotein(a) as coronary risk factor to type 2 diabetes mellitus and low-density lipoprotein cholesterol in patients > or = 65 years of age (The Italian Longitudinal Study on Aging). Am J Cardiol.2002;89:825-829.
Cantin B, et al. Association of fibrinogen and lipoprotein(a) as a coronary heart disease risk factor in men (The Quebec Cardiovascular Study). Am J Cardiol.2002;89:662-666.
von Eckardstein A, Schulte H, Cullen P, Assmann G. Lipoprotein(a) further increases the risk of coronary events in men with high global cardiovascular risk. J Am Coll Cardiol.2001;37:434-439.
Foody JM, et al. Homocysteine and lipoprotein(a) interact to increase CAD risk in young men and women. Arterioscler Thromb Vasc Biol.2000;20:493-499.
Gaw A, Boerwinkle E, Cohen JC, Hobbs HH. Comparative analysis of the apo(a) gene, apo(a) glycoprotein, and plasma concentrations of Lp(a) in three ethnic groups: evidence for no common "null" allele at the apo(a) locus. J Clin Invest.1994;93:2526-2534.
Graphic: https://www.amgen.com/stories/2023/02/8-things-to-know-about-lipoproteina

64

Lp (a) and CVD Risk

- Lp(a) competes with Plasminogen & prevents Fibrinolysis
  - Reduces activation of plasminogen to plasmin
    - Plasmin breaks down blood clots
- Lp(a) decreases ability to dissolve blood clots
- Atherogenic and Thrombotic
- Increases the risk of plaque rupture and thrombotic events (MI, Stroke, DVT)
- 3-5x greater risk of CVD if Lp(a) elevated
  - Completely missed on standard lipid panels

Beisiegel U, Niendorf A, Wolf K, Reblin T, Rath M. Lipoprotein(a) in the arterial wall. Eur Heart J. 1990 Aug;11 Suppl E:174-83.
Smith EB, Cochran S. Factors influencing the accumulation in fibrous plaques of lipid derived from low density lipoprotein. II. Preferential immobilization of lipoprotein (a) (Lp(a)). Atherosclerosis. 1990 Oct;84(2-3):173-81.
Assmann G, Schulte H, Eckardstein AV. Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for coronary events in middle-aged men. Am J Cardiol.. 1996;77:1179–1184.

65

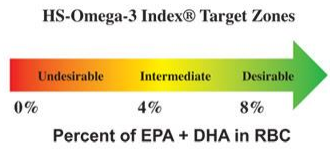
Particles Are Important




66

HS-Omega 3 Index

- Measure of the relative amounts of EPA + DHA in red blood cells
- Standardized analytical method
- Risk factor for sudden cardiac death and mortality due to CVD
- Ideal ≥ 8% - 11%
- Average American ~3.5-5%

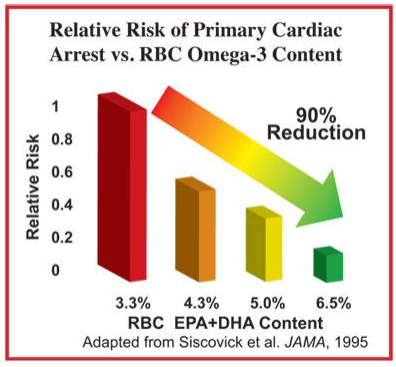


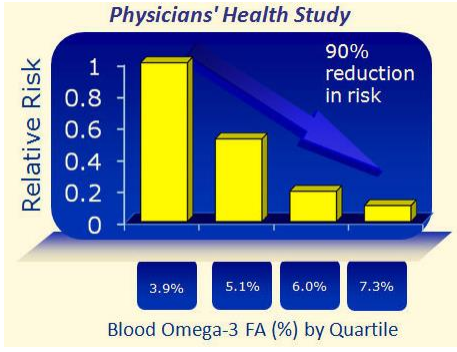
Harris W.S., von Schacky C., Park Y. Standardizing Methods for Assessing Omega-3 Biostatus. In: McNamara R.K., editor. The Omega-3 Deficiency Syndrome. Nova Publishers; Hauppauge, NY, USA: 2013. pp. 385–398.
Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med. 2004 Jul; 39(1):212-20.
Block RC, Harris WS, Reid KJ, et al. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. Atherosclerosis. 2008 Apr;197(2):821-8. Epub 2007 Sep 17.
Superko HR, Superko SM, Nasir K, et al. Omega-3 Fatty Acid Blood Levels. Circulation. 2013;128:2154-2161.
Von Schacky C. Omega-3 Index and Cardiovascular Health. Nutrients. 2014;6(2):799-814.

67

HS-Omega 3 Index and CVD

Optimized EPA+DHA levels dramatically decrease the risk of death from CVD





Siscovick DS, et al. Dietary Intake and Cell Membrane Levels of Long-Chain n-3 Polyunsaturated Fatty Acids and the Risk of Primary Cardiac Arrest. JAMA. 1995;274(17): 1363–1367.
Albert CM et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med. 2002; 346: 1113-1118.

68

EPA/DHA Dosing

- Need 1300-1500 mg *more* EPA+DHA/day to increase HS-Omega 3 Index from ~4% to ~8% in 5 months
  - + Omega Pure EPA-DHA 720: 1 cap BID wf

Flock MR, Skulas-Ray AC, Harris WS, et al. Determinants of Erythrocyte Omega-3 Fatty Acid Content in Response to Fish Oil Supplementation: A Dose-Response. Randomized Controlled Trial. J Am Heart Assoc, 2 (2013), p. e000513
Harris WS, et al. Erythrocyte long-chain omega-3 fatty acid levels are inversely associated with mortality and with incident cardiovascular disease: The Framingham Heart Study. Journal of Clinical Lipidology; 12(3):718-727.

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High sensitivity CRP (hs-CRP)

- Atherosclerosis is an inflammatory disorder
  - Inflammation can cause endothelial dysfunction
  - Oxidized lipoproteins initiate/propagate inflammatory response
  - Inflammation drives plaque formation & calcification
  - Inflammation increases likelihood of plaque rupture and thrombosis

- C-reactive protein (CRP) is a marker of systemic inflammation
- Studies have shown that:
  - hs-CRP elevations (>2.0 mg/L) are associated with acute CV events and mortality
  - hs-CRP is a stronger predictor of CVD events than LDL-C levels
  - **hs-CRP>3 has been shown to increase risk of CV event 300%**

Fuster V, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes (1) N Engl J Med. 1992;326:242–250.
Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352:1685–1695.
Ridker PM, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336:973–979.
Ridker PM, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002;347:1557–1565.
Buckley DI, et al. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151:483-95
Kaptoge S, et al, Emerging Risk Factors Collaboration C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375:132–140. doi: 10.1016/S0140-6736(09)61717-7.

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Homocysteine

- Homocysteine has been shown to both initiate and propagate atherosclerosis via:
  - Oxidative stress, platelet activation, endothelial dysfunction, hyper coagulability, vascular smooth muscle cell proliferation and mitochondrial stress
  - Causes oxidative stress, which inhibits L-arginine uptake, causes eNOS uncoupling and ↓ NO production
- Mild/moderate elevations, *even within the normal range*, increase risk of atherosclerosis/CVD

Mangoni AA, Jackson SH. Homocysteine and cardiovascular disease: current evidence and future prospects. Am J Med.2002;112:556-565.
De Bree A, et al. Homocysteine determinants and the evidence to what extent homocysteine determines the risk of coronary heart disease. Pharmacol Rev.2002;54:599-618.
Werstuck GH, et al. Homocysteine-induced endoplasmic reticulum stress causes dysregulation of the cholesterol and triglyceride biosynthetic pathways. J Clin Invest.2001;107:1263-1273.
Danesh J, Lewington S. Plasma homocysteine and coronary heart disease: systematic review of published epidemiological studies. J Cardiovasc Risk. 1998;5:229–232.
Homocysteine Studies Collaboration Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA. 2002;288:2015–2022.
Janaszak-Jasiecka, A., Płoska, A., Wierońska, J.M. et al. Endothelial dysfunction due to eNOS uncoupling: molecular mechanisms as potential therapeutic targets. Cell Mol Biol Lett 28, 21 (2023).

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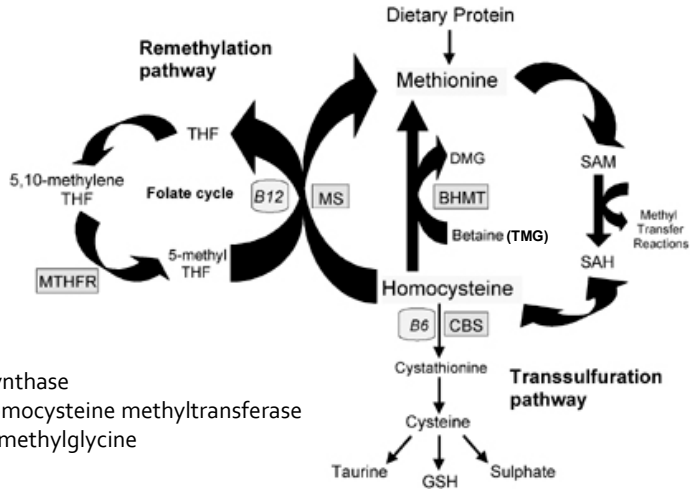
Homocysteine Metabolism



MS = methionine synthase
BHMT = betaine-homocysteine methyltransferase
Betaine = TMG = trimethylglycine

Mangoni AA, Jackson SH. Homocysteine and cardiovascular disease: current evidence and future prospects. Am J Med.2002;112:556-565.
De Bree A, et al. Homocysteine determinants and the evidence to what extent homocysteine determines the risk of coronary heart disease. Pharmacol Rev.2002;54:599-618.

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Causes of Elevated Homocysteine

- Genetic SNPs
  - Homozygous for MTHFR variant (677 C->T) present in ~15% of Caucasian population
  - Can increase homocysteine 25%
- Nutrient deficiency
  - B6, B12, folate – reduced forms often necessary
  - Trimethylglycine (TMG)
- Medications
  - Fibrates, cholestyramine, Glucophage/metformin, methotrexate

Frosst P, Blom HJ, Milos R. et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet.1995;10:111-113.
De Bree A, et al. Homocysteine determinants and the evidence to what extent homocysteine determines the risk of coronary heart disease. Pharmacol Rev.2002;54:599-618.
Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. BMJ.1998;316:894-898.
Desouza C, et al. Drugs affecting homocysteine metabolism: impact on cardiovascular risk. Drugs. 2002;62(4):605-16.

73

Getting the Information We Need

- ApoB-100 (ApoB) &/or LDL-P #
- Small, dense LDL-P (III/IV)
  - TG:HDL-C>4
- RLP-P
- Lp(a)
- HDL-P
  - HDL2b-P
- HS-Omega-3 Index
- hs-CRP
- Homocysteine

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CVD Risk Summary

- Patients at increased risk of CVD frequently have:
  - An atherogenic lipoprotein profile:
    - ↑ triglyceride-rich lipoproteins (VLDL-P, RLP-P)
    - ↑ small, dense LDL particles
    - ↑ Lp(a)
    - ↓ HDL particles (especially HDL2b)
  - Nitric oxide dysregulation

- Those with metabolic syndrome, T2D, hypertension
- Often presents with *normal* LDL-C
  - Completely missed with standard lipid panels
- 3-fold (300%) increase in CVD risk

Gordon T, Kannel WB, Castelli, et al. Lipoproteins, cardiovascular diseases and death. The Framingham Study. Arch Intern Med 1981;141:1128– 31.
Austin MA, McKnight B, Edwards KI, et al. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a 20-year prospective study. Circulation 2000;101:2777 – 82.
Twickler TB, Dallinga-Thie GM, Cohn JS, Chapman MJ. Elevated remnant-like particle cholesterol concentration: a characteristic feature of the atherogenic lipoprotein phenotype. Circulation 2004;109:1918– 25.

75

CVD Risk Summary

BEST PREDICTORS OF CVD RISK:

- ↑ Apo B-100 / ↑ LDL-P#
- ↑ Small LDL particles
  - Especially small, dense LDL-P
- ↑ RLP-P
- ↓ HDL2b
- ↓ Nitric oxide
- ↑ Blood pressure

CVD RISK MODIFIERS:

- Metabolic syndrome/ type II diabetes
- ↑ Lp(a)
- ↑ Hs-CRP
- ↑ Homocysteine
- ↓ HS-Omega-3 Index

- **If only have standard lipid testing:**
  - TG:HDL-C
  - Use to encourage advanced testing

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Optimal Values – Standard Testing

Marker	Optimal Value	Notes
Total Cholesterol	<200 mg/dl	
HDL-C	>60 mg/dl	
LDL-C	<100 mg/dl	
Triglycerides	<100 mg/dl	
TG/HDL-C (mg/dl)	**<2.0**	**Esp important for diabetes/insulin resistance**
TC/HDL-C	2.5-3.5	
Fasting glucose	80-90 mg/dl	
Nitric Oxide	Target level or higher	Nitric Oxide Indicator Strips
Systolic BP	<120 mmHg	
Diastolic BP	<80 mmHg	

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Optimal Values – Advanced Testing

Marker	Optimal Value	Notes
LDL-P	< 900 nmol/L	Especially important for diabetes, metabolic syndrome and ↑ TG/HDL-C
Apo B-100	<80 mg/dl; <70 mg/dl for high risk	
Non-HDL-P	< 800 nmol/L	
Dense LDL III	< 300 nmol/L	
Dense LDL IV	< 100 nmol/L	
Lp(a)	< 30 mg/dl; < 70 nmol/L	
VLDL-P	< 85 nmol/L; <30 mg/dl	
RLP-P	< 150 nmol/L	
HDL2b-P	> 1500 nmol/L	
hs-CRP	< 1.0 mg/L	
Homocysteine	< 7-10 mg/dl	
HS-Omega-3 Index	> 8%	
Fasting Insulin	7-9 µlU/ml	

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Getting an Update…

- We should not be using technology and data from the 70s & 80s when research from this century points us in a better direction

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Clinicians NEED Better Data

- Approximately 50% of all CVD-related deaths have no prior cardiac symptoms or diagnoses
  - We need a way to identify these people
- Current algorithms to identify CVD risk are heavily weighted for age
  - Nearly everyone over 65 is labeled borderline/high
  - Most everyone under 65 is labeled low risk
- We need more accurate ways to determine, communication and address CVD risk

Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56(25):e50–e103.
Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007;49(3):378–402.
Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary Calcium Score and Cardiovascular Risk. J Am Coll Cardiol 2018;72(4):434–447.

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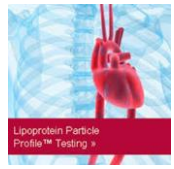
Advanced Diagnostic Tools

- Advanced Lipoprotein Testing
  - LPP+ Testing (Lipoprotein Particle Profile)
  - KBMO – CIT (Cardiovascular Inflammation Test)
- Omega-3 Index
- Nitric Oxide Indicator Strips



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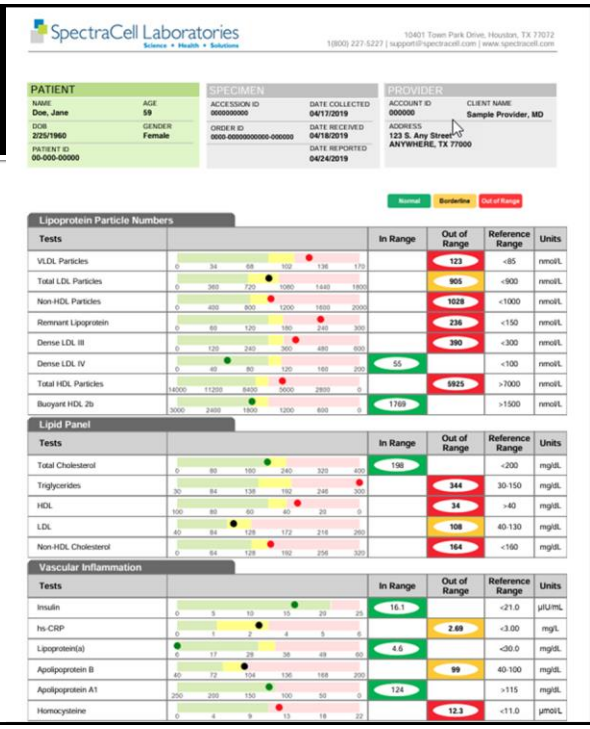
LPP+

- Provides direct measurement of:
  - VLD-P
  - Total LDL-P
  - RLP-P
  - Small dense LDL-P
    - LDL III/IV
  - HDL2b-P
  - Fasting insulin
  - hs-CRP
  - Lp(a)
  - ApoB
  - Homocysteine
- Requires a blood draw
- www.spectracell.com


SpectraCell Laboratories

PATIENT
NAME: Doe, Jane
AGE: 59
DOB: 2/25/1960
GENDER: Female
PATIENT ID: 00-000-00000

SPECIMEN
ACCESSION ID: 0000000000
DATE COLLECTED: 04/17/2019
ORDER ID: 0000-00000000000-000000
DATE RECEIVED: 04/18/2019
DATE REPORTED: 04/24/2019

PROVIDER
ACCOUNT ID: 000000
CLIENT NAME: Sample Provider, MD
ADDRESS: 123 S. Any Street ANYWHERE, TX 77000

Lipoprotein Particle Numbers

Tests	In Range	Out of Range	Reference Range	Units
VLDL Particles		123	<85	nmol/L
Total LDL Particles		905	<900	nmol/L
Non-HDL Particles		1028	<1000	nmol/L
Remnant Lipoprotein		236	<150	nmol/L
Dense LDL III		390	<300	nmol/L
Dense LDL IV	55		<100	nmol/L
Total HDL Particles		5925	>7000	nmol/L
Buoyant HDL 2b	1769		>1500	nmol/L

Lipid Panel

Tests	In Range	Out of Range	Reference Range	Units
Total Cholesterol	198		<200	mg/dL
Triglycerides		344	30-150	mg/dL
HDL		34	>40	mg/dL
LDL		108	40-130	mg/dL
Non-HDL Cholesterol		164	<160	mg/dL

Vascular Inflammation

Tests	In Range	Out of Range	Reference Range	Units
Insulin	16.1		<21.0	µIU/mL
hs-CRP		2.69	<3.00	mg/L
Lipoprotein(a)	4.6		<30.0	mg/dL
Apolipoprotein B		99	40-100	mg/dL
Apolipoprotein A1	124		>115	mg/dL
Homocysteine		12.3	<11.0	µmol/L

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Using the LPP+ to Address CVD

- Step 1: Primary Risk Assessment
  - High LDL particle number (<900) &/or Apo B (<80 mg/dL)
  - Elevated small/dense LDL (LDL III >300 nmol/L; LDL IV > 100 nmol/L)
  - Elevated RLP (150 nmol/L); Moderate/high Triglycerides (>150 mg/dL)
  - Low HDL2b (<1500 nmol/L)
- Step 2: Modify risk using Metabolic syndrome traits, Lp(a) & hs-CRP
  - Combine metabolic syndrome traits from LPP with blood pressure, obesity (WC/BIA) & fasting glucose
  - ↑ Lp(a) and/or ↑ hs-CRP and/or ↑ homocysteine
  - Also consider family Hx, medical Hx and smoking
  - Modify risk assessment and Tx goals from Step 1 based on these criteria
  - Use standard Lipid Panel at bottom to compare with previous labs
- Step 3: Determine Therapeutic Approach
  - Determine Tx goals and therapeutic approach to address each risk factor
  - Refer to LPP Therapeutic Guidelines

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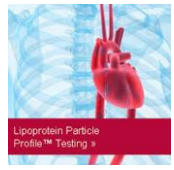
Who should take the LPP Test?



- All patients, and especially those who:
  - Have a family history of heart disease or diabetes
  - Have been diagnosed with heart disease or diabetes
  - Are already taking cholesterol-lowering medications
  - Have been diagnosed with Metabolic Syndrome (high blood pressure)
  - Are overweight
  - Have high LDL - the bad cholesterol
  - Have low HDL - the good cholesterol
  - Have high triglycerides
  - Anyone that wants to know their cardiovascular disease risk!
- Requires a blood draw; they have many draw sites available
  - If blood draw is not an option, run the KBMO CIT

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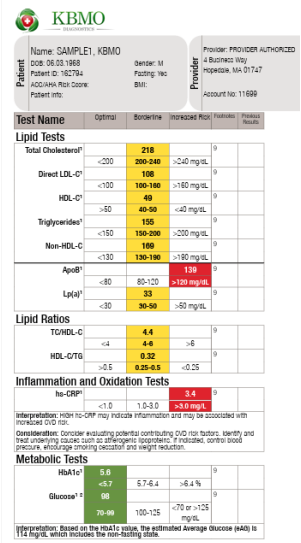
Cardiovascular Inflammation Test - CIT

- If blood draw is not an option, you the CIT from KBMO
- Provides a measure of:
  - ApoB
  - Lp(a)
  - TC/HDL-C ratio
  - HDL-C/TG ratio
    - <0.25 = Marker of insulin resistance and likelihood of small dense LDL-P (III/IV)
  - hs-CRP
  - HbA1C
  - Fasting glucose
- Speak to Ron/Nutri-Dyn rep to learn more


KBMO

Patient — Name: SAMPLE1, KBMO; DOB: 06.03.1968; Patient ID: 162794; ACC/AHA Risk Score:; Patient info:; Gender: M; Fasting: Yes; BMI:

Provider — Provider: PROVIDER AUTHORIZED; 4 Business Way; Hopedale, MA 01747; Account No: 11699

Test Name		Optimal	Borderline	Increased Risk	Footnotes	Previous Results
Lipid Tests						
Total Cholesterol[1]		<200	218 200-240	>240 mg/dL	0	
Direct LDL-C[1]		<100	108 100-160	>160 mg/dL	0	
HDL-C[1]		>50	49 40-50	<40 mg/dL	0	
Triglycerides[1]		<150	155 150-200	>200 mg/dL	0	
Non-HDL-C		<130	169 130-190	>190 mg/dL	0	
ApoB[1]		<80	80-120	139 >120 mg/dL	0	
Lp(a)[1]		<30	33 30-50	>50 mg/dL	0	
Lipid Ratios						
TC/HDL-C		<4	4.4 4-6	>6	0	
HDL-C/TG		>0.5	0.32 0.25-0.5	<0.25	0	
Inflammation and Oxidation Tests						
hs-CRP[1]		<1.0	1.0-3.0	3.4 >3.0 mg/L	0	
Metabolic Tests						
HbA1c[1]		5.6 <5.7	5.7-6.4	>6.4 %	0	
Glucose*[1]		98 70-99	100-125	<70 or >125 mg/dL	0	

Interpretation: HIGH hs-CRP may indicate inflammation and may be associated with increased CVD risk.

Consideration: Consider evaluating potential contributing CVD risk factors, identify and treat underlying causes such as atherogenic lipoproteins. If indicated, control blood pressure, encourage smoking cessation and weight reduction.

Interpretation: Based on the HbA1c value, the estimated Average Glucose (eAG) is 114 mg/dL which includes the non-fasting state.

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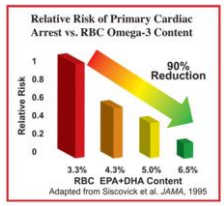
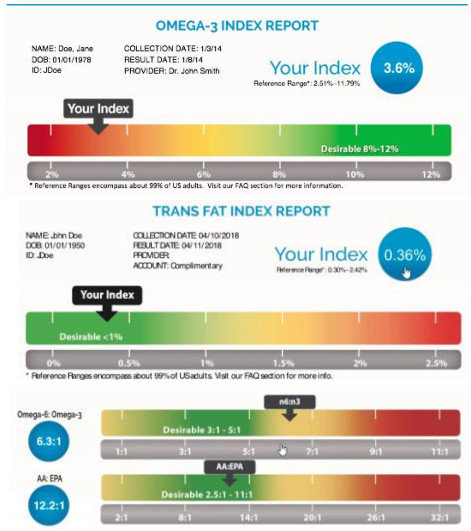
Omega-3 Index Plus Test

- Omega-3 Index Basic Test
  - Omega-3 Index
- Omega-3 Index Plus Test
  - Omega-3 Index
  - Trans Fat Index
  - Omega-6:Omega-3 Ratio
  - AA:EPA Ratio
- Available through Nutri-Dyn



- EFA dosing:
  - Add 1300-1500 mg EPA+DHA/day to increase Omega 3 Index from ~4% to ~8% in 5 months
- 90% reduction in risk of sudden cardiac death when Omega-3 Index >8%



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CVD Recommendations: Diet

- A diet high in vegetables and fruits decreases the risk of CVD and death
- Total fat intake does not appear to be an important risk factor for CVD*
  - Trans fats dramatically increase CVD and death
  - Replacing SFA with MUFA/PUFA reduces CVD risk
- A diet high in high-GI (Glycemic Index) foods increases risk for CVD
- A Mediterranean diet decreases CVD risk and can improve existing CVD
  - More effective than low-fat; low-carb; high-fat; high-protein; vegetarian or vegan diets in reducing CVD risk

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CVD Recommendations: Diet - References

Wang, X, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ. 349: g4490.
Walker C, Reamy BV (April 2009). "Diets for cardiovascular disease prevention: what is the evidence?". Am Fam Physician. 79 (7): 571–8.
Nordmann, AJ, et al. Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. The American Journal of Medicine. 124 (9): 841–51.e2.
Threapleton, DE, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ. 347 (dec19 2): f6879–f6879.
Fats and fatty acids in human nutrition Report of an expert consultation. World Health Organization. WHO/FAO. Archived from the original on 28 December 2014. Retrieved 20 December 2014.
Willett, WC (July 2012). "Dietary fats and coronary heart disease". Journal of Internal Medicine. 272 (1): 13–24.
Chowdhury R, et al. Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk. Annals of Internal Medicine. 160 (6): 398–406.
de Souza RJ, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 351 (h3978).
Ajala O, English P, Pinkney J. Systemic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013;97:505-16.
Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, et al.: Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999, 353:1547–1557.
Menotti A, Kromhout D, Blackburn H, et al.: Food intake patterns and 25-year mortality from coronary heart disease: cross-cultural correlations in the Seven Countries Study. The Seven Countries Study Research Group. Eur J Epidemiol 1999, 15:507–515.
Zhou BF, Stamler J, Dennis B, et al.: Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTER-MAP study. J Hum Hypertens 2003, 17:623–630.
Matalas AL: Disparities within traditional Mediterranean food patterns: an historical approach of the Greek diet. Int J Food Sci Nutr 2006, 57:529–536.
Stanhope JM, Sampson VM, Prior IA: The Tokelau Island Migrant Study: serum lipid concentration in two environments. J Chronic Dis 1981, 34:45–55.
Lindeberg S, Nilsson-Ehle P, Terent A, et al.: Cardiovascular risk factors in a Melanesian population apparently free from stroke and ischaemic heart disease: the Kitava study. J Intern Med 1994, 236:331–340.
Hooper, L, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database of Systematic Reviews.
Siri-Tarino PW, et al. Saturated fat, carbohydrate, and cardiovascular disease. American Journal of Clinical Nutrition. 91 (3): 502–509.
Micha, R; Mozaffarian, D (October 2010). "Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence". Lipids. 45 (10): 893–905.
Willett, WC (July 2012). "Dietary fats and coronary heart disease". Journal of Internal Medicine. 272 (1): 13–24.

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CVD Recommendations: Diet - References

Moreno JA,, et al.: A monounsaturated fatty acid-rich diet reduces macrophage uptake of plasma oxidised low-density lipoprotein in healthy young men. Br J Nutr 2008, 100:569–575.
Galgani JE, et al. Effect of the dietary fat quality on insulin sensitivity. Br J Nutr 2008, 100:471–479.
Mensink RP, et al. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003, 77:1146–1155.
Smith RD, et al.: Long-term monounsaturated fatty acid diets reduce platelet aggregation in healthy young subjects. Br J Nutr 2003, 90:597–606.
Cordain L, et al.: Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr 2005, 81:341–354.
Ervin RB, Wright JD, Wang CY, Kennedy-Stephenson J: Dietary intake of fats and fatty acids for the United States population: 1999–2000. Adv Data 2004, 1–6.
Cordain L, et al.: Fatty acid analysis of wild ruminant tissues: evolutionary implications for reducing diet-related chronic disease. Eur J Clin Nutr 2002, 56:181–191.
Ramsden, C.E. et al. Dietary fat quality and coronary heart disease prevention: A unified theory based on evolutionary, historical, global, and modern perspectives. Curr Treat Options Cardio Med (2009) 11: 289.
Rose GA, Thomson WB, Williams RT: Corn oil in treatment of ischaemic heart disease. Br Med J 1965, 1:1531–1533.
Djousse L, et al.: Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. Am J Clin Nutr 2001, 74:612–619.
Hu FB, et al.: Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997, 337:1491–1499.
Wada M, et al.: Enzymes and receptors of prostaglandin pathways with arachidonic acidderived versus eicosapentaenoic acid-derived substrates and products. J Biol Chem 2007, 282:22254–22266.
Lands WE: Diets could prevent many diseases. Lipids 2003, 38:317–321.
Baylin A, Campos H: Arachidonic acid in adipose tissue is associated with nonfatal acute myocardial infarction in the central valley of Costa Rica. J Nutr 2004, 134:3095–3099.
Ramsden, C.E. et al. Dietary fat quality and coronary heart disease prevention: A unified theory based on evolutionary, historical, global, and modern perspectives. Curr Treat Options Cardio Med (2009) 11: 289.
Christensen JH, et al. Alphalinolenic acid and heart rate variability in women examined for coronary artery disease. Nutr Metab Cardiovasc Dis 2005, 15:345–351.
German JB, et al. A reappraisal of the impact of dairy foods and milk fat on cardiovascular disease risk. Eur J Nutr. 2009;48:191–203.
Smit LA, Baylin A, Campos H: Conjugated linoleic acid in adipose tissue and risk of myocardial infarction. Am J Clin Nutr 2010, 92:34–40.
Wijendran V, Hayes KC. Dietary n-6 and n-3 fatty acid balance and cardiovascular health. Annu Rev Nutr. 2004;24:597–615.
De Oliveira Otto MC, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. Amer J Clin Nutr. 2012;96(2):397-404.
Sinha R, et al. Meat intake and mortality: a prospective study of over half a million people. Arch Intern Med 2009;169:562–71.
O'Sullivan TA, et al. Food Sources of Saturated Fat and the Association With Mortality: A Meta-Analysis. American Journal of Public Health. 2013;103(9):e31-e42. doi:10.2105/AJPH.2013.301492.
Astrup, A, et al. The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010?. The American Journal of Clinical Nutrition. 93 (4): 684–8.
Hayes KC, et al. Saturated fatty acids and LDL receptor modulation in humans and monkeys. Prostaglandins Leukot Essent Fatty Acids. 1997;57:411–418.
Dietschy JM. Dietary fatty acids and the regulation of plasma low density lipoprotein cholesterol concentrations. J Nutr. 1998;128(2 Suppl):444S–448S.

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Mediterranean Diet

- Shown to reduce mortality due to CVD by 70+%
- Also shown to ↓ risk of cancer, obesity, metabolic syndrome, diabetes, and Alzheimer's disease
  - High in plant foods and monounsaturated fats
  - Low in processed foods, trans fats and refined carbohydrates
  - Only modest reductions in total cholesterol, LDL-C, non-HDL-C and LDL-P #(~10%)
  - ➢ Other metabolic processes must account for CVD risk reduction

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Mediterranean Diet and CVD

- Broad range of beneficial cardiovascular effects:
  - ↓TG, TG/HDL-C, fasting glucose, fasting insulin
  - ↑ LDL particle size
  - ↓ inflammation
  - ↓ body fat/weight
  - ↓ blood pressure
  - Improve GI flora health & function
  - Favorably alters atherogenic gene expression

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Modified Mediterranean Diet

- Modified Mediterranean, Low-glycemic load Diet
  - High in deep colored (low glycemic index) vegetables, fruits, herbs and spices
  - Alcohol: ≤ 1 glass of red wine (4 oz.)/day
  - Limit whole grains to 1 serving/day
    - Improves weight loss, blood sugar control & ↓ cravings
  - Glycemic index of foods ≤ 55
    - ≤ 1 serving/day of deep colored vegetables (GI 55-70)
  - Omit all sweeteners except agave nectar & stevia

Riccardi G, Clemente G, Giacco R. Glycemic index of local foods and diets: the Mediterranean experience. Nutr Rev. 2003;61:S56–60.
Lerman RH, Minich DM, Darland G, et al. Enhancement of a modified Mediterranean-style, low glycemic load diet with specific phytochemicals improves cardiometabolic risk factors in subjects with metabolic syndrome and hypercholesterolemia in a randomized trial. Nutrition & Metabolism. 2008;5:29. doi:10.1186/1743-7075-5-29.

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Modified Mediterranean Diet Guidelines

Food Category	Average Serving Size	Daily Recommendation	Examples
Legumes	½ cup	At least 1 serving	Beans, hummus, green peas
Low GI* (<55) Vegetables	½ cup	At least 3 servings	Broccoli, celery, cabbage, spinach, mushrooms, tomatoes, sea vegetables, fresh juices made from acceptable vegetables
Moderate GI (55-70) Vegetables	½ cup	Only 1 serving	Beets, sweet potatoes, carrots
Concentrated Protein Sources		Unlimited	Eggs , fish, poultry, tofu, low-fat cottage cheese, low-fat mozzarella
Fruits	Specific quantities for each fruit to equal 80 kcal	2-3 servings	Apple, blueberries, cherries, grapes, orange
Nuts and Seeds	Approx. 1 scant handful or 2 TBSP nut butter	1 serving	Peanut butter, almonds, hazelnuts, walnuts
Oils	1 teaspoon or as indicated	4 servings	Flaxseed oil, olive oil, ripe green olives, avocado
Dairy	6 oz. or as indicated	(Optional)	Plain low-fat yogurt, 1% milk, soymilk (unsweetened)
Beverages		Unlimited	Decaffeinated, herbal, or green tea; decaffeinated coffee; water
		Limited	1 glass of red wine (4 oz.), 1-2 cups (8 oz.) of caffeinated coffee
Condiments		Unlimited	Cinnamon, mustard, soy sauce, flavored extracts
Allowable sweeteners			Agave nectar, stevia

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Modified Mediterranean Diet Guidelines

To be eliminated from diet	Examples
Trans fatty acids	Partially hydrogenated vegetable oil
Artificial sweeteners	Splenda® (sucralose), NutraSweet® (aspartame)
High GI fruits and vegetables	White potatoes, corn, bananas
Simple sugars	High fructose corn syrup, fruit juice, table sugar (sucrose), evaporated cane juice, honey, maple syrup

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Mediterranean Diet References

de Lorgeril M, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet. 1994;343:1454–1459.

Estruch R, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279–1290.

Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr. 2010;92:1189–1196.

de Lorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N. Mediterranean dietary pattern in a randomized trial: prolonged survival and possible reduced cancer rate. Arch Intern Med. 1998;158:1181–1187.

Damasceno NR, et al. Mediterranean diet supplemented with nuts reduces waist circumference and shifts lipoprotein subfractions to a less atherogenic pattern in subjects at high cardiovascular risk. Atherosclerosis. 2013 Oct;230(2):347-53.

Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. J Am Coll Cardiol. 2004;44:152–158.

Holven KB, Narverud I, Lindvig HW, Halvorsen B, Langslet G, Nenseter MS, Ulven SM, Ose L, Aukrust P, Retterstøl K. Subjects with familial hypercholesterolemia are characterized by an inflammatory phenotype despite long-term intensive cholesterol lowering treatment. Atherosclerosis. 2014;233:561–567.

de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999;99:779–785.

Chiuve SE, Fung TT, Rexrode KM, Spiegelman D, Manson JE, Stampfer MJ, Albert CM. Adherence to a low-risk, healthy lifestyle and risk of sudden cardiac death among women. JAMA. 2011;306:62–69.

Akesson A, Larsson SC, Discacciati A, Wolk A. Low-risk diet and lifestyle habits in the primary prevention of myocardial infarction in men: a population-based prospective cohort study. J Am Coll Cardiol. 2014;64:1299–1306.

Lerman RH, Minich DM, Darland G, et al. Enhancement of a modified Mediterranean-style, low glycemic load diet with specific phytochemicals improves cardiometabolic risk factors in subjects with metabolic syndrome and hypercholesterolemia in a randomized trial. Nutrition & Metabolism. 2008;5:29. doi:10.1186/1743-7075-5-29.

Ebbeling CB, et al. A reduced-glycemic load diet in the treatment of adolescent obesity. Arch Pediatr Adolesc Med. 2003;157:773–779.

Ebbeling CB, et al. Effects of an ad libitum low-glycemic load diet on cardiovascular disease risk factors in obese young adults. Am J Clin Nutr. 2005;81:976–982.

Maki KC, et al. Effects of a reduced-glycemic-load diet on body weight, body composition, and cardiovascular disease risk markers in overweight and obese adults. Am J Clin Nutr. 2007;85:724–734.

Sloth B, et al. No difference in body weight decrease between a low-glycemic-index and a high-glycemic-index diet but reduced LDL cholesterol after 10-wk ad libitum intake of the low-glycemic-index diet. Am J Clin Nutr. 2004;80:337–347.

Trichopoulou A, Bamia C, Trichopoulos D. Mediterranean Diet and Survival Among Patients With Coronary Heart Disease in Greece. Arch Intern Med. 2005;165(8):929–935.

https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-016-0677-4

Trichopoulou A, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study BMJ 2005; 330 :991.

Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Amer J Clin Nutr;97(3); 505–516.

Schwingshackl L, et al. Adherence to a Mediterranean diet and risk of diabetes: A systematic review and meta-analysis. Public Health Nutrition, 18(7), 1292-1299.

Schröder H, et al. Adherence to the Traditional Mediterranean Diet Is Inversely Associated with Body Mass Index and Obesity in a Spanish Population. J Nutri:134(12); 3355-61.

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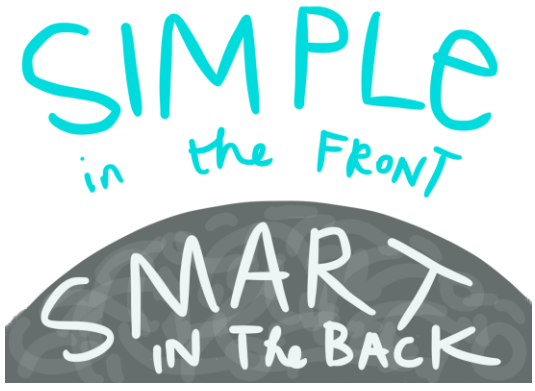
Dietary Recommendations - Overview

"We are going to include foods that speed up the healing process, and pull foods out that slow it down."



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Dietary Recommendations

- Change the quantity and quality of carbohydrates
- Focus on whole foods
  - Foods that don't need a label
  - Know the ingredients
- Small balanced meals – 4-6x/day
  - Space meals evenly – every 3-4 hours
- Balanced = carb + protein + healthy fats

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Quantity and Quality of Carbs

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Focus on Whole Foods






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Carbs and CVD

- Increasing simple/refined carbohydrate:
  - ↑ TC, TG, LDL-C & TC:HDL-C & ↓ HDL-C
  - ↑ small, dense LDL, oxidized LDL and vascular inflammation
  - Impairs glucose tolerance, ↑ insulin resistance & diabetes, ↑ body fat, alters platelet function & stimulates smooth muscle cell proliferation
- High-sugar diet ↑ risk of death from CVD 300%
- All these abnormalities can be reversed by following a low-sugar/low Glycemic Load diet

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Carbs and CVD References

Krauss RM, et al. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr. 2006;83:1025–1031.
Schaefer EJ, Gleason JA, Dansinger ML. Dietary fructose and glucose differentially affect lipid and glucose homeostasis. J Nutr. 2009;139:1257S–1262S.
Barclay AW, et al. Glycemic index, glycemic load, and chronic disease risk–a meta-analysis of observational studies. Am J Clin Nutr. 2008;87:627–637.
Pelkman CL. Effects of the glycemic index of foods on serum concentrations of high-density lipoprotein cholesterol and triglycerides. Curr Atheroscler Rep. 2001;3:456–461.
Parks EJ, Hellerstein MK. Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanisms. Am J Clin Nutr. 2000;71:412–433.
Stanhope KL, Havel PJ. Fructose consumption: recent results and their potential implications. Ann N Y Acad Sci. 2010;1190:15–24.
Welsh JA, Sharma A, Abramson JL, et al. Caloric sweetener consumption and dyslipidemia among US adults. JAMA. 2010;303:1490–1497.
Beulens JW., et al. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. J Am Coll Cardiol 2007;50:14–21.
Liu S, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71:1455–61.
Szanto S, Yudkin J. The effect of dietary sucrose on blood lipids, serum insulin, platelet adhesiveness and body weight in human volunteers. Postgrad Med J. 1969;45:602–7.
Szanto S, Yudkin J. Dietary sucrose and platelet behaviour. Nature. 1970;225:467–8.
Te Morenga LA, Howatson AJ, Jones RM, et al. Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. Am J Clin Nutr. 2014.
Kinosian B, Glick H, Preiss L, et al. Cholesterol and coronary heart disease: predicting risks in men by changes in levels and ratios. J Investig Med. 1995;43:443–50.
Stampfer MJ, Sacks FM, Salvini S, et al. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. N Engl J Med. 1991;325:373–81.
Albrink MJ, Meigs JW, Man EB. Serum lipids, hypertension and coronary artery disease. Am J Med. 1961;31:4–23.
Yudkin J, Kakkar VV, Szanto S. Sugar intake, serum insulin and platelet adhesiveness in men with and without peripheral vascular disease. Postgrad Med J. 1969;45:608–11.
Bruckdorfer KR, Worcester NA, Yudkin J. Influence of diet on rat platelet aggregation. Nutr Metab. 1977;21(Suppl 1):196–8.
Szanto S, Yudkin J. Plasma lipids, glucose tolerance, insulin levels and body-weight in men after diets rich in sucrose. Proc Nutr Soc. 1969;28:11a–2a.
Reiser S, Handler HB, Gardner LB, et al. Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. Am J Clin Nutr. 1979;32:2206–16.
Weidtmann A, et al. Mildly oxidized LDL induces platelet aggregation through activation of phospholipase A2. Arterioscler Thromb Vasc Biol. 1995;15:1131–8.
Daub K, Seizer P, Stellos K, et al. Oxidized LDL-activated platelets induce vascular inflammation. Semin Thromb Hemost. 2010;36:146–56.
Pfeifle B, Ditschuneit H. Effect of insulin on growth of cultured human arterial smooth muscle cells. Diabetologia. 1981;20:155–8.
Lustig RH. Fructose: metabolic, hedonic, and societal parallels with ethanol. J Am Diet Assoc. 2010;110:1307–21.
Yang Q, Zhang Z, Gregg EW, et al. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA internal medicine. 2014;174:516–24.
Hansen L, et al. Fruit and vegetable intake and risk of acute coronary syndrome. Br J Nutr. 2010;104:248–55.
Wang X, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ. 2014;349:g4490.
Ng SW, Slining MM, Popkin BM. Use of caloric and noncaloric sweeteners in US consumer packaged foods, 2005–2009. Journal of the Academy of Nutrition and Dietetics. 2012;112:1828–34. e1–6.

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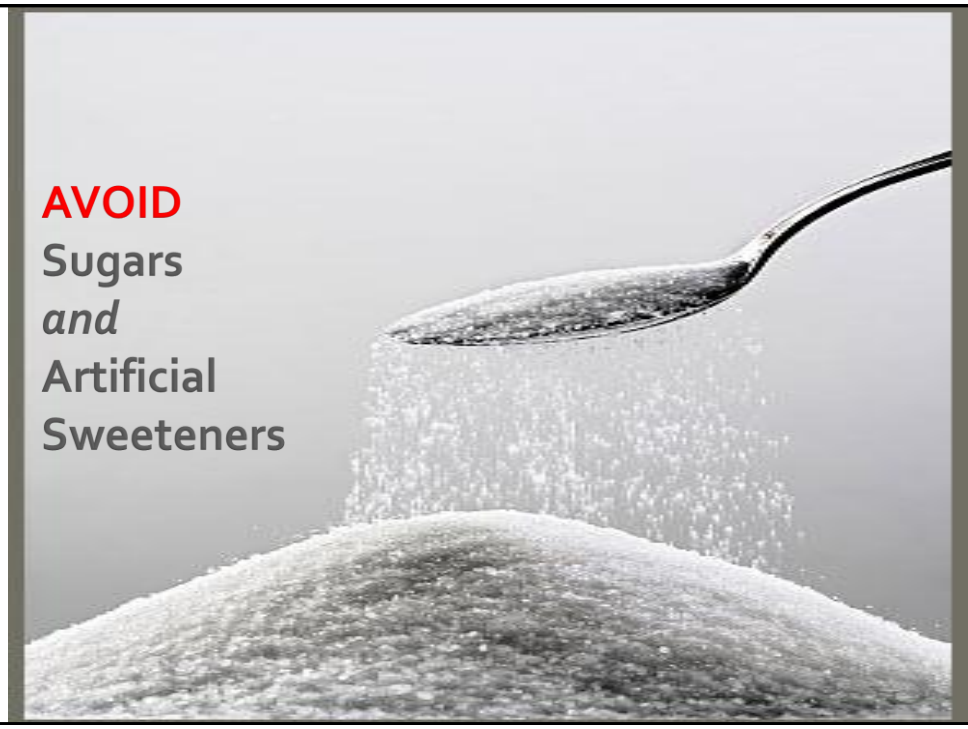

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Artificial Sweeteners

- Many names:
  - Saccharin: Sweet and Low, Sweet Twin, Sweet'N Low, Necta Sweet
  - Aspartame: Nutrasweet, Equal, Sugar Twin
  - Sucralose: Splenda
  - Acesulfame K: acesulfame potassium, Ace-K, Sunett
  - Now, starting to blend them together
    - NO studies have been done on safety

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Soft Drinks, CVD and Death

- SSB and ASB are associated with
  - Weight gain
  - ↑ risk of type 2 diabetes
  - ↑ risk of coronary heart disease
  - ↑ risk of stroke
  - ↑ risk of DEATH
- Consuming ≥ 2 servings/day ↑ risk of death 52%
  - Each serving ↑ risk of death from CVD 10-18%

SSB – Sugar Sweetened Beverages; ASB – Artificially Sweetened Beverages

Malik VS, et al. Long-Term Consumption of Sugar-Sweetened and Artificially Sweetened Beverages and Risk of Mortality in US Adults. Circulation 2019. 139:00.
Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. Am J Clin Nutr. 2013;98:1084–1102.
Malik VS, Popkin BM, Bray GA, et al. Sugar sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care. 2010;33:2477–2483.
Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr. 2009;89:1037–1042. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation. 2012;125:1735–41, S1.
Bernstein AM, de Koning L, Flint AJ, Rexrode KM, Willett WC. Soda consumption and the risk of stroke in men and women. Am J Clin Nutr. 2012;95:1190–1199.
Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern Med. 2014;174:516–524.

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Artificial Sweeteners (AS) and CVD

- AS can *increase* cravings for sugar and promote over-consumption of calories
- Regular AS consumption induces metabolic derangements
  - Alters gut microbiota
  - Damages blood vessel lining
  - Induces insulin resistance

- AS consumption *increases* the risk of obesity, metabolic syndrome, diabetes & CVD

Swithers SE; Davidson TL. A role for sweet taste: Calorie predictive relations in energy regulation by rats. Behavioral Neuroscience, Vol 122(1), Feb 2008, 161-173.
Davidson TL, et al. Intake of high-intensity sweeteners alters the ability of sweet taste to signal caloric consequences: Implications for the learned control of energy and body weight regulation.
Yang Q. Gain Weight by "going diet"? Artificial sweeteners and the neurobiology of sugar cravings. Yale J Biol Med. 2010.
Swithers, SE. Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements. Trends in Endocrinology & Metabolism , Volume 24 , Issue 9 , 431 – 441.
Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* **514,**181–186 (09 October 2014).
Hoffman BR, et al. The Influence of Sugar and Artificial Sweeteners on Vascular Health during the Onset and Progression of Diabetes. Published Online:20 Apr 2018Abstract Number:603.20.

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Eliminate Sugar & Artificial Sweeteners

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Lots of Non-Starchy Veggies

- Organic preferred (Dirty Dozen especially)
- More color the better
- Anything that grows above the ground (except corn)
- Starchy veggies: white potato, corn, parsnip

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CVD Recommendations: Diet

- Trans fats are devastating to human health
- Fat quantity matters less than fat quality
- Populations with low incidence of CVD:
  - Total fat ranges from <15% to 40+%
  - Minimal intake of trans fats
  - High intake of omega-3 PUFAs
  - Low intake of omega-6 PUFAs
  - High intake of monounsaturated fatty acids (MUFAs)
  - Low intake of saturated fats from animal protein/meat

Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, et al.: Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999, 353:1547–1557.

Menotti A, Kromhout D, Blackburn H, et al.: Food intake patterns and 25-year mortality from coronary heart disease: cross-cultural correlations in the Seven Countries Study. The Seven Countries Study Research Group. Eur J Epidemiol 1999, 15:507–515.

Zhou BF, Stamler J, Dennis B, et al.: Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTER-MAP study. J Hum Hypertens 2003, 17:623–630.

Matalas AL: Disparities within traditional Mediterranean food patterns: an historical approach of the Greek diet. Int J Food Sci Nutr 2006, 57:529–536.

Stanhope JM, Sampson VM, Prior IA: The Tokelau Island Migrant Study: serum lipid concentration in two environments. J Chronic Dis 1981, 34:45–55.

Lindeberg S, Nilsson-Ehle P, Terent A, et al.: Cardiovascular risk factors in a Melanesian population apparently free from stroke and ischaemic heart disease: the Kitava study. J Intern Med 1994, 236:331–340.

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Trans Fats

- The body cannot properly break down trans fats
- Incorporate into cell membranes – alter function
- In ALL partially hydrogenated & some hydrogenated oils
- NAS concluded in 2005: "there is no safe level of trans fat consumption"

Effects of Trans Fats on Health

⇑ LDL Cholesterol	⇑ risk of cardiovascular disease & death
⇓ HDL Cholesterol	⇓ mental performance
⇑ Triglycerides	⇑ risk of multiple sclerosis (MS)
⇑ small, dense LDL-P & Lp(a)	⇑ Insulin resistance & diabetes
⇑ inflammation	⇑ risk Parkinson's Disease
⇑ Weight gain & obesity	⇑ risk Alzheimer's Disease
⇑ Visceral fat accumulation	⇑ risk of hypertension

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Trans fats = MUST read labels

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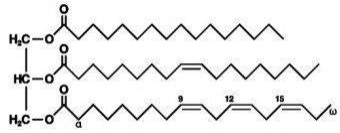
Types of Fat

- Lipids: any class of organic compounds that are fatty acids or their derivatives that are insoluble in water but soluble in organic solvents.
  - Includes fat, cholesterol and other fat-like substances, including triglycerides
- Triglycerides: an ester formed from glycerol and three fatty acid groups



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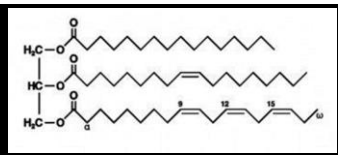
Triglycerides (TGs)



- 93% of dietary fats are TGs
  - Fatty acids may include any combination of SFAs, MUFAs and/or PUFAs
- Excess calories/glucose (from carbohydrates) can be made into TG in the liver
- 95% of the fat stored in the body are TGs
  - Energy source when plasma glucose is decreased

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Saturated fatty acids (SFAs)

- SFAs differ in chain-length and have dramatically different metabolic effects
  - Lauric acid (C12:0) reduces TC/HDL-C ratio
    - Raise TC, LDL-C and HDL-C, but raises HDL-C most
    - Shown to ↓ CVD risk
  - Myristic acid (C14:0) has no effect on TC/HDL-C
  - Palmitic acid (C16:0) raises TC/HDL-C and LDL-C
    - Also shown to increase blood clotting
    - Shown to ↑ CVD risk
  - Stearic acid (C18:0) has no effect on LDL-C, HDL-C or TC/HDL-C

Grundy SM: Influence of stearic acid on cholesterol metabolism relative to other long-chain fatty acids. Am J Clin Nutr 1994, 60(6 Suppl):986S–990S.

Mensink RP, Zock PL, Kester AD, Katan MB: Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003, 77:1146–1155.

Kelly FD, Sinclair AJ, Mann NJ, et al.: A stearic acid-rich diet improves thrombogenic and atherogenic risk factor profiles in healthy males. Eur J Clin Nutr 2001, 55:88–96.

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Fatty Acid Composition

Oil or Fat	Saturated					Mono unsaturated	Poly unsaturated	
	Capric Acid C10:0	Lauric Acid C12:0	Myristic Acid C14:0	Palmitic Acid C16:0	Stearic Acid C18:0	Oleic Acid C18:1	Linoleic Acid (ω6) C18:2	Alpha Linolenic Acid (ω3) C18:3
Almond Oil	-	-	-	7	2	69	17	-
Beef Tallow	-	-	3	24	19	43	3	1
Butterfat (cow)	3	3	11	27	12	29	2	1
Butterfat (goat)	7	3	9	25	12	27	3	1
Canola Oil	-	-	-	4	2	62	22	10
Cocoa Butter	-	-	-	25	38	32	3	-
Coconut Oil	6	47	18	9	3	6	2	-
Corn Oil (Maize Oil)	-	-	-	11	2	28	58	1
Flaxseed Oil	-	-	-	3	7	21	16	53
Lard (Pork fat)	-	-	2	26	14	44	10	-
Olive Oil	-	-	-	13	3	71	10	1
Palm Oil	-	-	1	45	4	40	10	-
Palm Kernel Oil	4	48	16	8	3	15	2	-
Peanut Oil	-	-	-	11	2	48	32	-
Safflower Oil*	-	-	-	7	2	13	78	-
Sesame Oil	-	-	-	9	4	41	45	-
Soybean Oil	-	-	-	11	4	24	54	7
Sunflower Oil*	-	-	-	7	5	19	68	1
Walnut Oil	-	-	-	11	5	28	51	5

* Not high-oleic variety

% by wt of total fatty acids

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Palmitic Acid

- Palmitic acid mostly from grain-fed meats and dairy products
- Grain-fed cattle contain 2-4x more SFAs/palmitic acid than pasture fed
- Palmitic acid raises LDL-C by decreasing synthesis of LDL receptor
  - Cholesterol is not removed from circulation and continues to circulate
- Replacement of palmitic acid with MUFAs has been shown to decrease CVD risk and provide cardiometabolic benefits

Ervin RB, Wright JD, Wang CY, Kennedy-Stephenson J: Dietary intake of fats and fatty acids for the United States population: 1999–2000. Adv Data 2004, 1–6.
Cordain L, Watkins BA, Florant GL, et al.: Fatty acid analysis of wild ruminant tissues: evolutionary implications for reducing diet-related chronic disease. Eur J Clin Nutr 2002, 56:181–191.

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Fats and Inflammation

- Saturated fats (from grain-fed red meat/dairy) increase inflammation
- Long-chain Ω-6 fatty acids (vegetable oil, red meat) increase inflammation
- MUFA (oleic acid) and Ω-3 EFAs decrease inflammation
  - Substituting MUFA and Ω-3 EFSs for SFA and Ω-6 has been shown to decrease inflammation

Shi H, et al. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 2006;116:3015–25.
Lee JY, et al. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. J Biol Chem 2001;276:16683–9.
Kennedy A, et al. Saturated fatty acid-mediated inflammation and insulin resistance in adipose tissue: mechanisms of action and implications. J Nutr 2009;139:1–4.
Baer DJ, et al. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. Am J Clin Nutr 2004;79:969–73.
Bellido C, et al. Butter and walnuts, but not olive oil, elicit postprandial activation of nuclear transcription factor kappaB in peripheral blood mononuclear cells from healthy men. Am J Clin Nutr 2004;80:1487–91.

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Effects of SFAs Determined by Diet

- SFA can have a detrimental impact on CVD if:
  - Accompanied by excess calories and/or dietary cholesterol
  - If the PUFA intake (LA & Ω-3s) is low
  - Consumed with simple sugars/carbohydrates
  - Consumed from red meat vs. dairy
    - Substitute 2% SF from meat to dairy, ↓ CVD risk 25%
- Fermentation of dairy (yogurt, kefir) and milk from pasture-fed cows lowers CVD risk

Hayes KC, et al. Saturated fatty acids and LDL receptor modulation in humans and monkeys. Prostaglandins Leukot Essent Fatty Acids. 1997;57:411–418.
Dietschy JM. Dietary fatty acids and the regulation of plasma low density lipoprotein cholesterol concentrations. J Nutr. 1998;128(2 Suppl):444S–448S.
German JB, et al. A reappraisal of the impact of dairy foods and milk fat on cardiovascular disease risk. Eur J Nutr. 2009;48:191–203.
Smit LA, Baylin A, Campos H: Conjugated linoleic acid in adipose tissue and risk of myocardial infarction. Am J Clin Nutr 2010, 92:34–40.
Wijendran V, Hayes KC. Dietary n-6 and n-3 fatty acid balance and cardiovascular health. Annu Rev Nutr. 2004;24:597–615.
De Oliveira Otto MC, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. Amer J Clin Nutr. 2012;96(2):397-404.
Sinha R, et al. Meat intake and mortality: a prospective study of over half a million people. Arch Intern Med 2009;169:562–71.
O'Sullivan TA, et al. Food Sources of Saturated Fat and the Association With Mortality: A Meta-Analysis. American Journal of Public Health. 2013;103(9):e31-e42. doi:10.2105/AJPH.2013.301492.

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Animal Fats

Comparison of Animals' Muscle Fatty Acid Concentrations
(mg fatty acids/100 g sample)

Fatty Acid	Elk	Mule Deer	Antelope	Pasture-Fed Steer	Grain-Fed Steer
Saturated	610	989	895	910	1909
Monounsaturated	507	612	610	793	1856
Total Polyunsaturated	625	746	754	262	341
Omega-3 PUFA	178	225	216	61	46
Omega-6 PUFA	448	524	536	138	243
Ratio ω-6: ω-3	2.5:1	2.3:1	2.5:1	2.3:1	5.3:1

- Organic, 100% pasture fed ideal

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Fatty Acid Composition of Nuts and Seeds

Nut	ω-6:ω-3 ratio	% MUFA	% PUFA	% SAT
Walnuts	4.2	23.6	69.7	6.7
Macadamia nuts	6.3	81.6	1.9	16.5
Pecans	20.9	59.5	31.5	9.0
Pine nuts	31.6	39.7	44.3	16.0
Cashews	47.6	61.6	17.6	20.8
Pistachios	51.9	55.5	31.8	12.7
Sesame seeds	58.2	39.5	45.9	14.6
Hazelnuts (filberts)	90	78.7	13.6	7.7
Pumpkin seeds	114.4	32.5	47.6	19.9
Brazil nuts	377.9	36.2	38.3	25.5
Sunflower seeds	472.9	20.0	69.0	11.0
Almonds	High (no ω-3)	66.6	25.3	8.1
Coconut	High (no ω-3)	4.4	1.3	94.3
Peanuts	High (no ω-3)	52.1	33.3	14.6

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Polyunsaturated fatty acids (PUFAs)

- Omega-6 PUFAs
  - Linoleic acid (LA)
    - Sunflower, safflower, soybean, corn, and canola oils
  - Arachidonic acid (AA)
    - Chicken, eggs, beef/pork, processed meats, animal milk, hard cheeses, farm raised fish (tilapia, catfish)
- Omega-3 PUFAs
  - α-Linolenic acid (ALA)
    - Flaxseed/oil, walnut/oil, pumpkin seeds/oil, canola oil
  - Eicosapentaenoic acid (EPA) & docosahexaenoic acid (DHA)
    - Deep sea, fatty fish (anchovies, Atlantic herring/mackerel, salmon, sardines), fish oils

Weaver KL, et al.: The content of favorable and unfavorable polyunsaturated fatty acids found in commonly eaten fish. J Am Diet Assoc 2008, 108:1178–1185.
Cordain L, et al.: Fatty acid analysis of wild ruminant tissues: evolutionary implications for reducing diet-related chronic disease. Eur J Clin Nutr 2002, 56:181–191.

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PUFAs and CVD risk

- Replacement of LA-rich oils with MUFA-rich oils and/or Omega-3 FAs can decrease CVD risk
- AA is prothrombotic and proinflammatory
  - Has a positive correlation with CHD mortality
  - Partial replacement with Omega-3s can provide significant CV benefits
- ALA has cardioprotective properties; maximum benefit with low-LA diet
- EPA & DHA have a wide array of cardiometabolic benefits

Rose GA, Thomson WB, Williams RT: Corn oil in treatment of ischaemic heart disease. Br Med J 1965, 1:1531–1533.
Djousse L, et al.: Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. Am J Clin Nutr 2001, 74:612–619.
Hu FB, et al.: Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997, 337:1491–1499.
Wada M, et al.: Enzymes and receptors of prostaglandin pathways with arachidonic acidderived versus eicosapentaenoic acid-derived substrates and products. J Biol Chem 2007, 282:22254–22266.
Lands WE: Diets could prevent many diseases. Lipids 2003, 38:317–321.
Baylin A, Campos H: Arachidonic acid in adipose tissue is associated with nonfatal acute myocardial infarction in the central valley of Costa Rica. J Nutr 2004, 134:3095–3099.
Ramsden, C.E. et al. Dietary fat quality and coronary heart disease prevention: A unified theory based on evolutionary, historical, global, and modern perspectives. Curr Treat Options Cardio Med (2009) 11: 289.
Christensen JH, et al. Alphalinolenic acid and heart rate variability in women examined for coronary artery disease. Nutr Metab Cardiovasc Dis 2005, 15:345–351.

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EPA/DHA and CVD Risk

- EPA & DHA have many beneficial CV effects:

⇑ HDL/HDL-C	Inhibition of early & late stage atherogenesis
⇓ TG, VLDL, IDL, RLP	Improve endothelial function
⇓ LDL-P and small, dense LDL	Plaque stabilization
⇓ Platelet aggregation	⇓ Ventricular arrhythmias
⇓ Blood pressure	

- High intakes of EPA/DHA reduces CVD risk and mortality
- EPA+DHA consumption effective in both primary and secondary CVD prevention
  - 850 mg/day reduced total morality by 20% and sudden death by 45% in post-MI patients
- 25% of US population consumes no EPA/DHA

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EPA/DHA References

Torrejon C, et al. n-3 Fatty acids and cardiovascular disease: actions and molecular mechanisms. Prostaglandins Leukot Essent Fatty Acids 2007, 77:319–326.
Leaf A, et al. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. Circulation 2003, 107:2646–2652.
Dyerberg J, Bang HO: Dietary fat and thrombosis. Lancet 1978, 1:152.
De Caterina R, Massaro M: Omega-3 fatty acids and the regulation of expression of endothelial pro-atherogenic and pro-inflammatory genes. J Membr Biol 2005, 206:103–116.
Aarsetoy H, et al. Long term influence of regular intake of high dose n-3 fatty acids on CD40-ligand, pregnancy-associated plasma protein A and matrix metalloproteinase-9 following acute myocardial infarction. Thromb Haemost 2006, 95:329–336.
Kagawa Y, Nishizawa M, Suzuki M, et al.: Eicosapolyenoic acids of serum lipids of Japanese islanders with low incidence of cardiovascular diseases. J Nutr Sci Vitaminol 1982, 28:441–453.
Lands WE: Diets could prevent many diseases. Lipids 2003, 38:317–321.
Iso H, et al.: Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation 2006, 113:195–202.
Dolecek TA, Granditis G: Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT). World Rev Nutr Diet 1991, 66:205–216.
Ervin RB, Wright JD, Wang CY, Kennedy-Stephenson J: Dietary intake of fats and fatty acids for the United States population: 1999–2000. Adv Data 2004, 1–6.
Harris WS: The omega-3 index as a risk factor for coronary heart disease. Am J Clin Nutr 2008, 87:1997S–2002S.
Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999, 354:447–455.
Yates A, Norwig J, Maroon JC, et al. Evaluation of Lipid Profiles and the Use of Omega-3 Essential Fatty Acid in Professional Football Players. Sports Health. 2009;1(1):21-30.

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Replacement of SFA with PUFA

- Replacement of SFA with PUFA:
  - ↓TC and LDL-C
  - ↓ HDL-C, but ↓ LDL-C more
    - HDL-C:LDL-C ↑ and TC:HDL-C ↓
  - Projected to ↓ CVD risk ~10% for each 5% energy (calorie) substitution
    - Likely underestimated because PUFA have other CV benefits beyond cholesterol metabolism, including improving insulin sensitivity and reducing inflammation

Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fat, carbohydrate, and cardiovascular disease. Am J Clin Nutr. 2010;91:502–509.
Mensink RP, et al. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr. 2003;77:1146–1155.
Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb. 1992;12:911–919.
Wijendran V, Hayes KC. Dietary n-6 and n-3 fatty acid balance and cardiovascular health. Annu Rev Nutr. 2004;24:597–615.
Micha R, Mozaffarian D: Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. Lipids 2010 Mar 31 [Epub ahead of print].
Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA. 2002;288:2569–2578.
Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2010;7:e1000252.

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Reshuffling fats

- Reducing SFA in-and-of itself has not consistently been shown to improve CVD risk
  - Palmitic acid does increase CVD risk (conventional red meat)
  - SFA only raise cholesterol/CVD risk when
    - PUFA:SFA <0.49 (PUFA<5-10% of calories)
    - Accompanied by excess calories &/or high cholesterol
- Replacement of SFA with PUFAs (esp Ω-3) or MUFAs can reduce CVD risk ~42%
- Replacement of SFA with carbohydrate:
  - ↓ CVD risk if use low glycemic index foods (vegetables, deep colored berries)
  - ↑ CVD risk if consume high glycemic foods
- Consuming 1-3 grams EPA+DHA daily is ideal

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Reshuffling fats references

Hu FB, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med. 1997;337:1491–1499.

Halton TL, et al. Low-carbohydrate-diet score and the risk of coronary heart disease in women. N Engl J Med. 2006;355:1991–2002.

Sacks FM. Dietary fats and coronary heart disease. Overview. J Cardiovasc Risk 1994;1:3–8.

Hu FB, et al. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. Am J Clin Nutr. 1999;70:1001–1008.

Jakobsen MU, et al.: Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr 2009, 89:1425–1432.

Jakobsen MU, et al.: Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. Am J Clin Nutr 2010, 91:1764–1768.

Mensink RP, et al. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials, Amer J Clin Nutr; 77(5):146–1155,

Dayton S, et al. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation 1969;40(suppl II):II-1–63.

Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am J Clin Nutr 2010;91:535–46.

Ness AR, Maynard M, Frankel S, et al. Diet in childhood and adult cardiovascular and all cause mortality: the Boyd Orr cohort. Heart 2005;91:894–8.

Hayes KC, Khosla P, Hajri T, Pronczuk A. Saturated fatty acids and LDL receptor modulation in humans and monkeys. Prostaglandins Leukot Essent Fatty Acids 1997;57:411–8.

Wijendran V, Hayes KC. Dietary n−6 and n−3 fatty acid balance and cardiovascular health. Annu Rev Nutr 2004;24:597–615.

Fielding CJ, Havel RJ, Todd KM, et al. Effects of dietary cholesterol and fat saturation on plasma lipoproteins in an ethnically diverse population of healthy young men. J Clin Invest 1995;95:611–8.

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Getting the Fatty Acid Balance Right

- If you choose to eat animal protein, choose fish high in omega-3s:
  - Anchovies, herring, mackerel (Atlantic), salmon (wild), sardines, trout, tuna (albacore)
- Eggs – organic, pasture fed
- Meat – organic, pasture/grass fed or wild
- Remember – 1 deck of cards sized flesh protein = ~20-25 grams protein
- Choose the right oils for cooking

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Cooking with Oils

Oil Usage at a Glance	
Best for Baking •Coconut oil •Palm oil •Safflower oil-high oleic •Sunflower oil-high oleic	**Best For Frying** •Coconut oil •Avocado oil •Palm oil •Sesame oil
Best For Sautéing •Canola oil •Coconut oil •Olive oil •Safflower oil-high oleic •Sesame oil •Sunflower oil-high oleic	**Best For Dressing, Marinades And Dipping** •Flax Oil •Udo's Oil •Hemp Oil •Olive oil •Toasted sesame oil

- Olive, coconut and flax/Udo's
- Store oils in cool, dark place
- Do NOT heat flax or Udo's oil – store in fridge
- Use a bit more flax than olive oil daily
- Do not use soybean (vegetable oil), wheat germ or peanut oils
  - Contain lectins that can adversely affect GI, immune and heart health

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Nuts and Seeds

Nut	ω-6:ω-3 ratio	% MUFA	% PUFA
Walnuts	4.2	23.6	69.7
Macadamia nuts	6.3	81.6	1.9
Pecans	20.9	59.5	31.5
Pine nuts	31.6	39.7	44.3
Cashews	47.6	61.6	17.6
Pistachios	51.9	55.5	31.8
Sesame seeds	58.2	39.5	45.9
Hazelnuts (filberts)	90	78.7	13.6
Pumpkin seeds	114.4	32.5	47.6
Brazil nuts	377.9	36.2	38.3
Sunflower seeds	472.9	20.0	69.0
Almonds	High	66.6	25.3

- Eat raw if possible – preserves ω-3
- Soaking nuts improves digestion
  - Soak overnight, drain and store in fridge for up to a week
- Flaxseeds – grind in coffee grinder; eat ~1 Tbsp/day
- Enjoy nuts/seeds as a snack/side dish, not a main dish☺

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Fat Summary

- Fats are necessary for optimal health; it's the type of fat that is important
- Avoid ALL trans fats and foods that have partially hydrogenated oils; limit animal fats
- High heat cooking – Coconut oil
- Medium/low heat cooking – olive oil
- Salad dressings/marinades – Flaxseed/olive oil
- Eat raw nuts and seeds, especially walnuts
- If you eat animal protein – choose wild caught fish, chicken, turkey, lamb, wild game or grass fed beef
- Get 1-2 Tbsp per day Flaxseed oil
- Get 2-10 grams EPA/DHA per day

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Modified Mediterranean Diet

- Shown to have the greatest influence on cardiometabolic risk
  - Ketogenic diet may be helpful for short-term weight loss in T2D
- Soluble and fermentable fibers have an especially profound impact on glycemic response
  - Not only of initial meal, but of *subsequent* meals
  - Pectins, beta-glucans, guar gum, inulin, cellulose, hemicellulose
  - Beans & legumes, oats, barley, nuts/seeds

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Diet and CVD – High-fat, low-carb

- High/moderate-fat, low carbohydrate diets:
  - ↓TG 25-40% & large VLDL 48%
  - ↓ small, dense LDL 30-55% and number LDL-P 10%
  - ↑ HDL particle size
  - ↓ body fat & abdominal fat
    - Can reduce inflammation and CVD risk
- Can work well for those with metabolic syndrome
  - ↓ high glycemic carbohydrates NOT low glycemic index vegetables and
- Reduce overall CVD risk; may be due to weight loss

Wood RJ, et al. Carbohydrate Restriction Alters Lipoprotein Metabolism by Modifying VLDL, LDL, and HDL Subfraction Distribution and Size in Overweight Men J Nutr; 136(2):384–389.
Volek JS, Westman EC. Very-low-carbohydrate weight-loss diets revisited. Cleve Clin J Med. 2002;69:849, 853, 856–848.
Volek JS, et al. Body composition and hormonal responses to a carbohydrate-restricted diet. Metabolism. 2002;51:864–70.
Krauss RM, et al. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr. 2006 May;83(5):1025-31; quiz 1205.
Parks EJ, et al. Effects of a low-fat, high-carbohydrate diet on VLDL-triglyceride assembly, production, and clearance. Journal of Clinical Investigation. 1999;104(8):1087-1096.
AHRENS EH Jr, et al. Carbohydrate-induced and fat-induced lipemia. Trans Assoc Am Physicians. 1961;74:134-46.

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Dietary Fiber & Health Benefits

Physiological Property	Proposed Effect	Health Benefit
Soluble dietary fiber	Delays gastric emptying	Contributes to satiety
	Prevents/delays nutrient uptake in small intestine	Lowers glucose, insulin and lipid level after meal
	Prevents reabsorption of bile acids	Lowers blood cholesterol levels
Insoluble dietary fiber	Increases stool weight	Reduces incidence of colorectal cancer and intestinal disease
	Accelerate transit time	Lowers glucose, insulin and lipid levels after meal
Fermentation	Growth of health-promoting bacteria	Protects against inflammation and colorectal cancer
	Production of short-chain fatty acids	Lowers blood cholesterol levels & protects against colorectal cancer

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Fiber Sources

- **Sources of soluble fiber:** oatmeal, oat cereal, lentils, apples, oranges, pears, oat bran, beans, dried peas, blueberries, psyllium, cucumbers, celery, and carrots.
- **Sources of insoluble fiber:** whole wheat, whole grains, wheat bran, corn bran, barley, couscous, brown rice, bulgur, zucchini, celery, broccoli, cabbage, onions, tomatoes, carrots, cucumbers, green beans, dark leafy vegetables, raisins, grapes, fruit, and root vegetable skins.

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Modified Mediterranean Diet

- Soluble and fermentable fibers have an especially profound impact on glycemic response
  - Not only of initial meal, but of *subsequent* meals
  - Pectins, beta-glucans, guar gum, inulin, cellulose, hemicellulose
  - Beans & legumes, oats, barley, nuts/seeds

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If sor EAT TO HEAL

- Eat Food. Not too much. Mostly Plants
  - Strictly avoid: alcohol, soda, sugar, white flour products, artificial sweeteners, trans fats (will need to read labels)
  - Eat: vegetables, fish, whole fruits
    - 50-75% (3/4 plate) alkaline foods: deep colored vegetables/fruit
    - 25% MAX (1/4 plate) HEALTHY acidic foods: fatty fish, raw nuts/seeds & some whole grains (~1-2 servings/day)
- Chew, chew chew! (At LEAST 30 times)
- Drink pure water throughout the day
  - *½ body weight in ounces every day in divided doses*

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When They are Ready: Modified Mediterranean Diet

Food Category	Average Serving Size	Daily Recommendation	Examples
Legumes	½ cup	At least 1 serving	Beans, hummus, green peas
Low GI* (<55) Vegetables	½ cup	At least 3 servings	Broccoli, celery, cabbage, spinach, mushrooms, tomatoes, sea vegetables, fresh juices made from acceptable vegetables
Moderate GI (55-70) Vegetables	½ cup	Only 1 serving	Beets, sweet potatoes, carrots
Concentrated Protein Sources		Unlimited	Eggs , fish, poultry, tofu, low-fat cottage cheese, low-fat mozzarella
Fruits	Specific quantities for each fruit to equal 80 kcal	2-3 servings	Apple, blueberries, cherries, grapes, orange
Nuts and Seeds	Approx. 1 scant handful or 2 TBSP nut butter	1 serving	Peanut butter, almonds, hazelnuts, walnuts
Oils	1 teaspoon or as indicated	4 servings	Flaxseed oil, olive oil, ripe green olives, avocado
Dairy	6 oz. or as indicated	(Optional)	Plain low-fat yogurt, 1% milk, soymilk (unsweetened)
Beverages		Unlimited	Decaffeinated, herbal, or green tea; decaffeinated coffee; water
		Limited	1 glass of red wine (4 oz.), 1-2 cups (8 oz.) of caffeinated coffee
Condiments		Unlimited	Cinnamon, mustard, soy sauce, flavored extracts
Allowable sweeteners			Agave nectar, stevia

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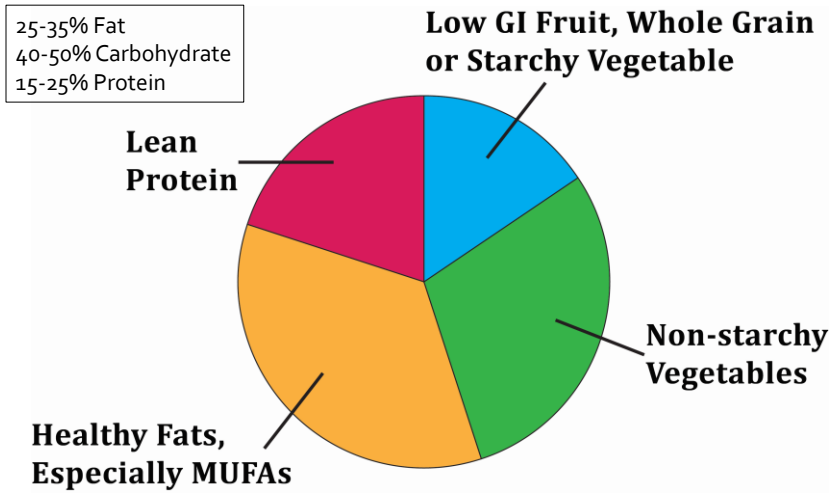
Modified Mediterranean Plate by Calorie



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Modified Mediterranean Plate






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Modified Mediterranean Diet: General Guidelines

- Choose organic, seasonal and locally-grown foods whenever possible
- Choose your veggies from a rainbow of colors
- High Fiber Carbs – eat whole foods that have been minimally processed
- Minimize gluten containing grains – wheat, rye, barley
- Low glycemic fruits – limit to 1-2 servings/day
- Avoid trans fats, partially/hydrogenated oils
- Water – ½ body weight in ounces daily in divided doses; limit to 4-8 oz. during meals
- Chew food until liquid before swallowing

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Modified Mediterranean Diet: Optimal Nutrient Choices

- Lean Protein
  - **Cold water fish – salmon, halibut, herring, mackerel, sardines, trout (also count as fat)**
  - Chicken
  - Turkey
  - Eggs
  - Whey, pea, rice or hemp protein powder
  - Lean red meats (beef, lamb)
  - Wild game
  - Greek-style yogurt and cottage cheese

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Modified Mediterranean Diet: Optimal Nutrient Choices

- Healthy Fats
  - **Raw nuts, nut butters** and seeds
  - **Avocado**
  - **Olive oil and olives**
  - Coconut milk, oil and shredded unsweetened flakes
  - Freshly ground flaxseed meal and oil

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Modified Mediterranean Diet: Optimal Nutrient Choices

- Non-Starchy Vegetables

Artichoke	Asparagus	Bamboo shoots	Beans: green, wax, Italian
Bean sprouts	Beets	Broccoli	Brussels sprouts
Cabbage	Carrots	Cauliflower	Celery
Cucumber	Eggplant	Garlic	Green onions, scallions
Greens: all	Hearts of palm	Jicama	Kohlrabi
Leeks	Lettuce: all	Mushrooms	Okra
Onions	Peas	Peppers: all	Radishes
Rutabaga	Spinach	Sprouts: all	Turnips
Squash: spaghetti, zucchini		Tomatoes	Water chestnuts

Serving size: ½ cup cooked; 2-3 cups raw (leafy greens); 1 cup raw (all others)

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Modified Mediterranean Diet: Optimal Nutrient Choices

- Low GI Fruit, Whole Grain, Starchy Vegetable

Berries: all	Apples	Citrus	Plums
100% whole wheat products	Brown rice	Legumes (beans, peas, lentils)	Millet
Sweet potato, yam	Steel cut oats	Barley	Rye
Bulgar	Buckwheat	Cooked carrots	Quinoa
Winter Squash: acorn, butternut, pumpkin			

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Modified Mediterranean Diet: Simple Meal Ideas

- Breakfast
  - Smoothie: 1-2 scoops Medical Food/Protein Powder; ½-1 cup berries; 1/8-1/4 cup coconut milk/oil or avocado; 1 Tbsp flaxseed meal, ¾ cup water
  - Eggs over easy on 100% whole grain toast with side of berries topped with chopped walnuts
  - Leftover grilled chicken breast or salmon with side green salad and vinaigrette dressing
  - Breakfast turkey sausage with side of chopped apples tossed with cinnamon, sliced almonds and drizzle of coconut milk
  - Greek-style yogurt topped with chopped berries and freshly ground flaxseed meal

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Modified Mediterranean Diet: Simple Meal Ideas

- Lunch & Dinner
  - Large green salad tossed with chopped non-starchy veggies, black beans, canned salmon, avocado; dress with olive oil vinaigrette
  - Grilled turkey burger on whole grain bun topped with mashed avocado and tomato slice, side of shredded cabbage with vinaigrette dressing
  - Grilled salmon filet, with sides of roasted asparagus and brown rice
  - Lean beef (loin), broiled and topped with sliced mushrooms and onions sautéed in olive oil, side green salad and sweet potato
  - Omelet loaded with sautéed spinach and mushrooms, side of sliced tomatoes

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Modified Mediterranean Diet: Simple Meal Ideas

- Healthy Snacks
  - Sliced apple with almond butter
  - Lettuce roll-up with sliced turkey and avocado
  - Celery stuffed with guacamole or nut butter
  - Mini-smoothie: ½ your morning smoothie recipe
  - Berries topped with chopped walnuts and cinnamon

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Alcohol

- Light alcohol consumption ↓ CVD risk 25-30%
  - 1-2 drinks/day ~3-4 days/week for CHD mortality
  - ≤1 drink/day for stroke mortality
- Moderate alcohol consumption ↑ CVD risk
  - 7-13 drinks/week can increase CVD risk 1.5x
- Heavy drinking ↑↑ CVD risk
  - 4+ drinks in 2 hrs (even if only 1-2x/week) or 6+ drinks/day increases CVD risk
  - >14 drinks/week can increase CVD risk 1.5-2x

Ronksley, Paul E.; et al. (2011-02-22). "Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis". BMJ. 342: d671.
Mostofsky, Elizabeth; et al. (2016-03-08). "Alcohol and Immediate Risk of Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis". Circulation. 133 (10): 979–987.
Holmes, Michael V.; Dale, Caroline E.; Zuccolo, Luisa; Silverwood, Richard J.; Guo, Yiran; Ye, Zheng; Prieto-Merino, David; Dehghan, Abbas; Trompet, Stella (2014-07-10). "Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data". BMJ. 349: g4164.
Klatsky AL (May 2009). "Alcohol and cardiovascular diseases". Expert Rev Cardiovasc Ther. 7 (5): 499–506.
Mukamal KJ, Conigrave KM, Mittleman MA, et al. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. N Engl J Med. 2003;348:109–118.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30134-X/fulltext#seccestitle70; accessed 03/11/2019
https://www.nbcnews.com/health/health-news/little-1-drink-day-linked-hypertension-new-study-finds-n980726; accessed 03/11/2019

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Our Body's Water Needs

- *Drink ½ your body weight in ounces every day + water lost during excessive sweating*
  - *Example: 150 lb person should drink ~75 oz. of water throughout the day + water lost through sweating*
  - *Sweating:*
    - *2-3 hours yardwork can cause 2-3 lbs of water loss*
    - *1 hour hard workout/practice can cause 2-5 lbs water loss*
    - *2 lbs water loss = 1 quart extra water needed*
- *Must drink in divided doses – 2-4 oz. every 20-30 minutes ideal; water lost from sweating should be replaced over next 12-18 hrs*
- Drink the purest water available – distilled, reverse osmosis, filtered bottled water (glass or hard plastic), bottled spring water (glass or hard plastic)

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Eating out

- It is likely that they are eating out the majority of the time
  - 83% of Americans eat fast food at least 1x/week
  - Average American eats out 4.5x/week
  - People in US spend more on dining out than groceries
- It's not ideal/desired, but they are likely going to do it, at least at first
  - Transition them to other options/cooking ASAP
  - Give them healthier options for when they eat out

http://www.bloomberg.com/news/articles/2015-04-14/americans-spending-on-dining-out-just-overtook-grocery-sales-for-the-first-time-ever
http://www.statista.com/topics/1957/eating-out-behavior-in-the-us/
https://www.zagat.com/b/the-state-of-american-dining-in-2015

150

Eating out - Recommendations

- Fast (American) food
  - Choose: None of them unless absolutely necessary
    - Grilled chicken/fish; sauce on side (use 1 Tbsp); no bun; extra veggies (toppings)
    - Green salad with dressing on side
  - AVOID: McDonalds, Burger King, Hardees, Culvers
    - If HAVE TO eat here, see above
    - Deep-fried anything; red meat/hamburger

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Eating out - Recommendations

- Mexican
  - Choose: Chipotle
    - Fajitas with grilled meats or beans + vegetables
    - Salads/burritos with beans, chicken or lean meat
    - Add black beans, salsa and guacamole
  - Avoid: Taco Bell
    - Cheese, anything deep fried, refried beans, large bowl(s) of tortilla chips, pitchers of margaritas

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Eating out - Recommendations

- Asian or Thai
  - Choose: Noodles, Chins, Sai Bai Thong, Bahn Tai
    - Stir-fried shrimp, chicken + veggies (+ little brown rice)
  - Avoid: Buffets
    - Dishes with thick, sweet/sour sauces (Kung Pao chicken), large bowls of rice, fried egg rolls, lo mein
    - Breaded or deep fried foods

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Eating out - Recommendations

- Subs and sandwiches
  - Choose: Jimmy John's – "unwich"
    - Uses lettuce leaves rather than bread
    - Veggies – especially sprouts, spinach, olives, etc.
    - Can add chicken or turkey
    - Salads or have open-faced sandwich (1/2 bun)
  - Avoid: Blimpie's, Quiznos, Subway
    - Cheese, mayo, lots of sauces

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Eating out - Recommendations

- Pizza
  - Choose: Papa John's
    - Thin crust, lots of veggies, hint of cheese (or none)
    - Vegan/vegetarian pizza
    - Salad bar – as a meal or side
  - Avoid: Pizza hut, Dominos, Toppers, Rocky's
    - Loads of cheese, meat lovers (aka cardiac arrest)
    - Alfredo/creamy sauces
    - Eating more than 1-2 slices

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Eating out - Tips

- Limit menu extras
  - Drinks, appetizers, soups, sides, desserts, sauces
    - Always choose salad/veggies for sides; limit sauces
- Eat slow and enjoy your food
  - Put your fork down between bites
  - Chew your food until it is a liquid before swallowing
- Make it two meals
  - Eat only ½ your plate; get a to-go box with meal
- Don't' eat more to be polite
  - Dining with another - ↑ intake 35%; 2 others - ↑ 75%
  - Be the last to start eating and leave food on your plate

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Eating out – Best Choices

- Salad bars/deli at co-ops and/or Whole Foods
- Always choose options with LOTS of veggies
- Protein: legumes, fish, chicken, turkey
- Always get sauces/dressings on the side
  - Use about ¼-1/2 of what you are given
- Consider eating something healthy before you go
- Avoid drinking alcohol before eating
  - Will eat 20-33% more if consume alcohol

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Quick Meal Ideas

- Get salads/meals at co-op/Whole Foods/grocery salad bar/deli
- Purchase frozen food entrees and compliment with salad bar
- Stir fry: buy pre-chopped veggies (salad bar), choose sauce, add protein; high heat 2-5 min
- Go Mediterranean: pick up some hummus, veggies (salad bar), olives, goat cheese

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Quick Meal Ideas

- Super-soups – add canned beans, fresh/frozen veggies, herbs and/or salsa to soups – put in crock pot and let simmer
- Mexican – chopped lettuce, mixed veggies, salsa, beans, avocado/guacamole
- Lettuce wraps – use toppings from salad bar
- Omelets – use leftover veggies/protein
- SALADS – salad bar or pre-washed; try different veggies/toppings
  - Nuts/seeds, dried fruit, herbs, oil/vinegar, veggies

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Dietary Recommendations Summary

- Use their food journal to get an overview
- Help them understand the NEED for dietary change
- Ask them if they want to go fast/slow
  - Eat to Heal
  - Modified Mediterranean Diet
- CHEW food until liquid (at *least* 30 times)
- Increase water intake throughout the day

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Dietary Recommendations Summary

- Give simple/easy meal ideas
- Help them make better choices when eating out
- Help them line up support needed
  - Significant other, friend, other
  - Plan for eating – where, when go/shop, how
- Keep in close contact for the first 4-8 weeks
  - Most crucial time to get them positioned for success



161

Supplements to Improve CVD

- More than 70% of condition-specific supplement sales are focused on CV health
  - Total market: ~$10.2 billion (2024)

Natural Practitioner, January/February 2018. p. 22.
https://www.grandviewresearch.com/industry-analysis/cardiovascular-health-supplements-market-report

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Dyslipidemia: Supplementation: Niacin

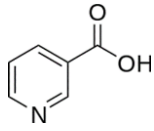
- Niacin (nicotinic acid)
  - Extensively studied
  - Inhibits free fatty acid release from adipose tissue
  - Controls activity of TG lipase and lipolysis
  - Decrease rate of liver synthesis of LDL & VLDL
  - Increases rate of TG removal from blood
  - Increases concentration of large, buoyant LDL-P
  - Significant ↓ TG, VLDL, LDL, TC, Lp(a)
    - ↓ TG: 20-52%, VLDL: 36%, LDL: 8-33%, TC: 8-22%, Lp(a)5-35%
  - Significantly ↑ HDL: 15-35% and LDL particle size

National Cholesterol Education Program. Cholesterol Lowering in the Patient with Coronary Heart Disease. 1997. Available at: http://www.nhlbi.nih.gov/health/prof/heart/chol/chol_low.pdf.
Wolfe ML, Vartanian SF, Ross JL, et al. Safety and effectiveness of Niaspan when added sequentially to a statin for treatment of dyslipidemia. Am J Cardiol 2001;87:476-9.
Altschul R, et al. Influence of nicotinic acid on serum cholesterol in man. Arch Biochem 1955;54(2):558-9.
McKenney J. New Perspectives on the Use of Niacin in the Treatment of Lipid Disorders. Arch Intern Med 2004;164(7):697-705.
Ito MK. Niacin-based therapy for dyslipidemia: past evidence and future advances. Am J Manag Care 2002;8(12 Suppl):S315-S322.

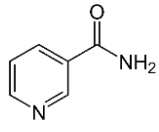
163

Which niacin to use for CVD

- Nicotinic acid – works
  - Immediate or slow/extended release & Rx



- Niacinamide (non-flush)
  - Does not positively effect dyslipidemias



Kruse W, et al. "Nocturnal inhibition of lipolysis in man by nicotinic acid and derivatives". European Journal of Clinical Pharmacology. 16 (1): 11–5.
Taheri, R (15 January 2003). "No-Flush Niacin for the Treatment of Hyperlipidemia". Medscape. Retrieved 31 March 2008.
Pieper JA. Overview of niacin formulations: differences in pharmacokinetics, efficacy, and safety. Am J Health Syst Pharm 2003;60(13 Suppl 2):S9-14.
Knopp RH. Evaluating niacin in its various forms. Am J Cardiol 2000;86(12A):51L-6L.

164

Dyslipidemia: Supplementation: Niacin

- Niacin causes vasodilation of blood vessels
  - Niacin flush
    - ***Flushing is not a sign of toxicity/allergy***
    - Can occur at 500 mg – 6 grams/day
    - Usually lasts 15-30 min
    - Tolerance will develop in ~2 weeks
  - Take with food and avoid alcohol & hot food/drink
  - Can also take aspirin/ibuprofen 30 minutes prior
- Liver toxicity possible – check liver enzymes
- Can increase uric acid levels (gout)

Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (2000). Washington, DC: National Academy Press, 2000.
McKenney J. New Perspectives on the Use of Niacin in the Treatment of Lipid Disorders. Arch Intern Med 2004;164(7):697-705.
Elam MB, Hunninghake DB, Davis KB et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. Arterial Disease Multiple Intervention Trial. JAMA 2000;284(10):1263-70.
Pan J, Lin M, Kesala RL, Van J, Charles MA. Niacin treatment of the atherogenic lipid profile and Lp(a) in diabetes. Diabetes Obes Metab 2002;4(4):255-61.

165

Dyslipidemia: Supplementation: Phytosterols

- Phytosterols – 2 grams/day
  - Plant sterols from fruits and vegetables
  - Recommended by National Institutes of Health (NIH) and American Heart Association (AHA)
  - Similar molecular structure to cholesterol
  - Act within the intestine to block absorption of both dietary and endogenous biliary cholesterol
    - ↓ LDL 8-13%
  - May also offer cancer/BPH protection
    - Colon, breast, prostate

Vanstone, et al. American Journal of Clinical Nutrition 2002; 76:1272-8.
Journal American Diet Association 2003; 76:577-81.
Journal of Nutrition 2000; 130:2127-30.
Cancer 1995; 345:1529-32
British Journal of Urology 1997; 80:427-32.

166

Dyslipidemia: Supplementation: Pantethine

- Pantethine
  - Vitamin B5-precursor
    - Produces cystamine which inhibits acetyl-CoA carboxylase
      - Reduces triglyceride (TG) synthesis
    - Reduces cholesterol synthesis by inhibiting HMG-CoA reductase
  - Significantly ↓ TG, TC, VLDL, LDL, LDL-P#
    - ↓ TG: 25-26%, VLDL: 28%, TC & LDL: 15-38%, LDL-P#: 16%
    - ↑ HDL & HDL2: 20-34%
  - Also inhibits lipid peroxidation of LDL and reduces platelet aggregation
  - Beneficial for fatty liver disease

Pins JJ. Journal of Diabetes 2004; 53(suppl)2:A 406.
Pins J. American College of Nutrition 2003 Oct.
Arsenio, et al. Clinical therapeutics (volume 8, No. 5, 1986).
Maggi, et al. Cur Ther Res 1982; 32:380-86.
Pins JJ, Keenan JM. Pantethine: a new option in managing dyslipidemia. J Am Coll Nutr. In press 2005
Osono Y, Hirose N, Nakajima K, Hata Y. The effects of pantethine on fatty liver and fat distribution. J Atheroscler Thromb 2000;7(1):55-8.

167

Dyslipidemia: Supplementation: Red Yeast Rice

- Red Yeast Rice – 1-5 grams/day
  - Bulgarian monascus strain (MB100BG)
    - Does NOT contain lovastatin
  - Contains monacolins – inhibit HMG-CoA reductase
    - Blocks cholesterol synthesis
  - Contains sterols
    - Blocks reuptake of cholesterol
  - Lowers TG: 63-66% and TC: 35-27%

Becker DJ, Gordon RY, Halbert SC, et al. Red yeast rice for dyslipidemia in statin-intolerant patients: A randomized trial. Ann Intern Med 2009;150:830-9.
Halbert SC, French B, Gordon RY, et al. Tolerability of red yeast rice (2,400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. Am J Cardiol 2010;105:198-204.
Zhao, S. P., Lu, Z. L., Du, B. M., Chen, Z., Wu, Y. F., Yu, X. H., Zhao, Y. C., Liu, L., Ye, H. J., and Wu, Z. H. Xuezhikang, an extract of cholestin, reduces cardiovascular events in type 2 diabetes patients with coronary heart disease: subgroup analysis of patients with type 2 diabetes from China coronary secondary prevention study (CCSPS). J Cardiovasc Pharmacol 2007;49(2):81-84.

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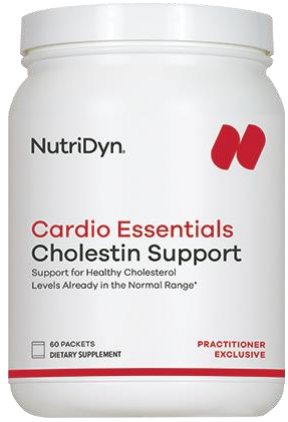
Dyslipidemia: Supplementation

Ingredient	Amount
Niacin (as nicotinic acid)	500 mg NE
Red Yeast Rice (seed; *Monascus purpureus*)	800 mg
Phytosterols	668 mg
Pantethine (Pantesin®)	200 mg



- Foundational Support
  - Provides multiple pathways to manage blood lipid metabolism in one synergistic formula
  - 1 packet 2x/day

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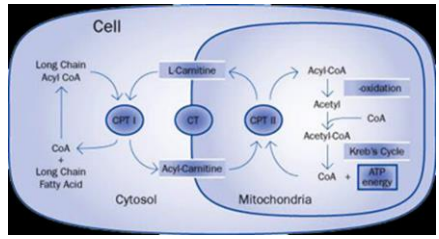
Dyslipidemia: Supplementation: L-Carnitine

- Can be synthesized by liver from lysine & methionine
  - Only accounts ~25% of daily need = supplementation required
- 95% is found in heart and skeletal muscle
- Many cardiovascular benefits:
  - ↓TG, VLDL-P , & RLP-P
    - ↓small LDL particles and ↑ LDL particle size
  - ↓Lp(a)
  - ↓OxLDL-C & Prevents oxidative stress



Sirtori CR, Calabresi L, Ferrara S, et al. L-Carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a). Nutr Metab Cardiovasc Dis 2000;10:247–51.
Casciani CU, Caruso U, Cravotto E, et al. Effect of L-carnitine on lipid pattern in haemodialysis. Lancet 1980;316:1309–10.
Brown GC, Borutaite V. Nitric oxide, cytochrome c and mitochondria. Biochem Soc Symp 1999;66:17–25.
Binienda ZK, Ali SF. Neuroprotective role of L-carnitine in the 3-nitropropionic acid induced neurotoxicity. Toxicol Lett 2001;125:67–73.
Malaguarnera M, et al; L-Carnitine supplementation reduces oxidized LDL cholesterol in patients with diabetes, The American Journal of Clinical Nutrition, 89(1); 71–76.
Malaguarnera M, et al. Effect of L-carnitine on the size of low-density lipoprotein particles in type 2 diabetes mellitus patients treated with simvastatin. Metabolism. 2009 Nov;58(11):1618-23.
Bremer J. Carnitine-metabolism and functions. Physiol. Rev. 1983;63:1420–1480. doi: 10.1152/physrev.1983.63.4.1420..
Vaz F.M., Wanders R.J. Carnitine biosynthesis in mammals. Biochem. J. 2002;361:417–429. doi: 10.1042/bj3610417.
Brass E.P. Pharmacokinetic considerations for the therapeutic use of carnitine in hemodialysis patients. Clin. Ther. 1995;17:176–185.

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L-Carnitine: Sources

- Food Sources:
  - Grass fed red meat
    - ~ 56-162 mg per serving

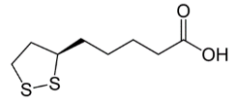
- Supplementation
  - Typically, 2-6 grams/day in divided doses
  - No more than 2 grams at one dose

Monograph. L-carnitine. Altern Med Rev. 2005 Mar;10(1):42-50

171

Dyslipidemia: Supplementation: Alpha-Lipoic Acid

- α-Lipoic Acid shown to have many cardiometabolic benefits:
  - Improved insulin sensitivity
  - ↓TG, TC, LDL-C & VLDL-C
  - ↓ small, dense LDL-C & oxLDL-C
  - ↓ free radicals/oxidative damage
  - ↓ endothelial dysfunction
  - ↓ inflammation



- Particularly useful for those metabolic syndrome/diabetes

Zhang Y, et al. Amelioration of Lipid Abnormalities by α-Lipoic acid Through Antioxidative and Anti-Inflammatory Effects. Obesity (Silver Spring). 2011 May 19.
Harding SV, et al. Evidence for Using Alpha-Lipoic Acid in Reducing Lipoprotein and Inflammatory Related Atherosclerotic Risk. Journal of Dietary Supplements, 9(2):116–127.

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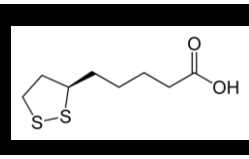
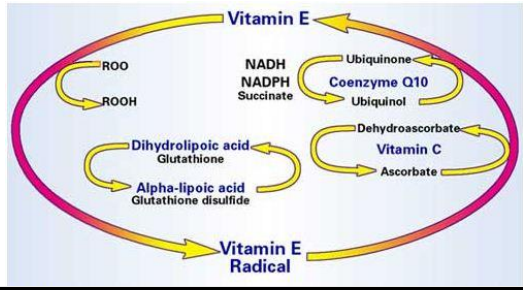
Alpha-lipoic acid (ALA)



- Potent antioxidant
  - ALA and metabolite DHLA both antioxidants
  - Increases production of glutathione
  - Water *and* fat soluble
  - Can also regenerate other antioxidants



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ALA: Toxicity and Dosing

- Toxicity rare; more likely if thiamine deficient
  - Alcoholics – supplement with thiamine
- Supplementation
  - ↓ small, dense LDL-C & oxidative damage: 600 mg/day
  - Peripheral arterial disease: 200 mg TID
  - Diabetes and peripheral neuropathy: 600-1200mg/day

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Dyslipidemia: Supplementation: Berberine

- Has unique ability to alter dyslipidemias
  - Upregulates # and function of the LDL receptor
- 500 mg BID for 3 months:
  - ↓TC 29%, TG 35% & LDL-C 25%
- Can be used with pharmaceuticals
- Shown to improve insulin sensitivity
  - Can ↓ FG 26%, HbA1c 18% (≈ to metformin/ rosiglitazone) as well as fasting insulin 28%
  - Especially useful for those with metabolic syndrome
- ➢ Use to ↓ RLP-P, small dense LDL-P, triglycerides, fasting glucose, HbA1c

Kong W, Wei J et al. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat Med. 2004; 10(12):1344-51.
Zhang H, et al. Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. Metabolism. Feb 2010;59(2):285-292.
Zeng XH, Zeng XJ, Li YY. Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 2003; 92(2):173-6.
Lau CW, Yao XQ, Chen ZY, Ko WH, Huang Y. Cardiovascular actions of berberine. Cardiovasc Drug Rev.2001; 19(3):234-44.
Ko BS, Choi SB et al. Insulin sensitizing and insulinotropic action of berberine from cortidis rhizoma. Biol Pharm Bull. 2005; 28(8):1431-7.
Zhang Y, Li X, Zou D, et al. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. J Clin Endocrinol Metab 2008;93:2559-65.

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Nitric Boost to Help Recouple NO Synthesis

Ingredients	Amount
Vitamin D3 (as cholecalciferol) (from lichen)	15 mcg
Thiamin (as thiamin mononitrate)	100 mg
Vitamin B12 (as adenosylcobalamin)	50 mcg
Magnesium (as magnesium ascorbate)	120 mg
Zinc (as zinc ascorbate)	7 mg
Potassium (as potassium nitrate)	150 mg
Beet Root Extract	375 mg
Pomegranate Extract (fruit; *Punica granatum*; 30% punicalagins) (Pomanox®)	200 mg
Montmorency Tart Cherry Extract (fruit; *Prunus cerasus*)	200 mg
French Maritime Pine Bark Extract (*Pinus pinaster*; 65-75% procyanidins) (Pycnogenol®)	50 mg
Grape Seed Extract (*Vitis vinifera*; 95% proanthocyanidins)	50 mg


NutriDyn.

Nitric Boost

Advanced Circulatory Support for Optimal Health*

Nitric Boost Supplementation

Nitric Boost is designed to support circulatory health, promote energy metabolism, and promote robust antioxidant support.* By increasing nitric oxide production, the formula promotes vasodilation, supports healthy blood flow, and supports cardiovascular function.* The combination of essential vitamins, minerals, and natural extracts works synergistically to support healthy oxidative stress response and promote healthy inflammatory markers.*

Nitric Boost is a scientifically formulated supplement that addresses multiple aspects of circulatory health.* This advanced formulation supports healthy nitric oxide production and optimal blood flow.* Supplementation with Nitric Boost includes these benefits:

- Promotes healthy blood flow and oxygen delivery*
- Supports cardiovascular health*
- Promotes healthy inflammatory markers*
- Promotes powerful antioxidant support*
- Supports exercise performance and endurance*
- Supports muscle recovery and reduces delayed onset muscle soreness*
- Promotes overall immune function and well-being*

How Nitric Boost Works

Nitric Boost represents a comprehensive approach to circulatory health, leveraging the latest scientific research on nitric oxide production and cardiovascular wellness with the following nutrients.*

Vitamin D3 enhances calcium absorption in the intestines, which is crucial for bone density and immune modulation.* Vitamin D3 supports macrophage activity and healthy inflammatory markers, promoting overall immune function and bone health.*[1,2,3]

Thiamin functions as a coenzyme in carbohydrate metabolism, aiding ATP production.* Thiamin is essential for nervous system health and supports cardiovascular function by maintaining proper nerve and muscle function.*[4,5,6]

Vitamin B12 acts as a coenzyme in energy production and myelin synthesis. Vitamin B12 supports red blood cell formation, DNA synthesis, and overall cognitive function.*[7,8,9]

Magnesium participates in over 300 enzymatic reactions, including ATP production and muscle contraction.* Magnesium is vital for healthy nerve function, blood glucose control, and healthy blood pressure already in the normal range, offering broad-spectrum health benefits.*[10,11,12]

For more information, visit: www.nutridyn.com

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Cardio Flow

Ingredient	Amount
Calories	15
Total Carbohydrate	4 g
Dietary Fiber	<1 g
Folate (as calcium L-5-methyltetrahydrofolate) (BioFolate®)	200 mcg DFE
Calcium	55 mg
Iron	1.3 mg
Magnesium (as magnesium bisglycinate chelate) (TRAACS™)	100 mg
Sodium	45 mg
L-Arginine	3 g
Beet Root Powder	2 g
Hibiscus Flower Powder	1.5 g
Taurine	1 g
L-Citrulline	1 g


NutriDyn.

Cardio Flow

Nutritional Support for Heart, Vascular, and Endothelial Function*

Cardio Flow Supplementation

Cardio Flow provides nutritional support for healthy endothelial function by promoting healthy vasodilation.* By releasing nitric oxide, the endothelium relaxes the vascular smooth muscle cells in vessel walls.* Endothelial dysfunction results in the inactivation of nitric oxide and loss of vascular tone.*

Key benefits of Cardio Flow include:

- Promotes endothelial health*
- Promotes heart health*
- Promotes vascular health*
- Promotes healthy inflammatory markers*

How Cardio Flow Works

The proprietary BioFolate® formula in Cardio Flow helps support homocysteine levels critical for healthy endothelial function by promoting nitric oxide bioavailability, healthy hemoglobin function, and healthy oxidative stress response.* BioFolate® provides biologically active and methylated pure calcium L-5-methyltetrahydrofolate for supporting healthy folate function.*

Cardio Flow also includes magnesium bisglycinate as patented TRAACS®, one of the most absorbable supplemental forms of chelated magnesium on the market. Magnesium is a key cofactor in more than 300 biological processes and may play a role in promoting healthy inflammatory markers in the endothelium as a natural calcium antagonist.*

The folate and magnesium in Cardio Flow are complemented with several clinically proven amino acids and herbal ingredients.* Through cardio-metabolic processes, the kidneys change L-citrulline into L-arginine to promote healthy nitric oxide production.* L-arginine is the biological precursor to nitric oxide and helps support healthy blood pressure already in a normal range by promoting healthy vasodilation.*

Beetroot powder is also known to promote healthy nitric oxide function.* Clinical studies have shown beetroot's promising ability to increase in vivo nitric oxide as it relates to healthy heart, vascular, and endothelial function.*

The inactivation of nitric oxide may also affect oxidative stress, further altering the function of the endothelium.* Oxidative stress and the resulting accompanying concerns may induce vascular and cardiovascular issues.*

For more information, visit: www.nutridyn.com

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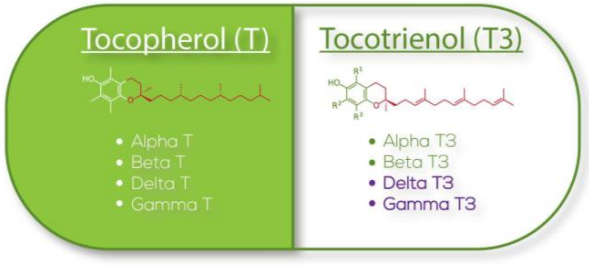
Tocotrienols

- Tocotrienols (T3) are part of Vitamin E family



- All tocopherols and tocotrienols are potent antioxidants
- T3 have an unsaturated side chain
  - Provides greater utility and benefits

Ahsan, H., Ahad, A., Iqbal, J. et al. Pharmacological potential of tocotrienols: a review. Nutr Metab (Lond) 11, 52 (2014)
Jiang Q, Christen S, Shigenaga MK, Ames BN. gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention. The American journal of clinical nutrition. 2001;74:714–722.
Brigelius-Flohe R, Traber MG. Vitamin E: function and metabolism. Faseb J. 1999;13:1145–1155.

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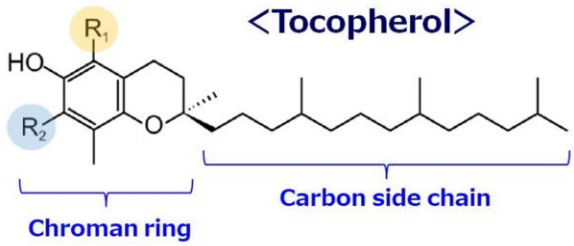
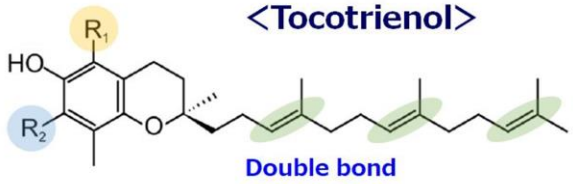
Tocopherol vs. Tocotrienol



form	R_1	R_2
α-	CH_3	CH_3
β-	CH_3	H
γ-	H	CH_3
δ-	H	H



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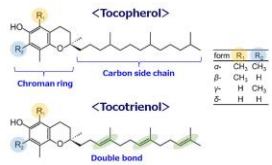
Tocotrienols: Unique Structure, Superior Benefits

- Unsaturated side chain allows for:
  - Better penetration/distribution through cell membranes
    - Absorbed into lipoprotein particles
  - More efficient penetration into tissues
    - Brain, liver, kidneys
- Unsubstituted R1 – γ & δ – forms:
  - Ability to trap reactive nitrogen species
    - Induced in chronic inflammatory conditions
  - Better able to neutralize lipid peroxides
    - Cardiovascular disease, cancer & neurodegenerative disorders



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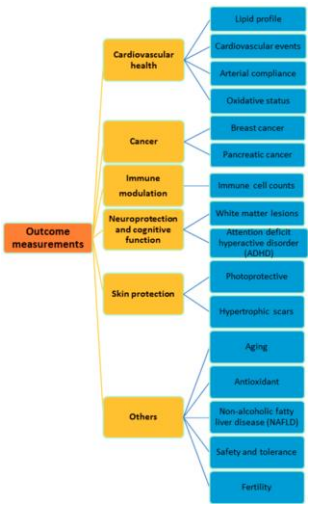
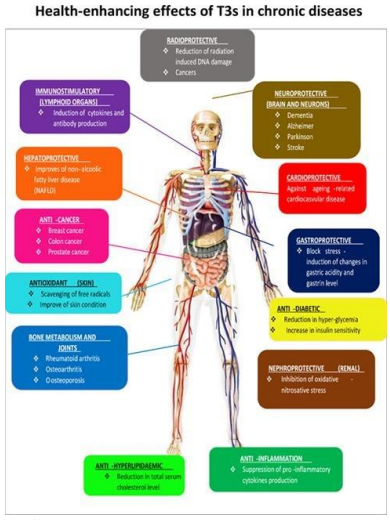
Tocotrienol Benefits





Meganathan, P.; Fu, J.-Y. Biological Properties of Tocotrienols: Evidence in Human Studies. Int. J. Mol. Sci. 2016, 17, 1682.
Zaida Zainal, Huzwah Khaza'ai, Ammu Kutty Radhakrishnan, Sui Kiat Chang, Therapeutic potential of palm oil vitamin E-derived tocotrienols in inflammation and chronic diseases: Evidence from preclinical and clinical studies, Food Research International, Volume 156, 2022.

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Tocotrienols: Unique Structure, Superior Benefits

- γT3 and δT3 are superior to α–tocopherol for:
  - Antioxidant protection: lipid peroxyl radicals, reactive nitrogen species, superoxide (O_2-) and H_2O_2
    - Up to 50x the antioxidant capacity of tocopherols
  - Cardiovascular health
    - γ-tocotrienol has 30-fold greater capacity to reduce cholesterol and atherogenic lipoprotein particles compared to α-tocopherol
  - Anti-inflammatory: ↓NF-κβ,iNOS, CRP, IL-6, TNF-α
  - ↓ Non-alcoholic fatty liver disease
  - Provides neuroprotection
  - Anti-Cancer benefits
    - Tocotrienols suppresses growth of human breast cancer cells & can augment chemotherapy
      - Tocopherols do not

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Tocotrienols: Unique Structure, Superior Benefits References

- Packer L, Weber SU, Rimbach G. Molecular aspects of alpha-tocotrienol antioxidant action and cell signaling. The Journal of nutrition. 2001;131:369S–373S.
- Wong RS, Radhakrishnan AK. Tocotrienol research: past into present. Nutrition reviews. 2012;70:483–490.
- Jiang Q, Christen S, Shigenaga MK, Ames BN. gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention. The American journal of clinical nutrition. 2001;74:714–722.
- Terashima K, Takaya Y, Niwa M. Powerful antioxidative agents based on garcinoic acid from Garcinia kola. Bioorganic & medicinal chemistry. 2002;10:1619–1625.
- Sen CK, Khanna S, Roy S. Tocotrienols: Vitamin E beyond tocopherols. Life Sci. 2006 Mar 27;78(18):2088-98.
- Suzuki YJ, Tsuchiya M, Wassall SR, Choo YM, Govil G, Kagan VE, Packer L. Structural and dynamic membrane properties of alpha-tocopherol and alpha-tocotrienol: implication to the molecular mechanism of their antioxidant potency. Biochemistry. 1993;32 (40):10692–10699.
- Serbinova E, Kagan V, Han D, Packer L. Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol. Free Radical Biology & Medicine. 1991;10 (5):263–275.
- Maniam S., Mohamed N., Shuid A.N., Soelaiman I.N. Palm tocotrienol exerted better antioxidant activities in bone than α-tocopherol. Basic Clin. Pharmacol. Toxicol. 2008;103:55–60.
- Sen CK, Khanna S, Roy S. Tocotrienols in health and disease: the other half of the natural vitamin E family. Mol Aspects Med. 2007 Oct-Dec;28(5-6):692-728.
- Khanna S, Roy S, Parinandi NL, Maurer M, Sen CK. Characterization of the potent neuroprotective properties of the natural vitamin E alpha-tocotrienol. J Neurochem. 2006
- Pearson CK, Barnes MM. The absorption and distribution of the naturally occurring tocochromanols in he rat. The British journal of nutrition. Jun 1970;24(2):581-587
- Palozza P, et al. Comparative antioxidant activity of tocotrienols and the novel chromanyl-polyisoprenyl molecule FeAox-6 in isolated membranes and intact cells. Molecular and cellular biochemistry. Jul 2006;287(1-2):21-32.
- Muller L, et al. In vitro antioxidant activity of tocopherols and tocotrienols and comparison of vitamin E concentration and lipophilic antioxidant capacity in human plasma. Molecular nutrition & food research. May 2010;54(5):731-742.

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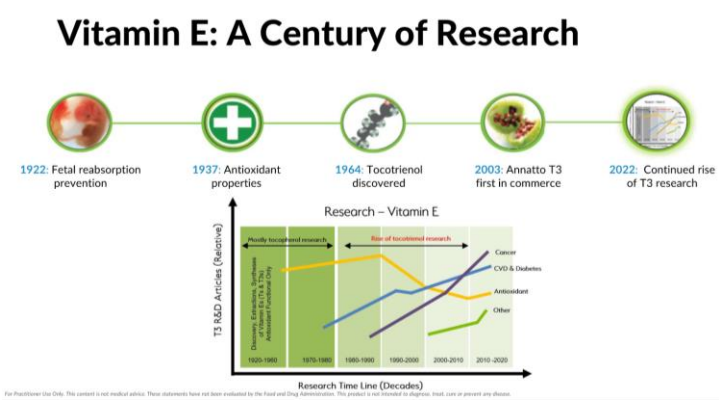
Tocotrienols: The Most Important Nutrient Your Patients Have Never Heard Of…



- Tocotrienol research:
  - ~1% of all vitamin E research published on PubMed
  - <1% of vitamin E research funded in last 30+ years
- More than 2/3 of the entire PubMed literature on tocotrienols has been published on/after 2000.

Sen CK, Khanna S, Rink C, Roy S. Tocotrienols: the emerging face of natural vitamin E. Vitam Horm. 2007;76:203-61.
Sen CK, Khanna S, Roy S. Tocotrienols in health and disease: the other half of the natural vitamin E family. Mol Aspects Med. 2007 Oct-Dec;28(5-6):692-728

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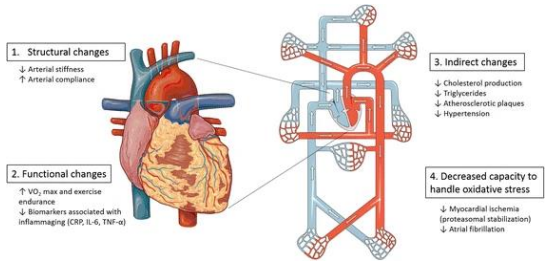
Tocotrienols: Cardiovascular Benefits

- Cardiovascular health improvements with tocotrienols
  - Cholesterol reduction: suppress the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase
    - Shown to significantly ↓ ApoB (15%), TC (30%), LDL-C (42%), TG (25%) and ↑ HDL-C (7%)
  - Reduce Lp(a) 17%
  - Decrease inflammation: CRP, inflammatory mediators
  - Reduce expression of cell adhesion molecules
    - Prevents initiation of atherosclerosis
  - Antithrombotic
  - Lower homocysteine
  - Protect against stroke
  - Improve insulin sensitivity
  - Slow progression of atherosclerosis
  - Stabilize atherosclerotic plaques



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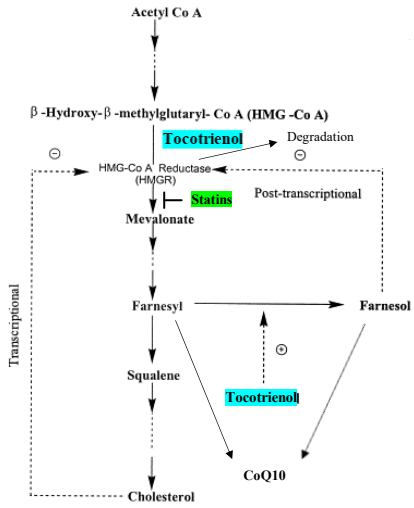
Tocotrienols & Statins

- Tocotrienols & statins both affect HMG-CoA Reductase
  - Statins inhibit HMGR
    - Can ↓ CoQ10 & LDL-C
  - Tocotrienols:
    - ↑ Degradation of HMGR
    - Catalyze Farnesyl to Farnesol
      - Allows CoQ10 production
    - Blocks translation of HMGR mRNA
- Statins & Tocotrienols can be used together
  - Synergistic effect



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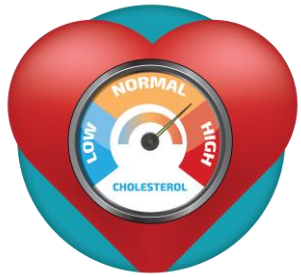
Tocotrienols & Statins

- 28 patients with high cholesterol, 25 weeks
  - All followed AHA Step-1 diet
  - 4 groups
    - A: 10 mg lovastatin
    - B: 50 mg tocotrienols
    - C: 10 mg lovastatin + 50 mg tocotrienols
    - D: 10 mg lovastatin + 50 mg α-tocopherol
  - Results
    - A: ↓ total cholesterol 13% & ↓ LDL-C 15%
    - B: ↓ total cholesterol 14% & ↓ LDL-C 18%
    - C: ↓ total cholesterol 20% & LDL-C 25%
    - D: ↓ total cholesterol 13% & ↓ LDL-C 15%



- Patients on Statins, add CoQ10 + Tocotrienols

Qureshi AA, Sami SA, et al. Synergistic effect of tocotrienol-rich fraction (TRF(25)) of rice bran and lovastatin on lipid parameters in hypercholesterolemic humans. J Nutr Biochem. 2001;12:318–329.

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Tocotrienols & Statins References

- Ramanathan, N., Tan, E., Loh, L.J. et al. Tocotrienol is a cardioprotective agent against ageing-associated cardiovascular disease and its associated morbidities. Nutr Metab (Lond) 15, 6 (2018).
- Meigs TE, Simoni RD. Farnesol as a Regulator of HMG-CoA Reductase Degradation: Characterization and Role of Farnesyl Pyrophosphatase. Arch Biochem Biophys. 1997;345:1–9.
- Meigs TE, Roseman DS, Simoni RD. Regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase degradation by the nonsterol mevalonate metabolite farnesol in vivo. J Biol Chem. 1996:271, 7916–7222.
- Cicero A.F., Gaddi A. Rice bran oil and gamma-oryzanol in the treatment of hyperlipoproteinaemias and other conditions. Phytother. Res., 15 (2001), pp. 277-289
- Andre Theriault, Jun-Tzu Chao, Qi Wang, Abdul Gapor, Khosrow Adeli, Tocotrienol: a review of its therapeutic potential, Clinical Biochemistry, Volume 32, Issue 5, 1999, Pages 309-319,
- Chen X, Jiang X, Xu M, Zhang M, Huang R, Huang J, Qi F. Co-production of farnesol and coenzyme Q10 from metabolically engineered Rhodobacter sphaeroides. Microb Cell Fact. 2019 May 31;18(1):98.
- Abdul-Majeed S, Mohamed N, Soelaiman IN. Effects of tocotrienol and lovastatin combination on osteoblast and osteoclast activity in estrogen-deficient osteoporosis. Evid Based Complement Alternat Med. 2012;2012:960742.
- Qureshi AA, Sami SA, Salser WA, Khan FA. Synergistic effect of tocotrienol-rich fraction (TRF(25)) of rice bran and lovastatin on lipid parameters in hypercholesterolemic humans. J Nutr Biochem. 2001;12:318–329.

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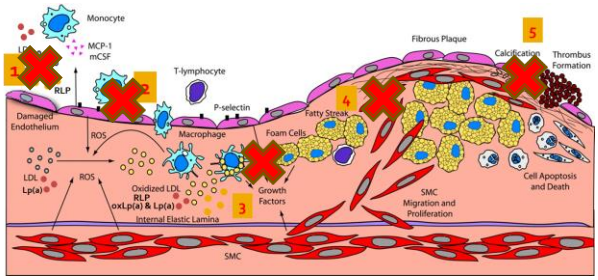
Tocotrienols Can Prevent & Stabilize Atherosclerotic Plaque



- Tocotrienols can inhibit the formation of atherogenic lipoprotein particles
- Decrease adhesion of monocytes to endothelium
- Prevent oxidation of lipoprotein particles & improve monocyte clearance of lipoprotein particles
- Inhibit the growth & proliferation of smooth muscle cells
- Stabilize atherosclerotic plaques and prevent thrombosis

- Prevent atherosclerosis development
- Can *reverse* arterial blockage

Altman R. Risk factor in coronary atherosclerosis athero-in-flammation: the meeting point. Thromb J. 2004;1:4–8.
Qureshi AA, Burger WC, Peterson DM, Elson CE. The structure of an inhibitor of cholesterol biosynthesis isolated from barley. J Biol Chem. 1986;261:10544–10550.
Vasanthi HR, Parameswari RP, Das DK. Multifaceted role of tocotrienols in cardioprotection supports their structure: function relation. Genes Nutr. 2012 Jan;7(1):19-28.

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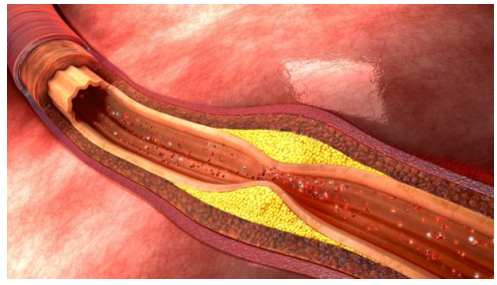
Tocotrienol and Plaque Regression Study

- 3-year double-blind study
- 50 patients with carotid stenosis
- Within 6 months of 240 mg tocotrienol complex/day
  - Tocotrienol group: 92% of patients had regression in carotid stenosis
  - Control: None had any improvement; 4% showed progression of carotid stenosis



Tomeo AC, Geller M, Watkins TR, Gapor A, Bierenbaum ML. Antioxidant effects of tocotrienols in patients with hyperlipidemia and carotid stenosis. Lipids. 1995;30:1179–1183.

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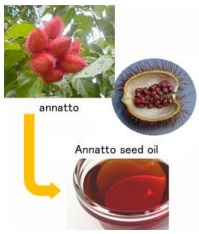
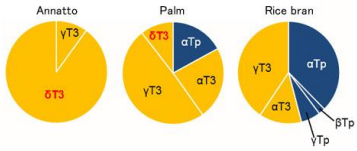
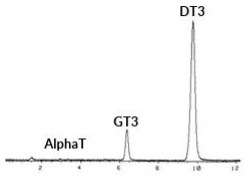
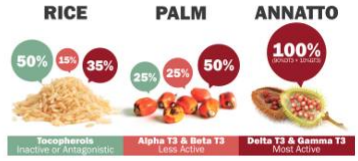
Tocotrienols: Maximizing the Benefits









- Plant-based
- Physical process
- Made in USA

- Only 3 sources (Rice, Palm, Annatto)
- Annatto is the most potent

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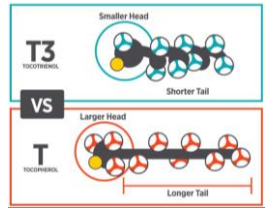
Tocopherols Interfere with Tocotrienols

- Studies suggest that **>15% tocopherols can prevent the cholesterol-lowering effects of tocotrienols**
- Tocopherols prevented the absorption and penetration of tocotrienols in several organs, interfering with tocotrienol benefits directly by:
  - ↓ cholesterol and triglyceride reduction
  - ↓ antioxidant capacity
  - Preventing anti-carcinogenic activity
  - Blocking tocotrienol absorption
  - ↑ tocotrienol break-down
  - Preventing adipose storage of tocotrienols



192

Tocopherols Interfere with Tocotrienols References

- Valastyan S, Thakur V, Johnson A, Kumar K, Manor D. Novel transcriptional activities of vitamin E: inhibition of cholesterol biosynthesis. Biochemistry. 2008;47:744–752
- Gee PT. Unleashing the untold and misunderstood observations on vitamin E. Genes Nutr. 2011 Feb;6(1):5-16.
- Ahsan, H., Ahad, A., Iqbal, J. et al. Pharmacological potential of tocotrienols: a review. Nutr Metab (Lond) 11, 52 (2014).
- Qureshi AA, Sami SA, et al. Synergistic effect of tocotrienol-rich fraction (TRF (25)) of rice bran and lovastatin on lipid parameters in hypercholesterolemic humans. J Nutr Biochem. 2001;12:318–329
- Qureshi AA, Pearce BC, Nor RM, Gapor A, Peterson DM, Elson CE. Dietary alpha-tocopherol attenuates the impact of gamma-tocotrienol on hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in chickens. J Nutr. 1996;126:389–394.
- Hun Teik K, Theng Theng N, Rajendran R. Dose-Dependent Cholesterolemic Activity of Tocotrienols and α-Tocopherol. Malays J Nutr. 2002;8:157–166.
- Shibata A, Kawakami Y, Kimura T, Miyazawa T, Nakagawa K. α-Tocopherol Attenuates the Triglyceride- and Cholesterol-Lowering Effects of Rice Bran Tocotrienol in Rats Fed a Western Diet. J Agric Food Chem. 2016;64:5361–5366.
- Yuen KH, Wong JW, Lim AB, Ng BH, Choy WP. Effect of Mixed-Tocotrienols in Hypercholesterolemic Subjects. Funct Foods Heal Dis. 2011;1:106–117.
- Mustad VA, Smith CA, Ruey PP, Edens NK, DeMichele SJ. Supplementation with 3 compositionally different tocotrienol supplements does not improve cardiovascular disease risk factors in men and women with hypercholesterolemia. The American journal of clinical nutrition. Dec 2002;76(6):1237-1243.

193

Tocopherols Interfere with Tocotrienols References

- Uchida T, Nomura S, Ichikawa T, Abe C, Ikeda S. Tissue distribution of vitamin E metabolites in rats after oral administration of tocopherol or tocotrienol. Journal of nutritional science and vitaminology. 2011;57(5):326-332.
- Shibata A, Nakagawa K, Tsuduki T, Miyazawa T. alpha-Tocopherol suppresses antiangiogenic effect of delta-tocotrienol in human umbilical vein endothelial cells. The Journal of nutritional biochemistry. Apr 2015;26(4):345-350.
- Shibata A, Kawakami Y, Kimura T, Miyazawa T, Nakagawa K. alpha-Tocopherol Attenuates the Triglyceride- and Cholesterol-Lowering Effects of Rice Bran Tocotrienol in Rats Fed a Western Diet. Journal of agricultural and food chemistry. Jul 6 2016;64(26):5361-5366.
- Khor HT, Ng TT. Effects of administration of alpha-tocopherol and tocotrienols on serum lipids and liver HMG CoA reductase activity. International journal of food sciences and nutrition. 2000;51 Suppl:S3-11.
- Shibata A, Nakagawa K, Sookwong P, Tsuduki T, Asai A, Miyazawa T. alpha-Tocopherol attenuates the cytotoxic effect of delta-tocotrienol in human colorectal adenocarcinoma cells. Biochemical and biophysical research communications. Jun 25 2010;397(2):214-219.
- Guthrie N, Gapor A, Chambers AF, Carroll KK. Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination. The Journal of nutrition. Mar 1997;127(3):544S-548S.
- Sontag TJ, Parker RS. Influence of major structural features of tocopherols and tocotrienols on their omega-oxidation by tocopherol-omega-hydroxylase. Journal of lipid research. May 2007;48(5):1090-1098.
- Uchihara Y, Kidokoro T, Tago K, Mashino T, Tamura H, Funakoshi-Tago M. A major component of vitamin E, alpha-tocopherol inhibits the anti-tumor activity of crizotinib against cells transformed by EML4-ALK. European journal of pharmacology. Apr 15 2018;825:1-9.

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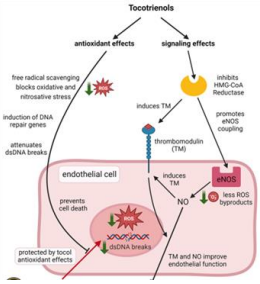
Annatto Pro 125

Ingredients	Amount
Tocotrienols (from annatto seed; *Bixa orellana*; 90% delta tocotrienols and 10% gamma tocotrienols) (DeltaGold®)	125 mg

- Target:
  - Cardiovascular health & lipid metabolism
    - ↑ Nitric Oxide production & release
    - ↓ RLP-P, Lp(a), small dense LDL
    - ↓ ApoB, hs-CRP, homocysteine
    - ↓ blood pressure
    - Improve insulin resistance
  - Liver health: NAFLD
  - Blood sugar imbalances, T2D
  - Brain health & cognition
  - Bone health: osteopenia/osteoporosis
  - Inflammatory conditions
  - Cancer



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Annatto Pro 125 References

- Vasanthi HR, Parameswari RP, Das DK. Genes Nutr. 2012;7:19–28.
- Fu JY, Che HL, Tan DMY, et al. Nutr Metab (Lond). 2014;11(5).
- Wong W-Y, Poudyal H, Ward LC, Brown L. Nutrients. 2012; 4(10):1527-1541.
- Ahsan H, Ahad A, Iqbal J, et al. Nutr Metab (Lond). 2014;11(52).
- Gopalan Y, Shuaib IL, Magosso E, et al. Stroke. 2014;45(5):1422-1428.
- Selvaraju TR, Khaza'ai H, Vidyadaran S, et al. Bosn J Basic Med Sci. 2014;14(4):195-204.
- Ming T. Ling, Sze U. Luk, Fares Al-Ejeh, Kum K. Khanna, Tocotrienol as a potential anticancer agent, Carcinogenesis, Volume 33, Issue 2, February 2012, Pages 233–239.
- Tham SY, Loh HS, Mai CW, Fu JY. Tocotrienols Modulate a Life or Death Decision in Cancers. Int J Mol Sci. 2019 Jan 16;20(2):372.
- Trujillo, M.; Kharbanda, A.; Corley, C.; Simmons, P.; Allen, A.R. Tocotrienols as an Anti-Breast Cancer Agent. Antioxidants 2021, 10, 1383.

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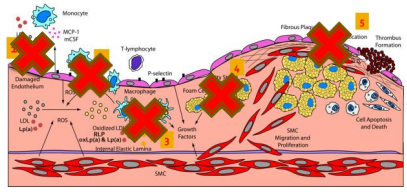
Tocotrienols: Foundational Therapy for Cardiovascular Disease

- All Patients with CVD risk:
  - Dyslipidemia
    - ↑ RLP-P, Lp(a), small dense LDL
    - ↑ApoB, hs-CRP, ↑ homocysteine
    - Statin + CoQ10: 100-200 mg BID + Annatto Pro 125: 1 cap QD/BID
  - High blood pressure
  - Insulin resistance



- Dosing:
  - 1 cap QD wf (maintenance)
  - 1 cap BID wf for those with CVD risk
- Take with some fat to optimize absorption
- Take ~6 hours apart from tocopherol-containing supplements

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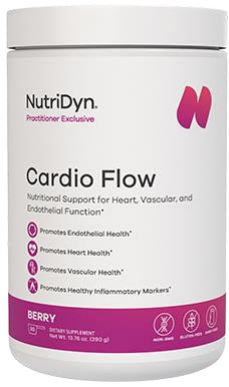
Foundational Support to Optimize NO Levels

- Incredible Foundation to recouple (repair) nitric oxide pathways and optimize NO levels



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Dyslipidemia: Supplemental Recommendations

Supplement	Rationale	Dosage
Phytosterols	• ↓ LDL-C	2 grams
Pantethine	• ↓ TG, TC, VLDL-C, LDL-C, Apo-B • ↑ HDL & HDL2, Apo A-1	600 mg/day
Niacin	• ↓ TG, VLDL, LDL, TC, Lp(a) • ↑ HDL & LDL-P size	500 mg – 4 grams SR: <2 grams
Red Yeast Rice	• ↓ TG and TC	1-5 grams/day
EPA & DHA	• ↓ TG, VLDL, IDL & small, dense LDL • ↓ lipid peroxidation • ↑ HDL2 & glutathione	

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Dyslipidemia: Supplemental Recommendations

Supplement	Rationale	Dosage
L-Carnitine	• ↓ TG, VLDL-C, TC & Lp(a) • ↓ small, dense LDL-C & ↑ LDL-P size • ↓ OxLDL-C & oxidative damage	1-2 grams QD/BID
α-lipoic acid	• ↑ insulin sensitivity • ↓ TG, TC, LDL-C & VLDL-C • ↓ small, dense LDL-C & oxLDL-C • ↓ free radicals/oxidative damage • ↓ inflammation	300 mg BID
Berberine	• ↓ TC, LDL, & TG • ↑ insulin sensitivity	600 mg/day
Garlic	• Prevents lipid peroxidation • Anti-atherogenic; anti-thrombotic	300 mg extract TID (1.3% alliin)
Tocotrienols	• ↓ lipid peroxidation & platelet aggregation; stabilize plaque	125 mg QD/BID

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Foundational Protocol for High ApoB/LDL-P

Recommendation	Dosage
Cardio Essential Cholestin Support and/or Cardio Essentials Niacin SR	*1 packet BID wf* *1 tab QD/BID/TID*
Omega Pure EPA-DHA 720	*1-2 softgels BID/TID wf*
Annatto Pro 125	***1 softgel BID***
Cardio Flow powder	***1 scoop QD (or ½ scoop BID)***
Nitric Boost	***3 caps/day wf***
Dynamic Cardio-Metabolic	1 scoop QD/BID (esp if ↑ blood sugar/insulin resistance)
Berberine Pro	1 cap BID wf PRN (esp if ↑ blood sugar/insulin resistance)
Diet: Modified Mediterranean: lots of deep colored vegetables/fruit (esp. berries/pomegranates); focus on MUFA (olives/olive oil, avocado/oil) – 1-2 Tbsp/day) and fish; nitrate-rich foods daily: Beets, carrots, lettuce, spinach, walnuts	
Exercise: 20-30 min 5x/week; interval/HIIT best + resistance training	
Stress management: daily; deep nasal breathing, humming, meditation, yoga, etc.	
Avoid: Antiseptic and/or alcohol/H2O2-based mouthwashes, Fluoride toothpaste, Antacids and PPIs	

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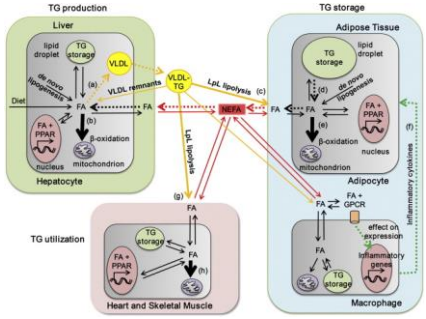
Triglyceride Control -> ↓ VLDL-P & RLP-P

- Triglyceride control
  - Omega-3 EFAs – 2-4 grams/day DHA + EPA
    - Reduce VLDL production by the liver
    - Increase TG & VLDL removal from blood
    - Activate PPAR process
      - Increase conversion of fatty acids to energy
    - Can reduce TG ~25%, large VLDL 92%, & small, dense LDL 21-48%
  - L-carnitine – 2 grams/day
    - Increase uptake/use of fatty acids for energy
    - Reduce TG 10-15% and reverse fatty liver disease



Guilliams TG. The use of fish oil supplements in clinical practice: a review. JANA. 2005; 8(1):21-34.
Rodriguez DR, endible A, Gomez N, and et al. Drug intervention program in dyslipemic children: use of L-carnitine. Revista Latina De Cardiologia - Euroamericana 1997;18(2):25-30.
Kelley DS, et al. Docosahexaenoic acid supplementation improves fasting and postprandial lipid profiles in hypertriglyceridemic men. Am J Clin Nutr. 2007 Aug;86(2):324-33.
Casciani CU, Caruso U, Cravotto E, et al. Effect of L-carnitine on lipid pattern in haemodialysis. Lancet 1980;316:1309–10.
Bae JC, et al. Improvement of Nonalcoholic Fatty Liver Disease With Carnitine-Orotate Complex in Type 2 Diabetes (CORONA): A Randomized Controlled Trial. Diabetes Care. 2015 Jul;38(7):1245-52.
Engler MM, Engler MB et al. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). Am J Cardiol. 2005; 95(7):869-71.
Gregory C. Shearer, Olga V. Savinova, William S. Harris. Fish oil — How does it reduce plasma triglycerides?, Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, Volume 1821, Issue 5, 2012, Pages 843-851.

202

Reducing TG, VLDL-P, RLP-P

Recommendation	Dosage
Cardio Essentials Niacin SR	***1 tab BID PRN wf***
Annatto Pro 125	***1 gelcap BID wf***
Omega Pure EPA-DHA 720 OR Omega Pure EPA-DHA 2400	***2-3 softgels BID/TID wf ½-1 tsp BID wf***
L-Carnitine/Acetyl-L-Carnitine (500 mg)	***2 capsule BID***
Cardio Metabolic	1 scoop QD/BID
N-acetyl cysteine (600 mg)	1 capsule BID wf PRN (if ↑VLDL &/or RLP)
Diet: Modified Mediterranean dietary guidelines; focus on MUFA & Ω-3 rich fish/foods for fats	
Exercise: 30 min 5x/week; interval/HIIT best; resistance training 2-4x/week	

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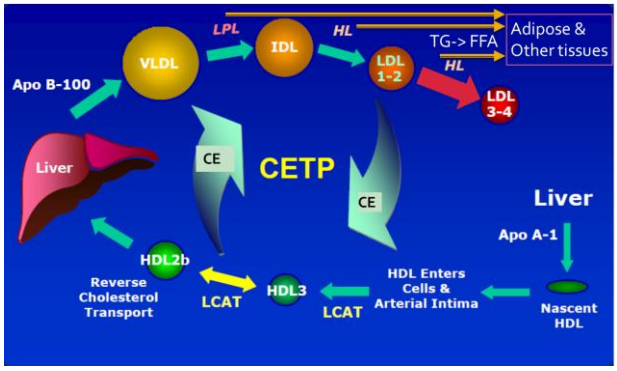
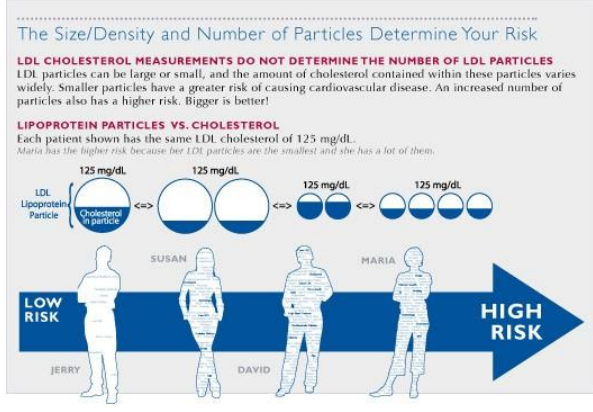
↑ VLDL-P & RLP-P -> ↑ small, dense LDL-P





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Increasing LDL Particle Size: ↓ Small, dense LDL-P (III/IV) or TG:HDL-C > 4

Recommendation	Dosage
Cardio-Metabolic	***1 scoop QD/BID***
Cardio Essentials Niacin SR	***1-2 tab BID***
Omega Pure EPA-DHA 720	***2 softgels BID/TID wf***
Annatto Pro 125	***1 gelcap BID wf***
L-Carnitine/Acetyl-L-Carnitine (500 mg)	***2 capsule BID w/of***
α-Lipoic Acid (200 mg)	***1 cap TID***
Berberine Pro	1 cap TID PRN
Diet: Modified Mediterranean Diet (low glycemic index, high fiber & MUFA)	
Exercise: 20-30 min 5x/week; interval/HIIT best + resistance training	

- If taking statin medications:
  - CoQ10 (100 mg) – 1-2 gelcaps BID

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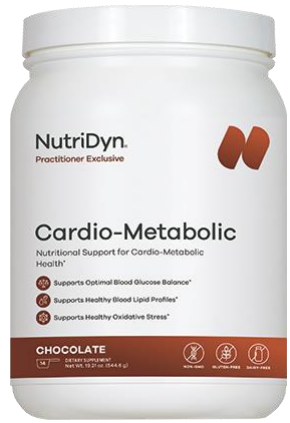
Cardio Metabolic: Optimize Blood Sugar

- Foundational blood sugar support
  - Especially for insulin resistance, T2D, ↑ fasting glucose
- Alters blood lipid metabolism
  - ↓ Small, dense LDL-P (III/IV)
  - ↓ TG, VLDL-P, RLP-P

Glucomannan (from umbrella arum root extract)	1.5 g
Gum Arabic Tree Gum Resin Powder	1.5 g
Plant Sterols	1.14 g
L-Lysine (as lysine HCl)	850 mg
L-Leucine	700 mg
L-Valine	500 mg
Bitter Melon Fruit Extract	250 mg
Organic Cassia Bark Powder	200 mg
Fenugreek Seed Extract	150 mg
Hops Aerial Parts Extract	125 mg
L-Isoleucine	100 mg
Gymnema Leaf Extract	67 mg



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Reducing Lp(a)

Recommendation	Dosage
Cardio Essentials Niacin SR	***1-2 tablets BID/TID wf***
Annatto Pro 125	***1 gelcap BID wf***
C Aspa Scorb / Vitamin C 1000 Complex	***½-1 tsp BID / 2 tablets BID wf***
CoQ10	***100-200 mg BID wf***
Natto NSK Mega	***1 cap BID w/of***
L-Carnitine	2 grams/day
NAC-600 (N-acetyl cysteine)	1 cap BID/TID wf

207

Reducing Lp(a) References

- Sirtori, C. R., Calabresi, L., Ferrara, S., Pazzucconi, F., Bondioli, A., Baldassarre, D., Birreci, A., and Koverech, A. L-carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a). Nutr Metab Cardiovasc.Dis. 2000;10(5):247-251.
- Zmunda JM, Thompson PD, Dickenson R, Bausserman LL. Testosterone decreases lipoprotein(a) in men. Am J Cardiol. 1996 Jun 1;77(14):1244-7.
- Marcovina SM, Lippi G, Bagatell CJ, Bremner WJ. Testosterone-induced suppression of lipoprotein(a) in normal men; relation to basal lipoprotein(a) level. Atherosclerosis. 1996 Apr 26;122(1):89-95.
- Ricci G, Tamaro G, Simeone R, et al. Lipoprotein(a) changes during natural menstrual cycle and ovarian stimulation with recombinant and highly purified urinary FSH. Hum Reprod. 2001 Mar;16(3):449-56.
- Pan J, Van JT, Chan E, et al. Extended-release niacin treatment of the atherogenic lipid profile and lipoprotein(a) in diabetes. Metabolism. 2002 Sep;51(9):1120-7.
- Shojaei M, et al. Effects of Carnitine and Coenzyme Q10 on Lipid Profile and Serum Levels of Lipoprotein(a) in Maintenance Hemodialysis Patients on Statin Therapy. Iran J Kidney Dis. 2011 Apr;5(2):114-8.
- Zmunda JM, et al. Testosterone decreases lipoprotein(a) in men. Am J Cardiol. 1996 Jun 1;77(14):1244-7.
- Marcovina SM, et al. Testosterone-induced suppression of lipoprotein(a) in normal men; relation to basal lipoprotein(a) level. Atherosclerosis. 1996 Apr 26;122(1):89-95.
- Kim CJ, et al. Effects of hormone replacement therapy on lipoprotein(a) and lipids in postmenopausal women. Arterioscler Thromb. 1994 Feb;14(2):275-81.
- Rath M. Lipoprotein-a reduction by ascorbate. J Orthomolec Med 1992;7:81-82.
- Cicero A, Derosa G, Miconi A et al. Possible role of ubiquinone in the treatment of massive hypertriglyceridemia resistant to PUFA and fibrates. Biomed Pharmacother 2005 Jul;59:312-7.

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Increasing HDL/HDL2b

- First line therapy: Lifestyle modifications
  - Weight loss
    - ↑ HDL-C 1 mg/dL per 3 kg loss
  - Diet rich in MUFA/PUFA
    - Up to 5% increase
  - Tobacco cessation
    - 5-10% increase
  - Moderate alcohol consumption
    - 5-15% increase
  - Exercise
    - 5-10% increase





Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA. 2007;298:786-798.

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Increasing HDL2b-P

Recommendation	Dosage
Cardio Essentials Cholestin Support and/or Cardio Essentials Niacin SR	*1 packet QD/BID wf* *1 tab BID PRN*
Omega Pure EPA-DHA 720	*2 softgels BID/TID wf*
Garlic Pro	1 cap QD/BID
Diet: Modified Mediterranean; 4 oz red wine 3-4x/week; eat 2+ cloves garlic daily	
Exercise: 30-60 min 3-5x/week; interval/HIIT + resistance training	
Stress management: daily	

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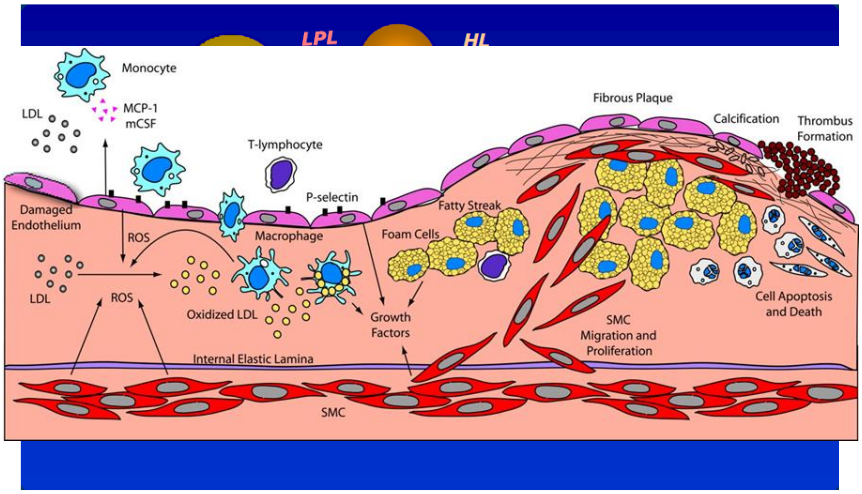
Reverse Cholesterol Transport



Brewer HB Jr, Santamarina-Fojo S. Clinical significance of high-density lipoproteins and the development of atherosclerosis: focus on the role of the adenosine triphosphate-binding cassette protein A1 transporter. Am J Cardiol. 2003 Aug 21;92(4B):10K-16K.

Rajman I, Eacho PI, Chowienczyk PJ, Ritter JM. LDL particle size: an important drug target? British Journal of Clinical Pharmacology. 1999;48(2):125-133.

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Dyslipidemia: Supplementation: Garlic

- Modest reductions in total/LDL-C
- Many other CVD benefits:
  - Prevents LDL oxidation
  - Profound anti-atherosclerotic activity
    - Reduces rate of atherosclerosis progression
    - Reduces coronary artery calcium progression
    - Improves vascular elasticity & endothelial function
  - Improves fibrinolytic activity
  - Inhibits platelet aggregation
  - Acts as an anti-hypertensive agent
- Dosing: 1 cap QD/BID

Banerjee SK, Maulik SK. Effect of garlic on cardiovascular disorders: a review. Nutr J. 2002; 1:4.

Lau BH. Suppression of LDL oxidation by garlic. J Nutr. 2001; 131(3s):985S-8S.

Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. J Hypertens. 1994;12(4):463-8.

Orekhov AN, Sobenin IA, Korneev NV, et al. Anti-atherosclerotic therapy based on botanicals. Recent Pat Cardiovasc Drug Discov 2013;8(1):56-66.

Ahmadi N, Nabavi V, Hajsadeghi F, et al. Aged garlic extract with supplement is associated with increase in brown adipose, decrease in white adipose tissue and predict lack of progression in coronary atherosclerosis. Int J Cardiol 2013;168(3):2310-4.

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Managing Inflammation

- Determine and address the cause(s)
- Modulate the inflammatory process
  - Chiropractic adjustment(s)
  - Dietary Interventions
    - Modified Mediterranean Diet
    - Anti-Inflammatory Diet
  - Weight loss
  - Stress management
  - Meditation and visualization
  - Supplementation

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Reducing Inflammation/hs-CRP

Recommendation	Dosage
Inflam-Eze and/or Inflam-Eze Plus	***1 scoop BID 1-2 caps BID/TID PRN***
C Aspa Scorb	***1 tsp in each serving Inflam-Eze***
PRM Resolve	***2 gelcaps BID (up to 8 gelcaps/day) wf***
Annatto Pro 125	***1 gelcap QD/BID wf***
D3-5000 + K2 (based on testing)	***1 capsule QD/BID wf***
Anti-inflammatory diet and/or Modified Mediterranean; eliminate food allergens/triggers	
Water – ½ body weight in ounces/day; ~1/4-½ cup every ½ hour	

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Reducing Homocysteine

- Quit smoking (!)
- Improve digestion/eliminate need for gastric acid inhibitors (reduce intrinsic factor/B12 absorption)
- Diet – decrease coffee/black tea & alcohol; increase vegetables/fiber & may need to reduce protein
- Exercise – HIIT: 30 min 3-5x/week; especially for men

- Methyl Complete – 2 tablets daily cf
  - L-5-MTHF (folate), methylcobalamin (B12), vitamin B6, trimethylglycine and choline + Intrinsic factor
- May require 5-MTHF: up to 2-5 mg/day & TMG: 1.5-6 g/day
- N-acetylcysteine (NAC) – 1800 mg/day if needed

Mennen LI, et al. Homocysteine, cardiovascular disease risk factors, and habitual diet in the French Supplementation with Antioxidant Vitamins and Minerals Study. Am J Clin Nutr. 2002; 76: 1279–1289.
Stolzenberg-Solomon R, et al. Association of dietary protein intake and coffee consumption with serum homocysteine concentrations in an older population. Am J Clin Nutr 1999;69:467–75.
Oshaug A, Bugge KH, Refsum H. Diet, and independent determinant for plasma total homocysteine. A cross sectional study of Norwegian workers on platforms in the North Sea. Eur J Clin Nutr 1998,52:7–11.
Mennen LI, et al; Homocysteine, cardiovascular disease risk factors, and habitual diet in the French Supplementation with Antioxidant Vitamins and Minerals Study, The American Journal of Clinical Nutrition, Volume 76, Issue 6, December 2002, pp.1279–1289.
Nygard O, Vollset SE, Refsum H, et al. Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. JAMA 1995;274:1526–33.
Stanford JL, et al. Oral folate reduces plasma homocyst(e)ine levels in hemodialysis patients with cardiovascular disease. Cardiovasc Surg. 2000;8(7):567-571.
Steenge GR, Verhoef P, Katan MB. Betaine supplementation lowers plasma homocysteine in healthy men and women. J Nutr. 2003;133(5):1291-1295.
Ventura P, Panini R, Abbati G, Marchetti G, Salvioli G. Urinary and plasma homocysteine and cysteine levels during prolonged oral N-acetylcysteine therapy. Pharmacology. 2003;68(2):105-114.

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You want me to do what…???

216

Establish a Foundation for CV Health

- Standard lipid testing only and/or Foundational Support
  - ***Cardio Essentials Cholestin Support***: 1 packet BID
    - If too much, start with ***Cardio Essentials Niacin SR***: 1 tab QD->BID in 2 weeks
  - ***Omega Pure EPA-DHA 720***: 1 gelcap BID
    - If high triglycerides, increase to 2 BID
  - ***Annatto Pro 125*** – 1 gelcap BID
  - ***D3-5000+K2*** – 1 cap QD/BID (based on Vitamin D labs)

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Build on the Foundation

- Nitric Oxide Strips suboptimal and/or hypertension, add
  - ***Cardio Flow***: 1 scoop QD
  - ***Nitric Boost***: 3 caps/day
  - Add others if/when possible or if more support needed
- If they complete LPP+ or KBMO CIT, use appropriate protocols
  - Begin with products that are ***bold & italic***
  - Add others if/when possible or if more support needed

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Cardiovascular Disease Review

- Cardiovascular diseases are multifactorial
  - Lipoprotein metabolism
  - Nitric Oxide dysregulation
- CVD develops over time, often silently
  - Begins in 20s, 30s & 40s
- Accurate and early assessment is important
- 90% of CVD is preventable
- CVD is reversible

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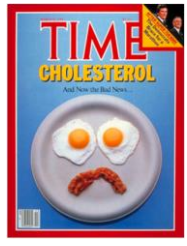
Standard Lipid Testing is Insufficient

- Calculated LDL-C = TC – (HDL-C + TG/5)
  - Inaccurate assessment of CVD risk
    - "Constant" 5 varies between 2-12 in real life
    - Calc LDL-C includes cholesterol from many lipoproteins with varying degrees of atherogenicity
    - Doesn't take into account particle size/density
    - Not an accurate measure of LDL-P
- Cholesterol does NOT provide an accurate assessment of CVD risk



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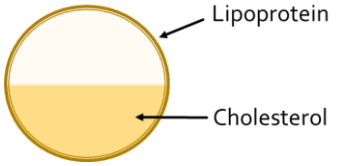
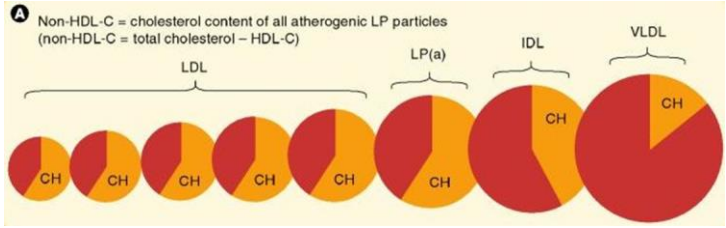
Lipoproteins vs. Cholesterol

- Lipoproteins matter A LOT





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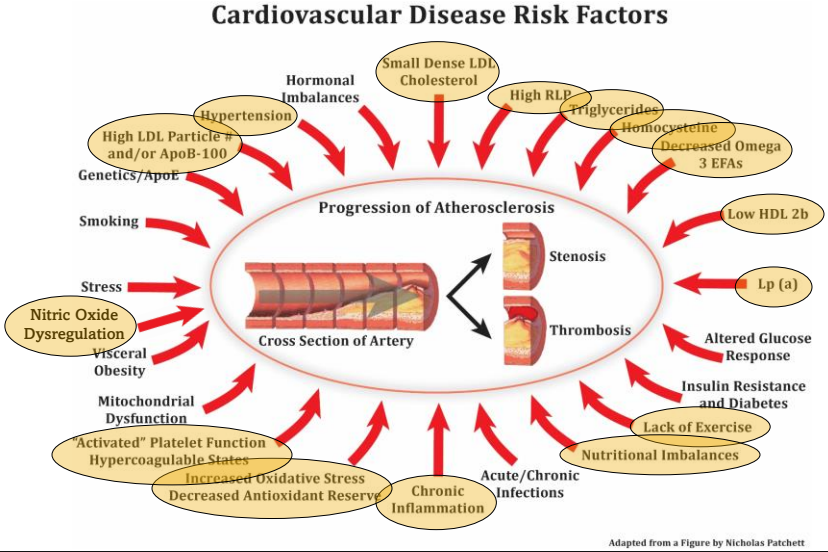
Cardiovascular Disease Risk Factors



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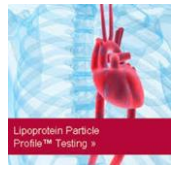
Get Testing Done

- Advanced Lipoprotein Testing
  - LPP+ Testing (Lipoprotein Particle Profile)
  - KBMO – CIT (Cardiovascular Inflammation Test)
- Omega-3 Index
- Nitric Oxide Indicator Strips



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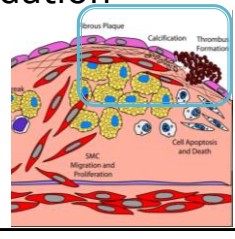
Advanced CVD Markers Summary

- ApoB or LDL-P#: ↑#, more particles, ↑ probability of arterial penetration

- ↑ Small (dense) LDL: ↑ penetration/oxidation



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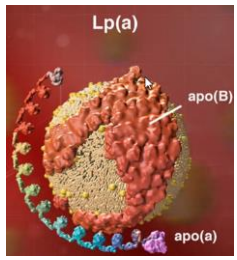
Advanced CVD Markers Summary

- RLP: VERY atherogenic
  - Can greatly accelerate atherosclerosis
  - Does NOT correlate with LDL-C; ↑ in 25% of population
  - Common with metabolic syndrome
- Lp(a): VERY atherogenic & thrombotic
  - Genetic component of CVD
  - ↑ in 20-25% of pop
  - CVD risk 3-5x greater if Lp(a) ↑



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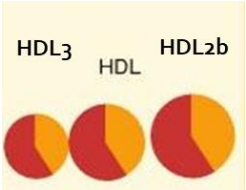
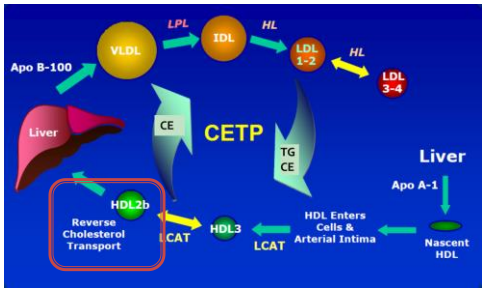
Advanced CVD Markers Summary

- HDL2b-P
  - Inversely associated with CVD risk
  - Measure of rate of reverse cholesterol transport
  - Low HDL2b common with metabolic syndrome





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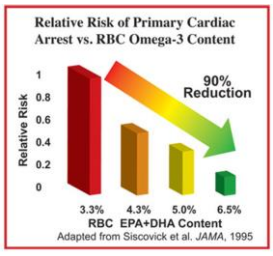
Advanced CVD Markers Summary

- HS-Omega 3 Index
  - < 8.0% = ↑ risk of sudden death due to CVD
- hs-CRP
  - Marker of inflammation
  - >2.0 mg/L associated with acute CVD events and mortality



- Homocysteine
  - Causes oxidative stress, which inhibits L-arginine uptake & causes ↓ NO production
  - Can initiate and propagate atherosclerosis

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Dyslipidemia Case Study: Matt

- 68 yo male
- 69" tall, 199.2 lbs; BF: 28.3%; SMM: 34.3%
- Triple bypass surgery in Oct 2015
  - Rx: pravastatin (40 mg); metoprolol succinate ER (12.5 mg), baby aspirin (81 mg)
- Decrease in energy & libido since Rx
- Client goal: improve CV health and reduce/eliminate need for Rx
- Labs: Vit D: 23 ng/ml; cholesterol panel

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Matt: Standard Lipid Testing Results

	Date	TC	LDL-C Calc	HDL-C	TG	TC:HDL-C	TG:HDL-C
Triple bypass surgery ->	09/24/15	231	160	35	181	6.6	5.2
	11/19/15	167	103	29	174	5.8	6.0
	09/19/16	160	101	34	124	4.7	3.6
	Goal (NCEP)	<200	<130	>40	<150	<5.0	n/a (<3)

- Put on Pravastatin (40 mg), Metoprolol ER (12.5 mg) and baby aspirin (81 mg) 10/13/15
- Told that risk of future CV event was being mitigated by medications & "not to worry"

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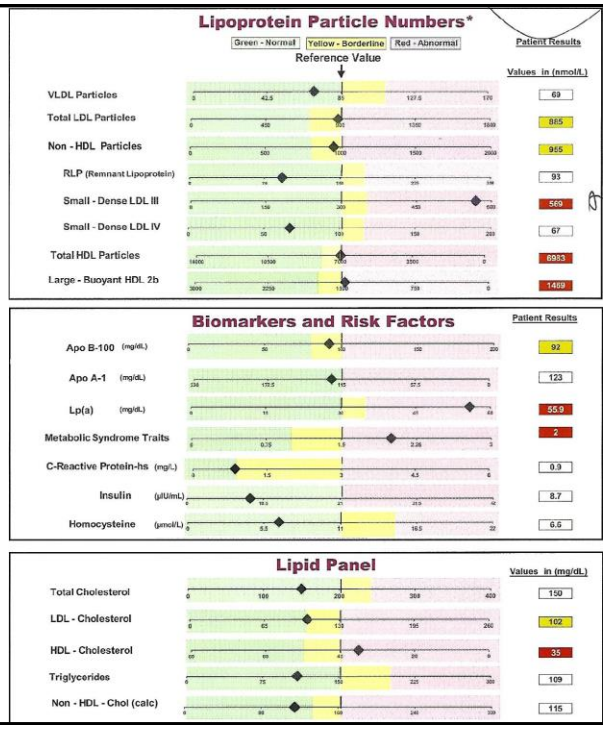

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Matt: Initial LPP Results

Biomarker	Reference Value	Sept 2016
Total Cholesterol	<200	150
LDL-C	<130	102
HDL-C	>40	35
Trigs	<150	109
LDL-P #	<900	885
Dense LDL III	<300	569
Dense LDL IV	<100	67
Total HDL-P	>7000	6983
Buoyant HDL2b	>1500	1469
Lp(a)	<30	55.9

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Using the LPP+ to Address CVD

- Step 1: Primary Risk Assessment
  - ✓ High LDL particle number (<900) & Apo B (<80 mg/dL)
  - ✓ Elevated small/dense LDL (LDL III >300 nmol/L; LDL IV > 100 nmol/L)
  - Elevated RLP (150 nmol/L); Moderate/high Triglycerides (>150 mg/dL)
  - ✓ Low HDL2b (<1500 nmol/L)
- Step 2: Modify risk using Metabolic syndrome traits, Lp(a) & hs-CRP
  - Combine metabolic syndrome traits from LPP with blood pressure, obesity (WC/BIA) & fasting glucose
  - ✓ ↑ Lp(a) and/or ↑ hs-CRP and/or ↑ homocysteine
  - ✓ Also consider family Hx, medical Hx and smoking
  - Modify risk assessment and Tx goals from Step 1 based on these criteria
  - Use standard Lipid Panel at bottom to compare with previous labs
- Step 3: Determine Therapeutic Approach
  - ➢ Significant risk of future cardiovascular event
  - Determine Tx goals and therapeutic approach to address each risk factor

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Matt: Initial Recommendations

Remedy/Supplement	Upon rising	Breakfast	Lunch	Dinner	Before retiring
Dynamic Cardio Metabolic		1 scoop			
Cardio Essentials Cholestin Support ->		2		2	
Cardio Essentials Niacin SR		1		1	
Omega Pure EPA-DHA 720				2	
Berberine Pro		2		1	
CoQ10 (100 mg)		2		2	
L-Carnitine 500		2		2	
Garlic Pro				1	
D3 10,000 with K2		1			

- **Water** – drink 2.5 quarts of water/tea daily in divided doses (4 oz. (1/2 cup) every 30 minutes optimal); Green & Rooibos Tea – 2-5 cups/day
- **Exercise –** increase resistance training – 3x/week with trainer; 1-2x/week on your own; Burst/High-intensity interval training – 3x/week – 5 min warm up , 10 x 1 min intervals (20 min); 5 min cool down
- **Dietary recommendations** – Modified Mediterranean Diet;
- **Deep breathing** – do 10 deep breaths first thing in the morning and before bed; every time you send or receive and email, take a deep breath
- **Sleep** – 8-9 hours nightly

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Matt: Follow up

- Within 1 week, ↑ energy & libido
  - Continue to improve over next several months
- Flushed with CE Niacin SR; reduced and slowly ↑
- 6 months later:
  - Wt: 181.2 lbs (-18 lbs)
  - BF: 23.1% (-5.2%, 14.5 lbs)
  - SMM: 36.5% (+2.2%)
  - Good compliance with diet & exercise
    - Treadmill: HIIT 40-60 min; 3-4x/week
    - Dumbbells at home: 2-3x/week

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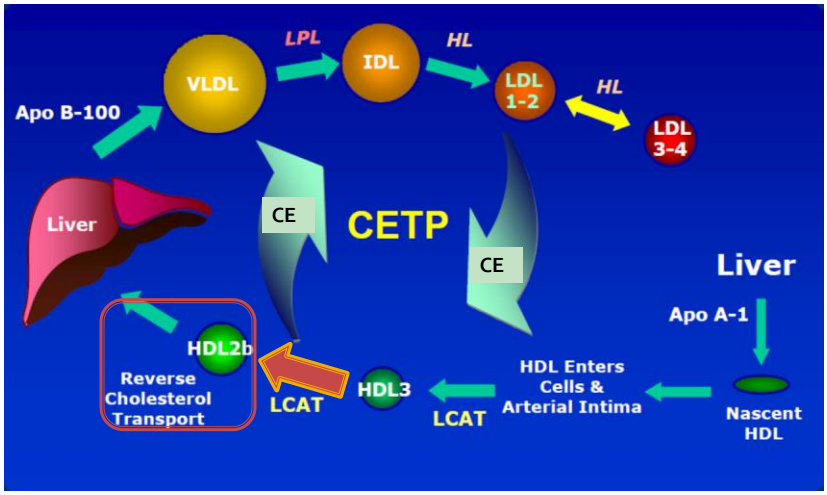
Matt: Follow up LPP Results



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Matt: Follow Up Recommendations

Remedy/Supplement	Upon rising	Breakfast	Lunch	Dinner	Before retiring
Dynamic Cardio Metabolic		1 scoop			
Cardio Essentials Niacin SR		1		1	
Omega Pure EPA-DHA 720				2	
Berberine Pro		1	1	1	
CoQ10 (100 mg)		2		2	
L-Carnitine 500		2		2	
Garlic Pro				1	
D3 10,000 with K2		1			

- **Water** – drink 2.5 quarts of water/tea daily in divided doses (4 oz. (1/2 cup) every 30 minutes optimal); **Green & Rooibos Tea – 2-5 cups/day**
- **Exercise –** increase resistance training – 3x/week with trainer & gym; 1-2x/week on your own; Continue HIIT 3-4x/week 40-60 min
- **Dietary recommendations** – Modified Mediterranean Diet; 50+% of plate deep colored vegetables/berries
- **Deep breathing** – do 10 deep breaths first thing in the morning and before bed; every time you send or receive and email, take a deep breath
- **Sleep** – 8-9 hours nightly
- Speak with MD about possibility of reducing Rx

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Start Here

- Determine CVD Risk
  - Testing to complete:
    - LPP+ or KBMO CIT, Omega 3 Index, Nitric Oxide Indicator Strips
- Address what you find
  - Provide/use the protocols
    - If needed, Establish a Foundation & Build upon it

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Establish a Foundation for CV Health

- Standard lipid testing only and/or Foundational Support
  - ***Cardio Essentials Cholestin Support***: 1 packet BID
    - If too much, start with ***Cardio Essentials Niacin SR***: 1 tab QD->BID in 2 weeks
  - ***Omega Pure EPA-DHA 720***: 1 gelcap BID
    - If high triglycerides, increase to 2 BID
  - ***Annatto Pro 125*** – 1 gelcap BID
  - ***D3-5000+K2*** – 1 cap QD/BID (based on Vitamin D labs)

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Build on the Foundation

- Nitric Oxide Strips suboptimal and/or hypertension, add
  - ***Cardio Flow***: 1 scoop QD
  - ***Nitric Boost***: 3 caps/day
  - Add others if/when possible or if more support needed
- If they complete LPP+ or KBMO CIT, use appropriate protocols
  - Begin with products that are ***bold & italic***
  - Add others if/when possible or if more support needed

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NO Boosting Supplementation

Recommendation	Dosage
Cardio Flow powder	***1 scoop QD (or ½ scoop BID)***
Nitric Boost	***3 caps/day cf***
Annatto Pro 125	***1 gelcap QD/BID cf (esp if ↑ RLP-P)***
C Aspa Scorb	½ tsp BID with food
N-acetyl cysteine (600 mg)	1 capsule BID cf (esp if ↑ RLP-P)
Brain Support	2 caps BID (esp for cognition)
Inflam-Eze Plus	1-2 caps BID/TID (esp for inflammation)
Diet – Modified Mediterranean: lots of low GI deep colored vegetables/fruit (esp. berries/pomegranates); focus on MUFA (Oleic acid (olives/olive oil, avocado/oil) – 1-2 Tbsp/day) and Fish/fish oils; nitrate-rich foods daily: Beets, carrots, lettuce, spinach, walnuts	
Exercise – moderate aerobic exercise – 30 min 5x/week; HIIT 2-3x/week	
Stress management – daily; deep nasal breathing, humming, meditation, yoga, etc.	
Avoid: Antiseptic and/or alcohol/H_2O_2-based mouthwashes, Fluoride toothpaste, Antacids and PPIs	

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Foundational Protocol for High ApoB/LDL-P

Recommendation	Dosage
Cardio Essential Cholestin Support and/or Cardio Essentials Niacin SR	*1 packet BID wf 1 tab QD/BID/TID*
Omega Pure EPA-DHA 720	*1-2 softgels BID/TID wf*
Annatto Pro 125	***1 softgel BID***
Cardio Flow powder	***1 scoop QD (or ½ scoop BID)***
Nitric Boost	***3 caps/day wf***
Dynamic Cardio-Metabolic	1 scoop QD/BID (esp if ↑ blood sugar/insulin resistance)
Berberine Pro	1 cap BID wf PRN (esp if ↑ blood sugar/insulin resistance)
Diet: Modified Mediterranean: lots of deep colored vegetables/fruit (esp. berries/pomegranates); focus on MUFA (olives/olive oil, avocado/oil) – 1-2 Tbsp/day) and fish; nitrate-rich foods daily: Beets, carrots, lettuce, spinach, walnuts	
Exercise: 20-30 min 5x/week; interval/HIIT best + resistance training	
Stress management: daily; deep nasal breathing, humming, meditation, yoga, etc.	
Avoid: Antiseptic and/or alcohol/H_2O_2-based mouthwashes, Fluoride toothpaste, Antacids and PPIs	

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Reducing TG, VLDL-P, RLP-P

Recommendation	Dosage
Cardio Essentials Niacin SR	***1 tab BID PRN wf***
Annatto Pro 125	***1 gelcap BID wf***
Omega Pure EPA-DHA 720 OR Omega Pure EPA-DHA 2400	***2-3 softgels BID/TID wf ½-1 tsp BID wf***
L-Carnitine/Acetyl-L-Carnitine (500 mg)	***2 capsule BID***
Cardio Metabolic	1 scoop QD/BID
N-acetyl cysteine (600 mg)	1 capsule BID wf PRN (if ↑VLDL &/or RLP)
Diet: Modified Mediterranean dietary guidelines; focus on MUFA & Ω-3 rich fish/foods for fats	
Exercise: 30 min 5x/week; interval/HIIT best; resistance training 2-4x/week	

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Increasing LDL Particle Size: ↓ Small, dense LDL-P (III/IV) or TG:HDL-C > 4

Recommendation	Dosage
Cardio-Metabolic	***1 scoop QD/BID***
Cardio Essentials Niacin SR	***1-2 tab BID***
Omega Pure EPA-DHA 720	***2 softgels BID/TID wf***
Annatto Pro 125	***1 gelcap BID wf***
L-Carnitine/Acetyl-L-Carnitine (500 mg)	***2 capsule BID w/of***
α-Lipoic Acid (200 mg)	***1 cap TID***
Berberine Pro	1 cap TID PRN
Diet: Modified Mediterranean Diet (low glycemic index, high fiber & MUFA)	
Exercise: 20-30 min 5x/week; interval/HIIT best + resistance training	

- If taking statin medications:
  - CoQ10 (100 mg) – 1-2 gelcaps BID

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Reducing Lp(a)

Recommendation	Dosage
Cardio Essentials Niacin SR	***1-2 tablets BID/TID wf***
Annatto Pro 125	***1 gelcap BID wf***
C Aspa Scorb / Vitamin C 1000 Complex	***½-1 tsp BID / 2 tablets BID wf***
CoQ10	***100-200 mg BID wf***
Natto NSK Mega	***1 cap BID w/of***
L-Carnitine	2 grams/day
NAC-600 (N-acetyl cysteine)	1 cap BID/TID wf

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Increasing HDL2b-P

Recommendation	Dosage
Cardio Essentials Cholestin Support and/or Cardio Essentials Niacin SR	*1 packet QD/BID wf 1 tab BID PRN*
Omega Pure EPA-DHA 720	*2 softgels BID/TID wf*
Garlic Pro	1 cap QD/BID
Diet: Modified Mediterranean; 4 oz red wine 3-4x/week; eat 2+ cloves garlic daily	
Exercise: 30-60 min 3-5x/week; interval/HIIT + resistance training	
Stress management: daily	

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Reducing Inflammation/hs-CRP

Recommendation	Dosage
Inflam-Eze and/or Inflam-Eze Plus	***1 scoop BID 1-2 caps BID/TID PRN***
C Aspa Scorb	***1 tsp in each serving Inflam-Eze***
PRM Resolve	***2 gelcaps BID (up to 8 gelcaps/day) wf***
Annatto Pro 125	***1 gelcap QD/BID wf***
D3-5000 + K2 (based on testing)	***1 capsule QD/BID wf***
Anti-inflammatory diet and/or Modified Mediterranean; eliminate food allergens/triggers	
Water – ½ body weight in ounces/day; ~1/4-½ cup every ½ hour	

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Reducing Homocysteine

- Quit smoking (!)
- Improve digestion/eliminate need for gastric acid inhibitors (reduce intrinsic factor/B12 absorption)
- Diet – decrease coffee/black tea & alcohol; increase vegetables/fiber & may need to reduce protein
- Exercise – HIIT: 30 min 3-5x/week; especially for men

- Methyl Complete – 2 tablets daily cf
  - L-5-MTHF (folate), methylcobalamin (B12), vitamin B6, trimethylglycine and choline + Intrinsic factor
- May require 5-MTHF: up to 2-5 mg/day & TMG: 1.5-6 g/day
- N-acetylcysteine (NAC) – 1800 mg/day if needed

Mennen LI, et al. Homocysteine, cardiovascular disease risk factors, and habitual diet in the French Supplementation with Antioxidant Vitamins and Minerals Study. Am J Clin Nutr. 2002; 76: 1279–1289.
Stolzenberg-Solomon R, et al. Association of dietary protein intake and coffee consumption with serum homocysteine concentrations in an older population. Am J Clin Nutr 1999;69:467–75.
Oshaug A, Bugge KH, Refsum H. Diet, and independent determinant for plasma total homocysteine. A cross sectional study of Norwegian workers on platforms in the North Sea. Eur J Clin Nutr 1998;52:7–11.
Mennen LI, et al; Homocysteine, cardiovascular disease risk factors, and habitual diet in the French Supplementation with Antioxidant Vitamins and Minerals Study, The American Journal of Clinical Nutrition, Volume 76, Issue 6, December 2002, pp.1279–1289.
Nygard O, Vollset SE, Refsum H, et al. Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. JAMA 1995;274:1526–33.
Stanford JL, et al. Oral folate reduces plasma homocyst(e)ine levels in hemodialysis patients with cardiovascular disease. Cardiovasc Surg. 2000;8(7):567-571.
Steenge GR, Verhoef P, Katan MB. Betaine supplementation lowers plasma homocysteine in healthy men and women. J Nutr. 2003;133(5):1291-1295.
Ventura P, Panini R, Abbati G, Marchetti G, Salvioli G. Urinary and plasma homocysteine and cysteine levels during prolonged oral N-acetylcysteine therapy. Pharmacology. 2003;68(2):105-114.

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HBP Supplement Recommendations

Recommendation	Dosage
Cardio Flow powder	***1 scoop QD (or ½ scoop BID)***
Nitric Boost	***3 caps/day cf***
Annatto Pro 125	***1 gelcap QD/BID cf (esp if ↑ RLP-P)***
CoQ10 (100 mg)	***1 gelcap BID cf***
C Aspa Scorb	***½ tsp BID with food***
Omega Pure EPA-DHA 720	***2 gelcaps TID cf***
N-acetyl cysteine (600 mg)	1 capsule BID cf (esp if ↑ RLP-P)
Diet: Modified Mediterranean: lots of deep colored vegetables/fruit (esp. berries/pomegranates); focus on MUFA (olives/olive oil, avocado/oil) – 1-2 Tbsp/day) and fish; nitrate-rich foods daily: Beets, carrots, lettuce, spinach, walnuts; water – ½ body weight in ounces throughout the day	
Exercise: 20-30 min 5x/week; interval/HIIT best + resistance training	
Stress management: daily; deep nasal breathing, humming, meditation, yoga, etc.	
Avoid: Antiseptic and/or alcohol/H_2O_2-based mouthwashes, Fluoride toothpaste, Antacids and PPIs	

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Motivation

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Questions???

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For More Information

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