



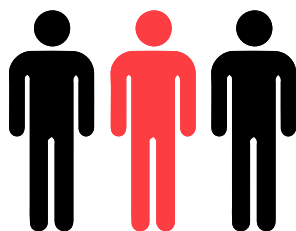
ONNA LO MD

Getting to the **Heart** of Cardiovascular Disease

Written By: Dr. Sachin Patel & Dr. Jared Seigler

Cardiovascular disease (CVD) primarily involves the heart and blood vessels but its detriment can affect the brain, limbs and other systems in the body. It can increase the risk for heart attack, heart failure, sudden death, and stroke, to name a few. The end result is a significantly decreased quality of life and life expectancy. CVD is often termed the “silent killer” because many times the first sign or symptom is a fatal heart attack. Despite billions of dollars being spent on research and medications, it seems we are fighting a losing battle. CVD is the ultimate interplay between genetics, environment and biochemistry.





1 in 3
American Adults has
some form of
Cardiovascular Disease.



600,000 People Die from
CVD per year
Worldwide.



\$444
BILLION = In **2010** the
TOTAL COST
of CVD in
the USA

Cardiovascular disease (CVD) is still the number one cause of death in the United States and it affects over 26 million Americans. One out of three American adults has some form of CVD and it kills almost 600,000 people per year. Death rates alone cannot describe the burden of CVD. In 2010, the total costs of CVD in the United States were estimated to be \$444 billion. Treatment of this epidemic accounts for about \$1 of every \$6 spent on health care in this country. Sadly, these numbers are only expected to rise as cardiovascular disease becomes more prevalent. This article hopes to shed light on this devastating disease, how to accurately assess risk factors, and how functional medicine and lifestyle medicine can help you prevent, address and reverse cardiovascular disease.

A Failing Approach

Much effort has been made by many organizations to push for heart health. Still most Americans do not view themselves as being at risk, while others choose not to do anything about it. The sad truth is, despite the efforts of the American Heart Association, heart disease continues to be mainly a lifestyle condition that is preventable and in many cases reversible through the correct interventions. This approach requires an active and participating patient that is given a sense of direction and guidance, not more prescription medications. A pill can never compensate for poor lifestyle choices, nor do medications result in better bio-chemistry.

Interestingly, cardiovascular drugs are some of the most prescribed medications in this country. Medications to treat high blood pressure and high cholesterol do not address the root cause of the problem, they simply make you look better on paper as the disease progresses in

the background. It is critical to ask the right questions if you are going to get to the heart of the matter.

If the current paradigm of heart disease management were correct then logic would dictate that the incidence of cardiovascular disease would be lower or trending in the right direction, clearly that is not the case. We have written this summary to give you a much better understanding of how we at The Living Proof Institute tackle this massive problem.



Is cholesterol the real enemy?

Debunking the Cholesterol Myth

High cholesterol was once considered anything above 300mg/dl until cholesterol lowering drugs were developed, the value has now dropped down to 200mg/dl. Many patients are placed on cholesterol lowering drugs even if their values are below 200mg/dl. Almost half of all heart disease occurs in those with low or normal cholesterol. In fact a cholesterol lower than 180 mg/dl has been associated with increase risk of stroke.

Is your body making a mistake?

Your body never makes mistakes, it simply responds and adapts to it's environment. You see, cholesterol is the building block of not only stress hormones, but also sex hormones such as testosterone and estrogen. As stress (inflammation, emotions, injury) increases the body requires more cholesterol to fulfill the demand of the environment, a highly intelligent response.

Interesting Cholestrol Facts:

The Framingham Heart Study showed that people with a cholesterol lower than 200 suffer from 40% of heart attacks.

There is clearly more to this problem than simply lowering cholesterol.



Many people who have heart attacks are on cholesterol lowering medications.

Research shows that people that have a cholesterol lower than 180 mg/dl are three times more likely to have a stroke.

Demands that will increase cholesterol requirements include stress, inflammation and elevated demands on insulin (high carbohydrate intake). The cholesterol levels in your body are determined by your environment, **choose wisely.**

The Role of Cholesterol

Cholesterol is necessary for
your very survival.

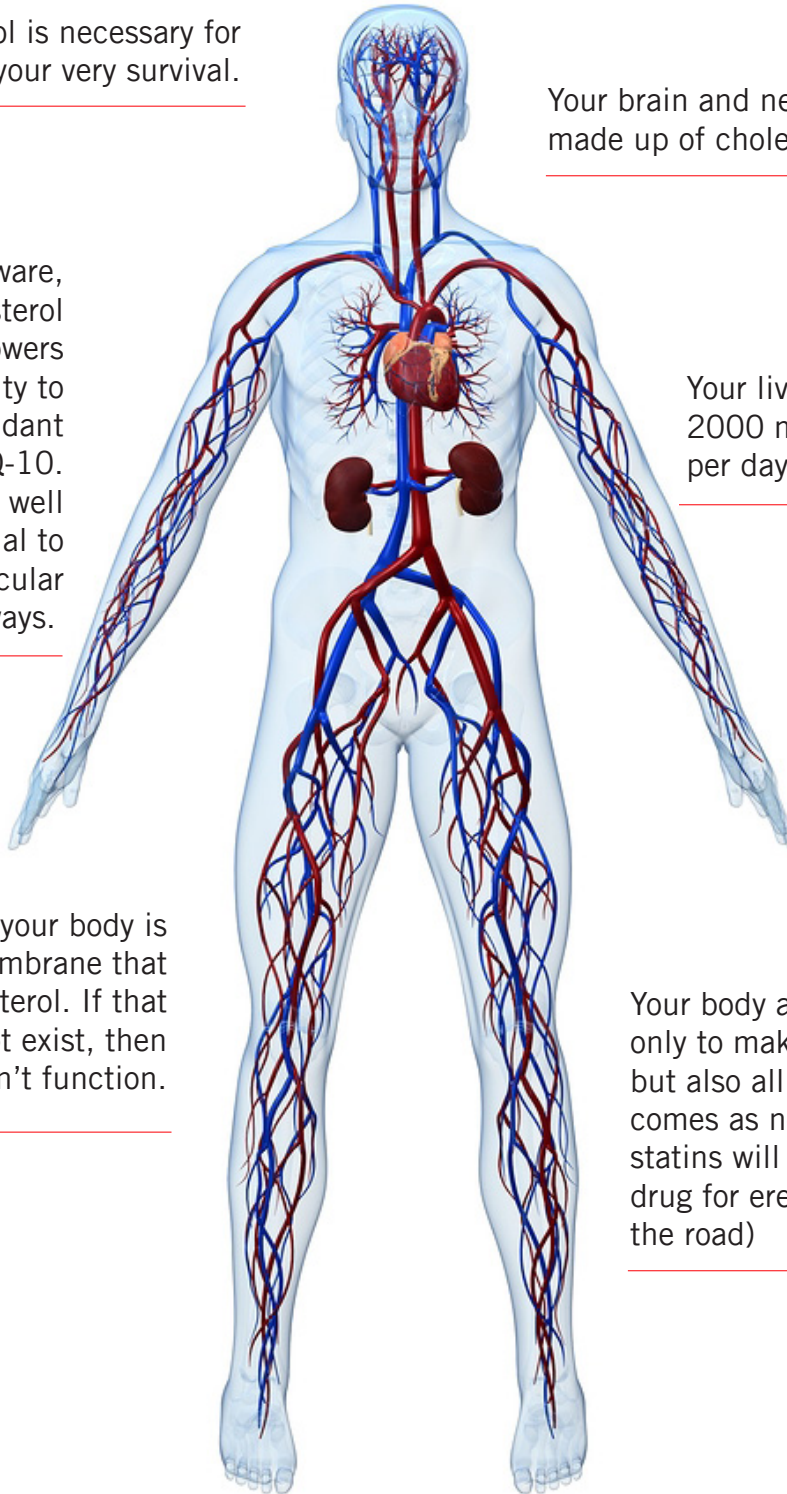
Your brain and nerves are
made up of cholesterol.

As most people are aware,
taking a statin (cholesterol
lowering drug) also lowers
your body's ability to
make an anti-oxidant
called Coenzyme Q-10.
Coenzyme Q-10 is well
known to be beneficial to
numerous cardiovascular
and metabolic pathways.

Your liver produces around
2000 milligrams of cholesterol
per day, on purpose!

Every cell in your body is
surrounded by a membrane that
is made up of cholesterol. If that
membrane did not exist, then
your cells couldn't function.

Your body also uses cholesterol not
only to make your stress hormones,
but also all your sex hormones. (It
comes as no surprise that men on
statins will usually have to take a
drug for erectile dysfunction down
the road)





Size Does Matter

When most patients get tests their doctors measure 4 values; total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. Not much attention is given to the size of the actual particle - the real risk factor. Particle size of the LDL molecule is of particular importance, not just the number.

For example, three people have an LDL number of 125mg/dl, under traditional assessment each would be perceived as having the same risk value. This is far from true. Each of those people should be put into different risk categories based on the size of the LDL particles. Standard blood tests do not measure the size of the LDL particles. This must be done by a special test that your doctor can order to determine particle size. The smaller the particle size, the higher the risk for CVD. These smaller particles can get stuck between the endothelial cells and cause a build-up that starts the plaque process. Over decades this damage will block the arteries.

One particularly damaging particle known is as lipoprotein (a). This destructive particle has a tendency to promote clotting and inflammation worse than other LDL particles because it oxidizes (rusts), faster than other LDL particles. Currently, the only two reliable agents known to lower lipoprotein (a) is Niacin and L-carnitine, not a medication. Ask your doctor to measure your Lp(a).

Methylation - A critical process to monitor CVD

Methylation is just a fancy word for the transfer of a carbon group from one molecule to another. There are hundreds of forms of methylation that happen inside the body, but there is one methylation process that is of vital importance in CVD risk, homocysteine.

Homocysteine is measured in the blood and is usually high due to a lack of vitamin B6, folic acid, B12 and methyl donors. Think of these methyl donors as workers that move the carbon group from one molecule to another. High levels of homocysteine have several negative effects on blood vessels. These include higher levels of atherosclerosis (plaque formation), impaired function of the cells that make up blood vessels (endothelial cells), hardening of arteries, and an increase risk of clotting.

High levels of homocysteine have been shown to almost double the risk of a cardiovascular event. Simply lowering this number is not enough, addressing why this number is high in the first place is a better long-term strategy.

Cold Heart Fact

CVD is often a disease of personal responsibility and is rooted in lifestyle disorders in most cases. CVD is rooted in Metabolic Syndrome which leads to insulin resistance. Metabolic Syndrome is a preventable condition that is heavily influenced by lifestyle and environment. Metabolic Syndrome consists of elevated fasting blood sugars, high blood pressure, high triglycerides, high LDL ("bad" cholesterol), low HDL ("good" cholesterol), and central obesity, thus leading to insulin resistance.

Insulin resistance is the catalyst of many health issues since it results in high insulin levels, poor cell communication, increases cholesterol, elevates blood pressure and lowered magnesium levels to name a few of its damaging effects.

High levels of insulin have also been proven to increase sodium retention, lower HDL levels and increase the risk of blood-clotting.

Therefore, a more logical step in people with high cholesterol and symptoms of Metabolic Syndrome is to consider strategies to support healthy insulin levels and increase insulin receptor sensitivity. These strategies should include reducing carbohydrate intake, moderate physical activity, weight reduction, blood pressure control, correction of the ratio of "good" and "bad" cholesterol, and blood sugar control have been proven beneficial in reversing the risk of a cardiovascular event. The cold heart fact is, you are in control.



Understanding Blood Markers related to CVD

To give you a better understanding of the markers associated to cardiovascular disease review the chart below. Each lab will use different ranges. Only your doctor can determine the right values for you once they understand your history.

Marker	Significance
Fasting Glucose and Fasting Insulin	Blood sugar handling issues such as diabetes can play a tremendous role in the risk for CVD. High insulin causes an increase in blood pressure, higher cholesterol, and causes more inflammation which can increase clotting risks.
Cholesterol	Although not as sensitive a marker for CVD as drug companies would have people believe, it still does play a role. As you have read, a low number can be just as bad as a high number. Cholesterol can be raised by stress and high levels of insulin, and these contributing factors can be addressed through lifestyle interventions. Remember, your body only makes as much as it needs.
Triglycerides	Usually the first sign of insulin resistance. This can be very beneficial for the younger population to address dietary changes before the effects can snowball into something much worse. Also, this number can change dramatically over a short period if the right intervention is used and therefore, can be a marker to gauge the success of any intervention.
HDL Cholesterol	This “good” cholesterol is the particle that takes cholesterol from the inside of blood vessels to the liver to be broken down. This marker is heavily influenced by physical activity, good-to-bad fat ratios, and diet.
VLDL Cholesterol	This is considered a “bad” cholesterol, mainly because it has the highest amount of triglycerides packed onto it for transport. By lowering triglycerides, this number can be affected as well.
LDL Cholesterol	This is the remains of VLDL. This particle’s job is to take leftover cholesterol from the liver and stick it to blood vessels walls that have been damaged by inflammation. Remember size matters with these particles, the bigger the better.
Total Cholesterol/HDL ratio	This marker is a ratio of cholesterol to HDL. The higher the ratio, the higher the risk of a CVD event such as a heart attack or stroke.
Homocysteine	This is an direct measurement of methylation occurring in the body. This marker is much more sensitive than cholesterol in determining the risk of a person with CVD. Homocysteine can be influenced by certain vitamin and nutrient deficiencies, as well as inflammation.
C-Reactive Protein	This is a very sensitive marker for inflammation occurring in the body.
Plasminogen Activator Inhibitor-1 (PAI-1)	This is a marker that can help determine the risk of clotting in a person’s blood vessels. Remember, heart attacks and most strokes are due to a build up of clotted material. This marker can be influenced by high levels of insulin.

Blood Markers (cont'd)

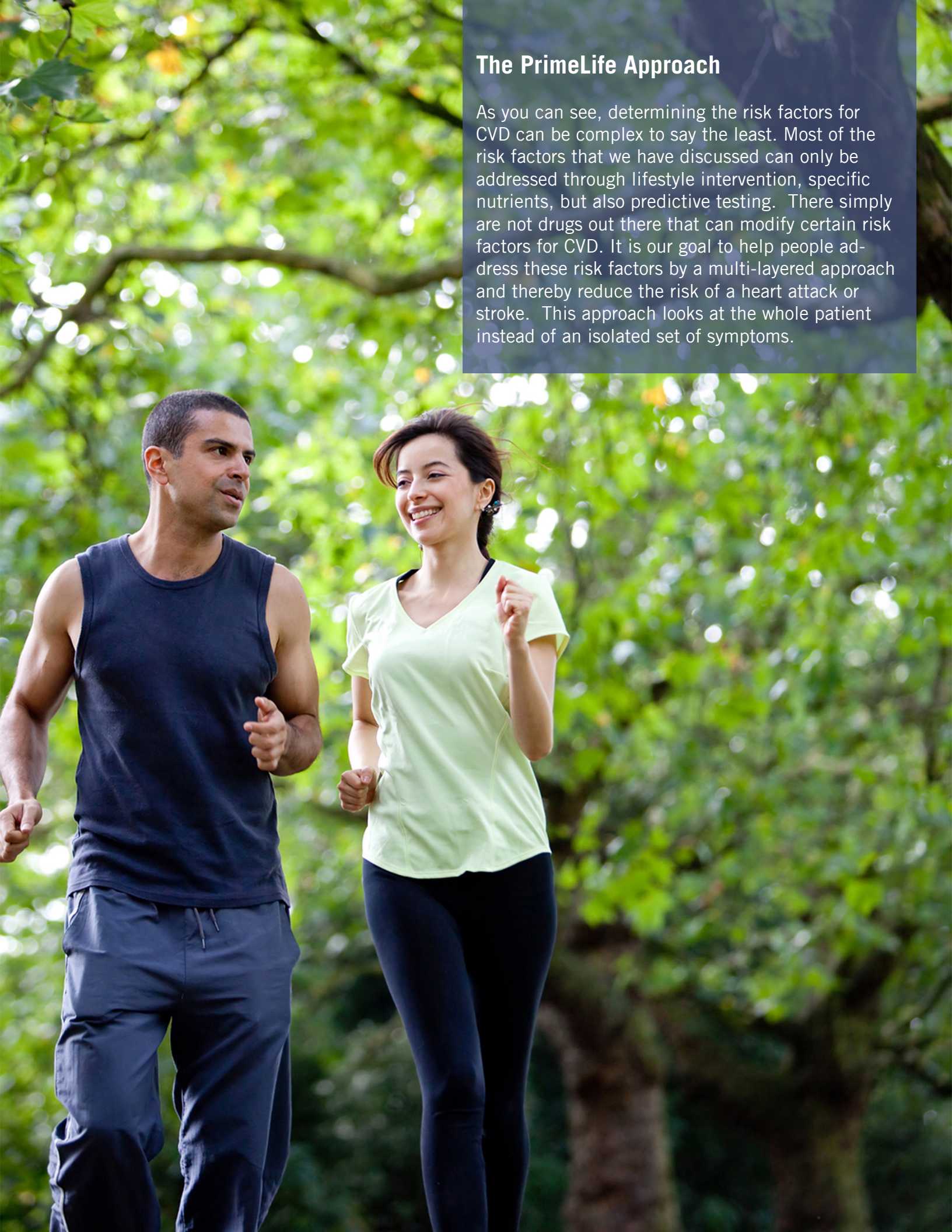
Marker	Significance
Fibrinogen Activity	This is another marker used to determine the risk of clotting. The more active a person's fibrinogen, the higher the risk of build up. The most common causes of increased clotting are Cardio-Metabolic Syndrome, estrogen replacement therapy, and smoking.
Lipoprotein Phenotype Profile (LPP)	This test is extremely valuable at determining not only the different types of particles that make up a person's HDL and LDL, but also the size of the particles. These factors can be indexed to determine a person's future risk of CVD as well as ways to modify and lessen these risk factors through certain nutrients and lifestyle interventions.
Omega-3 Index	The Omega-3 Index ultimately determines how your body handles inflammation on a cellular level. The fats a person consumes through their diet ultimately become chemical messengers and parts of cell walls that dictate how that cell handles a stimulus. The response is either pro-inflammatory or anti-inflammatory depending on this index.
Testosterone	Low testosterone is a component of Metabolic Syndrome.
GGT	This liver marker predicts the onset of Metabolic Syndrome and cardiovascular risk.
Folic acid and B12	Both of these markers play a huge role in methylation and therefore must be monitored in those with high homocysteine.
Ferritin	Ferritin is an iron protein complex and is found in most tissues. It is also an acute phase protein and may be increased in inflammation, malignancy, and liver disease.
Thyroid Hormones	Low levels of thyroid hormone can increase risk of CVD
Vitamin D	Low levels of vitamin D are associated with CVD for many reasons.
Vitamin K	A co-factor in clotting.
Heavy Metals	Heavy metals like cadmium, lead and mercury are extremely toxic and inflammatory.
Potassium	Low potassium will increase calcium excretion and raise blood pressure.
Sodium	Sodium imbalance is more to blame for increase fluid retention and increased calcium secretion. Sodium to potassium ratios are very important.
Calcium	Reduced dietary calcium intake is consistent predictor for high blood pressure.
Magnesium	Magnesium regulates blood pressure, calcium, potassium and sodium levels inside the cell, insulin sensitivity and arterial compliance.

Why didn't my doctor tell me this?

We get this question quite often. The role of a traditional allopathic physician is similar to that of a fire fighter. A fire fighter will put out a fire without asking many questions. A fire fighter will not help you rebuild your house. You need the fire fighter to put out the fire but what you also need is someone that is going to help you rebuild your home and make sure it does not burn down again. CVD is a result of a chronic lifestyle disorder. Most medical practitioners are not trained to address lifestyle disorders, they are trained to diagnose and put out fires. Unfortunately there are often no warning signs of CVD, it is up to the patient to take an assertive role in their health and to demand answers.

Many of the tools that are used by most doctors are outdated by as long as 17 years behind the research. The current model of simply measuring a lipid profile and providing a drug to lower total cholesterol without any other type of intervention is an ineffective model to address the complexity of cardiovascular disease. There is no doubt that lifestyle choices, diet, and proper nutrition can virtually reverse all of the major risk factors for cardiovascular disease, as discussed.



A man and a woman are jogging through a lush green park. The man, on the left, is wearing a dark blue tank top and dark blue athletic pants. The woman, on the right, is wearing a light green short-sleeved shirt and dark blue leggings. They are both smiling and looking towards the right. The background is filled with out-of-focus green trees and foliage, creating a bokeh effect. A semi-transparent dark blue box is overlaid on the top right of the image, containing white text.

The PrimeLife Approach

As you can see, determining the risk factors for CVD can be complex to say the least. Most of the risk factors that we have discussed can only be addressed through lifestyle intervention, specific nutrients, but also predictive testing. There simply are not drugs out there that can modify certain risk factors for CVD. It is our goal to help people address these risk factors by a multi-layered approach and thereby reduce the risk of a heart attack or stroke. This approach looks at the whole patient instead of an isolated set of symptoms.

References

1. Filipovsky J, Ducimetare P, Eschwaeger E, Richard JL, Rosselin G, Claude JR. The relationship of blood pressure with glucose, insulin, heart rate, free fatty acids and plasma cortisol levels according to degree of obesity in middle-aged men. *J Hypertens* 1996;14(2):229-35.
2. Fredrickson M, Tuomisto M, Bergman-Losman B. Neuroendocrine and cardiovascular stress reactivity in middle-aged normotensive adults with parental history of cardiovascular disease. *Psychophysiol* 1991;28(6):656-64.
3. Stahl F, Schnorr D, Pilz C, Dörner G. Dehydroepiandrosterone (DHEA) levels in patients with prostatic cancer, heart diseases and under surgery stress. *Exp Clin Endocrin* 1992;99:68-70.
4. English KM, Steeds R, TH Jones, Channer KS. Testosterone and coronary heart disease: is there a link? *QJM* 1997;90:787-791.
5. Phillips GB, Pinkernell BH, Tian-Yi J. The association of hypotestosterone with coronary artery disease in men. *Arterioscler Thromb* 1994;14(5):701-706. Chute CG, Baron JA, Plymate SR, Kiel DP, Pavia AT, et. al. Sex hormones and coronary artery disease. *Am J Med* 1987;85:853-859.
6. Sewdarsen M, Vythilingum S, Jialil I, Desai RK, Becker P. Abnormalities in sex hormones are a risk factor for premature manifestation of coronary artery disease in South African Indian men. *Atherosclerosis* 83:111-117.
7. Alexandersen P, Haarbo J, Christiansne C. The relationship of natural androgens to coronary heart disease in males: a review. *Atherosclerosis* 1996;125(1-13).
8. Stampfer MJ, Malinow MR, Willet WC, Newcomer LM, Upson B, Ullmann D, et al. A prospective study of plasma homocyst(e)ine and risk of myocardial infarction in US physicians. *JAMA* 1992;268(7):877-881.
9. Miller AL, Kelly GS. Homocysteine Metabolism: Nutritional modulation and impact on health and disease. *Alt Med Rev* 1997;2(4):234-254.
10. Hiraga T, Shimada M, Tsukada T, Murase T. Hypertriglyceridemia, but not hypercholesterolemia, is associated with the alterations of fibrinolytic system. *Horm Metab Res* 1996; 28(11):603-6.
11. Davignon J, Cohn JS. Triglycerides: a risk factor for coronary heart disease. *Atherosclerosis* 1996;124:S57-64.
12. Frohlich JJ. Lipoproteins and homocysteine as risk factors for atherosclerosis: assessment and treatment. *Can J Cardiol* 1995;11(Suppl C): 18C-23C.
13. Grau AJ, Buggle F, Beeher H,etal. The association of leukocyte count, fibrinogen, and c-reactive protein with vascular risk factors and ischemic vascular diseases. *Thromb Res* 1996; 82(3):245- 255.
14. Ridker PM, Cushman M, Stampher MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336(14):973-9.
15. Assman G, Schulte H. Triglycerides and atherosclerosis: results from the prospective cardiovascular Münster study. *Atheroscler Rev* 1991; 22:51-63.
16. National Institutes of Health:Conference Statement: Triglyceride High Sensity Lipoprotein and Coronary Heart Disease. *JAMA* 1993;269:505-510.
17. Lloyd-Jones DM, Wilson PW et al. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. *Arch Intern Med.* 2003; 163(16):1966-72.Castelli WP. Cholesterol and lipids in the risk of coronary artery disease--the Framingham Heart Study. *Can J Cardiol.* 1988; 4 Suppl A:5A-10A.
18. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002; 106(25):3143-421.
19. Grundy SM, Cleeman JI, Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004; 110(2):227-39.
20. Gordon DJ, Probstfield JL, Garrison RJ et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation.* 1989; 79(1):8-15.
21. Maron DJ. The epidemiology of low levels of high-density lipoprotein cholesterol in patients with and without coronary artery disease. *Am J Cardiol.* 2000;86(12A):11L-14L.
22. Gotto AM Jr. High-density lipoprotein cholesterol and triglycerides as therapeutic targets for preventing and treating coronary artery disease. *Am Heart J.* 2002;144(6 Suppl):S33-42.
23. Robins SJ, Collins D, Wittes JT et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA.* 2001; 285(12):1585-91.
24. Wierzbicki AS, Mikhailidis DP. Beyond LDL-C--the importance of raising HDL-C. *Curr Med Res Opin.* 2002;18(1):36-44.
25. Packard CJ, Saito Y. Non-HDL cholesterol as a measure of atherosclerotic risk. *J Atheroscler Thromb.* 2004;11(1):6-14.
26. Frost PH, Havel RJ. Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol.* 1998; 81(4A):26B-31B.
27. Gotto AM Jr. Triglyceride as a risk factor for coronary artery disease. *Am J Cardiol.* 1998; 82(9A):22Q-25Q.
28. Krauss RM. Triglycerides and atherogenic lipoproteins: rationale for lipid management. *Am J Med.* 1998;105(1A):58S-62S.
29. Martins IJ, Redgrave TG Obesity and post-prandial lipid metabolism. Feast or famine? *J Nutr Biochem.* 2004; 15(3):130-41.
30. Hyson D, Rutledge JC, Berglund L. Postprandial lipemia and cardiovascular disease. *Curr Atheroscler Rep.* 2003; 5(6):437-44.

31. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*. 2001; 358(9298):2026-33.
32. Sattar N, Williams K et al. Comparison of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with other cardiovascular risk factors in patients with the Metabolic Syndrome in the Insulin Resistance Atherosclerosis Study. *Circulation*. 2004; 110(17):2687-93.
33. Williams K, Sniderman AD et al. Comparison of the associations of apolipoprotein B and low-density lipoprotein cholesterol with other cardiovascular risk factors in the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation*. 2003; 108(19):2312-6.
34. Sniderman AD. How, when, and why to use apolipoprotein B in clinical practice. *Am J Cardiol*. 2002;90(8A):48i-54i.
35. Walldius G, Jungner I, Aastveit AH, Holme I, Furberg CD, Sniderman AD. The apoB/apoA-I ratio is better than the cholesterol ratios to estimate the balance between plasma proatherogenic and antiatherogenic lipoproteins and to predict coronary risk. *Clin Chem Lab Med*. 2004;42(12):1355-63.
36. Wallenfeldt K, Bokemark L, Wikstrand J, Hulthe J, Fagerberg B. Apolipoprotein B/apolipoprotein A-I in relation to the Metabolic Syndrome and change in carotid artery intima-media thickness during 3 years in middle-aged men. *Stroke*. 2004; 35(10):2248-52.
37. van Lennep JE, Westerveld HT et al. Apolipoprotein concentrations during treatment and recurrent coronary artery disease events. *Arterioscler Thromb Vasc Biol*. 2000;20(11):2408-13.
38. Kwiterovich PO Jr. Lipoprotein heterogeneity: diagnostic and therapeutic implications. *Am J Cardiol*. 2002;90(8A):1i-10i.
39. Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyper apo B: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Ann Intern Med*. 2001; 135(6):447-59.
40. Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. *Circulation*. 2004;109(23 Suppl 1):II12-7.
41. St-Pierre AC, Cantin B, Dagenais GR et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol*. 2005; 25(3):553-9.
42. Berneis K, Jeanneret C, Muser J, Felix B, Miserez AR. Low-density lipoprotein size and subclasses are markers of clinically apparent and non-apparent atherosclerosis in type 2 diabetes. *Metabolism*. 2005;54(2):227-34.
43. Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care*. 2004; 27(6):1496-504. 29. Garin MC, Kalix B, Morabia A, James RW. Small, dense lipoprotein particles and reduced paraoxonase-1 in patients with the Metabolic Syndrome. *J Clin Endocrinol Metab*. 2005; 90(4):2264-9.
44. Berneis K, Rizzo M. LDL size: does it matter? *Swiss Med Wkly*. 2004;134(49-50):720-4.
45. Lamarche B, St-Pierre AC, Ruel IL et al. A prospective, population-based study of low density lipoprotein particle size as a risk factor for ischemic heart disease in men. *Can J Cardiol*. 2001; 17(8):859-65. 32. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol*. 2002; 90(8A):22i-29i
46. Morgan J, Carey C, Lincoff A, Capuzzi D. High-density lipoprotein subfractions and risk of coronary artery disease. *Curr Atheroscler Rep*. 2004; 6(5):359-65.
47. Lamarche B, Moorjani S, Cantin B et al. Associations of HDL2 and HDL3 subfractions with ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol*. 1997; 17(6):1098-105.
48. Cromwell WC, Otvos JD. Low-density lipoprotein particle number and risk for cardiovascular disease. *Curr Atheroscler Rep*. 2004; 6(5):381-7.
49. Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation*. 2002; 106(15):1930-7.
50. Festa A, Williams K, Hanley AJ, Otvos JD, Goff DC, Wagenknecht LE, Haffner SM. Nuclear magnetic resonance lipoprotein abnormalities in prediabetic subjects in the Insulin Resistance Atherosclerosis Study. *Circulation*. 2005; 111(25):3465-72.
51. Adiels M, Boren J et al. Overproduction of VLDL1 driven by hyperglycemia is a dominant feature of diabetic dyslipidemia. *Arterioscler Thromb Vasc Biol*. 2005; 25(8):1697-703
52. Berglund L, Ramakrishnan R. Lipoprotein(a): an elusive cardiovascular risk factor. *Arterioscler Thromb Vasc Biol*. 2004; 24(12):2219-26.
53. Nielsen LB. Atherogenicity of lipoprotein(a) and oxidized low density lipoprotein: insight from in vivo studies of arterial wall influx, degradation and efflux. *Atherosclerosis*. 1999;143(2):229-43.
54. von Depka M, Nowak-Gottl U et al. Increased lipoprotein (a) levels as an independent risk factor for venous thromboembolism. *Blood*. 2000; 96(10):3364-8.
55. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation*. 2000; 102(10):1082-5.
56. Seman LJ, DeLuca C et al. Lipoprotein(a)-cholesterol and coronary heart disease in the Framingham Heart Study. *Clin Chem*. 1999; 45(7):1039-46.
57. Stein JH, Rosenson RS. Lipoprotein Lp(a) excess and coronary heart disease. *Arch Intern Med*. 1997; 157(11):1170-6.
58. Pan J, Van JT, Chan E, Kesala RL, Lin M, Charles MA. Extended-release niacin treatment of the atherogenic lipid profile and lipoprotein(a) in diabetes. *Metabolism*. 2002; 51(9):1120-7.
59. Tsimikas S, Brilakis ES et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med*. 2005; 353(1):46-57.
60. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA*. 2002; 288(20):2569-78. 48. Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. *J Am Coll Nutr*. 2001; 20(1):5-19.

61. Hu FB. Plant-based foods and prevention of cardiovascular disease: an overview. *Am J Clin Nutr.* 2003;78(3 Suppl):544S-551S.
62. Masson LF, McNeill G, Avenell A. Genetic variation and the lipid response to dietary intervention: a systematic review. *Am J Clin Nutr.* 2003; 77(5):1098-111.
63. Tsunoda F, Koba S, Hirano T, Ban Y, Iso Y, Suzuki H, Geshi E, Katagiri T. Association between small dense low-density lipoprotein and postprandial accumulation of triglyceride-rich remnant-like particles in normotriglyceridemic patients with myocardial infarction. *Circ J.* 2004; 68(12):1165-72.
64. Sacks FM, Katan M. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. *Am J Med.* 2002; 113 Suppl 9B:13S-24S.
65. Mauger JF, Lichtenstein AH et al. Effect of different forms of dietary hydrogenated fats on LDL particle size. *Am J Clin Nutr.* 2003; 78(3):370-5.
66. Matthan NR, Welty FK et al. Dietary hydrogenated fat increases high-density lipoprotein apoA-I catabolism and decreases low-density lipoprotein apoB-100 catabolism in hypercholesterolemic women. *Arterioscler Thromb Vasc Biol.* 2004; 24(6):1092-7.
67. Dumesnil JG, Turgeon J et al. Effect of a low-glycaemic index-low-fat-high protein diet on the atherogenic metabolic risk profile of abdominally obese men. *Br J Nutr.* 2001; 86(5):557-68.
68. Krauss RM, Deckelbaum RJ et al. Dietary guidelines for healthy American adults. A statement for health professionals from the Nutrition Committee, American Heart Association. *Circulation.* 1996; 94(7):1795-800.
69. Sloth B, Krog-Mikkelsen I 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(2):337-47.
70. Sharman MJ, Gomez AL, Kraemer WJ, Volek JS. Very low-carbohydrate and low-fat diets affect fasting lipids and postprandial lipemia differently in overweight men. *J Nutr.* 2004; 134(4):880-5.
71. Stern L, Iqbal N et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med.* 2004; 140(10):778-85.
72. Seshadri P, Iqbal N, Stern L et al. A randomized study comparing the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and C-reactive protein levels in patients with severe obesity. *Am J Med.* 2004; 117(6):398-405.
73. Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA.* 2004; 292(20):2482-90.
74. Ebbeling CB, Leidig MM 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(5):976-82.
75. Noakes M, Keogh JB, Foster PR, Clifton PM. Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. *Am J Clin Nutr.* 2005; 81(6):1298-306.
76. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metab.* 2003; 88(4):1617-23.
77. Sharman MJ, Kraemer WJ, Love DM, Avery NG, Gomez AL, Scheett TP, Volek JS. A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. *J Nutr.* 2002; 132(7):1879-85.
78. Lupton JR, Turner ND. Dietary fiber and coronary disease: does the evidence support an association? *Curr Atheroscler Rep.* 2003; 5(6):500-5.
79. Davy BM, Davy KP, Ho RC, Beske SD, Davrath LR, Melby CL. High-fiber oat cereal compared with wheat cereal consumption favorably alters LDL-cholesterol subclass and particle numbers in middle-aged and older men. *Am J Clin Nutr.* 2002; 76(2):351-8.
80. Jenkins DJ, Kendall CW et al. Soluble fiber intake at a dose approved by the US Food and Drug Administration for a claim of health benefits: serum lipid risk factors for cardiovascular disease assessed in a randomized controlled crossover trial. *Am J Clin Nutr.* 2002; 75(5):834-9.
81. Anderson JW, Davidson MH et al. Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *Am J Clin Nutr.* 2000; 71(6):1433-8.
82. Anderson JW, Allgood LD et al. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. *Am J Clin Nutr.* 2000;71(2):472-9.
83. Lucas EA, Wild RD et al. Flaxseed improves lipid profile without altering biomarkers of bone metabolism in postmenopausal women. *J Clin Endocrinol Metab.* 2002; 87(4):1527-32.
84. Berg A, Konig D et al. Effect of an oat bran enriched diet on the atherogenic lipid profile in patients with an increased coronary heart disease risk. A controlled randomized lifestyle intervention study. *Ann Nutr Metab.* 2003;47(6):306-11.
85. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr.* 1999; 69(1):30-42.
86. Moreyra AE, Wilson AC, Koraym A. Effect of combining psyllium fiber with simvastatin in lowering cholesterol. *Arch Intern Med.* 2005; 165(10):1161-6.
87. Kelley GA, Kelley KS, Tran ZV. et al. Walking and Non-HDL-C in adults: a meta-analysis of randomized controlled trials. *Prev Cardiol.* 2005 Spring;8(2):102-7.
88. Orchard TJ, Temprosa M, Goldberg R et al. The effect of metformin and intensive lifestyle intervention on the Metabolic Syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med.* 2005;142(8):611-9.

89. Aldana SG, Greenlaw RL et al. Effects of an intensive diet and physical activity modification program on the health risks of adults. *J Am Diet Assoc.* 2005; 105(3):371-81.
90. Petrella RJ, Lattanzio CN et al. Can adoption of regular exercise later in life prevent metabolic risk for cardiovascular disease? *Diabetes Care.* 2005; 28(3):694-701.
91. Varady KA, St-Pierre AC, Lamarche B, Jones PJ. Effect of plant sterols and endurance training on LDL particle size and distribution in previously sedentary hypercholesterolemic adults. *Eur J Clin Nutr.* 2005; 59(4):518-25.
92. Tedde R, Sechi LA, Marigliano A, Palo A, Scano L. Antihypertensive effect of insulin reduction in diabetic hypertensive patients. *Am J Hypertens* 1989;2:163-170.
93. Randeree H, Omar MA, Motala AA, Seedet MA. Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure. *Diabetes Care* 1992;15:1258-1263.
94. Zavaroni I, Mazza S, Dall'aglio E, et al. Prevalence of hyperinsulinemia in patients with high blood pressure. *J Int Med* 1992;231:235-240.
95. Potter van Loon, et al. The cardiovascular risk factor plasminogen activator inhibitor type I is related to insulin resistance. *Metabolism* 1993;42:946-949.
96. Juhan-Vague, et al. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *Circulation* 1996;94(9):2057-2063.
97. Dietschy JM, Brown MS. Effect of alteration of the specific activity of the intracellular acetyl CoA pool apparent rates of hepatic cholesterogenesis. *J Lipid Res* 1974;15:508-516.
98. Swensen TL. The role of cholesteryl ester transfer protein in lipoprotein metabolism. *Diabetes Metab Res* 1991;7:139-153.
99. Sowers JR. Update on the cardioMetabolic Syndrome. *Clin Cornerstone.* 2001;4(2):17-23.
100. Castro JP, El-Atat FA, McFarlane SI, Aneja A, Sowers JR. CardioMetabolic Syndrome: pathophysiology and treatment. *Curr Hypertens Rep.* 2003 oct;5(5):393-401.
101. Redon J, Cifkova R, Laurent S, Nilsson P, Narkiewicz K, Erdine S, Mancia G; Scientific Council of the European Society of Hypertension: European society of hypertension position statement. *J Hypertens.* 2008 oct;26(10):1891-900.
102. Culotta E, Koshland DE Jr. NO news is good news. *Science.* 1992;258:1862-5.
103. Li H, Forstermann U. Nitric oxide in the pathogenesis of vascular disease. *J Pathol.* 2000 Feb;190(3):244-54.
104. Guthikonda S, Haynes WG. Homocysteine: role and implications in atherosclerosis. *Curr Atheroscler Rep.* 2006 Mar;8(2):100-6.
105. Hoffman M. Hypothesis: hyperhomocysteinemia is an indicator of oxidant stress. *Med Hypothesis.* 2011 Dec;77(6):1088-93.
106. Welsh A and Ede M, Inositol hexanicotinate for improve nicotinic acid therapy. *Int Record Med* 174:9-15, 1961.
107. El-Enein A, Hafez Y, Salem H and Abedel M. The role of nicotinic acid and inositol hexaniacinate as anticholesterolemic and antilipemic agents. *Nutr Rep Intl* 28:899-911, 1983.
108. Sunderland G, Belch J, Sturrod R, et al. A double-blind randomized placebo-controlled trial of hexopal in primary Raynaud's disease. *Clin Rheumatol* 7:46-49, 1988.
109. Canner P and the Coronary Drug Project Group. Mortality In Coronary Drug Project patients during a nine-year post-treatment period. *J Am Coll Cardiol* 8:1245-1255, 1986.
110. The expert panel on detection, evaluation, and treatment of high cholesterol in adults. *Arch Int Med* 148:136-169, 1988.
111. Havel R. Dietary Supplement or drug? The case of cholestin. *Am J Clin Nutr.* 1999;69(2):175-76.
112. Li C, Zhu Y, Wang Y, Zhue J, Chang J, Kritchevsky D. *Monascus Purpureus*_Fermented Rice (Red Yeast Rice): A natural food product that lowers blood cholesterol in animal models of hypercholesterolemia. *Nutrition Research.* 1998;18(1):71-81.
113. Ma J, Li Y, Ye Q, Li J, Hua Y, Ju D, et al. Constituents of red yeast rice, a trictional Chinese food and medicine. *J agric Food Chem.* 200;48:5220-5225.
114. Heber D, Yip I, Ashley JM, Elashoff DA, Go VLW. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. *Am J Clin Nutr.* 1999;69:231-236.
115. Bonovich K, Colfer H, Davidson M, Dujovne C, Greenspan M, Karlberg R, et al. A multi-center, Self-controlled study of cholestin in subjects with elevated cholesterol. American Heart Association. 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, Orlando, FL. March 1999. [Abstract]
116. Qin S Zhang W, Qi P, Zhao M, Dong Z, Liy, et al. Elderly patients with primary hyperlipidemia benefited from treatment with a *Monacus purpureus* rice preparation: A placebo-controlled, double-blind clinical trial. American Heart Association. 39th Annual conference on cardiovascular disease epidemiology and Prevention, Orland, FL. March 1999. [Abstract]
117. Wang J, Lu Z, Chi J, Wang W, Su M, Kuo W, et al. Multicenter clinical trial of serum lipid-lowering effects of a *Monascus purpureus* (red yeast) rice preparation from traditional chinese medicine. *Curr Ther REs.* 1997;58(12):964-978.
118. Stevinson C, Pittler MH, Ernse E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. *Ann Intern Med* 2000 sep 19;133(6):420-9.
119. Bertolini S, Donati C, Elicio N, et al. Lipoprotein changes induced by pantethine in hyperlipoproteinemic patients: adults and children. *Int J Clin Pharmacol Ther Toxicol.* 1986;24:630-637.
120. Coronel F, Tornero F, Torrente J, et al. Treatment of hyperlipemia in diabetic patients on dialysis with a physiological substance. *Am J Nephrol.* 1991;11:32-36.
121. Gaddi A, Descovich GC, Nosedà G, et al. Controlled evaluation of pantethine, a natural hypolipidemic compound in patients with different forms of hyperlipoproteinemia. *Atherosclerosis.* 1984;50:73-83.
122. Gordon JB. An easy and inexpensive way to lower cholesterol? *West J Med.* 1991 Mar;154(3):352.

123. Hermann J, Arquitt A, Stoecker B. Effects of chromium supplementation of plasma lipids, apolipoproteins, and glucose in elderly subjects. *Nutr Res.* 1994;14(5):671-674.
124. Press RI, Geller J, Evans GW. The effect of chromium picolinate on serum cholesterol and apolipoprotein fractions in human subjects. *Western J Med.* 1993;152:41-45.
125. PTrow LG, Lewis J, Greenwood RH, Sampson MJ, Self KA, Crews HM, et al. Lack of effects of dietary chromium supplementation in glucose tolerance, plasma insulin, and lipoprotein levels in patients with type 2 diabetes. *Int J Vitam Nutr Res.* 2000;70(1):14-18.
126. Khanna , A.K. Ramesh Chander and N.K. Kapoor (1996) - terminalia arjuna: an ayurvedic cardioprotective, regulates lipid metabolism in hyperlipaemic rats, *Phytotherapy Research* 10, 8, 663-665. [on Terminalia arjuna (Roxb. ex DC.) Wight et Arn.]
127. Zhongguo Zhong Xi Yi Jie He Za Zhi. Study on effects of Codonopsis eupolyphaga anti-obesity powder in mice with nutritive obesity 1997 Dec;17(12):739-41.
128. Satyavati G. Gum Gugul (Commiphora mukul)- the success story of an ancient insight leading to a modern discovery. *Ind J Med Res* 87:327-335, 1988.
129. Nityanand S, Srivastava J, and Asthana O. Clinical trials with gugulipic, a new hypolipidaemic agent. *J Assoc Phys India* 36:321-328, 1989.
130. Inflammation in Atherosclerosis: From Vascular Biology to Biomarker Discovery and Risk Prediction, Rene S. Packard and Peter Libby, *Clinical Chemistry* 54:1, 24-39 (2008)
131. Macrophage Differentiation to Foam Cells, Pavel Shashkin, Bojan Dragulev, and Klaus Ley, *Current Pharmaceutical Design*, 2005, 11, 3061-3072
132. The Macrophage Foam Cell as a Target for Therapeutic Intervention, Andrew C. Li, Christopher K. Glass, *Nature Medicine*, Vol. 8, No. 11, November 2002
133. Atherothrombosis: Role of Inflammation: Introduction, McGraw-Hill Companies, Chapter 52
134. Endothelial Dysfunction and Oxidative Stress During Estrogen Deficiency in Spontaneously Hypertensive Rats, Sven Wassmann, MD, Anselm T. Baumer, MD, Kerstin Strehlow, MD, Martin van Eickels, MD, Christian Grohe, MD, Katja Ahlborn, MS, Renate Rosen, MD, Michael Böhm, MD, George Nickenig, MD, American Heart Association, *Circulation* 2001;103:435
135. Inflammation and Atherosclerosis, Peter Libby, Paul M. Ridker, and Attilio Maseri, *Circulation* 2002;105:1135-1143 DOI: 10.1161/hc0902.104353
136. Ameliorating Hypertension and Insulin Resistance in Subjects at Increased Cardiovascular Risk. Effects of Acetyl-L-Carnitine Therapy, Piero Ruggenenti, Dario Cattaneo, Giacomina Loriga, Franca Ledda, Nicola Motterlini, Giulia Gherardi, Silvia Orsio, Giuseppe Remuzzi, American Heart Association, July 2009, DOI: 10.1161/HYPERTENSIONAHA.109.132522
137. Hypoadiponectinemia in Obesity and Type 2 Diabetes: Close Association with Insulin Resistance and Hyperinsulinemia, Christian Weyer, Tooru Funahashi, Sachiyo Tanaka, Kikuko Hotta, Yuji Matsuzawa, Richard E. Pratley, P. Antonio Tataranni, *J. Clin. Endocrinol. Metab.* 2001 86: 1930-1935, doi: 10.1210/jc.86.5.1930
138. Gamma Glutamyl Transferase and Metabolic Syndrome, Cardiovascular Disease, and Mortality Risk, Douglas S. Lee, Jane C. Evans, Sander J. Robins, Peter W. Wilson, Irene Albano, Caroline S. Fox, Thomas J. Wang, Emelia J. Benjamin, Ralph B. D. Agostino, Ramachandran S. Vasan, *Arterioscler Thromb Vasc Biol.* DOI: 10.1161/01.ATV.0000251993.20372.40
139. Is Vitamin D as Vital to Cardiovascular Health as it Appears?, Chris Longenecker, Rebecca Boxer, McGraw Hill, July 29, 2010
140. Vitamin K Supplementation and Progression of Coronary Artery Calcium in Older Men and Women, M. Kyla Shea, Christopher J. O'Donnell, Udo Hoffmann, Gerard E. Dallal, Bess Dawson-Hughes, Jose M. Ordovas, Paul A. Price, Matthew K. Williamson, Sarah L. Booth, *Am J. Clin. Nutr* 2009;89:1799-807
141. Low Testosterone and Risk of Premature Death in Older Men: Analytical and Preanalytical Issues in Measuring Circulating Testosterone, Elizabeth A. Platz, *Clinical Chemistry* 54:7, 1110-1112 (2008)
142. Textbook of Nutritional Medicine, Melvyn R. Werbach, M.D., Jeffrey Moss, DDS, CNS, CCN
143. The Role of Vascular Biology, Nutrition and Nutraceuticals in the Prevention and Treatment of Hypertension, Mark C. Houston, MD, SCH, FACP, FAHA, Supplement No. 1, JANA
144. Laboratory Evaluations for Integrative and Functional Medicine, 2nd ed., Richard S. Lord, J. Alexander Bralley
145. Homocysteine and MTHFR Mutations: Relation to Thrombosis and Coronary Artery Disease, Elizabeth A. Varga, Amy C. Sturm, Caron P. Misita and Stephan Moll, *Circulation* 2005; 111:3289-3293 DOI: 10.1161/01.Cir.0000165142.37711.E7, The American Heart Association 2005
146. Effect of Fenugreek Seeds on Blood glucose and Serum Lipids in Type I Diabetes, Sharma RD, Raghuram TC, Rao NS, National Institute of Nutrition, *Eur J. Clin. Nutr.* 1990 Apr; 44(4):301-6
147. Licorice: A Traditional Herb and Its Modern Effects on Humans, P. Bouras, M. Skouroiadiou, S. Tsonas, *EHP*, Dec 2001, Vol. 7, No. 4
148. Should We Measure Asymmetric Dimethylarginine in Patients with Coronary Artery Disease? The Ludwigshafen Risk and Cardiovascular Health Study, *Clinical Chemistry* 53, No. 2, 2007
149. Asymmetric Dimethylarginine as a Mediator of Vascular Dysfunction and a Marker of Cardiovascular Disease and Mortality: An Intriguing Interaction with Diabetes Mellitus, Maïke Anderssohn, Edzard Schwedhelm, Nicole Lüneburg, Ramachandran S. Vasan and Rainer H. Böger, *Diabetes and Vascular Disease Research* 2010 7:105 DOI: 10.1177/1479164110366053
150. Lipoprotein Lipase and Atherosclerosis, K. Tsutsumi, *Current Vascular Pharmacology*, 2003, 1, 11-17
151. Insulin inhibits Na⁺/H⁺ Exchange in Vascular Smooth Muscle and Endothelial Cells in Situ: Involvement of H2O2 and Tyrosine Phosphatase SHP-2, Ebbe Boedtker and Christian Aalkjaer, *Am J. Physiol Heart Circ Physiol* 296: H247-H255, 2009
152. Inflammation and Cardiovascular Disease Mechanisms, Peter Libby, *Am J. Clin Nutr* 2006;

153. 83(suppl):456S-60S. Printed in USA
154. The Atherosclerosis Time-Line and the Role of the Endothelium, R. Kharbanda and R.J. MacAllister, Curr. Med. Chem.-Immun., Endoc., & Metab. Agents 2005, 5, 47-52
155. Heart Disease & Stroke Statistics, American Heart Association, 2010 Update At-A-Glance
156. Annals of Internal Medicine; American College of Physicians; March 2007
157. PubMed: PJ Clin Epidemiol. 1992 Oct; 45(10):1101-9
158. Journal of Diagnostic Medical Sonography 20:5-13, Jan/Feb 2004
159. Lowering Your Blood Pressure with DASH, NIH (2006)
160. Integrative Medicine, David Rakel, M.D
161. Botanical Influences on Illness, A Sourcebook of Clinical Research, 2nd ed., Melvyn R. Werbach, M.D, Michael T. Murray, MD