

LE Magazine May 2006

REPORT

New Blood Test Better Predicts Heart Attack Risk

By William Davis, MD, FACC



Marc, a successful architect, had rigorously monitored his cholesterol levels every six months since his mother's difficult recovery from a coronary bypass operation at the age of 63.

Over the years, Marc's low-density lipoprotein (LDL), a component of a standard cholesterol panel, wavered within a narrow range that never exceeded 95 milligrams per deciliter (mg/dL). "Your cholesterol profile is excellent, as always," his family doctor declared.

Nevertheless, a heart attack struck Marc down without warning at the age of 54, leaving him breathless and exhausted from performing the most ordinary activities. Demoralized and frightened, Marc pressed his doctor to explain why he had a heart attack despite his excellent cholesterol values. "Marc, some people have heart attacks because of genetics," his doctor replied. "There's not a whole lot we can do about that."

If you ask your doctor whether heart disease lurks silently within you, chances are your doctor will have no idea. Too often, an attempt will be made to predict your future by evaluating standard cholesterol tests. As a result, your risk, like Marc's, may be frightfully misjudged.

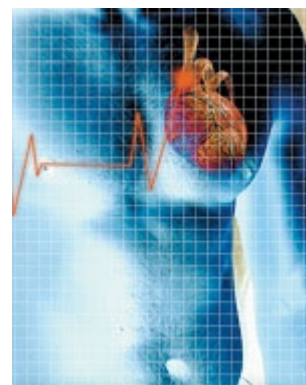
The shocking reality is that heart disease is the number-one killer of men and women in the US, yet most physicians have no idea how to diagnose the presence of hidden heart disease. If you go to an emergency room having suffered a heart attack, the doctor will usually make the correct diagnosis. But most heart disease is silent and unsuspected. The first symptom is often the last: sudden death. If you rely on your doctor to detect hidden heart disease, you may not get an accurate assessment. It does not have to be this way.

LIMITS OF LDL TESTING

The patient previously described suffered a heart attack despite having an LDL level of 95 mg/dL. Is this unusual? Consider 100 other heart attack survivors. What would you predict their cholesterol levels to be? You would probably expect them to be high. The average LDL level in heart attack survivors is 140 mg/dL. Compare this to the average LDL for all Americans, which is 134 mg/dL.¹⁻³ These values are so close, it is no wonder that predicting heart attack risk based on LDL values is an imprecise science at best.

There is tremendous overlap in LDL values between people destined to have a heart attack and those who will never have one. Except at the extremes, I challenge anyone to distinguish who has hidden heart disease and who does not—and who will suffer a heart attack and who will not—just by looking at cholesterol values.

Relying on cholesterol values to identify the presence of hidden heart disease is about as good as tossing a coin to do so. If we focus only on people with LDL levels greater than 130 mg/dL, for example, we will miss half of all those who will suffer a heart attack. Should we treat you to prevent a future heart attack—heads or tails? Since it is foolish to gamble with the precious asset of health, we must dig deeper to identify the factors that accurately predict heart disease.



LIMITATIONS OF STANDARD LIPID TESTING

For years, physicians have relied on the standard lipid panel—including total cholesterol, LDL, high-density lipoprotein (HDL), and triglycerides—to assess their patients' cardiovascular disease risk. It is increasingly apparent that this approach fails to detect many individuals at risk for heart disease.

This focus on standard lipid testing causes individuals and doctors to neglect all the other causes of heart disease, some of

which are more important than cholesterol. Can you have a heart attack if you have low cholesterol? You sure can. Can you survive to the age of 95, outlive all your neighbors, and never have a heart attack despite high cholesterol? Absolutely. Can you suffer a debilitating or fatal heart attack with “normal” cholesterol? It happens every day—1,152 times a day nationwide, to be exact, according to a 2004 report by the American Heart Association.



Yet most of the time, doctors attempt to assess heart disease risk by looking only at a standard cholesterol panel. The truth is, many risk factors are involved in the development of heart disease. Most people with coronary disease do not have just one contributing cause but rather five, six, or more contributing factors. High cholesterol is, at best, just one item on this list.

Cholesterol can be a useful tool in risk assessment. Several large studies have demonstrated that cholesterol levels are related statistically to the risk of heart disease. The higher your cholesterol levels (total and LDL), the greater the likelihood of heart disease. The Multiple Risk Factor Intervention Trial, or MR FIT, showed that the likelihood of heart attack

in the people with cholesterol levels in the highest 20% was three times that of people whose levels were in the lowest 20%.⁴ The well-known Framingham trial also illustrated this phenomenon.⁵

In both studies, however, a significant number of heart attacks still occurred in people with low or “normal” cholesterol values. In the Framingham study, four of five people fell into a large middle range of cholesterol levels, whether or not they developed heart disease. Those with extremely low total cholesterol (less than 150 mg/dL) had low (though not zero) risk for heart attack; those with extremely high cholesterol (greater than 300 mg/dL) had high risk for heart attack (threefold higher). But the great majority of people fell in between these extremes, and the greatest number of heart attacks developed in people with cholesterol levels in this middle range.

People with low or middle-range cholesterol values vastly outnumber those with high cholesterol levels. As a result, there are at least as many heart attack victims with low and intermediate cholesterol levels as there are those with high cholesterol. The higher the cholesterol, the higher the statistical risk of heart attack, but a frightening number of heart attacks still occur in people who have favorable cholesterol values.

The lesson: Unless you belong to the minority of people who have either extremely high or extremely low levels, you will not know whether heart disease is in your future simply by relying on cholesterol alone. There is a world of causes of heart attack beyond cholesterol. Lipoproteins are one such major group of causes.

TESTING LIPOPROTEINS, NOT LIPIDS

Cholesterol can be thought of as a passenger on a family of protein particles called “lipoproteins” (that is, lipid-carrying proteins). The protein component steers the lipoprotein particle and determines its fate—whether it interacts with the blood vessel wall to create atherosclerotic plaque, extracts cholesterol from plaque, or passes through the liver for disposal. In other words, the protein component of the particle determines the behavior of the lipoprotein particle. The cholesterol component just goes along for the ride.⁶

Low-density lipoprotein, routinely measured as LDL, actually comprises a varied mixture of particle types that differ in their potential to cause heart disease. You cannot assess heart disease risk simply from knowing that your LDL level is 150 mg/dL. LDL at this level could signal high risk for heart disease, or it could signal low risk. Lipoproteins can help decipher the difference.

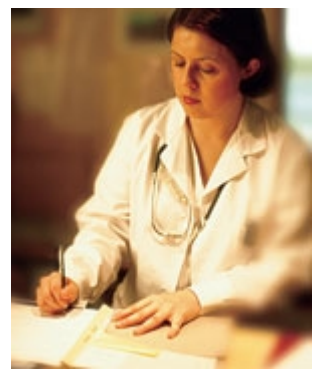
Likewise, high-density lipoprotein (HDL) is also a heterogeneous mixture of particles. Large HDL particles are responsible for extracting cholesterol from plaque and other beneficial actions. Smaller HDL particles are essentially useless. The total HDL level provided on standard cholesterol panels lumps all HDL, large and small, together, while specialized lipoprotein testing distinguishes the various subgroups.⁷

Lipoprotein testing provides insight into just how likely different particles are to deposit their cholesterol in plaque, and does not rely just on the relatively passive cholesterol part of the particle. Until recently, measuring lipoproteins was a cumbersome process that was available only in research laboratories. But testing technology has advanced considerably and several methods are now widely available.

Measuring lipoproteins rather than just lipids changes the whole language of cholesterol and the factors that cause the accumulation of coronary plaque. With LDL, for example, we are concerned less with the total LDL value and more with “LDL particle number” and “LDL particle size.”

Let us now review the various measures obtained through lipoprotein testing:

- LDL particle number
- Small LDL
- HDL and its subclasses
- Intermediate-density lipoproteins (IDL)
- Triglycerides and very low-density lipoprotein (VLDL)
- Lipoprotein (a).



REPORT

New Blood Test Better Predicts Heart Attack Risk

By William Davis, MD, FACC

LDL Particle Number

The Quebec Cardiovascular Study was the first large study demonstrating that heart attack can occur when a person's LDL particle number is high and LDL level is low.⁸ This has been repeatedly confirmed in other studies, most recently in the AMORIS study, which enrolled a remarkable 175,000 participants and demonstrated the superiority of LDL particle number (measured as apoprotein B) in predicting heart attack risk.⁹ This measure can be thought of as actually counting the number of LDL particles in one cubic centimeter, or one milliliter of blood.

LDL particle number is among the most powerful tools we have to predict the risk of heart attack. It can be measured directly as LDL particle number by the nuclear magnetic resonance spectroscopy method or indirectly as apoprotein B, which is a more widely available method. Apoprotein B is the major protein particle of LDL, with a single protein per LDL particle. Apoprotein B thus provides a "count" of LDL particles.

How can LDL level be low when the particle number is high? Because the amount of cholesterol contained per particle can vary widely. If you have many LDL particles that contain less cholesterol in each particle, the conventionally measured LDL level will be low, but your heart disease risk will be high. Greater numbers of cholesterol-containing particles in the blood means more cholesterol deposition in plaque. The combination of low LDL level and high LDL particle number is very common, creating a situation whereby many people are mistakenly told that they are not at risk for heart attack.



High LDL particle number responds to the same treatments as high LDL level, but this method of assessment provides greater confidence in determining who to treat and how intensively to do so. Statin prescription drugs lower LDL particle number, as does the non-statin prescription drug ezetimibe, though it is less potent. Niacin (vitamin B3) lowers LDL particle number less potently than the statins, but will achieve a 10-20% reduction. In addition to prescription medicines, many nutritional strategies can lower LDL particle number.

High LDL particle number can be a source of danger even when LDL level has been reduced by treatments such as cholesterol-lowering statin drugs. This is why people who take a cholesterol-lowering medication can still suffer a heart attack. LDL particle number provides much more powerful feedback on the adequacy of treatment and is therefore a tool for further reduction of risk.^{10,11}

Small LDL

LDL particles vary in size—big, medium, and small. The size difference is crucial. Small LDL particles are a far more destructive force than their larger counterparts. Like finely tuned weapons designed to wreak maximum damage, smaller particles more effectively penetrate the cellular barrier and enter arterial walls, contributing to atherosclerotic plaque. They also persist longer in the circulation, which allows more opportunity to cling like little magnets to tissues within the walls.

Once in the arterial wall, small LDL particles are more prone to oxidation, which stimulates the release of inflammatory and adhesive proteins. Small, dense LDL promotes endothelial dysfunction and enhanced production of pro-coagulants by endothelial cells. Small, dense LDL thus appears to be more atherogenic—that is, more likely to contribute to the build-up of plaque within arteries—than normal LDL.^{12,13}

Small LDL can be an inherited predisposition that is activated by unhealthy lifestyles and weight gain. When the genetic factors are strong, it can occur in healthy people who are not overweight. It frequently causes heart disease and is found in more than half of all people who suffer heart attacks. Small LDL particles triple the likelihood of developing coronary plaque and suffering a heart attack.¹⁴

This one little measure also holds a world of hidden information. Not only does it indicate a higher risk for heart attack, but small LDL suggests that you are more resistant to insulin and more likely to develop metabolic syndrome, or even diabetes, if you become overweight.¹⁵ It also suggests that a very low-fat diet (deriving less than 20% of calories from fat) may paradoxically heighten your heart disease risk.¹⁶

Small LDL can augment the dangers of other cardiac risk factors, such as high total cholesterol, increased LDL particle number, or high C-reactive protein (a measure of inflammation). Researchers have noted that while elevated small LDL particle count alone can raise heart attack risk by up to 300%, heart attack risk is sixfold higher (600%) when elevated C-reactive protein is also present.¹⁷

Despite its dangers, small LDL is easy to treat. Weight loss is a powerful way to increase LDL particle size. Exercise also provides a modest benefit. Niacin in doses of 500-1500 mg daily (depending on your weight and genetic factors) effectively corrects LDL size. In doses exceeding 500 mg/day, niacin is best prescribed by a physician who is experienced with its peculiar, mostly harmless side effects, like feeling flushed or itchy. Slow-release preparations are available, but consult your doctor in choosing forms that have been shown to be safe.^{18,19} Exercise may also help to optimize lipoprotein profiles.²⁰



Dietary strategies that slow or reduce sugar release into the bloodstream can be helpful. These include high-fiber foods and foods with a low glycemic index, as well as supplements such as flaxseed, glucomannan, oat bran, psyllium fiber, raw nuts like almonds and walnuts, and the “starch blocker” white bean extract.²¹

Oat bran is a great way not only to lower LDL particle number, but also to increase LDL particle size. Add two tablespoons daily to yogurt, fruit smoothies, cereal, or other foods.²² Omega-3 fatty acids from fish oil increase LDL size modestly, particularly if triglyceride levels are high.²³

HDL and HDL Subclasses

Many people with low HDL have been told their heart disease has no known cause or that its cause is untreatable. Both statements are simply untrue. Low HDL (below 40 mg/dL) is common, affecting more than half of all people with heart disease. Deficiency of the protective subclass within HDL is even more common, affecting most people with heart disease.^{24,25}

Like LDL, HDL comprises a family of HDL particles. The truly beneficial HDL is “large” HDL, sometimes also known as “HDL2b.” Large HDL is responsible for “reverse cholesterol transport,” or the extraction of cholesterol from plaque. Large HDL therefore plays a protective role and is crucial for regression (shrinkage) of coronary plaque.

As a rule, a deficiency of protective large HDL goes hand in hand with low total HDL levels of less than 40 mg/dL. In other words, if your HDL is less than 40 mg/dL, you are highly likely to have a marked deficiency of protective large HDL. If your total HDL is above 60 mg/dL, you probably have a favorable quantity of large HDL. If you are between 40 and 60 mg/dL, you may or may not have a deficiency of protective large HDL. Lipoprotein assessment is then necessary to measure large HDL.^{26,27}

Strategies that increase total HDL will also increase one’s proportion of large HDL. Strict low-fat diets (less than 20% of calories from fat) lower HDL and push HDL to the undesirable smaller size. Low-fat diets are therefore not advised when total HDL is low or when large HDL is deficient. People with low HDL do better by adding dietary sources of plentiful monounsaturated fatty acids (especially raw nuts, flaxseed products, and olive and canola oils), eating unprocessed foods with a low glycemic index, and increasing lean protein intake.²⁸ Omega-3 fatty acids from fish oil have a modest effect in raising total HDL and increasing large HDL.²⁹ The medical treatments to raise HDL are identical to those used to treat small LDL particle size.

Intermediate-Density Lipoproteins (IDL)

While many health-conscious adults are familiar with low-density lipoprotein (LDL) and high-density lipoprotein (HDL), they may not be aware of intermediate-density lipoprotein, or IDL. Though intermediate in density, there is nothing “intermediate” about IDL as a risk factor for heart disease. IDL is a potent contributor to heart attack risk. Elevated IDL means that the body struggles to clear fat from the blood after eating, with many more hours required to clear the blood than normal. The longer these lipoproteins persist in the blood, the more opportunity they have to create plaque, which may ultimately lead to a heart attack.



Only about 10% of people with heart disease have elevated IDL levels. While there is no specific treatment for high IDL, it does respond to a broad variety of treatments, particularly cholesterol-lowering medicines, niacin, fish oil, and weight loss. Knowing that you have a high IDL may mean that your treatment needs to be intensified, as IDL may persist even when LDL or other parameters are corrected.³⁰⁻³²

REPORT

New Blood Test Better Predicts Heart Attack Risk

By William Davis, MD, FACC

Triglycerides and VLDL

For several decades, researchers have debated the question of whether triglycerides contribute to heart disease risk. The issue has been conclusively settled: while triglycerides by themselves do not cause heart attacks, they are the driving force behind lipoprotein particles that are potent causes of heart disease, such as small LDL and very low-density lipoprotein (VLDL).³³ This phenomenon occurs when triglyceride levels are in the 100–400 mg/dL range. Levels over 400 mg/dL may also contribute to heart disease, but your doctor will need to consider a number of other issues, such as thyroid and kidney disease.

VLDL particles are the most densely triglyceride-packed lipoprotein. Triglycerides and VLDL particles commonly go hand in hand, but excessive VLDL can be present even when triglycerides are low. This is when specific measurement of VLDL is most helpful. When plentiful, VLDL particles circulate in the blood and interact with other lipoprotein particles such as LDL and HDL. This interaction forces triglycerides into LDL and HDL particles, and is the initial step in the formation of undesirable small LDL and deficient large HDL.³⁴

VLDL and triglycerides respond to the same treatments. In general, aim for a triglyceride level below 100 mg/dL, as all triglyceride-rich particles (including small LDL) are minimized at this level. Fish oil in higher doses (4000–10,000 mg/day) is an effective way to lower triglycerides and VLDL by 30–50%.²⁹ This is likely at least part of the reason fish oil has such a powerful impact on reducing death from cardiovascular events. Increasing the fiber content of your diet to 50 grams/day, adding raw nuts, maintaining healthy body weight, and avoiding foods with a high glycemic index are healthy strategies that may contribute to lowering triglycerides to the desired level of less than 100 mg/dL, thereby reducing or eliminating VLDL.³⁵

Lipoprotein (a)

Lipoprotein (a), or Lp(a), is a powerful, much underappreciated cause of heart disease. Up to 20% of people with heart disease will have increased Lp(a), which can lead to heart attacks early in life, often in a person's forties or fifties. Lp(a) not only is a direct cause of plaque growth and the plaque rupture that can cause a heart attack, but it also magnifies the dangers of all other risk factors, especially LDL particle size and number.³⁶

Treatment for elevated Lp(a) is controversial. Most experts agree that, at the very least, Lp(a) should be lowered to a level no higher than 30 mg/dL, and that this significantly reduces heart attack risk.³⁷ Niacin is the most effective direct treatment for lowering Lp(a), though higher doses are required than for other abnormalities (1000–4000 mg per day, which should be prescribed and monitored by a physician).

In females, the use of estrogen preparations may lower Lp(a), generally around 25%, though estrogen presents other issues that should be fully discussed with your doctor. Testosterone can be very helpful for men, and may lower Lp(a) by 25%. The supplement L-carnitine can be a useful adjunct; 2000 mg per day (1000 mg twice a day) can reduce Lp(a) by 7-8% and occasionally by up to 20%.³⁸ Other nutritional strategies that help lower Lp(a) include ground flaxseed (2 tablespoons daily), raw almonds (1/4 cup daily), and vitamin C (more than 1000 mg daily), with reported reductions of approximately 7%.³⁹⁻⁴¹

LESSONS BILL CLINTON'S DOCTORS SHOULD LEARN

Shortly after the release of his autobiography, former President Bill Clinton developed unstable symptoms that warned of impending heart attack. Extensive blockages of all three coronary arteries (greater than 90%) were diagnosed through heart catheterization, and Mr. Clinton underwent a quadruple coronary bypass operation.

According to a USA Today report, "Dr. Allan Schwartz, chief of cardiology at the hospital, said that given the extent of Clinton's blockage, there was a 'substantial likelihood that he would have suffered a substantial heart attack in the near future.' Doctors stopped Clinton's heart for 73 minutes and put him on a heart/lung machine, a common practice in bypass surgery. [Surgeon Craig] Smith said that it was 'obvious relatively quickly that what he needed was an operation.' "

After the procedure, the doctors addressing the media corps at New York-Presbyterian Hospital/Columbia boasted of their success, calling the procedure lifesaving. Media reports glowed with descriptions of the high-tech hospital care Mr. Clinton received. Senator Hillary Rodham Clinton publicly expressed her and daughter Chelsea's gratitude for the high-quality care the

former President received in the hospital.

QUESTIONS THE MEDIA OVERLOOKED

Before congratulating our medical system, several important questions need to be answered. Mr. Clinton had passed an annual thallium stress test for the preceding five years. His cholesterol was reported in the press as excellent at 179 mg/dL, and doctors monitored his cholesterol values frequently. Mr. Clinton jogged and complained of no symptoms with vigorous exercise.

If coronary disease takes years to develop, why was it not recognized earlier, before it became life threatening? How could stress test after stress test be normal when extensive coronary disease was present? How could doctors be satisfied with cholesterol values that permit life-threatening disease to develop? The answers to these questions are already available to us.

Had Mr. Clinton and his doctors been better informed, it is highly likely that his procedure would not have been necessary.

WHAT SHOULD HAVE HAPPENED

Mr. Clinton's doctors might have suggested that he undergo lipoprotein testing. Through no more effort than administering a conventional cholesterol test, they would have obtained insight into several previously unrecognized and potent causes of heart disease. These hidden causes could have been easily corrected, potentially reducing Mr. Clinton's coronary plaque.

Alternatively, had Mr. Clinton's doctors simply advised him in, say, 1996 (on assuming the presidency for his second term) to take a 30-second heart scan, they would have been shocked to learn that his "score" was very high—probably over 400 (desirable is 0), signifying extensive hidden coronary plaque. Once Mr. Clinton's high heart scan score was identified, a search for the causes should have ensued, followed by corrective measures.

Had his doctors been really smart, they would have had Mr. Clinton undergo a heart scan and lipoprotein testing. With five minutes of Mr. Clinton's time, a powerful prevention program could have been devised. This kind of information would likely have eliminated Mr. Clinton's need for bypass surgery.

HOW NOT TO MAKE THE SAME MISTAKES

Learn from the mismanagement of Mr. Clinton's health and do not wait for the appearance of symptoms before you take action to prevent heart disease. If you have no symptoms, a stress test, even with blood-flow images, like the thallium stress test, is virtually useless and does not accurately predict the potential for heart attack in the vast majority of cases. Do not rely on cholesterol to predict your potential for heart attack. Look at the complete picture: do you have high blood pressure, a history of heart disease or stroke in your family, diabetes, or smoking now or in the past? Consider monitoring your lipoproteins to better assess your sources of risk.

OTHER MEASURES OF HEART DISEASE RISK

Several other measures are important components of a comprehensive assessment of heart disease risk. Although not lipoproteins, these measures are often included in cardiovascular health panels.

Homocysteine

Homocysteine was first suspected to be a cause of heart disease when children with a rare metabolic disorder called "homocystinuria" were observed to develop coronary disease. High levels of homocysteine—often greater than 200 micromoles per liter (mmol/L)—were recorded in the blood of these children.

Since these preliminary observations, it has become clear that elevated homocysteine levels are associated with coronary disease risk in adults, and that this risk occurs at levels far below 200 mmol/L. In adults, homocysteine levels in the 15-50 mmol/L range are associated with a significantly increased risk of heart disease, while some evidence suggests that levels as low as 8-10 mmol/L may elevate risk.

Homocysteine causes arterial injury, increases oxidization of LDL particles (thereby making them more damaging), constricts arteries, and provokes blood clot formation. The net result is a threefold increase in heart attack risk. Many people with heart disease have elevated homocysteine levels.⁴²⁻

43

Once you have recognized that your homocysteine is elevated, management is relatively easy and consists of B vitamin supplementation. Common starting regimens are vitamin B6 (25-50 mg), vitamin B12 (1000 mcg or more), and folic acid (1000-5000 mcg). Folic acid can be obtained over the counter in doses up to 800



mcg. Higher doses are available by prescription. Very rarely, taking folic acid by itself will “mask” hidden vitamin B12 deficiency, causing red tongue, anemia, and neurological effects. Therefore, folic acid is best taken in combination with vitamins B12 and B6. For modestly elevated homocysteine levels, a combination B vitamin complex is a good way to begin.

REPORT

New Blood Test Better Predicts Heart Attack Risk

By William Davis, MD, FACC

C-Reactive Protein

Inflammation is fuel for the fire that leads to coronary plaque rupture, resulting in heart attack. Inflammation may also contribute to other diseases, such as diabetes, cancer, and arthritis. A number of proteins circulate in the blood, signaling heightened states of inflammation. The most clinically studied of these is C-reactive protein (CRP).

Dr. Paul Ridker of Harvard University is the nation's foremost authority on CRP. He has demonstrated that high CRP levels increase heart attack risk threefold, even when LDL level is low. When elevated CRP occurs in the company of small LDL particle size, a very high risk for heart attack can develop—a risk that is sixfold greater.¹⁷

Scientists have developed a way to measure CRP, called “high-sensitivity” CRP, that can detect low levels of inflammation. While highly elevated levels nearly always represent inflammation outside the heart (e.g., arthritis) and should not be used to prognosticate coronary risk, modestly elevated levels can be used to gauge low-grade inflammation that contributes to coronary plaque rupture.

Healthy lifestyle choices, such as restricting saturated fat, choosing low-glycemic-index foods, and engaging in regular exercise, are the best way to lower CRP. Fish oil can be a useful adjunct in your program for turning off inflammation and lowering CRP.⁴⁴ Prescription agents like the cholesterol drug ezetimibe (Zetia®) and the diabetes drugs Actos® and Avandia® can lower CRP. Aspirin lowers CRP modestly,⁴⁵ as does alpha tocopherol (vitamin E).⁴⁶ Plant-based compounds called flavonoids, including olive oil polyphenols, are emerging as potentially important factors in lowering inflammation and CRP levels, though further investigation is warranted.^{46,47}

Fibrinogen

Our blood maintains a precarious balance between being able to flow freely into the smallest capillaries and being capable of clotting in response to injury. Clotting proteins circulating in the blood help maintain this balance. Fibrinogen is a principal clotting protein. With the appropriate stimulation (injury or stress), fibrinogen is modified to form a smaller protein called fibrin. Thousands of strands of fibrin accumulate at an injury site to form a blood clot.

When greater blood levels of fibrinogen are present, the balance is tipped in favor of blood clot formation, even when it may not be appropriate. This can happen, for instance, at the site of a ruptured coronary plaque. The injured plaque surface causes fibrinogen to be converted to fibrin, forming a blood clot, which may result in heart attack. Fibrinogen can also promote atherosclerotic plaque growth, even without blood clot formation. Elevated fibrinogen levels are associated with an increased risk of heart attack.⁴⁸⁻⁵⁰

The modern American lifestyle of sedentary occupations and excessive intake of high-fat foods and refined starches increases fibrinogen. Estrogen raises fibrinogen levels, which may account for some of the increased blood-clotting tendency observed with estrogen replacement.

Fish oil at doses of 3000 mg or greater daily does a good job of lowering fibrinogen.⁵¹ Combine this with a diet rich in green vegetables and fiber, low in saturated and hydrogenated fat, and physical activity, and fibrinogen levels usually drop into a favorable range. For the occasional person who requires more intensive effort, the fibric acid class of drugs, especially fenofibrate, can lower fibrinogen by 15-40%. Niacin also helps by lowering fibrinogen by 10-30%.⁵²

NUTRITIONAL SUPPLEMENTS THAT LOWER LDL PARTICLE NUMBER

- Oat bran, ground flaxseed, or ground psyllium seed: 2 tablespoons/day. Oat bran and flaxseed are the most versatile, great either in hot cereal or added to yogurt or fruit smoothies.⁵³⁻⁵⁶
- Raw almonds, walnuts, or pecans: 1/4-1/2 cup/day.³⁹
- Soy protein powder: 3 tablespoons (25 gm)/day of this supplement added to yogurt or fruit smoothies is among the most effective nutritional methods for lowering LDL particle number, by suppressing the liver's production of cholesterol.⁵⁴ Other convenient sources of soy protein include soy cheese, low-carbohydrate pasta, and soy milk.

- Stanol/sterol esters: found in some butter substitutes and fortified orange juice products.⁵⁴
- Beans: lima, Spanish, black, red, etc.: 1/2-1 cup/day.⁵⁵
- Chitosan: 1200 mg per day lowers LDL level by around 10%.^{57,58}
- Pectin: citrus fruit rinds can be an effective adjunct for lowering cholesterol.⁵⁹ Pectin can also be taken as a supplement.
- Glucomannan: this fiber from konjac root decreases LDL level by around 10%, while lowering blood sugar and promoting weight loss by providing a feeling of fullness.⁵⁸ A dose of 1500 mg before meals works well, and should be consumed with plenty of water, since it is highly water-absorbing.

HOW AND WHEN TO GET THESE TESTS

If you have already been diagnosed with coronary or vascular disease, or have a history of heart attack, coronary stent, angioplasty, or bypass surgery, your doctor may have failed to identify many of the underlying causes of your condition. Uncovering the hidden causes of your heart disease can make a profound difference to your future. After all, how can an effective prevention program be devised without identifying all causes of your heart disease? It is not unusual for lipoprotein assessment to identify three, four, or five risk factors of heart disease. The good news is that this information can help you and your doctor to implement new treatments to comprehensively reduce your risk.

If you do not have known heart disease but have reason to believe that you are at high risk—due to family history of the disease, diabetes in yourself or your family, being overweight or obese, or having had significant cholesterol or triglyceride abnormalities identified—strongly consider lipoprotein testing to shed more light on the extent of your risk factors. Better information can mean more effective prevention and thus better health. The same advice applies if a computed tomography (CT) heart scan has revealed that you suffer from arterial calcification.



Even if you are simply concerned about heart disease risk, you might consider lipoprotein testing. The blood draw is no different than that for a cholesterol panel and is performed at virtually no risk to you.

Thankfully, more and more physicians are recognizing the deficiencies of conventional lipid assessment and have turned to lipoprotein testing for better answers. Laboratories around the country are now offering advanced lipoprotein testing. Life Extension now offers the Vertical Auto Profile, or VAP™, method of advanced lipoprotein testing.

CONCLUSION

Advanced lipoprotein testing can help provide great insight into your risks for heart disease, filling the gaping deficiencies of mainstream cholesterol or lipid testing. The superior information provided by lipoprotein testing can help you and your physician to devise an effective program to prevent future heart attacks.

If you have a family history of heart disease, high blood pressure, diabetes, or any measure of coronary plaque, you should strongly consider lipoprotein testing. If you have had coronary disease already diagnosed—that is, if you have had a heart attack, angina, or a heart procedure like coronary angioplasty or bypass surgery—then lipoprotein testing can be a crucial part of your program to prevent future cardiac catastrophes, particularly if conventional lipid testing has failed to pinpoint the cause of your disease.

GLYCEMIC INDEX: AN IMPORTANT FACTOR WHEN LIPOPROTEIN PARTICLE SIZE COUNTS

Being aware of the glycemic-index values of different foods is very important when you have small LDL particles, low total HDL, deficient large HDL, or increased triglycerides or VLDL. This means choosing foods that release sugars slowly, an effect that may help improve all of these risk factors. Abrupt spikes in sugar release help create these abnormalities and lead to both coronary plaque growth and diabetes. By contrast, foods that release sugars slowly or contain little or no sugar can help correct these patterns.^{60,61}

The glycemic index is calculated by comparing a food's ability to raise blood sugar to that of either white table sugar or white bread, two foods that are processed by the body like pure sugar. The height of the blood sugar peak is then measured. A glycemic index of 100 would be equal in sugar-release properties to sugar or white bread; an index below 100 would mean less sugar release. In general, proteins and fats have lower glycemic index values, while carbohydrates and refined foods have higher values.

Carbohydrates are a potential problem for glycemic index control. Processed foods like breakfast cereals, white bread, other

white flour products, and sweets are clearly the worst culprits, causing big spikes in blood sugar after ingestion. Desirable carbohydrate sources with lower glycemic indexes include foods containing oats, whole fruits and vegetables (the pulp and fiber slow sugar release, unlike their juices), and beans.

Healthy oils, like canola, olive, and flaxseed oils, slow the sugar-release effect of other foods. Foods rich in fiber, such as oat bran, whole grains, and raw nuts (almonds, walnuts, pecans), tend to slow sugar release. Supplements containing glucomannan and other fibers are very viscous, which slows sugar release and also promotes satiety, thereby supporting weight loss.

A website managed by the University of Sydney (www.glycemicindex.com) has an excellent searchable database that allows you to enter the food in question and obtain its glycemic index. Dr. Jennie Brand-Miller has published extensively on the glycemic index, and the complete glycemic index tables generated by her research are also available in her book *The Glucose Revolution* (Marlowe and Company, 1999).

Dr. William Davis is an author, lecturer, and practicing cardiologist focusing on coronary disease regression. He is author of the book, Track Your Plaque: The only heart disease prevention program that shows you how to use the new heart scans to detect, track, and control coronary plaque. He can be contacted through www.trackyourplaque.com.

References

1. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ*. 2002 Jun 29;324(7353):1570-6.
2. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? *J Am Coll Cardiol*. 2003 May 7;41(9):1475-9.
3. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2001 Sep 4;104(10):1108-113.
4. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986 Nov 28;256(20):2823-8.
5. Castelli WP, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol*. 1992 Jan;2(1-2):23-8.
6. Sniderman AD, Pedersen T, Kjekshus J. Putting low-density lipoproteins at center stage in atherogenesis. *Am J Cardiol*. 1997 Jan 1;79(1):64-7.
7. Cheung MC, Brown BG, Wolf AC, Albers JJ. Altered particle size distribution of apolipoprotein A-I-containing lipoproteins in subjects with coronary artery disease. *J Lipid Res*. 1991 Mar;32(3):383-94.
8. Lamarche B, Despres JP, Moorjani S, et al. Prevalence of dyslipidemic phenotypes in ischemic heart disease (prospective results from the Quebec Cardiovascular Study). *Am J Cardiol*. 1995 Jun 15;75(17):1189-95.
9. Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*. 2001 Dec 15;358(9298):2026-33.
10. van Lennep JE, Westerveld HT, van Lennep HW, et al. Apolipoprotein concentrations during treatment and recurrent coronary artery disease events. *Arterioscler Thromb Vasc Biol*. 2000 Nov;20(11):2408-13.
11. Gotto AM, Jr., Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation*. 2000 Feb 8;101(5):477-84.
12. St-Pierre AC, Ruel IL, Cantin B, et al. Comparison of various electrophoretic characteristics of LDL particles and their relationship to the risk of ischemic heart disease. *Circulation*. 2001 Nov 6;104(19):2295-9.
13. Kwiterovich PO, Jr. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol*. 2002 Oct 17;90(8A):30i-47i.

14. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. *Circulation*. 1997 Jan 7;95(1):69-75.
15. de Bruin TW. Lipid metabolism. *Curr Opin Lipidol*. 1998 Jun;9(3):275-8.
16. Krauss RM. Dietary and genetic effects on LDL heterogeneity. *World Rev Nutr Diet*. 2001;89:12-22.
17. St-Pierre AC, Bergeron J, Pirro M, et al. Effect of plasma C-reactive protein levels in modulating the risk of coronary heart disease associated with small, dense, low-density lipoproteins in men (The Quebec Cardiovascular Study). *Am J Cardiol*. 2003 Mar 1;91(5):555-8.
18. Morgan JM, Carey CM, Lincoff A, Capuzzi DM. The effects of niacin on lipoprotein subclass distribution. *Prev Cardiol*. 2004;7(4):182-7.
19. Guyton JR, Goldberg AC, Kreisberg RA, et al. Effectiveness of once-nightly dosing of extended-release niacin alone and in combination for hypercholesterolemia. *Am J Cardiol*. 1998 Sep 15;82(6):737-43.
20. Superko HR. Exercise and lipoprotein metabolism. *J Cardiovasc Risk*. 1995 Aug;2(4):310-5.
21. Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. *J Lipid Res*. 2002 Sep;43(9):1363-79.
22. Davy BM, Davy KP, Ho RC, et al. 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 Aug;76(2):351-8.
23. Griffin BA. The effect of n-3 fatty acids on low density lipoprotein subfractions. *Lipids*. 2001;36 SupplS91-7.
24. Gordon DJ, Rifkind BM. High-density lipoprotein—the clinical implications of recent studies. *N Engl J Med*. 1989 Nov 9;321(19):1311-6.
25. Miller NE. Associations of high-density lipoprotein subclasses and apolipoproteins with ischemic heart disease and coronary atherosclerosis. *Am Heart J*. 1987 Feb;113(2 Pt 2):589-97.
26. Syvanne M, Ahola M, Lahdenpera S, et al. High density lipoprotein subfractions in non-insulin-dependent diabetes mellitus and coronary artery disease. *J Lipid Res*. 1995 Mar;36(3):573-82.
27. Johansson J, Carlson LA, Landou C, Hamsten A. High density lipoproteins and coronary atherosclerosis. A strong inverse relation with the largest particles is confined to normotriglyceridemic patients. *Arterioscler Thromb*. 1991 Jan;11(1):174-82.
28. Bays H. Existing and investigational combination drug therapy for high-density lipoprotein cholesterol. *Am J Cardiol*. 2002 Nov 20;90(10B):30K-43K.
29. Thomas TR, Smith BK, Donahue OM, et al. Effects of omega-3 fatty acid supplementation and exercise on low-density lipoprotein and high-density lipoprotein subfractions. *Metabolism*. 2004 Jun;53(6):749-54.
30. Tsunoda F, Koba S, Hirano T, et al. 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 Dec;68(12):1165-72.
31. Chung BH, Cho BH, Liang P, et al. Contribution of postprandial lipemia to the dietary fat-mediated changes in endogenous lipoprotein-cholesterol concentrations in humans. *Am J Clin Nutr*. 2004 Nov;80(5):1145-58.
32. Rivellese AA, Maffettone A, Vessby B, et al. Effects of dietary saturated, monounsaturated and n-3 fatty acids on fasting lipoproteins, LDL size and post-prandial lipid metabolism in healthy subjects. *Atherosclerosis*. 2003 Mar;167(1):149-58.
33. Otvos J. Measurement of triglyceride-rich lipoproteins by nuclear magnetic resonance spectroscopy. *Clin Cardiol*. 1999 Jun;22(6 Suppl):II21-7.
34. Zilversmit DB. Atherogenic nature of triglycerides, postprandial lipidemia, and triglyceride-rich remnant lipoproteins. *Clin*

35. Chan DC, Barrett HP, Watts GF. Dyslipidemia in visceral obesity: mechanisms, implications, and therapy. *Am J Cardiovasc Drugs*. 2004;4(4):227-46.

36. Berglund L, Ramakrishnan R. Lipoprotein(a): an elusive cardiovascular risk factor. *Arterioscler Thromb Vasc Biol*. 2004 Dec;24(12):2219-26.

37. Maher VM, Brown BG, Marcovina SM, et al. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). *JAMA*. 1995 Dec 13;274(22):1771-4.

38. 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 Oct;10(5):247-51.

39. Jenkins DJ, Kendall CW, Marchie A, et al. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. *Circulation*. 2002 Sep 10;106(11):1327-32.

40. Marcovina SM, Koschinsky ML, Albers JJ, Skarlatos S. Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein(a) and Cardiovascular Disease: recent advances and future directions. *Clin Chem*. 2003 Nov;49(11):1785-96.

41. Berglund L. Diet and drug therapy for lipoprotein (a). *Curr Opin Lipidol*. 1995 Feb;6(1):48-56.

42. Anon. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA*. 2002 Oct 23;288(16):2015-22.

43. Refsum H, Ueland PM, Nygard O, Vollset SE. Homocysteine and cardiovascular disease. *Annu Rev Med*. 1998;49:31-62.

44. Ciubotaru I, Lee YS, Wander RC. Dietary fish oil decreases C-reactive protein, interleukin-6, and triacylglycerol to HDL-cholesterol ratio in postmenopausal women on HRT. *J Nutr Biochem*. 2003 Sep;14(9):513-21.

45. Fredrikson GN, Hedblad B, Nilsson JA, et al. Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma C-reactive protein levels. *Metabolism*. 2004 Nov;53(11):1436-42.

46. Patrick L, Uzick M. Cardiovascular disease: C-reactive protein and the inflammatory disease paradigm: HMG-CoA reductase inhibitors, alpha-tocopherol, red yeast rice, and olive oil polyphenols. A review of the literature. *Altern Med Rev*. 2001 Jun;6(3):248-71.

47. Phillips T, Childs AC, Dreon DM, Phinney S, Leeuwenburgh C. A dietary supplement attenuates IL-6 and CRP after eccentric exercise in untrained males. *Med Sci Sports Exerc*. 2003 Dec;35(12):2032-7.

48. Chambless LE, Folsom AR, Sharrett AR, et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol*. 2003 Sep;56(9):880-90.

49. Koenig W. Fibrin(ogen) in cardiovascular disease: an update. *Thromb Haemost*. 2003 Apr;89(4):601-9.

50. Palmieri V, Celentano A, Roman MJ, et al. Relation of fibrinogen to cardiovascular events is independent of preclinical cardiovascular disease: the Strong Heart Study. *Am Heart J*. 2003 Mar;145(3):467-74.

51. Vanschoonbeek K, Feijge MA, Paquay M, et al. Variable hypocoagulant effect of fish oil intake in humans: modulation of fibrinogen level and thrombin generation. *Arterioscler Thromb Vasc Biol*. 2004 Sep;24(9):1734-40.

52. de Maat MP. Effects of diet, drugs, and genes on plasma fibrinogen levels. *Ann NY Acad Sci*. 2001;936:509-21.

53. Berg A, Konig D, Deibert P, 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.

54. Kerckhoffs DA, Brouns F, Hornstra G, Mensink RP. Effects on the human serum lipoprotein profile of beta-glucan, soy protein and isoflavones, plant sterols and stanols, garlic and tocotrienols. *J Nutr*. 2002 Sep;132(9):2494-505.

55. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr*.

56. Anderson JW, Allgood LD, Lawrence A, 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 Feb;71(2):472-9.
57. Bokura H, Kobayashi S. Chitosan decreases total cholesterol in women: a randomized, double-blind, placebo-controlled trial. *Eur J Clin Nutr.* 2003 May;57(5):721-5.
58. Gallaher DD, Gallaher CM, Mahrt GJ, et al. A glucomannan and chitosan fiber supplement decreases plasma cholesterol and increases cholesterol excretion in overweight normocholesterolemic humans. *J Am Coll Nutr.* 2002 Oct;21(5):428-33.
59. Anderson JW, Tietyen-Clark J. Dietary fiber: hyperlipidemia, hypertension, and coronary heart disease. *Am J Gastroenterol.* 1986 Oct;81(10):907-19.
60. Harbis A, Perdreau S, Vincent-Baudry S, et al. Glycemic and insulinemic meal responses modulate postprandial hepatic and intestinal lipoprotein accumulation in obese, insulin-resistant subjects. *Am J Clin Nutr.* 2004 Oct;80(4):896-902.
61. Pelkman CL. Effects of the glycemic index of foods on serum concentrations of high-density lipoprotein cholesterol and triglycerides. *Curr Atheroscler Rep.* 2001 Nov;3(6):456-61.

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.