Arteriosclerotic Vascular Disease

*Atherosclerosis* (also known as *Arteriosclerotic Vascular Disease* or *ASVD*) is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low density (especially small particle) lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). It is commonly referred to as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries.

The *atheromatous plaque* is divided into three distinct components:

1. The atheroma (‘lump of wax’, from *Athera*, wax in Greek,), which is the nodular accumulation of a soft, flaky, yellowish material at the center of large plaques, composed of macrophages nearest the lumen of the artery
2. Underlying areas of cholesterol crystals
3. Calcification at the outer base of older/more advanced lesions.

The following terms are similar, yet distinct, in both spelling and meaning, and can be easily confused: arteriosclerosis, arteriolosclerosis, and atherosclerosis.

*Arteriosclerosis* is a general term describing any hardening (and loss of elasticity) of medium or large arteries (from the Greek *Arterio*, meaning *artery*, and *sclerosis*, meaning *hardening*);

*Arteriolosclerosis* is any hardening (and loss of elasticity) of arterioles (small arteries);
Atherosclerosis is a hardening of an artery specifically due to an atheromatous plaque. Therefore, atherosclerosis is a form of arteriosclerosis.

Atherosclerosis, though typically asymptomatic for decades, eventually produces two main problems:

- **First**, the atheromatous plaques, though long compensated for by artery enlargement, eventually lead to plaque ruptures and clots inside the artery lumen over the ruptures. The clots heal and usually shrink but leave behind stenosis (narrowing) of the artery (both locally and in smaller downstream branches), or worse, complete closure, and, therefore, an insufficient blood supply to the tissues and organ it feeds.

- **Second**, if the compensating artery enlargement process is excessive, then a net aneurysm results.

These complications of advanced atherosclerosis are chronic, slowly progressive and cumulative. Most commonly, soft plaque suddenly ruptures, causing the formation of a thrombus that will rapidly slow or stop blood flow, leading to death of the tissues fed by the artery in approximately 5 minutes. This catastrophic event is called an infarction. One of the most common recognized scenarios is called coronary thrombosis of a coronary artery, causing myocardial infarction (a heart attack).

Even worse is the same process in an artery to the brain, commonly called stroke.

Another common scenario in very advanced disease is claudication from insufficient blood supply to the legs, typically due to a combination of both stenosis and aneurysmal segments narrowed with clots.

Since atherosclerosis is a body-wide process, similar events occur also in the arteries to the brain, intestines, kidneys, legs, etc.
Yet, many infarctions involve only very small amounts of tissue and are termed clinically silent, because the person having the infarction does not notice the problem, does not seek medical help or when they do, physicians do not recognize what has happened.

**Causes**

Atherosclerosis develops from low-density lipoprotein molecules (LDL) becoming oxidized (ldl-ox) by free radicals, particularly oxygen free radicals (ROS). When oxidized LDL comes in contact with an artery wall, a series of reactions occur to repair the damage to the artery wall caused by oxidized LDL. The LDL molecule is globular shaped with a hollow core to carry cholesterol throughout the body to generate brain tissues, vitamin D, and so on. Cholesterol does not dissolve in water. Blood is 70% water. Cholesterol can move in the bloodstream only by being transported by LDL.

The body’s immune system responds to the damage to the artery wall caused by oxidized LDL by sending specialized white blood cells (macrophages and T-lymphocytes) to absorb the oxidized-LDL forming specialized foam cells. Unfortunately, these white blood cells are not able to process the oxidized-LDL, and ultimately grow then rupture, depositing a greater amount of oxidized cholesterol into the artery wall. This triggers more white blood cells, continuing the cycle.

Eventually, the artery becomes inflamed. The cholesterol plaque causes the muscle cells to enlarge and form a hard cover over the affected area. This hard cover is what causes a narrowing of the artery, reduces the blood flow and increases blood pressure.

Some researchers believe that atherosclerosis may be caused by an infection of the vascular smooth muscle cells. Chickens, for example, develop atherosclerosis when infected with the Marek’s disease herpes virus. Herpes virus infection of arterial smooth muscle cells has been shown to cause cholesteryl ester (CE) accumulation. Cholesteryl ester accumulation is associated with atherosclerosis.
Also, cytomegalovirus (CMV) infection is associated with cardiovascular diseases.

**Symptoms**

Atherosclerosis typically begins in early adolescence, and is usually found in most major arteries, yet is asymptomatic and not detected by most diagnostic methods during life. Atheroma in arm, or more often in leg arteries, which produces decreased blood flow, is called peripheral artery occlusive disease (PAOD).

According to United States data for the year 2004, for about 65% of men and 47% of women, the first symptom of atherosclerotic cardiovascular disease is heart attack or sudden cardiac death (death within one hour of onset of the symptom).

Most artery flow disrupting events occur at locations with less than 50% lumen narrowing (~20% stenosis is average). Cardiac stress testing, traditionally the most commonly performed non-invasive testing method for blood flow limitations, in general, detects only lumen narrowing of ~75% or greater, although some physicians claim that nuclear stress methods can detect as little as 50%.

**Atherogenesis**

Atherogenesis is the developmental process of atheromatous plaques. It is characterized by a remodeling of arteries involving the concomitant accumulation of fatty substances called plaques. One recent theory suggests that, for unknown reasons, leukocytes, such as monocytes or basophiles, begin to attack the endothelium of the artery lumen in cardiac muscle. The ensuing inflammation leads to formation of atheromatous plaques in the arterial tunica intima, a region of the vessel wall located between the endothelium and the tunica media. The bulk of these lesions are made of excess fat, collagen, and elastin.
At first, as the plaques grow, only wall thickening occurs without any narrowing, stenosis of the artery opening, called the lumen; stenosis is a late event, which may never occur and is often the result of repeated plaque rupture and healing responses, not just the atherosclerosis process by itself.

*Cellular*

*Micrograph of an artery that supplies the heart with significant atherosclerosis and marked luminal narrowing. Masson’s trichrome.*

The first step of atherogenesis is the development of so called ‘fatty streaks’, which are small sub-endothelial deposits of monocyte-derived macrophages. The primary documented driver of this process is oxidized Lipoprotein particles within the wall, beneath the endothelial cells, though upper normal or elevated concentrations of blood glucose also plays a major role and not all factors are fully understood. Fatty streaks may appear and disappear.

Low Density Lipoprotein particles in blood plasma, when they invade the endothelium and become oxidized create a risk for cardiovascular disease. A complex set of biochemical reactions regulates the oxidation of LDL, chiefly stimulated by presence of enzymes, e.g. Lp-LpA2 and free radicals in the endothelium or blood vessel lining.

The initial damage to the blood vessel wall results in a ‘call for help’, an inflammatory response. Monocytes (a type of white blood cell)
enter the artery wall from the bloodstream, with platelets adhering to the area of insult. This may be promoted by redox signaling induction of factors such as VCAM-1, which recruit circulating monocytes.

The monocytes differentiate macrophages, which ingest oxidized LDL, slowly turning into large ‘foam cells’ – so-described because of their changed appearance resulting from the numerous internal cytoplasmic vesicles and resulting high lipid content. Under the microscope, the lesion now appears as a fatty streak.

Foam cells eventually die, and further propagate the inflammatory process. There is also smooth muscle proliferation and migration from tunica media to intima responding to cytokines secreted by damaged endothelial cells. This would cause the formation of a fibrous capsule covering the fatty streak.

*Calcification and lipids*

Intracellular micro-calcifications form within vascular smooth muscle cells of the surrounding muscular layer, specifically in the muscle cells adjacent to the atheromas.

In time, as cells die, this leads to extra-cellular calcium deposits between the muscular wall and outer portion of the atheromatous plaques. A similar form of an intramural calcification, presenting the picture of an early phase of arteriosclerosis, appears to be induced by a number of drugs that have an anti-proliferative mechanism of action.

Cholesterol is delivered into the vessel wall by cholesterol-containing low-density lipoprotein (LDL) particles. To attract and stimulate macrophages, the cholesterol must be released from the LDL particles and oxidized, a key step in the ongoing inflammatory process. The process is worsened if there is insufficient high-density lipoprotein (HDL), the lipoprotein particle that removes cholesterol from tissues and carries it back to the liver.
The foam cells and platelets encourage the migration and proliferation of smooth muscle cells, which in turn ingest lipids, become replaced by collagen and transform into foam cells themselves. A protective fibrous cap normally forms between the fatty deposits and the artery lining (the intima).

These capped fatty deposits (now called ‘atheromas’) produce enzymes that cause the artery to enlarge over time. As long as the artery enlarges sufficiently to compensate for the extra thickness of the atheroma, then no narrowing (‘stenosis’) of the opening (‘lumen’) occurs. The artery becomes expanded with an egg-shaped cross-section, still with a circular opening. If the enlargement is beyond proportion to the atheroma thickness, then an aneurysm is created.

*Visible features*

![Severe atherosclerosis of the aorta. Autopsy specimen.](image)

Although arteries are not typically studied microscopically, two plaque types can be distinguished:

www.healthoracle.org
1. The *fibro-lipid (fibro-fatty) plaque* is characterized by an accumulation of lipid-laden cells underneath the intima of the arteries, typically without narrowing the lumen due to compensatory expansion of the bounding muscular layer of the artery wall. Beneath the endothelium there is a ‘fibrous cap’ covering the atheromatous ‘core’ of the plaque. The core consists of lipid-laden cells (macrophages and smooth muscle cells) with elevated tissue cholesterol and cholesterol ester content, fibrin, proteoglycans, collagen, elastin, and cellular debris. In advanced plaques, the central core of the plaque usually contains extra-cellular cholesterol deposits (released from dead cells), which form areas of cholesterol crystals with empty, needle-like clefts. At the periphery of the plaque are younger ‘foamy’ cells and capillaries. These plaques usually produce the most damage to the individual when they rupture.

2. The *fibrous plaque* is also localized under the intima, within the wall of the artery resulting in thickening and expansion of the wall and, sometimes, spotty localized narrowing of the lumen with some atrophy of the muscular layer. The fibrous plaque contains collagen fibers (eosinophilic), precipitates of calcium (hematoxylinophilic) and, rarely, lipid-laden cells.

In effect, the muscular portion of the artery wall forms small aneurysms just large enough to hold the atheroma that are present. The muscular portion of artery walls usually remains strong, even after they have remodeled to compensate for the atheromatous plaques.

However, atheromas within the vessel wall are soft and fragile with little elasticity. Arteries constantly expand and contract with each heartbeat, i.e., the pulse. In addition, the calcification deposits between the outer portion of the atheroma and the muscular wall, as
they progress, lead to a loss of elasticity and stiffening of the artery as a whole.

The calcification deposits, after they have become sufficiently advanced, are partially visible on coronary artery computed tomography or electron beam tomography (EBT) as rings of increased radiographic density, forming halos around the outer edges of the atheromatous plaques, within the artery wall. On CT, >130 units on the Hounsfield scale (some argue for 90 units) has been the radiographic density usually accepted as clearly representing tissue calcification within arteries. These deposits demonstrate unequivocal evidence of the disease, relatively advanced, even though the lumen of the artery is often still normal by angiographic or intravascular ultrasound.

**Rupture and stenosis**

Although the disease process tends to be slowly progressive over decades, it usually remains asymptomatic until an atheroma ulcerates which leads to immediate blood clotting at the site of atheroma ulcer. This triggers a cascade of events that leads to clot enlargement which may quickly obstruct the lumen (opening) of the artery itself. A complete blockage leads to ischemia of the myocardial (heart) muscle and damage. This process is the myocardial infarction or ‘heart attack.’

If the heart attack is not fatal, fibrous organization of the clot within the lumen ensues, covering the rupture but also producing stenosis or closure of the lumen, or over time and after repeated ruptures, resulting in a persistent, usually localized stenosis or blockage of the artery lumen. Stenosis can be slowly progressive, whereas plaque ulceration is a sudden event that occurs specifically in atheromas with thinner/weaker fibrous caps that have become ‘unstable.’

Repeated plaque ruptures, ones not resulting in total lumen closure, combined with the clot patch over the rupture and healing response to stabilize the clot is the process that produces most stenosis over
time. The stenotic areas tend to become more stable, despite increased flow velocities at these narrowings. Most major blood-flow-stopping events occur at large plaques, which, prior to their rupture, produced very little if any stenosis.

From clinical trials, 20% is the average stenosis at plaques that subsequently rupture with resulting complete artery closure. Most severe clinical events do not occur at plaques that produce high-grade stenosis. From clinical trials, only 14% of heart attacks occur from artery closure at plaques producing a 75% or greater stenosis prior to the vessel closing.

If the fibrous cap separating a soft atheroma from the bloodstream within the artery ruptures, tissue fragments are exposed and released, and blood enters the atheroma within the wall and sometimes results in a sudden expansion of the atheroma size. Tissue fragments are very clot-promoting, containing collagen and tissue factor; they activate platelets and activate the system of coagulation. The result is the formation of a thrombus (blood clot) overlying the atheroma, which obstructs blood flow acutely. With the obstruction of blood flow, downstream tissues are starved of oxygen and nutrients. If this is the myocardium (heart muscle), angina (cardiac chest pain) or myocardial infarction (heart attack) develops.

**Diagnosis of plaque-related disease**

![Microphotography of arterial wall with calcified (violet colour) atherosclerotic plaque (haematoxillin & eosin stain)](www.healthoracle.org)
Areas of severe narrowing, stenosis, detectable by angiography, and to a lesser extent ‘stress tests’ have long been the focus of human diagnostic techniques for cardiovascular disease, in general.

However, these methods focus on detecting only severe narrowing, not the underlying atherosclerosis disease. As demonstrated by human clinical studies, most severe events occur in locations with heavy plaque, yet little or no lumen narrowing present before debilitating events suddenly occur. Plaque rupture can lead to artery lumen occlusion within seconds to minutes, and potential permanent debility and sometimes sudden death.

Plaques that have ruptured are called complicated plaques. The lipid matrix breaks through the thinning collagen gap and when the lipids come in contact with the blood, clotting occurs. After rupture the platelet adhesion causes the clotting cascade to contact with the lipid pool causing a thrombus to form. This thrombus will eventually grow and travel throughout the body. The thrombus will travel through different arteries and veins and eventually become lodged in an area that narrows. Once the area is blocked, blood and oxygen will not be able to supply the vessels and will cause death of cells and lead to necrosis and poisoning. Serious complicated plaques can cause death of organ tissues, causing serious complications to that organ system.

Greater than 75% lumen stenosis used to be considered by cardiologists as the hallmark of clinically significant disease because it is typically only at this severity of narrowing of the larger heart arteries that recurring episodes of angina and detectable abnormalities by stress testing methods are seen. However, clinical trials have shown that only about 14% of clinically-debilitating events occur at locations with this, or greater severity of narrowing. The majority of events occur due to atheroma plaque rupture at areas without narrowing sufficient enough to produce any angina or stress test abnormalities. Thus, since the later-1990s, greater attention is being focused on the ‘vulnerable plaque.’
Though any artery in the body can be involved, usually only severe narrowing or obstructions of some arteries, those that supply more critically-important organs are recognized. Obstruction of arteries supplying the heart muscle results in a heart attack. Obstruction of arteries supplying the brain results in a stroke. These events are life-changing, and often result in irreversible loss of function because lost heart muscle and brain cells do not grow back to any significant extent, typically less than 2%.

Over the last couple of decades, methods other than angiography and stress-testing have been increasingly developed as ways to better detect atherosclerotic disease before it becomes symptomatic. These have included both (a) anatomic detection methods and (b) physiologic measurement methods.

Examples of anatomic methods include:

1. coronary calcium scoring by CT,
2. carotid IMT (intimal media thickness) measurement by ultrasound,
3. IVUS.

Examples of physiologic methods include:

1. Lipoprotein subclass analysis
2. HbA1c
3. CRP and High sensitivity CRP
4. Homocysteine

The example of the metabolic syndrome combines both anatomic (abdominal girth) and physiologic (blood pressure, elevated blood glucose) methods.
Advantages of these two approaches:

The anatomic methods directly measure some aspect of the actual atherosclerotic disease process itself, thus offer potential for earlier detection, including before symptoms start, disease staging and tracking of disease progression.

The physiologic methods are often less expensive and safer and changing them for the better may slow disease progression, in some cases with marked improvement.

Disadvantages of these two approaches:

The anatomic methods are generally more expensive and several are invasive, such as IVUS.

The physiologic methods do not quantify the current state of the disease or directly track progression.

For both, clinicians and third party payers have been slow to accept the usefulness of these newer approaches.

Physiologic factors that increase risk.

Various anatomic, physiological and behavioral risk factors for atherosclerosis are known. These can be divided into various categories: congenital vs. acquired, modifiable or not, classical or non-classical. The points labelled ‘+’ in the following list form the core components of ‘metabolic syndrome’.

Factors add to each other multiplicatively, with two factors increasing the risk of atherosclerosis fourfold. Hyperlipidemia, hypertension and cigarette smoking together increases the risk seven times.

Modifiable

- Having diabetes or Impaired glucose tolerance (IGT) +
• Dyslipoproteinemia (unhealthy patterns of serum proteins carrying fats & cholesterol): +
  o High serum concentration of low-density lipoprotein (LDL, ‘bad if elevated concentrations and small’), and / or very low density lipoprotein (VLDL) particles, i.e., ‘lipoprotein subclass analysis’
  o Low serum concentration of functioning high density lipoprotein (HDL ‘protective if large and high enough’ particles), i.e., ‘lipoprotein subclass analysis’
  o An LDL:HDL ratio greater than 3:1
• Tobacco smoking, increases risk by 200% after several pack years
• Having high blood pressure +, on its own increasing risk by 60%
• Elevated serum C-reactive protein concentrations

**Nonmodifiable**

• Advanced age
• Male sex
• Having close relatives who have had some complication of atherosclerosis (eg. coronary heart disease or stroke)
• Genetic abnormalities, e.g. familial hypercholesterolemia

**Lesser or uncertain**

The following factors are of relatively lesser importance, are uncertain or nonquantitated:

• Being obese (in particular central obesity, also referred to as *abdominal* or *male-type* obesity) +
• A sedentary lifestyle
• Postmenopausal estrogen deficiency
• High carbohydrate intake
• Intake of trans fat
• Elevated serum levels of triglycerides +
• Elevated serum levels of homocysteine
• Elevated serum levels of uric acid (also responsible for gout)
• Elevated serum fibrinogen concentrations
• Elevated serum lipoprotein(a) concentrations
• Chronic systemic inflammation as reflected by upper normal WBC concentrations, elevated high sensitivity-CRP and many other blood chemistry markers, most only research level at present, not clinically done.
• Stress or symptoms of clinical depression
• Hyperthyroidism (an over-active thyroid)
• Elevated serum insulin levels +
• Short sleep duration
• Chlamydia pneumoniae infection

Dietary risk factors

The relation between dietary fat and atherosclerosis is a contentious field. The USDA, in its food pyramid, promotes a low-fat diet, based largely on its view that fat in the diet is atherogenic. The American Heart Association, the American Diabetes Association and the National Cholesterol Education Program make similar recommendations.

In contrast, Prof Walter Willett (Harvard School of Public Health, PI of the second Nurses’ Health Study) recommends much higher levels, especially of monounsaturated and polyunsaturated fat. Writing in Science, Gary Taubes detailed that political considerations played into the recommendations of government bodies. These differing views reach a consensus, though, against consumption of trans fats.

The role of dietary oxidized fats / lipid peroxidation (rancid fats) in humans is not clear. Laboratory animals fed rancid fats develop atherosclerosis. Rats fed DHA-containing oils experienced marked disruptions to their antioxidant systems, as well as accumulated significant amounts of peroxide in their blood, livers and kidneys. In another study, rabbits fed atherogenic diets containing various oils
were found to undergo the greatest amount of oxidative susceptibility of LDL via polyunsaturated oils. In a study involving rabbits fed heated soybean oil, ‘grossly induced atherosclerosis and marked liver damage were histologically and clinically demonstrated’.

Rancid fats and oils taste very bad even in small amounts; people avoid eating them. It is very difficult to measure or estimate the actual human consumption of these substances. In addition, the majority of oils consumed are refined, bleached, deodorized and degummed by manufacturers. The resultant oils are colorless, odorless, and tasteless and have a longer shelf life than their unrefined counterparts. This extensive processing serves to make peroxidated, rancid oils much more elusive to detection via the various human senses than the unprocessed alternatives.

The French paradox is the observation that despite having a diet similar to those United States in terms of fat intake, rates of heart disease are lower in France. There is evidence to suggest the French paradox is due to underestimation of the rates of heart disease in France.

**Prognosis**

Lipoprotein imbalances, upper normal and especially elevated blood sugar, i.e., diabetes and high blood pressure are risk factors for atherosclerosis; homocysteine, stopping smoking, taking anticoagulants (anti-clotting agents), which target clotting factors, taking omega-3 oils from fatty fish or plant oils such as flax or canola oils, exercising and losing weight are the usual focus of treatments that have proven to be helpful in clinical trials. The target serum cholesterol level is ideally equal or less than 4 mmol/L (160 mg/dL), and triglycerides equal or less than 2 mmol/L (180 mg/dL).

Evidence has increased that people with diabetes, despite their not having clinically-detectable atherosclerotic disease, have more severe debility from atherosclerotic events over time than even non-diabetics that have already suffered atherosclerotic events. Thus
diabetes has been upgraded to be viewed as an advanced atherosclerotic disease equivalent.

*Treatment*

If atherosclerosis leads to symptoms, some symptoms such as angina pectoris can be treated. Non-pharmaceutical means are usually the first method of treatment, such as cessation of smoking and practicing regular exercise.

If these methods do not work, medicines are usually the next step in treating cardiovascular diseases, and, with improvements, have increasingly become the most effective method over the long term. However, medicines are criticized for their expense, patented control and occasional undesired effects.

*Statins*

In general, the group of medications referred to as statins has been the most popular and are widely prescribed for treating atherosclerosis and cardiovascular diseases. These are nothing but ‘costly aspirins’. They have not shown any extra ordinary benefits when tested under stringent conditions. They are big time money spinners for the drug companies. Most of the favorable reports presented are Drug Company sponsored. A medical multimillion dollar scam, in short.

The newest statin, rosuvastatin, has been the first to demonstrate regression of atherosclerotic plaque within the coronary arteries by IVUS (intravascular ultrasound evaluation). The study was set up to demonstrate effect primarily on atherosclerosis volume within a 2 year time-frame in people with active/symptomatic disease (angina frequency also declined markedly) but not global clinical outcomes, which was expected to require longer trial time periods; these longer trials remain in progress.
The success of statin drugs in clinical trials is based on some reductions in mortality rates, however by trial design biased toward men and middle-age, the data is as, as yet, less strongly clear for women and people over the age of 70.

*Dietary Approach*

However, for most people, changing their physiologic behaviors, from the usual high risk to greatly reduced risk, requires a combination of several compounds, taken on a daily basis and indefinitely. More and more human treatment trials have been done and are ongoing that demonstrate improved outcome for those people using more-complex and effective treatment regimens that change physiologic behaviour patterns to more closely resemble those that humans exhibited at a time before fatty streaks begin forming.

Combinations of nutritive supplements and vitamins intake have been most successful in changing common but sub-optimal lipoprotein patterns and group outcomes. In the many secondary prevention and several primary prevention trials, several classes of lipoprotein expression (less correctly termed ‘cholesterol-lowering’) altering agents have consistently reduced not only heart attack, stroke and hospitalization but also all-cause mortality rates.

Vitamin B3, AKA niacin, in pharmacologic doses, (generally 1,000 to 3,000 mg/day), tends to improve

(a) HDL levels, size and function

(b) Shift LDL particle distribution to larger particle size

(c) Lower lipoprotein (a), an atherosclerosis promoting genetic variant of LDL.

Additionally, individual responses to daily niacin, while mostly evident after a month at effective doses, tends to continue to slowly
improve further over time. Research work on increasing HDL particle concentration and function, beyond the usual niacin effect/response, even more important, is slowly advancing.

Dietary changes to achieve benefit have been more controversial, generally far less effective and less widely adhered to with success. One key reason for this is that most cholesterol, typically 80-90%, within the body is created and controlled by internal production by all cells in the body (true of all animals), with typically slightly greater relative production by hepatic/liver cells. Cell structure relies on fat membranes to separate and organize intracellular water, proteins and nucleic acids and cholesterol is one of the components of all animal cell membranes.

While the absolute production quantities vary with the individual, group averages for total human body content of cholesterol within the population commonly run about ~35,000 mg (assuming lean build; varies with body weight and build) and ~1,000 mg/day ongoing production.

Dietary intake plays a smaller role, 200-300 mg/day being common values; for pure vegetarians, essentially 0 mg/day, but this typically does not change the situation very much because internal production increases to largely compensate for the reduced intake.

For many, especially those with greater than optimal body mass and increased glucose levels, reducing carbohydrate (especially simple forms) intake, not fats or cholesterol, is often more effective for improving lipoprotein expression patterns, weight and blood glucose values. For this reason, medical authorities much less frequently promote the low dietary fat concepts than was commonly the case prior to about year 2005.

However, evidence has increased that processed, particularly industrial non-enzymatic hydrogenation produced trans fats, as opposed to the natural cis-configured fats, which living cells primarily produce, is a significant health hazard.
Dietary supplements of Omega-3 oils, especially those from the muscle of some deep salt water living fish species, also have clinical evidence of significant protective effects as confirmed by 6 double blind placebo controlled human clinical trials.

There is also a variety of evidence, though less robust, that homocysteine and uric acid levels, including within the normal range promote atherosclerosis and that lowering these levels is helpful, up to a point.

Vitamin C

In animals Vitamin C deficiency has been confirmed as an important role in development of hypercholesterolemia and atherosclerosis, but due to ethical reasons placebo-controlled human studies are impossible to do. Vitamin C acts as an antioxidant in vessels and inhibits inflammatory process. It has therapeutic properties on high blood pressure and its fluctuation, and arterial stiffness in diabetes. Vitamin C is also a natural regulator of cholesterol and higher doses (over 150 mg/kg daily) may confer significant protection against atherosclerosis even in the situation of elevated cholesterol levels.

The scale of vitamin C benefits on cardiovascular system led several authors to the theory, that vitamin C deficiency is the primary cause of cardiovascular diseases.\(^1\) The theory was unified by twice Nobel Prize winner Linus Pauling and Matthias Rath. They suggest, that clinical manifestations of cardiovascular diseases are merely overshoot of body defense mechanisms that are involved in stabilization of vascular wall, after it is weakened by the vitamin C deficiency and the subsequent collagen degradation. They discuss several metabolic and genetic predispositions and their pathomechanism.

Other Agents
Trials on Vitamin E have been done, but they have failed to find a beneficial effect, for various reasons, but for some patients at high risk for atherosclerosis there may be some benefits.

Menaquinone (Vitamin K2), but not phylloquinone (Vitamin K1), intake is associated with reduced risk of CHD mortality, all-cause mortality and severe aortic calcification.

It has been suggested that excess iron may be involved in development of atherosclerosis, but one study found reducing body iron stores in patients with symptomatic peripheral artery disease through phlebotomy did not significantly decrease all-cause mortality or death plus nonfatal myocardial infarction and stroke. Further studies may be warranted.

**Surgical intervention**

Other physical treatments, helpful in the short term, include minimally invasive angioplasty procedures that may include stents to physically expand narrowed arteries and major invasive surgery, such as bypass surgery, to create additional blood supply connections that go around the more severely narrowed areas.

This procedure is now become an industry—another multimillion dollar medical scam. Most of the surgeries undertaken are not warranted to say the least. Multiple bypass surgeries are performed on the same person.

Further, the surgical procedure is limited to certain specific regions and does not address all the other areas which are susceptible to blockages. Finally surgery is only an interim solution, if at all. It is not a solution to the problem.

**Prophylaxis**

Patients at risk for atherosclerosis-related diseases are increasingly being treated prophylactically with low-dose aspirin and a statin. The
high incidence of cardiovascular disease led Wald and Law to propose a *Polypill*, a once-daily pill containing these two types of drugs in addition to an ACE inhibitor, diuretic, beta blocker, and folic acid. They maintain that high uptake by the general population by such a *Polypill* would reduce cardiovascular mortality by 80%. It must be emphasized however that this is purely theoretical, as the Polypill has never been tested in a clinical trial. This is probably another scam in the making; duly sponsored by drug companies who can smell the moola.

Medical treatments often focus predominantly on the symptoms. The problem is that this is a disease that can remain asymptomatic during the early days. However, over time, the treatments which focus on decreasing the underlying atherosclerosis processes, as opposed to simply treating the symptoms resulting from the atherosclerosis, have been shown by clinical trials to be more effective.

In summary, the key to the more effective approaches has been better understanding of the widespread and insidious nature of the disease and to combine multiple different treatment strategies, not rely on just one or a few approaches. In addition, for those approaches, such as lipoprotein transport behaviors, which have been shown to produce the most success, adopting more aggressive combination treatment strategies has generally produced better results, both before and especially after people is symptomatic.

Because many blood thinners, particularly salicylates such as warfarin and aspirin thin the blood by interfering with Vitamin K, there is recent evidence that blood thinners which work by this mechanism can actually worsen arterial calcification in the long term even though they thin the blood in the short term.

*Recent research*

An indication of the role of HDL on atherosclerosis has been with the rare Apo-A1 Milano human genetic variant of this HDL protein. A small short-term trial using bacterial synthesized human Apo-A1
Milano HDL in people with unstable angina produced fairly dramatic reduction in measured coronary plaque volume in only 6 weeks vs. the usual increase in plaque volume in those randomized to placebo. The trial was published in JAMA in early 2006. Ongoing work starting in the 1990s may lead to human clinical trials—probably by about 2008. These may use synthesized Apo-A1 Milano HDL directly. Or they may use gene-transfer methods to pass the ability to synthesize the Apo-A1 Milano HD Lipoprotein.

Methods to increase high-density lipoprotein (HDL) particle concentrations, which in some animal studies largely reverses and remove atheromas, are being developed and researched.

Niacin has HDL raising effects (by 10 - 30%) and showed clinical trial benefit in the Coronary Drug Project and is commonly used in combination with other lipoprotein agents to improve efficacy of changing lipoprotein for the better. However most individuals have nuisance symptoms with short term flushing reactions, especially initially, and so working with a physician with a history of successful experience with niacin implementation, careful selection of brand, dosing strategy, etc. are usually critical to success.

The ASTEROID trial used a high-dose of rosuvastatin—the statin with typically the most potent dose/response correlation track record (both for LD Lipoproteins and HD Lipoproteins.) It found plaque (intima + media volume) reduction. Several additional rosuvastatin treatment/placebo trials for evaluating other clinical outcomes are in progress.

The actions of macrophages drive atherosclerotic plaque progression. *Immunomodulation of atherosclerosis* is the term for techniques which modulate immune system function in order to suppress this macrophage action. Immunomodulation has been pursued with considerable success in both mice and rabbits since about 2002. Plans for human trials, hoped for by about 2008, are in progress.
Research on genetic expression and control mechanisms is progressing. Topics include

- PPAR, known to be important in blood sugar and variants of lipoprotein production and function;
- The multiple variants of the proteins that form the lipoprotein transport particles.

Some controversial research has suggested a link between atherosclerosis and the presence of several different nanobacteria in the arteries, e.g., Chlamydophila pneumoniae, though trials of current antibiotic treatments known to be usually effective in suppressing growth or killing these bacteria have not been successful in improving outcomes.

The immunomodulation approaches mentioned above, because they deal with innate responses of the host to promote atherosclerosis, have far greater prospects for success.

The National Heart, Lung, and Blood Institute (NHLBI) and National Center for Complementary and Alternative Medicine (NCCAM) sponsored The Trial to Assess Chelation Therapy (TACT). The purpose of this study is to determine the safety and effectiveness of ethylene diamine tetra-acetic (EDTA) chelation therapy in individuals with coronary artery disease. EDTA chelation therapy involves repeated administrations of a synthetic amino acid to reduce atherosclerotic plaque and other mineral deposits throughout the cardiovascular system. The results of TACT will provide either a significant positive result or an informative null result upon which rational clinical decision-making and health policy can be based.

*The Hemorheologic-Hemodynamic Theory*

The theory of atherogenesis described above is presented largely as fact. While representing the mainstream view, this theory has several weaknesses. Aggressive reduction of serum LDL-cholesterol using
high dose statin therapy still leaves significant risk of adverse cardiovascular events in high-risk patients. Despite lowering serum LDL-cholesterol to less than 100 mg/dL, the estimated risk of adverse events in patients with established coronary artery disease is estimated to be 9% per year. This, in conjunction with the failure of torcetrapib in clinical trials, should prompt reexamination of mainstream atherogenesis theory.

Further, oxidized LDL is widely distributed in both arteries and veins, the latter of which do not develop atherosclerosis. The distribution of the putative precursor lesion, the fatty streak, correlates poorly with the distribution of fibrous plaques.

The mainstream theory of atherogenesis does not explain the localization of fibrous plaques to the vicinity of changing arterial geometry, such as branches, curves, and dilatations. Mainstream theory provides no explanation for accelerated atherosclerosis associated with hypertension. Finally, mainstream theory cannot explain the presence of fibrous plaques in synthetic arteriovenous grafts.

The \textit{hemorheologic–hemodynamic} theory holds that atherosclerosis is a disease of stasis of blood, which promotes the organization of a thrombus into an atherosclerotic plaque. Stasis of blood predisposes to thrombosis, as described in Virchow’s triad. Risk factors for atherosclerosis create larger areas of decreased shear (flow) by increasing blood viscosity, arterial stiffness, or both. Both of these abnormalities are seen in association with aging, hypertension, diabetes mellitus, cigarette smoking, and obesity.

The hemorheologic-hemodynamic theory posits that the same pathologic process, thrombosis, leads to plaque development and its complication, superimposed thrombosis and infarction. The name reflects the fact that the interaction of hemorheologic, i.e., blood flow, and hemodynamic, i.e., blood velocity, pulsatility, and arterial geometry, factors lead to atherosclerosis.
Viscosity and localized stasis

In arteries during systole, there is a gradient of blood velocity with the highest velocity in the center of the vessel and the lowest against the arterial wall. In areas of vascular branching, curving and dilatation, focal blood pooling occurs in the low shear environment against the arterial wall if blood velocity exceeds a critical value of Reynolds number. This phenomenon is seen in nature when rapidly flowing water encounters an obstruction, forming eddies and pools. Blood is a non-Newtonian fluid, and its viscosity progressively increases with decreasing shear. In areas of pooling, a vicious cycle can develop in which increased viscosity leads to decreased flow, further increasing viscosity and decreasing flow, leading ultimately to stasis and thrombosis in the absence of adequate fibrinolytic activity.

Decreased blood flow promotes thrombosis by decreasing influx of fibrinolytic molecules and decreasing efflux of activated clotting factors. Platelets activated by high shear in the central column of blood can be directed to the vicinity of the arterial wall by eddy currents. In these areas, decreased blood flow decreases endothelial production of molecules with antithrombotic activity such as nitric oxide and prostacyclin, further promoting thrombosis. This is akin to endothelial dysfunction which in mainstream atherogenesis theory is thought to be caused by putative cytopathic effects of oxidized low-density lipoprotein.

Arterial stiffening

Increased arterial stiffness accelerates atherosclerosis by increasing peak arterial blood velocity, thereby increasing Reynolds’s number, which indicates the propensity for a flowing fluid to develop pools and eddy currents in association with changing arterial geometry. In the normally compliant aorta, a portion of each stroke volume is stored in systole and propelled with lower velocity in diastole, creating blood flow throughout most of the cardiac cycle. An area of pooling created by high velocity would disappear during slow
diastolic flow, and any accumulated microthrombus would be dispersed. In a perfectly stiff aorta, the entire stroke volume would be expelled in systole. Given constant stroke volume, conservation of mass requires increasing peak arterial blood velocity with increasing arterial stiffness. In addition, no low velocity diastolic flow will occur, so that a pool formed during high velocity systolic flow will persist throughout the cardiac cycle. This will allow the time necessary for thrombus growth and subsequent organization. Additionally, increased peak arterial velocity will augment shear-mediated platelet actiavation.

Organization of mural thrombi

J.B. Duguid promoted the idea that atherosclerotic plaques develop from organization of mural thrombi in the 1940s and 50s. Arterial thrombi tend to remain localized to the low shear environment of the arterial wall because of high blood velocity in the central portion of the artery. These thrombi are known as ‘mural’ or ‘parietal.’ In veins, the velocity gradient between the center of the vessel and the vessel wall is small. Thus, thrombi in veins are more likely to become occlusive, as in deep venous thrombosis. This is why atherosclerosis is limited to arteries. If thrombi persist, whether in arteries or veins, they undergo organization, in which circulating fibrocytes colonize the thrombus and differentiate into cells capable of producing collagen and markers of smooth muscle differentiation, such as smooth muscle actin.

Role of lipoproteins in atherogenesis

The hemorheologic-hemodynamic theory predicts that low-density lipoprotein (LDL) should increase blood viscosity and high-density lipoprotein (HDL) should decrease blood viscosity, which has been demonstrated experimentally. Erythrocytes are separated by a minimum intercellular distance of approximately 15 nanometers caused by electrostatic repulsion due to sialic acid on the cell membrane surface.
LDL has a particle diameter of 18 to 40 nanometers, large enough to simultaneously bind to two erythrocytes and form erythrocyte aggregates. Erythrocyte aggregates increase blood viscosity at low shear by increasing the inertia of the suspended particles.

HDL, with a particle diameter of 8 to 12 nanometers, is too small to promote erythrocyte aggregation. Instead, by competing with LDL for binding to erythrocytes, it antagonizes erythrocyte aggregation and decreases blood viscosity. Erythrocyte aggregates are weak, and progressively disrupted with increasing shear.

Given the relationship of LDL to blood viscosity, it is not surprising that hypercholesterolemia is a risk factor for both atherosclerosis and deep venous thrombosis.

*Insights provided by the hemorheologic–hemodynamic theory*

The hemorheologic-hemodynamic theory explains the significant remaining risk of adverse cardiovascular events in patients with established coronary artery disease despite aggressive lowering of LDL-cholesterol using high dose statin therapy. Despite lowering serum LDL-cholesterol to less than 100 mg/dL, the risk of major cardiovascular events in these patients is estimated to be 9% per year. Such therapy does not address the adverse consequences of arterial stiffening, or increased blood viscosity caused by other factors.

The hemorheologic-hemodynamic theory explains the existence of atherosclerotic plaques in synthetic arteriovenous grafts. These provide an extreme hemodynamic environment, where extremely high velocity blood flows through a curved vessel. These vessels are prone to thrombosis and development of atherosclerotic plaques despite anticoagulation. These vessels lack a tunica media, which perceived wisdom maintains is the origin of smooth muscle cells in atherosclerotic plaques via migration.

The identification of the fibrocyte provides an alternative explanation for the origin of smooth muscle cells in atherosclerotic plaques.
Being largely inanimate, the capacity of these vessels to respond to an injury with an inflammatory response, the inciting cause of atherosclerosis according to mainstream atherogenesis theory, would be very limited. Further, this theory explains the benefit of blood donation and drinking large quantities of water. Both of these very low risk interventions reduce blood viscosity.

The hemorheologic-hemodynamic eliminates reliance on the fatty streak in atherogenesis. Fatty streaks routinely resolve without sequelae. This is acknowledged in by mainstream atherogenesis theory, which is unable to predict why a particular fatty streak progresses into an atherosclerotic plaque while the majority regress.

Increased HDL particle size and increased low-shear blood viscosity caused by torcetrapib therapy could account for the increased cardiovascular mortality seen in clinical trials.

Increased peak arterial blood velocity and arterial stiffening may also play a role in sudden cardiac death associated with physical exertion. Physical exertion results in increased cardiac output and increased blood pressure, both of which could increase peak arterial velocity, although the effect of increased cardiac output on peak arterial blood velocity in this situation has not been studied. Increased Reynolds number could lead to acute coronary thrombosis as described above.

The future

Validation of the hemorheologic-hemodynamic theory will require a prospective study to determine if measuring blood viscosity and peak arterial blood velocity identifies subjects at high risk for symptomatic atherosclerosis better than routine markers such as lipid analysis.