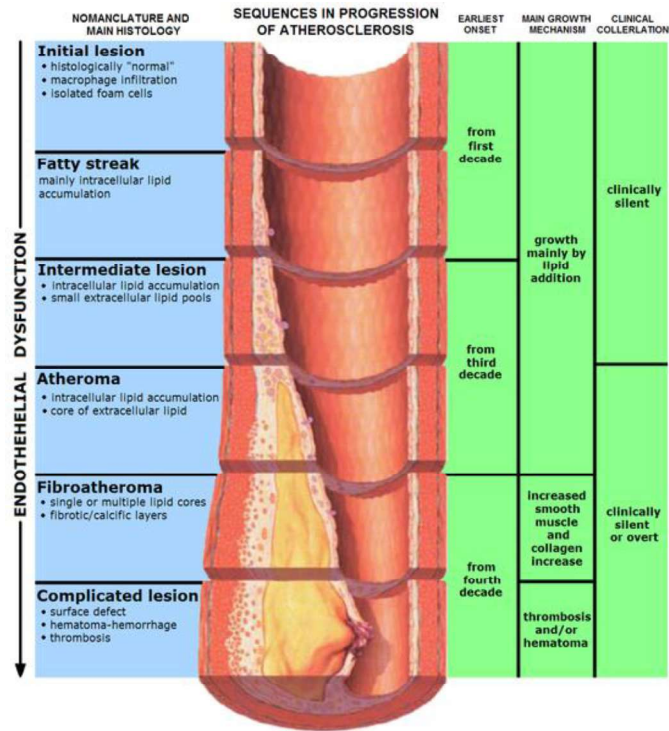# Atherosclerosis information sheet

Atherosclerosis, or athero for short, is the progressive buildup of plaque – fatty deposits and other cells – in the walls of the arteries. Its name comes from the Greek words *athero* (meaning gruel or paste) and *sclerosis* (hardness).

There are two types of plaque that can form in the artery walls:

- **Stable** plaque has a thick fibrous cap made of smooth muscle cells covered by endothelial cells. As plaque grows, it can reduce blood flow to the brain, heart, or other parts of the body.
- **Unstable** plaque is more dangerous because it has a thin cap. As a result, it may rupture, causing an acute, life-threatening thrombosis – when this occurs in the heart it is termed a myocardial infarction, or heart attack.

NOMANCLATURE AND MAIN HISTOLOGY

Initial lesion
- histologically "normal"
- macrophage infiltration
- isolated foam cells

Fatty streak
mainly intracellular lipid accumulation

Intermediate lesion
- intracellular lipid accumulation
- small extracellular lipid pools

Atheroma
- intracellular lipid accumulation
- core of extracellular lipid

Fibroatheroma
- single or multiple lipid cores
- fibrotic/calcific layers

Complicated lesion
- surface defect
- hematoma-hemorrhage
- thrombosis

ENDOTHEHELIAL DYSFUNCTION

SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS

EARLIEST ONSET
- from first decade
- from third decade
- from fourth decade

MAIN GROWTH MECHANISM
- growth mainly by lipid addition
- increased smooth muscle and collagen increase
- thrombosis and/or hematoma

CLINICAL COLLERATION
- clinically silent
- clinically silent or overt

Atherosclerotic cardiovascular disease is the leading cause of death in the world. Atherosclerosis typically begins in early adolescence, and is found in major arteries, yet is asymptomatic and not detected by most diagnostic methods during life. Traditional risk factors for atherosclerosis are high low density lipoprotein (LDL) cholesterol, high blood pressure, family history, diabetes, smoking, obesity, being post-menopausal for women and being older than 45 for men. As the patient ages, arterial plaque can build up and restrict blood flow. Over time this disease can eventually chronically clog the arteries, or result in an acute thrombotic event, limiting or blocking blood flow. According to United States data for the year 2004, for about 66% of men and 47% of women, the first sign of atherosclerotic cardiovascular disease is heart attack or sudden cardiac death (death within one hour of onset of the symptom).

Diagnosis

Areas of severe narrowing, stenosis, detectable by angiography, and to a lesser extent "stress testing" 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.

Consequences

Because plaque tends to build up slowly in the arteries, atherosclerosis may have no symptoms until the artery becomes severely narrowed or completely blocked. The consequences of atherosclerosis can be severe and far-reaching, including:

- **Coronary artery disease** (CAD) can result when blood flow is restricted to parts of the heart. Restricted blood flow may cause chest pain (also called angina) and heart attack, while other complications include post-myocardial infarction heart failure.
- **Stroke and transient ischemic attack** (TIA). Atherosclerosic plaques can rupture generating a thrombus that can travel to the brain. TIAs can occur if blood supply to part(s) of the brain is temporarily blocked but flow is restored before significant damage. Stroke can occur when the blockage persists long enough to impart permanent damage, and can be very serious. TIA often has some of the same symptoms as stroke, although symptoms normally pass within one hour up to 24 hours. It may not be as serious as stroke, but it is considered a warning for future attacks and stroke.
- **Peripheral arterial disease** (PAD) occurs when blood flow to the arms or legs is limited. PAD can cause pain and numbness and, if left unchecked, can result in tissue death or gangrene.
- **High blood pressure or kidney failure,** if atherosclerosis happens in the arteries leading to kidneys.

Treatment options

Living a healthy lifestyle that incorporates good nutrition, weight management and routine physical activity can play a big role in avoiding atherosclerosis. However, for most people, pharmacologic treatment of risk factors, described below, has proven to be a more effective strategy toward cardiovascular disease risk reduction compared with lifestyle modification. 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.

LDL-lowering agents

An elevated level of LDL is a major risk factor for atherosclerosis. Since 1987, statins, or HMG-CoA reductase inhibitors, have been used to reduce LDL cholesterol levels in patients with hypercholesterolemia. Statins have relatively few short- or long-term undesirable side-effects and have become the standard-of-care for treatment of hypercholesterolemia and CAD risk reduction. Several clinical trials comparing statin treatment with placebo have consistently shown strong effects in reducing atherosclerotic disease 'events' (e.g., heart attack) and cardiovascular mortality by about 25-35%.

Relatively newer drugs for hypercholesterolemia include cholesterol absorption inhibitors (e.g., ezetimibe), which modestly reduce LDL cholesterol levels when given as monotherapy, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. The latter class of drugs include therapeutic antibodies (Praluent, Repatha) and small interfering RNA (Leqvio). Both approaches robustly reduce LDL cholesterol, with Leqvio offering the additional convenience of twice-yearly dosing.

Anti-platelet medications.

Anti-platelet medications, such as aspirin, can reduce the likelihood that platelets will clump in narrowed arteries, form a blood clot and cause further blockage.

Primary and secondary prevention

Combinations of statins, intestinal cholesterol absorption-inhibiting supplements (ezetimibe and others, and to a much lesser extent fibrates) have been the most successful in changing common but sub-optimal lipoprotein patterns and group outcomes (although fibrates have not yet been shown to affect outcomes). Recently, a clinical trial with an antibody to the pro-inflammatory cytokine IL-1β, has proven that suppression of inflammation is beneficial in patients with cardiovascular disease and high inflammation. Administration of the antibody, even in patients with good lipid levels, reduced the frequency of cardiovascular events.

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.

Diet and dietary supplements

Dietary, rather than pharmacologic, interventions to achieve benefit have been controversial, generally far less effective and less widely adhered to with success. One 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. From a dietary perspective, the primary driver of hypercholesterolemia is intake of saturated fat.

Facts and Figures

Cardiovascular disease is the leading cause of death and disability worldwide

Enormous patient impact

- 471 million people[1]

- 17.6 million deaths annually[1]
  - 8.9 million from ischemic heart disease[2]

- >200 million years of life lost from premature death

Enormous economic burden

- Nearly $1 trillion globally in 2015[3]

- US costs estimated to exceed $1 trillion by 2035[1]

- 55% are direct healthcare costs

1. Benjamin et al, Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation* 2019; 2. Institute for Health Metrics and Evaluation. Global Burden of Disease. http://ghdx.healthdata.org; 3. Driving Sustainable action for Circulatory Health. White Paper on Circulatory Health. Geneva, Switzerland. Global Coalition for Circulatory Health 2018.