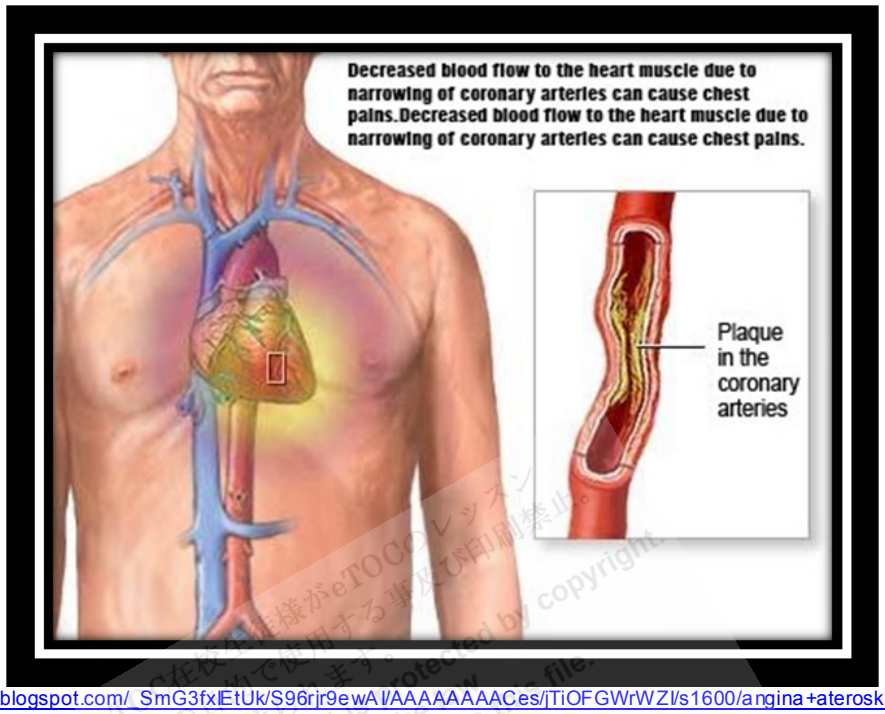
Arteriosclerosis



http://1.bp.blogspot.com/_SmG3fxlEtUk/S96rjr9ewAI/AAAAAAAACes/jTiOFGWrWZI/s1600/angina+atherosklerosis.jpg

Definition of Arteriosclerosis

Arteriosclerosis is a general term for several disorders that cause thickening and loss of elasticity in the arterial wall. Atherosclerosis, the most common form, is also the most serious and clinically relevant because it causes coronary artery disease and cerebrovascular disease. Non-atheromatous forms of arteriosclerosis include arteriolosclerosis and Mönckeberg arteriosclerosis.

*Atherosclerosis is characterized by **patchy intimal plaques** (atheromas) that **encroach** on the lumen of medium-sized and large arteries; the plaques contain **lipids**, inflammatory cells, smooth muscle cells, and connective tissue. Risk factors include **dyslipidemia**, diabetes, cigarette smoking, family history, **sedentary lifestyle**, obesity, and hypertension. Symptoms develop when growth or rupture of the plaque reduces or **obstructs** blood flow; symptoms vary by artery affected. Diagnosis is clinical and confirmed by angiography, ultrasonography, or other imaging tests. Treatment includes risk factor, lifestyle, and dietary modification, physical activity, antiplatelet drugs, and antiatherogenic drugs.*

Atherosclerosis can affect all large and medium-sized arteries, including the coronary, carotid, and cerebral arteries; the aorta; its branches; and major arteries of the

extremities. It is the leading cause of **morbidity** and **mortality** in the US and in most developed countries. In recent years, age-related mortality **attributable** to **atherosclerosis** has been decreasing, but in 2008, cardiovascular disease, primarily coronary and **cerebrovascular atherosclerosis** still caused almost 812,000 deaths in the US (more than cancer and almost 7 times more than injuries). Atherosclerosis is rapidly increasing in **prevalence** in developing countries, and as people in developed countries live longer, incidence will increase. By 2020, atherosclerosis is expected to be the leading cause of death worldwide.

Pathophysiology

The earliest visible lesion of atherosclerosis is the fatty streak, which is an accumulation of **lipid-laden foam cells** in the **intimal layer** of the artery. The hallmark of atherosclerosis is the **atherosclerotic plaque**, which is an evolution of the **fatty streak** and has 3 major components:

- **Lipids**
- Inflammatory and smooth muscle cells
- A **connective tissue matrix** that may contain **thrombi** in various stages of organization and **Ca deposits**

All stages of atherosclerosis—from initiation and growth to complication of the plaque—are considered an inflammatory response to injury mediated by specific **cytokines**. **Endothelial** injury is thought to have a primary initiating or inciting role.

Atherosclerosis preferentially affects certain areas of the arterial tree. **Non-laminar** or **turbulent blood flow** (eg, at branch points in the arterial tree) leads to **endothelial dysfunction** and inhibits **endothelial production** of nitric oxide, a potent vasodilator and anti-inflammatory molecule. Such blood flow also stimulates endothelial cells to produce adhesion molecules, which recruit and bind inflammatory cells. Risk factors for atherosclerosis (eg, **dyslipidemia**, diabetes, cigarette smoking, hypertension), oxidative stressors (eg, **superoxide radicals**), **angiotensin II**, and systemic infection and inflammation also inhibit nitric oxide production and stimulate production of adhesion molecules, **proinflammatory cytokines**, **chemotactic proteins**, and **vasoconstrictors**; exact mechanisms are unknown. The net effect is **endothelial binding** of **monocytes** and **T cells**, migration of these cells to the **subendothelial space**, and initiation and perpetuation of a local vascular inflammatory response. **Monocytes** in the subendothelium transform into macrophages. Lipids in the blood, particularly **low-density lipoprotein** (LDL) and **very-low-density lipoprotein** (VLDL), also bind to **endothelial cells** and are **oxidized** in the **subendothelium**. Uptake of

oxidized lipids and **macrophage** transformation into **lipid-laden** foam cells result in the typical early atherosclerotic lesions called fatty streaks. Degraded **erythrocyte membranes** that result from rupture of **vasa vasorum** and **intraplaque** hemorrhage may be an important additional source of lipids within plaques.

Macrophages elaborate **proinflammatory cytokines** that recruit smooth muscle cell migration from the media and that further attract and stimulate growth of macrophages. Various factors promote smooth muscle cell replication and increase production of dense extracellular matrix. The result is a **subendothelial fibrous plaque** with a **fibrous cap**, made of intimal smooth muscle cells surrounded by connective tissue and intracellular and extracellular lipids. A process similar to bone formation causes calcification within the plaque.

Atherosclerotic plaques may be stable or unstable. Stable plaques regress, remain static, or grow slowly over several decades until they may cause stenosis or occlusion. Unstable plaques are vulnerable to spontaneous erosion, fissure, or rupture, causing acute thrombosis, occlusion, and infarction long before they cause **hemodynamically significant stenosis**. Most clinical events result from unstable plaques, which do not appear severe on **angiography**; thus, plaque stabilization may be a way to reduce morbidity and mortality.

The strength of the fibrous cap and its resistance to rupture depend on the relative balance of collagen deposition and degradation. Plaque rupture involves secretion of **metalloproteinases**, **cathepsins**, and **collagenases** by activated **macrophages** in the plaque. These enzymes digest the fibrous cap, particularly at the edges, causing the cap to thin and ultimately rupture. T cells in the plaque contribute by secreting cytokines. Cytokines inhibit smooth muscle cells from synthesizing and depositing **collagen**, which normally reinforces the plaque.

Once the plaque ruptures, plaque contents are exposed to circulating blood, triggering **thrombosis**; **macrophages** also stimulate thrombosis because they contain tissue factor, which promotes thrombin generation in vivo. One of 5 outcomes may occur:

- The resultant thrombus may organize and be incorporated into the plaque, changing the plaque's shape and causing its rapid growth.
- The thrombus may rapidly occlude the vascular lumen and precipitate an acute ischemic event.
- The **thrombus** may **embolize**.
- The plaque may fill with blood, balloon out, and immediately occlude the artery.

- Plaque contents (rather than thrombus) may embolize, occluding vessels downstream.

Plaque stability depends on multiple factors, including plaque composition (**relative proportion of lipids**, **inflammatory cells**, **smooth muscle cells**, **connective tissue**, and **thrombus**), **wall stress** (**cap fatigue**), size and location of the **core**, and **configuration of the plaque in relation to blood flow**. By contributing to rapid growth and **lipid deposition**, **intraplaque hemorrhage** may play an important role in transforming stable into unstable plaques. In general, unstable **coronary artery plaques** have a high **macrophage content**, a thick **lipid core**, and a thin **fibrous cap**; they narrow the vessel lumen by < 50% and tend to rupture unpredictably. Unstable **carotid artery** plaques have the same composition but typically cause problems through severe stenosis and occlusion or deposition of **platelet thrombi**, which **embolize** rather than rupture. Low-risk plaques have a thicker cap and contain fewer lipids; they often narrow the **vessel lumen** by > 50% and may produce predictable exercise-induced stable **angina**.

Clinical consequences of plaque rupture in coronary arteries depend not only on plaque anatomy but also on relative balance of **procoagulant** and **anticoagulant** activity in the blood and on the vulnerability of the **myocardium** to **arrhythmias**.

A link between infection and **atherosclerosis** has been observed, specifically an association between serologic evidence of certain infections (eg, ***Chlamydia pneumoniae***, **cytomegalovirus**) and **coronary artery disease** (CAD). Putative mechanisms include indirect effects of chronic inflammation in the bloodstream, cross-reactive antibodies, and inflammatory effects of infectious **pathogens** on the **arterial wall**.

Risk Factors

There are numerous risk factors. Certain factors tend to cluster as the metabolic syndrome, which is becoming increasingly prevalent. This syndrome includes **abdominal obesity**, **atherogenic** dyslipidemia, hypertension, insulin resistance, a **prothrombotic state**, and a **proinflammatory state** in **sedentary patients**. **Insulin resistance** is not synonymous with the **metabolic syndrome** but may be key in its **etiology**.

Table 1

Risk Factors for Atherosclerosis

Status	Risk Factor
Nonmodifiable	Age Family history of premature atherosclerosis* Male sex
Modifiable, established	Certain **dyslipidemias** (high total or **LDL** level, low **HDL** level, increased total-to-HDL cholesterol ratio) Tobacco smoking **Diabetes mellitus** Hypertension
Modifiable, under study or emerging	Alcohol intake (other than moderate) Heart transplantation ***Chlamydia pneumoniae* infection** High **CRP** level High level of small, dense LDL High lipoprotein (a) level **Hyperhomocysteinemia** **Hyperinsulinemia** **Hypertriglyceridemia** **5-Lipoxygenase polymorphisms** Low intake of fruits and vegetables Obesity or the metabolic syndrome **Prothrombotic states** (eg, **hyperfibrinogenemia**, **high plasminogen activator inhibitor level**) Psychosocial factors (eg, type A personality, depression, anxiety, work characteristics, socioeconomic status) Radiation therapy to thorax **Renal insufficiency** **Sedentary lifestyle**†

*__Atherosclerosis__ is premature when it occurs in a 1st-degree relative before age 55

for men and before age 65 for women.

†How much this factor contributes independent of other frequently associated risk factors (eg, diabetes, dyslipidemia) is unclear.

CRP = C-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Dyslipidemia (high total, high LDL, or low high-density lipoprotein [HDL] cholesterol), hypertension, and diabetes promote **atherosclerosis** by amplifying or augmenting **endothelial dysfunction** and inflammatory pathways in **vascular endothelium**.

In **dyslipidemia**, **subendothelial uptake** and **oxidation of LDL** increases; oxidized lipids stimulate production of adhesion molecules and inflammatory cytokines and may be antigenic, inciting a T cell–mediated immune response and inflammation in the arterial wall. HDL protects against **atherosclerosis** via reverse cholesterol transport; it may also protect by transporting antioxidant enzymes, which can break down and neutralize oxidized lipids. The role of hypertriglyceridemia in **atherogenesis** is complex, although it may have a small independent effect.

Hypertension may lead to vascular inflammation via angiotensin II–mediated mechanisms. Angiotensin II stimulates **endothelial cells**, **vascular smooth muscle cells**, and **macrophages** to produce **proatherogenic mediators**, including **proinflammatory cytokines**, **superoxide anions**, **prothrombotic factors**, growth factors, and **lectin-like oxidized LDL receptors**.

http://patsfarmacy.files.wordpress.com/2012/03/canstockphoto35182522.jpg

Diabetes leads to the formation of advanced **glycation** end products, which increase the production of **proinflammatory cytokines** from **endothelial cells**. **Oxidative** stress and reactive **O_2 radicals**, generated in diabetes, directly injure the **endothelium** and promote **atherogenesis**.

http://upload.wikimedia.org/wikipedia/commons/thumb/9/94/Bittermelonfruit.jpg/280px-Bittermelonfruit.jpg

Tobacco smoke contains nicotine and other chemicals that are toxic to **vascular endothelium**. Smoking, including passive smoking, increases **platelet reactivity** (possibly promoting **platelet thrombosis**) and plasma **fibrinogen levels** and **Hct** (increasing blood viscosity). Smoking increases LDL and decreases HDL; it also promotes **vasoconstriction**, which is particularly dangerous in arteries already narrowed by **atherosclerosis**. HDL increases by about 6 to 8 mg/dL (0.16 to 0.21 mmol/L) within 1 mo of smoking cessation.

http://t0.gstatic.com/images?q=tbn:ANd9GcSg_G28CUHXeGsjvEo1cyKm_t5QKYLCAwjb8uioNnAyiO1yvdqnbQ

Hyperhomocysteinemia increases risk of **atherosclerosis**, although not as much as the above risk factors. It may result from folate deficiency or a **genetic metabolic defect**. The **pathophysiologic mechanism** is unknown but may involve direct endothelial injury, stimulation of monocyte and T-cell recruitment, LDL uptake by macrophages, and smooth muscle cell proliferation.

Lipoprotein (a) is a modified form of LDL that has a **cysteine-rich** region **homologous** with the fibrin-binding domain of **plasminogen**. High levels of **lipoprotein**(a) may compete with fibrin to bind with plasminogen and thus interfere with **thrombolysis**, predisposing to **atherothrombosis**.

A **high level of small, dense LDL**, characteristic of diabetes, is highly **atherogenic**. Mechanisms may include increased susceptibility to oxidation and nonspecific **endothelial binding**.

A **high C-reactive protein (CRP) level** does not reliably predict extent of atherosclerosis but can predict increased likelihood of ischemic events. In the absence of other inflammatory disorders, it may indicate increased risk of **atherosclerotic plaque rupture**, ongoing **ulceration** or **thrombosis**, or increased activity of lymphocytes and macrophages. CRP may have a direct role in **atherogenesis** through multiple mechanisms, including **downregulation** of nitric oxide synthesis and **upregulation** of **angiotensin** type I receptors, **chemoattractant** proteins, and adhesion molecules.

*C. **pneumoniae*** **infection** or other infections (eg, viral, ***Helicobacter pylori***) may cause **endothelial dysfunction** through direct infection, exposure to **endotoxin**, or stimulation of systemic or **subendothelial inflammation**.

Renal insufficiency promotes development of **atherosclerosis** via several pathways, including worsening hypertension and insulin resistance; decreased **apolipoprotein** A-I levels; and increased **lipoprotein**(a), **homocysteine**, **fibrinogen**, and **CRP** levels.

Accelerated **coronary atherosclerosis** is often observed after heart transplantation and is likely related to immune-mediated endothelial injury. Accelerated coronary atherosclerosis is also observed after thoracic radiation therapy and is likely the result of radiation-induced **endothelial injury**.

Prothrombotic states increase likelihood of **atherothrombosis**.

5-Lipoxygenase polymorphisms (deletion or addition of alleles) may promote atherosclerosis by increasing **leukotriene** production within plaques, which causes vascular **permeability** and **monocyte-macrophage migration**, thus increasing **subendothelial inflammation** and dysfunction.

Documented vascular disease: The presence of **atherosclerotic disease** in one vascular territory increases the likelihood of disease in other vascular territories. Patients with **noncoronary atherosclerotic vascular disease** have cardiac event rates comparable to those of patients with known CAD, and they are now considered to have a CAD risk equivalent and should be treated as aggressively.

Symptoms and Signs

Atherosclerosis is initially **asymptomatic**, often for decades. Symptoms and signs develop when lesions impede blood flow. Transient ischemic symptoms (eg, stable **exertional angina**, **transient ischemic attacks**, **intermittent claudication**) may develop when stable plaques grow and reduce the arterial lumen by > 70%. **Vasoconstriction** can change a lesion that does not limit blood flow into a severe or complete stenosis. Symptoms of unstable angina or infarction, ischemic stroke, or rest pain in the limbs may develop when unstable plaques rupture and acutely occlude a major artery, with superimposition of **thrombosis** or **embolism**. **Atherosclerosis** may also cause sudden death without preceding stable or unstable **angina pectoris**.

Atherosclerotic involvement of the arterial wall can lead to **aneurysms** and arterial **dissection**, which can manifest as pain, a **pulsatile mass**, **absent pulses**, or sudden death.

Diagnosis

Approach depends on the presence or absence of symptoms.

Symptomatic patients: Patients with symptoms and signs of **ischemia** are evaluated for the amount and location of **vascular occlusion** by various **invasive** and **noninvasive tests**, depending on the organ involved (see elsewhere in THE MANUAL). Such patients also should be evaluated for **atherosclerosis** risk factors by using

- History and physical examination
- **Fasting lipid profile**
- **Plasma glucose** and **glycosylated hemoglobin** (HbA_{1c}) levels

Patients with documented disease at one site (eg, **peripheral arteries**) should be evaluated for disease at other sites (eg, **coronary and carotid arteries**).

Because not all **atherosclerotic** plaques have similar risk, various imaging technologies are being studied as a way to identify plaques especially vulnerable to rupture. CT angiography is often used as an initial screening test, but catheter-based tests, including **intravascular ultrasonography** (which uses an ultrasound transducer on the tip of a catheter to produce images of the arterial lumen and wall), **angioscopy**, **plaque thermography** (to detect the increased temperature in plaques with active inflammation), **optical coherence tomography** (which uses infrared laser light for imaging), and **elastography** (to identify soft, **lipid-rich plaques**) are also used. **Immunoscintigraphy** is a noninvasive alternative using radioactive tracers that localize in vulnerable plaque.

Some clinicians measure **serum markers** of inflammation. CRP levels > 3 mg/dL (> 3000 µg/L) are highly predictive of cardiovascular events. High levels of **lipoprotein-associated phospholipase** A2 appear to predict cardiovascular events in patients with a normal or low LDL level.

Asymptomatic patients (screening): In patients with risk factors for atherosclerosis but no symptoms or signs of ischemia, the role of additional testing beyond the fasting lipid profile is unclear. Although imaging studies such as **electron beam** or **multidetector row CT**, **MRI**, and **ultrasonography** can detect atherosclerotic plaque, they probably do not improve prediction of **ischemic events** over assessment of risk factors or established prediction tools (eg, **Framingham risk index**)

Urinary microalbuminuria (> 30 mg albumin/24 h) is a marker for renal disorders and their progression, as well as a strong predictor of cardiovascular and noncardiovascular morbidity and mortality; however, the direct relationship between **microalbuminuria** and **atherosclerosis** has not been established.

Treatment

- Lifestyle changes (diet, smoking, physical activity)
- Drug treatment of diagnosed risk factors
- **Antiplatelet drugs**
- Possibly **statins, ACE inhibitors, β-blockers**

Treatment involves aggressive modification of risk factors to slow progression and induce regression of existing plaques. Recent evidence suggests that LDL should be < 70 mg/dL (< 1.81 mmol/L) in patients with disease or at high risk of cardiovascular events. Lifestyle changes include diet modification, smoking cessation, and regular participation in physical activity. Drugs to treat dyslipidemia, hypertension, and diabetes

are often required. These lifestyle changes and drugs directly or indirectly improve endothelial function, reduce inflammation, and improve clinical outcome. The statins can decrease atherosclerosis-related morbidity and mortality even when serum cholesterol is normal or slightly high. Antiplatelet drugs help all atherosclerotic patients. Patients with CAD may benefit additionally from ACE inhibitors and β-blockers.

http://2.bp.blogspot.com/-EddnMCe98wk/TbvzoDVHyLI/AAAAAAAACJ8/5GGqJqJSRfA/s1600/Heart-Check-America-6.jpg

Diet: Several changes are beneficial:

- Less saturated fat
- No trans fats
- More fruits and vegetables
- More fiber
- Moderate (if any) alcohol

Substantial decreases in saturated fat and refined and processed carbohydrates and increases in carbohydrates with fiber (eg, fruits, vegetables) are recommended. These dietary changes are a prerequisite for lipid control and weight reduction and are essential for all patients. Calorie intake should be limited to keep weight within the normal range.

Small decreases in fat intake do not appear to lessen or stabilize **atherosclerosis**. Effective change requires limiting fat intake to 20 g/day, consisting of 6 to 10 g of **polyunsaturated fat** with ω-6 (**linoleic acid**) and ω-3 (**eicosapentaenoic acid**,

docosahexaenoic acid) fatty acids in equal proportion, ≤ 2 g of **saturated fat**, and the rest as **monounsaturated fat**. **Trans fats**, which are highly **atherogenic**, should be avoided.

http://us.123rf.com/400wm/400/400/torky/torky0911/torky091100003/5839716-bio-food-healthy-heart.jpg

Increasing carbohydrates to compensate for decreasing saturated fats in the diet increases plasma **triglyceride** levels and reduces HDL levels. Thus, any caloric deficiency should be made up with proteins and unsaturated fats rather than simple carbohydrates. Excessive fat and refined sugar intake should be avoided especially in people at risk of diabetes, although sugar intake has not been directly related to cardiovascular risk. Instead, consumption of complex carbohydrates (eg, vegetables, whole grains) is encouraged.

Fruits and vegetables (5 daily servings) seem to decrease risk of **coronary atherosclerosis**, but whether this effect is due to **phytochemicals** or to a proportional decrease in saturated fat intake and increase in fiber and vitamin intake is unclear. Phytochemicals called **flavonoids** (in red and purple grapes, red wine, black teas, and dark beers) appear especially protective; high concentrations in red wine may help explain why incidence of coronary atherosclerosis in the French is relatively low, even though they use more tobacco and consume more fat than Americans do. But no

clinical data indicate that eating **flavonoid-rich** foods or using supplements instead of foods prevents atherosclerosis.

Increased fiber intake decreases total cholesterol and may have a beneficial effect on glucose and insulin levels. Daily intake of at least 5 to 10 g of soluble fiber (eg, oat bran, beans, soy products, **psyllium**) is recommended; this amount decreases LDL by about 5%. **Insoluble fiber** (eg, cellulose, lignin) does not appear to affect cholesterol but may confer additional health benefits (eg, reduced risk of colon cancer, possibly by stimulating bowel movement or reducing contact time with **dietary carcinogens**). However, excessive fiber interferes with the absorption of certain minerals and vitamins. In general, foods rich in phytochemicals and vitamins are also rich in fiber.

Alcohol increases HDL and has poorly defined **antithrombotic**, **antioxidant**, and anti-inflammatory properties. These effects appear to be the same for wine, beer, and hard liquor, and occur at moderate levels of consumption; about 30 mL of ethanol (1 oz, contained in about 2 average servings of typical alcoholic beverages) 5 to 6 times/wk protects against coronary atherosclerosis. However, at higher doses, alcohol can cause significant health problems. Thus, the relationship between alcohol and total mortality rate is J-shaped; mortality rate is lowest for men who consume <14 drinks/wk and women who consume < 9 drinks/wk. People who consume greater amounts of alcohol should cut back. However, clinicians are hesitant to recommend that nondrinkers begin consuming alcohol based on any apparent protective effect.

There is little evidence that dietary supplementation with vitamins, phytochemicals, and trace minerals reduces risk of atherosclerosis. The one exception is fish oil supplements. Although alternative medicines and health foods are becoming more popular, and some may have minor effects on blood pressure or cholesterol, these treatments are not always proven safe or effective and may have negative interactions with proven drugs. Levels of **coenzyme Q10**, which is necessary for the basic functioning of cells, tend to decrease with age and may be low in patients with certain heart and other chronic diseases; thus, coenzyme Q10 supplementation has been used or recommended, but its therapeutic benefit remains controversial.

Physical activity: Regular physical activity (eg, 30 to 45 min of walking, running, swimming, or cycling 3 to 5 times/wk) reduces incidence of some risk factors (hypertension, dyslipidemia, diabetes), CAD (eg, MI), and death attributable to atherosclerosis in patients with and without previous ischemic events. Whether the association is causal or merely indicates that healthier people are more likely to exercise regularly is unclear. Optimal intensity, duration, frequency, and type of exercise

have not been established, but most evidence suggests an inverse linear relationship between aerobic physical activity and risk. Walking regularly increases the distance patients with peripheral vascular disease can walk without pain.

http://1.bp.blogspot.com/-_FjUXUHfiqY/UDk-DRPvc0I/AAAAAAAAATk/vniuf8p9RXo/s1600/aerobics.jpg

An exercise program that involves **aerobic exercise** has a clear role in preventing atherosclerosis and promoting weight loss. Before starting a new exercise program, the elderly and people who have risk factors for atherosclerosis or who have had recent ischemic events should be evaluated by a physician. Evaluation includes history, physical examination, and assessment of risk factor control.

Antiplatelet drugs: Oral **antiplatelet drugs** are essential because most complications result from plaque fissure or rupture, leading to platelet activation and thrombosis. The following are used:

- **Aspirin**
- **Thienopyridine** drugs such as **clopidogrel**, **prasugrel**, and **ticagrelor**

Aspirin is most widely used but, despite its proven benefits, remains underused. It is indicated for secondary prevention and recommended for primary prevention of coronary atherosclerosis in patients at high risk (eg, patients with diabetes with or without atherosclerosis, patients with ≥ 20% risk of cardiac events within 10 yr). Optimal dose and duration are unknown, but 81 to 325 mg po once/day indefinitely is commonly used for primary and secondary prevention. However, 81 mg is preferred because this dose may minimize the risk of bleeding, particularly when aspirin is used in combination with other antithrombotic drugs. In about 10 to 20% of patients taking aspirin for

secondary prevention, ischemic events recur. The reason may be aspirin resistance; assays to detect lack of thromboxane suppression (indicated by elevated urinary **11-dehydrothromboxane B_2**) are being studied for clinical use.

Some evidence suggests that ibuprofen can interfere with aspirin's antithrombotic effect, so other NSAIDs are recommended for patients taking aspirin for prevention. However, all NSAIDs, some more than others, including **COX-2 selective inhibitors** (eg, **rofecoxib**), appear to increase cardiovascular risks.

Clopidogrel (usually 75 mg/day) is substituted for aspirin when ischemic events recur in patients taking aspirin and in patients intolerant of aspirin. **Clopidogrel** in combination with aspirin is effective in treating acute ST-segment and non-ST-segment elevation MI; the combination is also given for 9 to 12 mo after percutaneous intervention (PCI) to reduce risk of recurrent ischemic events. Resistance **toclopidogrel** also occurs. **Prasugrel** and **ticagrelor** are newer and more effective drugs **thanclopidogrel** for coronary disease prevention in select patient groups.

Ticlopidine is no longer widely used because it causes severe **neutropenia** in 1% of users and has severe GI adverse effects.

Other drugs: ACE inhibitors, angiotensin II receptor blockers, statins, and **thiazolidinediones** (eg, **pioglitazone**) have anti-inflammatory properties that reduce risk of atherosclerosis independent of their effects on BP, lipids, and glucose.

ACE inhibitors inhibit the contributions of **angiotensin** to **endothelial dysfunction** and inflammation.

Statins enhance **endothelial nitric oxide production**, stabilize **atherosclerotic plaques**, reduce lipid accumulation in the arterial wall, and induce regression of plaques. Routine use of statins for primary prevention of ischemic events is controversial. However, several well-controlled studies support their use in high-risk patients (eg, patients with diabetes and normal BP and lipid levels and patients with multiple risk factors, including **hyperlipidemia** and/or hypertension). There is also support for the use of statins in patients with normal LDL but high CRP.

Thiazolidinediones may control expression of **proinflammatory genes**, although recent studies suggest that they may increase the risk of coronary events.

Folate (folic acid) 0.8 mg po bid has been previously used to treat **hyperhomocysteinemia** but does not appear to reduce the risk of acute coronary events. Vitamins B_6 and B_{12} also lower **homocysteine levels**, but current data do not justify their use alone or in combination with folate.

Macrolide and other antibiotics given to treat chronic occult *C. **pneumoniae*** infections (and thereby suppress inflammation and theoretically alter the course and manifestations of atherosclerosis) have not been shown useful.

Key Points

- Risk factors include dyslipidemia, diabetes, cigarette smoking, family history, sedentary lifestyle, obesity, and hypertension.
- Unstable plaques often cause < 50% stenosis yet are more prone to rupture and cause acute **thrombosis** or **embolic phenomena** than are larger, stable plaques.
- In **asymptomatic patients**, imaging tests to detect atherosclerosis probably do not help predict ischemic events better than standard assessment of risk factors.
- Stopping smoking, exercising, eating a diet low in saturated fat and refined carbohydrates and high in fiber and possibly consuming omega-3 fatty acids and moderate amounts of alcohol help in prevention and treatment.
- Antiplatelet drugs, and depending on patient factors, statins and/or **ACE inhibitors** also are helpful.

Reference: http://www.merckmanuals.com