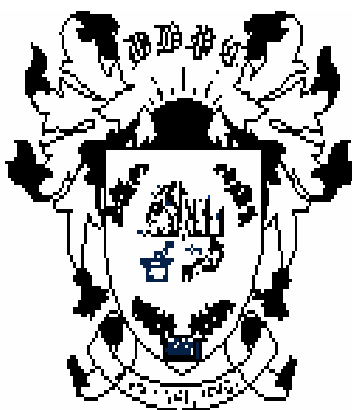


**TREATMENT OF ATHEROSCLROSIS  
AND CORONARY ARTERY DISEASE- A REVIEW**

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**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.

Atherosclerosis is a slow, complex disease that typically starts in childhood and often progresses when people grow older. In some people it progresses rapidly, even in their third decade. Many scientists think it begins with damage to the innermost layer of the artery. This layer is called the endothelium. Causes of damage to the arterial wall include:

- elevated levels of cholesterol and triglyceride in the blood
- high blood pressure
- tobacco smoke
- diabetes

Tobacco smoke greatly worsens atherosclerosis and speeds its growth in the coronary arteries, the aorta and arteries in the legs. (The coronary arteries bring blood to the heart muscle; the aorta is the large vessel that the heart pumps blood through to the body.)

Because of the damage to the endothelium, fats, cholesterol, platelets, cellular waste products, calcium and other substances are deposited in the artery wall. These may stimulate artery wall cells to produce other substances that result in further buildup of cells. These cells and surrounding material thicken the endothelium significantly. The artery's diameter shrinks and blood flow decreases, reducing the oxygen supply. Often a blood clot forms near this plaque and blocks the artery, stopping the blood flow.

**Coronary artery disease** (CAD)(or atherosclerotic heart disease) is the end result of the accumulation of atheromatous plaques within the walls of the coronary arteries that supply the myocardium (the muscle of the heart) with oxygen and nutrients. It is sometimes also called coronary heart disease (CHD), but although CAD is the most common cause of CHD, it is not the only cause. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. When plaque builds up in the arteries, the condition is called atherosclerosis

CAD is the leading cause of death worldwide. While the symptoms and signs of coronary artery disease are noted in the advanced state of disease, most individuals with coronary artery disease show no evidence of disease for decades as the disease progresses before the first onset of symptoms, often a "sudden" heart attack, finally arises. After decades of progression, some of these atheromatous plaques may rupture and (along with the activation of the blood clotting system) start limiting blood flow to the heart muscle.

## **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.

### **Alternative treatment**

1. Herbal medicine: Ginger, Garlic, Pepper.
2. Yoga & relaxation therapy.
3. Vitamin & mineral therapy.
  1. Vit C, E, B Complex, Cr,Mg, Se,Zn.
4. Chinese medicine: Massage & Accupunture.

## **DRUG THERAPY**

### **Anticoagulants**

**Direct thrombin inhibitors** (DTIs) are a class of medication that act as anticoagulants (delaying blood clotting) by directly inhibiting the enzyme thrombin. Some are in clinical use, while others are undergoing clinical development. Several members of the class are expected to replace heparin (and derivatives) and warfarin in various clinical scenarios.

### **Types**

There are two types of DTIs, dependent on their interaction with the thrombin molecule. *Bivalent* DTIs (hirudin and analogs) bind both to the active site and exosite 1, while univalent DTIs bind only to the active site.

### **Bivalent**

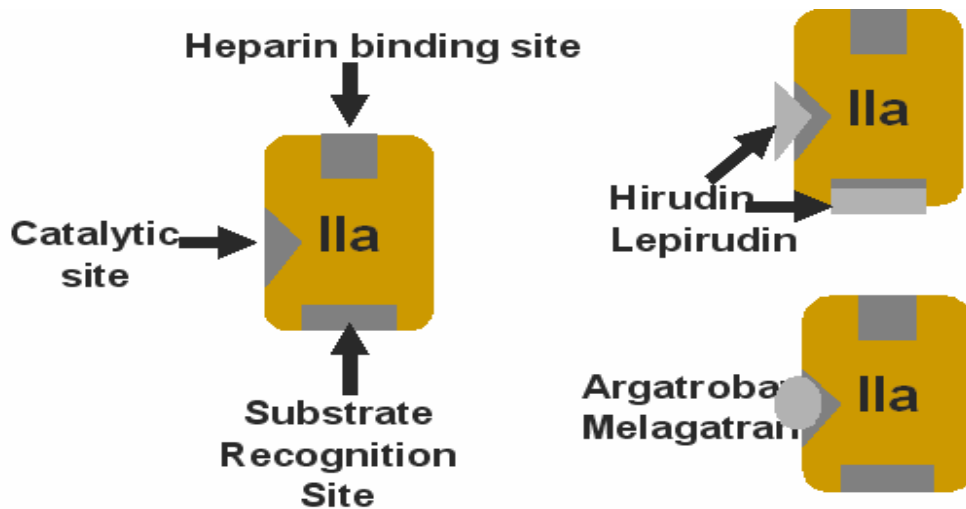
Hirudin and derivatives were originally discovered in *Hirudo medicinalis*:

- Hirudin
- Bivalirudin (transient inhibition - is cleaved by thrombin)
- Lepirudin
- Desirudin

### **Univalent**

Univalent DTIs include:

- Argatroban
- Melagatran (and its prodrug ximelagatran)
- Dabigatran



**Figure 1. Direct Thrombin Inhibitors**

### **Hirudin**

- Powerful & specific thrombin inhibitor, even inhibit clot bound thrombin.
- Obtained from medicinal leech (*Hirudo medicinalis*).
- Different from other anticoagulants :does not interfere with the biosynthesis of clotting factors
- Independent of antithrombin III

### **Lepirudin(Refludian®)**

Recombinant form ( Leu-Thr-63-desulfohirudin)

#### **Mechanism of action**

- ❖ Bind to both catalytic & substrate recognition site
- ❖ Inactivate fibrin bound thrombin in thrombi
- ❖ Independent of antithrombin III

#### **Administered:**

- ❖ Parentrally

#### **Pharmacokinetics**

- ❖ cleared by kidney and not given to patient with renal insufficiency.
- ❖ Binds tightly to the enzyme, forming a slowly reversible complex.
- ❖ Develop antithrombin antibodies, cause increase in aPTT:-daily monitoring is reqd.

### **Bivalirudin (Hirulog or AngiomaxR )**

Specific and reversible direct thrombin inhibitor.

#### **Chemistry & Pharmacology**

- Bivalent inhibitor of thrombin

- An active site-directed moiety, D-Phe-Pro-Arg-Pro, linked via a tetraglycine spacer to a dodecapeptide that interacts with catalytic site on thrombin.
- Only transient inhibition of the active site of thrombin, because, once bound, thrombin cleaves the Pro-Arg bond within the amino-terminal of bivalirudin. Consequently, substrates can compete with cleaved bivalirudin for access to catalytic site.

#### **Pharmacokinetics**

- Plasma half-life(i.v infusion): 25 min.
- Excreted by renal route & Proteolysis

#### **Indications:**

- PTCA

#### **Adverse effect:**

- Bleeding
- back pain
- headache
- Hypotension

#### **Argatroban**

- Small molecular weight compound Binds only to catalytic site

#### **Ximelagatran**

- First oral direct thrombin inhibitor
- Prodrug of melagatran

#### **Pharmacokinetics**

- Well absorbed from GI tract Peak absorption in 15-30 minutes
- Peak levels in 2-3 hours
- Not protein bound
- Half-life 3-4 hours
- Eliminated via kidneys

#### **USES**

Bivalent DTIs enjoy limited use in circumstances where heparin would be indicated but cannot be used, such as the acute coronary syndrome ("unstable angina"). As they are administered by injection (intravenous, intramuscular or subcutaneous), they are less suitable for long-term treatment.

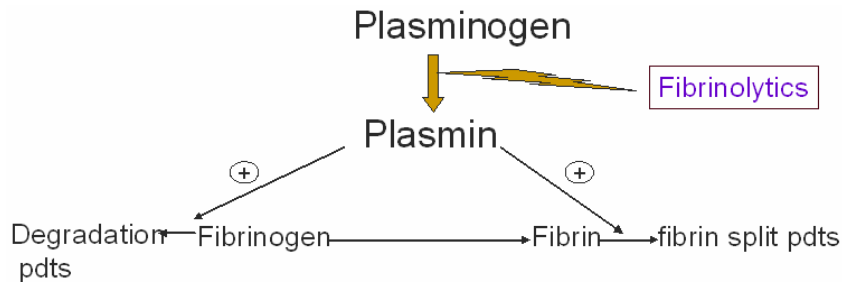
Argatroban (as well as the hirudins) are used for heparin-induced thrombocytopenia, a rare but serious complication of heparin treatment that requires anticoagulation (as it increases both arterial and venous thrombosis risk) but not with the putative agent, heparin.

Ximelagatran showed good efficacy compared with warfarin in several trials in prevention and treatment of deep vein thrombosis and as thromboprophylaxis in atrial fibrillation.<sup>[1]</sup> Development was stopped by manufacturer AstraZeneca, however, because

of reports of liver enzyme derangements and liver failure. Dabigatran is under development for similar indications. Recent studies have indicated Dabigatran is slightly more effective for stroke thromboprophylaxis in the setting of atrial fibrillation than coumadin.

### Fibrinolytics

Recom. tPA



#### 1. Alteplase(Activase) & Duteplase

- Single chain & Double chain r-tPA
- Clot selective
- Non antigenic
- Short half life so i.v infusion

#### 2. Reteplase (r-PA):

Deletion of epidermal growth factor region, the finger domain and kringle1.



longer half life

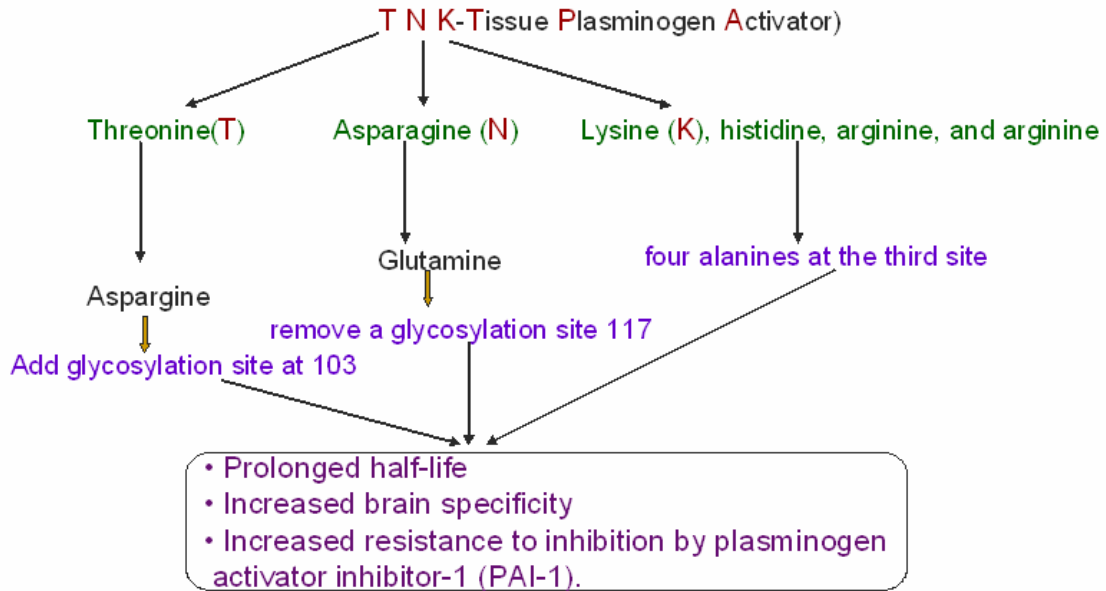
#### 3. Lanoteplase

- Deletion of fibronectin finger-like and epidermal growth factor domains
- Change in 117 AAs: deleted Glycosylation site Prolonged half life-Single bolus dose.

**ADR:** Bleeding, GI Haemorrhage, Stroke

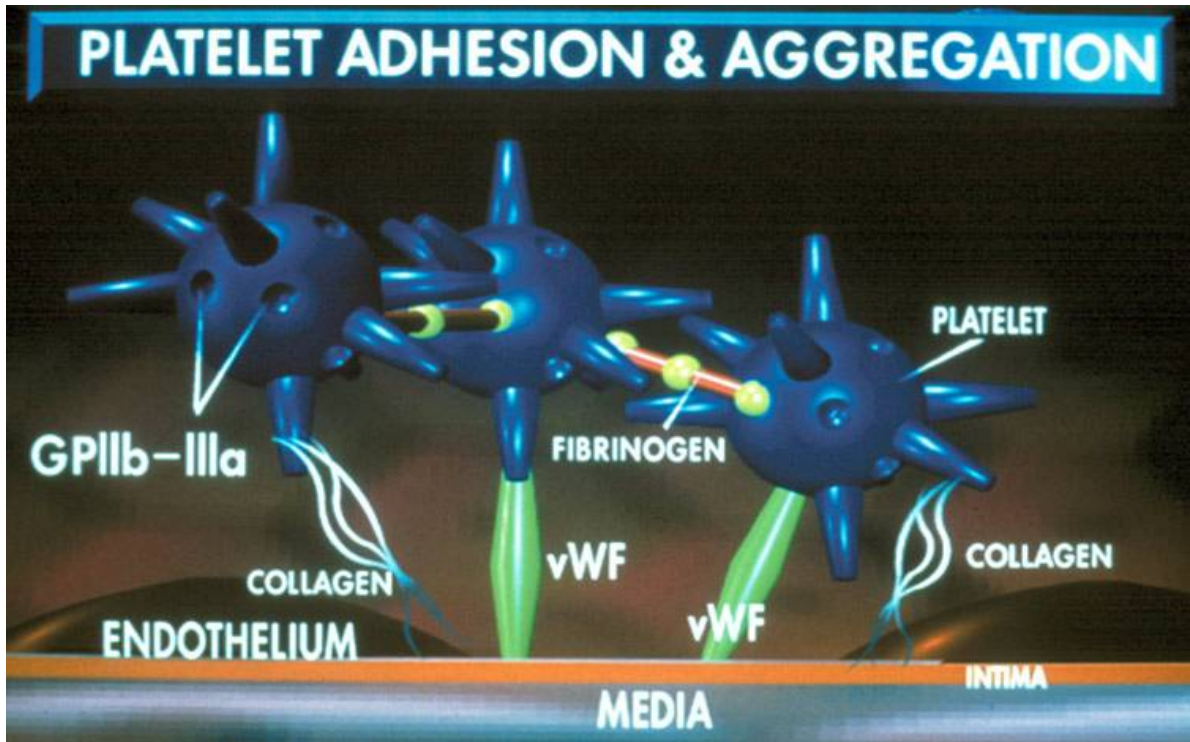
**Contraindications:** Internal bleeding  
Haemorrhagic cerebrovascular disease  
Pregnancy  
Uncontrolled HT

**TNK-tPA**



**ANTIPLATELETS**

GPIIb/IIIa Inhibitors



**Figure 2. Platelet Adhesion & Aggregation**

Fall into 3 chemically distinct groups:

1. Monoclonal Ab (murine) abciximab –
  - Slow dissociation from the receptor (antiplatelet effect last for ~10 hrs after administration) and immunogenic.
  - Binds to other integrin receptors e.g. vitronectin blocking platelet-endothelium and platelet-SMC interactions.
2. Peptide Antagonists (Eptifibatide) – rapid receptor binding/dissociation and high systemic clearance. Only available for IV use.
3. Non-peptide Antagonists (Tirofiban) – developed with a view to oral administration, but have failed to show clinical efficacy by this route.

In medicine, **glycoprotein IIb/IIIa inhibitors**, also **GpIIb/IIIa inhibitors**, is a class of antiplatelet agents.

Several GpIIb/IIIa inhibitors exist:

- abciximab (ReoPro)
- eptifibatide (Integrilin)
- tirofiban (Aggrastat)

### **Abciximab(ReoProRM)**

First GP IIb/IIIa receptor inhibitor

**Other name** : c7E3 Fab

#### **Chemistry & Pharmacology**

Chimeric mouse-human monoclonal antibody directed against the GP IIb/IIIa receptor.

#### **Mechanism of Action:**

steric hindrance of the receptor

inhibits the vitronectin (av b3)receptor

Administered by i.v injection

#### **Clearance :**

- unbound substance via proteolytic cleavage with half life of 30 min
- Bound antibodies remain bound for 18-24hrs after infusion is stopped

#### **Indications:**

- Percutaneous coronary intervention
- Prevent restenosis
- Recurrent MI

#### **Adverse Reaction:**

- Thrombocytopenia



- Hemorrhage
- uncontrolled hypertension
- Vascular malformation
- aneurysm or neoplasm

### **EPTIFIBATIDE (Integrelin)**

#### **Chemistry & Pharmacology**

- Synthetic cyclic heptapeptide
- Physiologic arginine-glycine-aspartate(RGD:-recognition site for integrin Receptor) sequence in adhesive ligands like von Willebrand's factor, fibrinogen, etc
- Lysine-glycine-aspartate amino acid sequence within its structure
- Substitution of lysine for arginine on the binding site in eptifibatide.
- Bound only to  $\alpha$ IIb $\beta$ 3 not to vitronectin receptor

#### **Pharmacokinetic**

- Short half-life: 1 to 2 hours.
- Eliminated by both renal and non-renal mechanisms.

#### **Indications:**

- Angioplastic coronary interventions
- Unstable angina

#### **Adverse reactions**

- Haemorrhagic complications
- Hypotention
- Thrombocytopenia and need for platelet transfusion

#### **Contraindications**

- Thrombolytics in acute myocardial infarction.
- Does not induce antibody formation like that of abciximab
- As an add-on therapy to heparin

### **Tirofiban(Aggrastat<sup>RM</sup>)**

#### **Chemistry & Pharmacology**

Small molecule nonpeptide inhibitor of the platelet glycoprotein (GP) IIb/IIIa receptor and not vitronectin receptor half-life of 2 hours

#### **Indications:**

- safe and effective agent in combination with heparin
- patients with CAD who undergo angioplasty and/or directional coronary atherectomy.
- Warnings: Known thrombocytopenia, concomitant warfarin use, hemorrhagic retinopathy

**Use**

Glycoprotein IIb/IIIa inhibitors are frequently used during percutaneous coronary interventions (angioplasty with or without intracoronary stent placement).

They work by preventing platelet aggregation and thrombus formation. They do so by inhibition of the GpIIb/IIIa receptor on the surface of the platelets. They may also be used to treat acute coronary syndromes, without percutaneous coronary intervention, depending on TIMI risk.

They should be given intravenously. The oral form is associated with increased mortality and hence should not be given. In integrin nomenclature glycoprotein IIb/IIIa is called  $\alpha$ IIb $\beta$ 3.

<b>Class</b>	<b>Drugs</b>	<b>Recent</b>
<b>Anticoagulants</b>	Warfarin, Heparin, LMWH, UFH	Direct Thrombin inhibitors:- hirudin, Lepuridin, Bivaluridin, Agravatran
<b>Fibrinolytics:</b>	Streptokinase, Anistreptase, Urokinase.	Alteplase(t-PA) Retenplase(r-PA), Lanoteplase, TNK-tPA
<b>Antiplatelets</b>	CoxI: Aspirin, Sulphinpyrazone ADPI: Ticlopidine, Clopidogrel PDEI: Dipyridamole, Cilostazole Synthetic prostacyclin Epoprostenol	GPIIB/IIIa INHIBITOR

**Table 1. Classification of Drug Therapy**

**STATINS**

In general, the group of medications referred to as statins has been the most popular and are widely prescribed for treating atherosclerosis. They have relatively few short-term or longer-term undesirable side-effects, and multiple comparative treatment/placebo trials have fairly consistently shown strong effects in reducing atherosclerotic disease 'events' and generally ~25% comparative mortality reduction in clinical trials, although one study design, ALLHAT, (1) was less strongly favorable.

The newest statin, rosuvastatin, has been the first to demonstrate regression of atherosclerotic plaque within the coronary arteries by IVUS (intravascular ultrasound

evaluation) (2). 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.

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 exhibit in childhood at a time before fatty streaks begin forming.

The statins, and some other medications, have been shown to have antioxidant effects, possibly part of their basis for some of their therapeutic success in reducing cardiac 'events'.

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 (3). For example, in the Scandinavian Simvastatin Survival Study (4S), the first large placebo controlled, randomized clinical trial of a statin in people with advanced disease who had already suffered a heart attack, the overall mortality rate reduction for those taking the statin, vs. placebo, was 30%. For the subgroup of people in the trial that had Diabetes Mellitus, the mortality rate reduction between statin and placebo was 54%. 4S was a 5.4-year trial that started in 1989 and was published in 1995 after completion. There were 3 more dead women at trial's end on statin than in the group on placebo drug whether chance or some relation to the statin remains unclear. The ASTEROID trial has been the first to show actual disease volume regression; however, its design was not able to "prove" the mortality reduction issue since it did not include a placebo group, the individuals offered treatment within the trial had advanced disease and promoting a comparison placebo arm was judged to be unethical.

### **PRIMARY AND SECONDARY PREVENTION**

Combinations of statins, niacin, 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. 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. The first of the large secondary prevention comparative statin/placebo treatment trials was the Scandinavian Simvastatin Survival Study. (4S) with over 15 more extending through the more recent ASTEROID trial published in 2006. The first primary prevention comparative treatment trial was AFCAPS/TexCAPS (4) with multiple later comparative statin/placebo treatment trials including EXCEL (5), ASCOT (6) and SPARCL (7-8) While the statin trials have all been clearly favorable for improved human outcomes, only ASTEROID showed evidence of atherosclerotic regression (slight). For both human and animal trials, those which have shown evidence

of disease regression had all utilized more aggressive combination agent treatment strategies, nearly always including niacin.

### **DIET AND DIETARY SUPPLEMENTS**

Vitamin B3, AKA niacin, in pharmacologic doses, (generally 1,000 to 3,000 mg/day), sold in many OTC and prescription formulations, tends to improve (a) HDL levels, size and function, (b) shift LDL particle distribution to larger particle size and (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. (However, careful patient understanding of how to achieve this without nuisance symptoms is needed, though not often achieved.) 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 U.S. 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.

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. 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 stabilisation 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.

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.

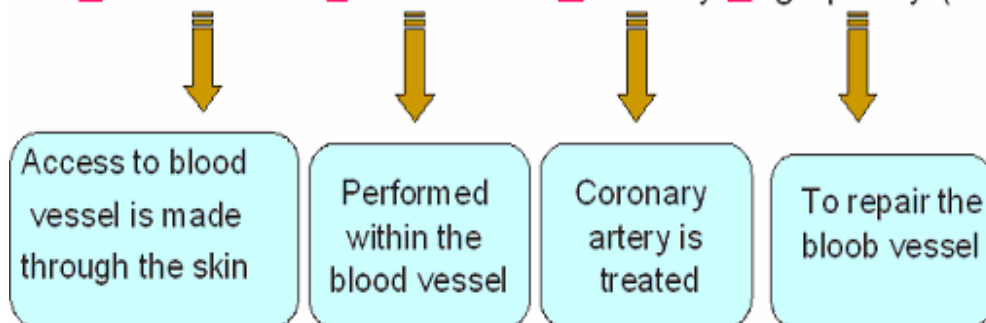
Menaquinone (Vitamin K2), but not phylloquinone (Vitamin K1), intake is associated with reduced risk of CHD mortality, all-cause mortality and severe aortic calcification.

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**

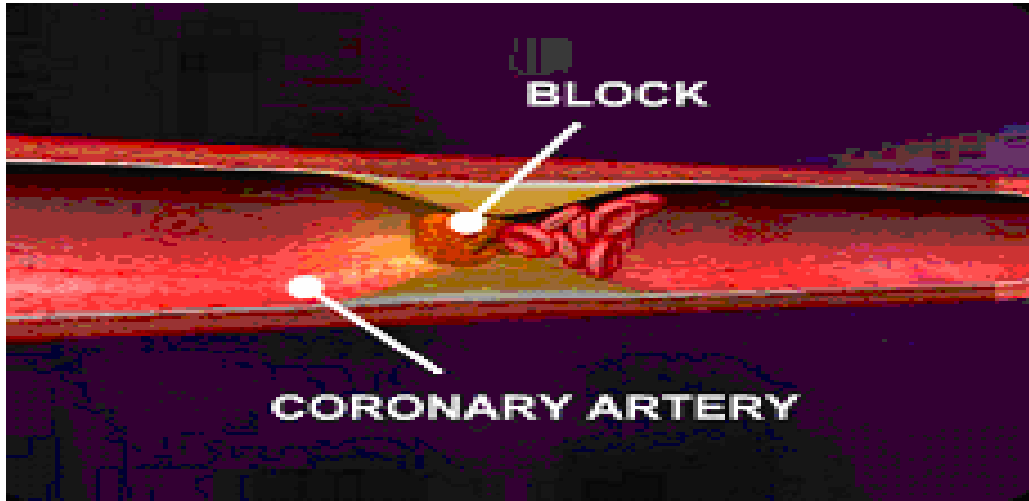
Other physical treatments, helpful in the short term, include minimally invasive angioplasty procedures that may include stents to physically expand narrowed arteries and major invasive surgery, such as bypass surgery, to create additional blood supply connections that go around the more severely narrowed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

#### ■ **P**ercutaneous **T**ransluminal **C**oronary **A**ngioplasty (PTCA)



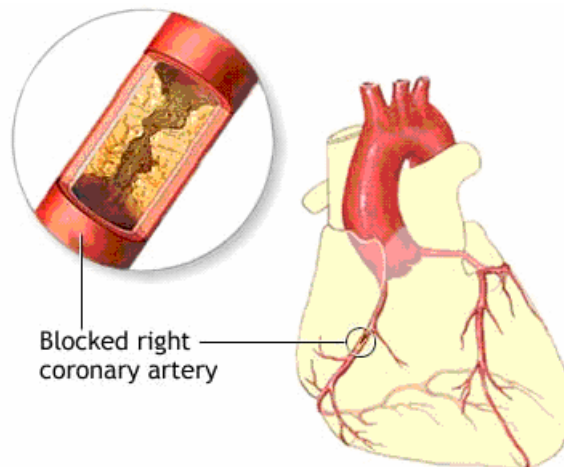
#### ■ **C**oronary **A**rtery **B**ypass **G**rafting (CABG)

### PTCA: BLOCKED CORONARY ARTERY



**Figure 3.** Blocked coronary artery

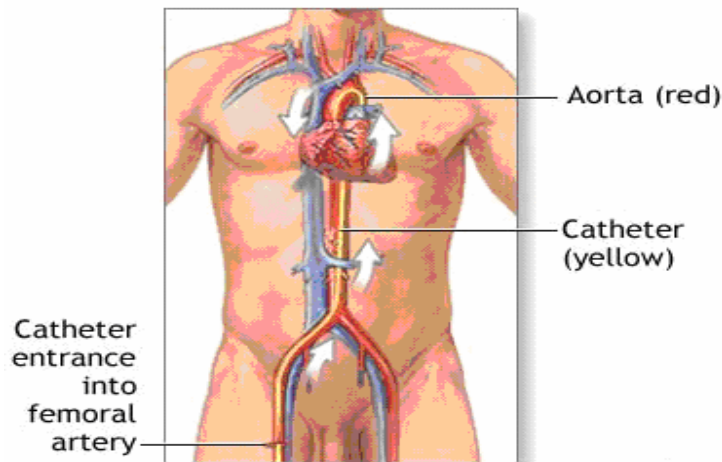
The coronary arteries supply blood to the heart muscle. The right coronary artery supplies both the left and the right heart; the left coronary artery supplies the left heart.



**Figure 4.** Blocked right coronary artery

Fat and cholesterol accumulates on the inside of arteries (atherosclerosis). The small arteries of the heart muscle (the coronary arteries) can be narrowed or blocked by this accumulation. If the narrowing is small, percutaneous transluminal coronary angioplasty, or PTCA for short, may be recommended for treatment. PTCA is a minimally invasive procedure to open up blocked coronary arteries, allowing blood to circulate unobstructed to the heart muscle. The indications for PTCA are:

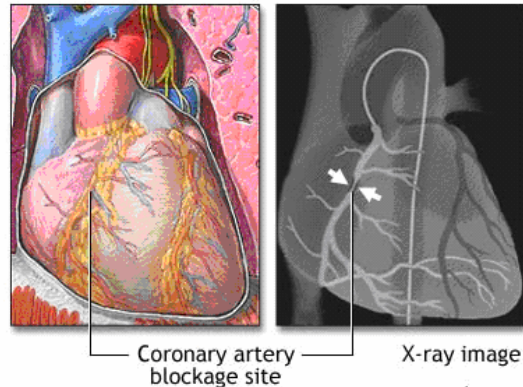
- An acute, full thickness heart attack
- Persistent chest pain (angina) despite medication



**Figure 5. Catheter entrance into femoral artery**

While the patient is awake and pain-free (local anesthesia), a catheter is inserted into an artery at the top of the leg (the femoral artery). The procedure begins with the doctor injecting some local anesthesia into the groin area and putting a needle into the femoral artery (the blood vessel that runs from the heart down the leg). Once the needle is inserted, a guide wire is placed through the needle, into the blood vessel. Following this step, the guide wire is left in the blood vessel and the needle is removed. A large needle called an introducer is then placed over the guide wire and the guide wire is removed.

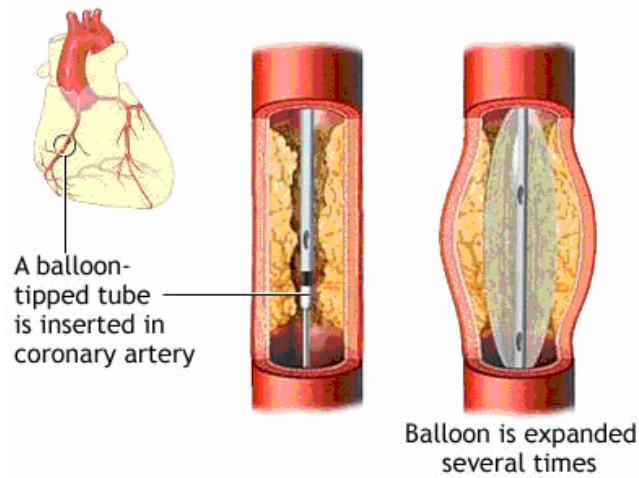
Dye is injected into the coronary arteries



**Figure 6. X-ray image**

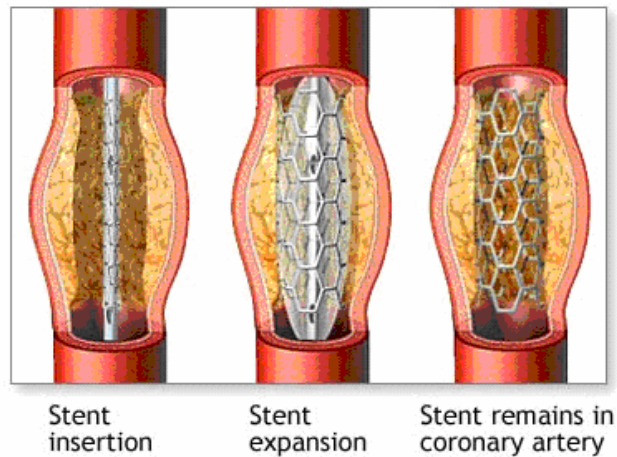
Next, a diagnostic catheter, which is a long narrow tube, is advanced through the introducer over a .035" guidewire, into the blood vessel. This catheter is then guided to the aorta and the guidewire is removed. Once the catheter is placed in the opening or ostium of one of the coronary arteries, the doctor injects dye and takes a series of x-rays.





**Figure 7. A balloon tipped tube**

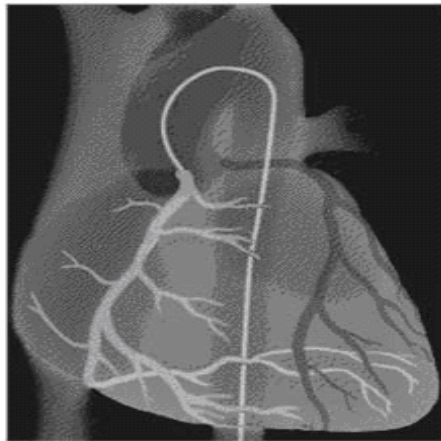
The first catheter is exchanged out over the guidewire for a guiding catheter and the guidewire is removed. A smaller guidewire is advanced across the blocked section of the coronary artery and a balloon -tipped tube is positioned so the balloon part of the tube is beside the blockage. The balloon is then inflated for a few seconds to compress the blockage against the artery wall. Then the balloon is deflated. The doctor may repeat this a few times, each time pumping up the balloon a little more to widen the passage for the blood to flow through. This treatment may be repeated at each blocked site in the coronary arteries.



**Figure 8. Stent remains in coronary artery**

A device called a stent may be placed. A stent is a latticed, metal scaffold that is placed within the coronary artery to keep the vessel open.



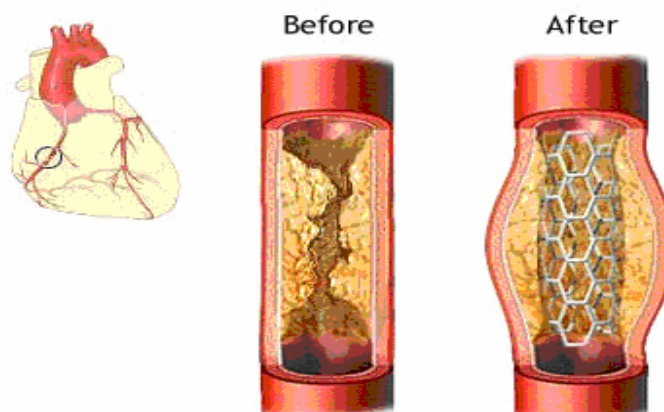


Contrast media  
(dye: in white)  
is injected to  
check the arteries

**Figure 9.** Check the artery

Once the catheter has been positioned at the coronary artery origin, contrast media is injected and a series of x-rays are taken to check for any change in the arteries. Following this, the catheter is removed and the procedure is completed.

This procedure can greatly improve the blood flow through the coronary arteries and to the heart tissue in about 90% of patients and may eliminate the need for coronary artery bypass surgery. The outcome is relief from chest pain symptoms and an improved exercise capacity. In 2 out of 3 cases, the procedure is considered successful with complete elimination of the narrowing or blockage. This procedure treats the condition but does not eliminate the cause, and recurrences happen in 1 out of 3 to 5 cases. Patients need medication, diet, medically directed exercise, and stress reduction measures. If adequate widening of the narrowing is not accomplished, heart surgery (coronary artery bypass graft surgery, also called a CABG) may be recommended.



**Figure 10.** Before and after artery

Before coronary angioplasty is done, your doctor will need to know whether your coronary arteries are blocked. If one or more of your arteries are blocked, your doctor will need to know where and how severe the blockages are.

To find out, your doctor will do an angiogram and take an x-ray picture of your arteries. During an angiogram, a small tube called a catheter with a balloon at the end is put into a large blood vessel in the groin (upper thigh) or arm. The catheter is then threaded to the coronary arteries. A small amount of dye is injected into the coronary arteries and an x-ray picture is taken.

This picture will show any blockages, how many, and where they're located. Once your doctor has this information, the angioplasty can proceed. Your doctor will blow up (inflate) the balloon in the blockage and push the plaque outward against the artery wall. This opens the artery more and improves blood flow.

### **CORONARY BALLOON ANGIOPLASTY**

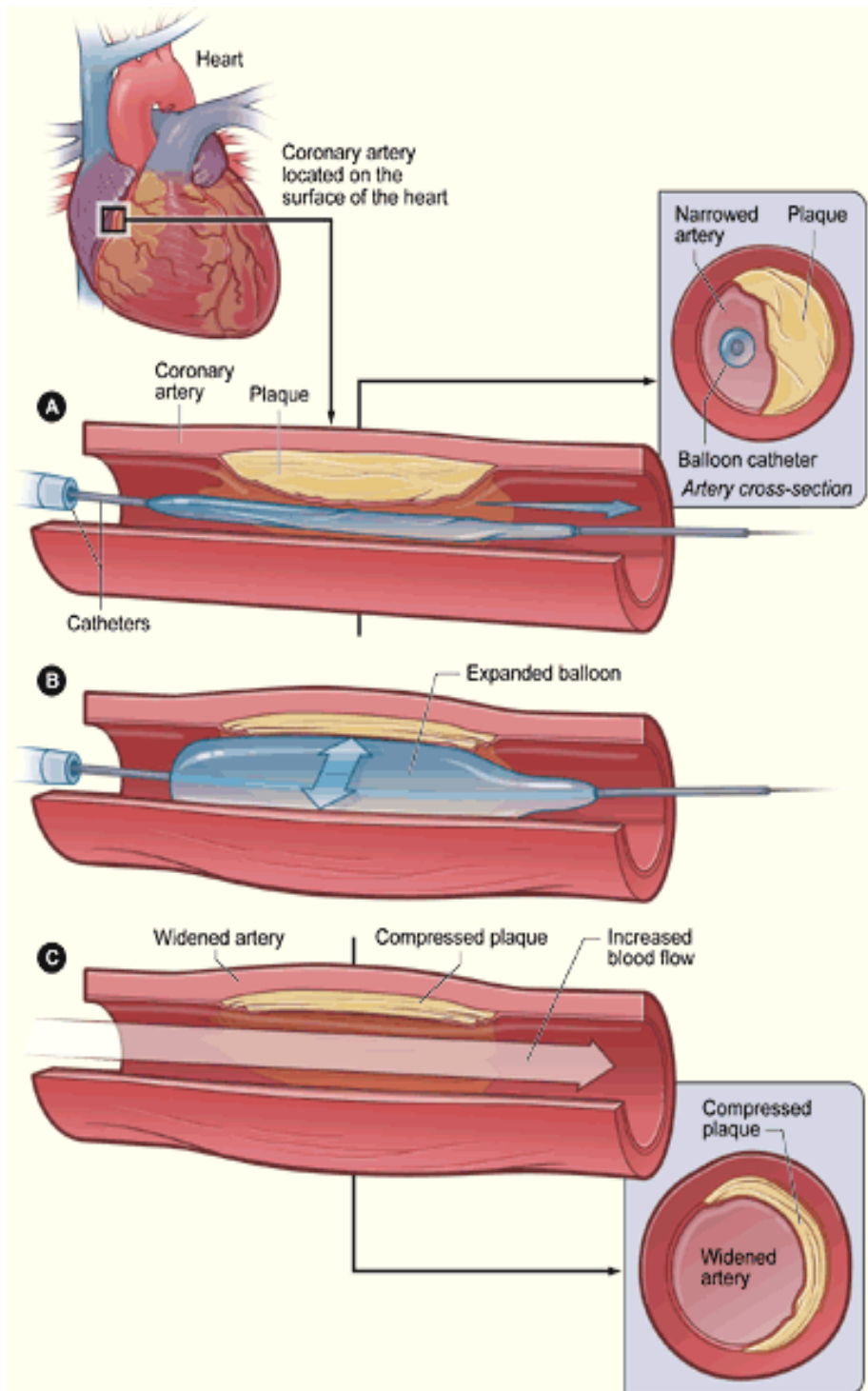
The illustration shows a cross-section of a coronary artery with plaque buildup. The coronary artery is located on the surface of the heart. **Figure A** shows the deflated balloon catheter inserted into the narrowed coronary artery. In **figure B**, the balloon is inflated, compressing the plaque and restoring the size of the artery. **Figure C** shows the widened artery.

A small mesh tube called a stent is usually placed in the newly widened part of the artery. The stent holds up the artery and lowers the risk of the artery renarrowing. Stents are made of metal mesh and look like small springs.

Some stents, called drug-eluting stents, are coated with medicines that are slowly and continuously released into the artery. These medicines help prevent the artery from becoming blocked again from scar tissue that grows around the stent.

The illustration shows the placement of a stent in a coronary artery with plaque buildup. **Figure A** shows the deflated balloon catheter and closed stent inserted into the narrowed coronary artery. The inset image on **figure A** shows a cross-section of the artery with the inserted balloon catheter and closed stent. In **figure B**, the balloon is inflated, expanding the stent and compressing the plaque to restore the size of the artery. **Figure C** shows the stent-widened artery. The inset image on **figure C** shows a cross-section of the compressed plaque and stent-widened artery.

In some cases, plaque is removed during angioplasty. In a procedure called atherectomy (ath-er-EK-toe-me), a catheter with a rotating shaver on its tip is inserted into the artery to cut away plaque. Lasers also are used to dissolve or break up the plaque. These procedures are now rarely done because angioplasty gives better results for most patients.



**Figure 11.** Coronary Balloon Angioplasty

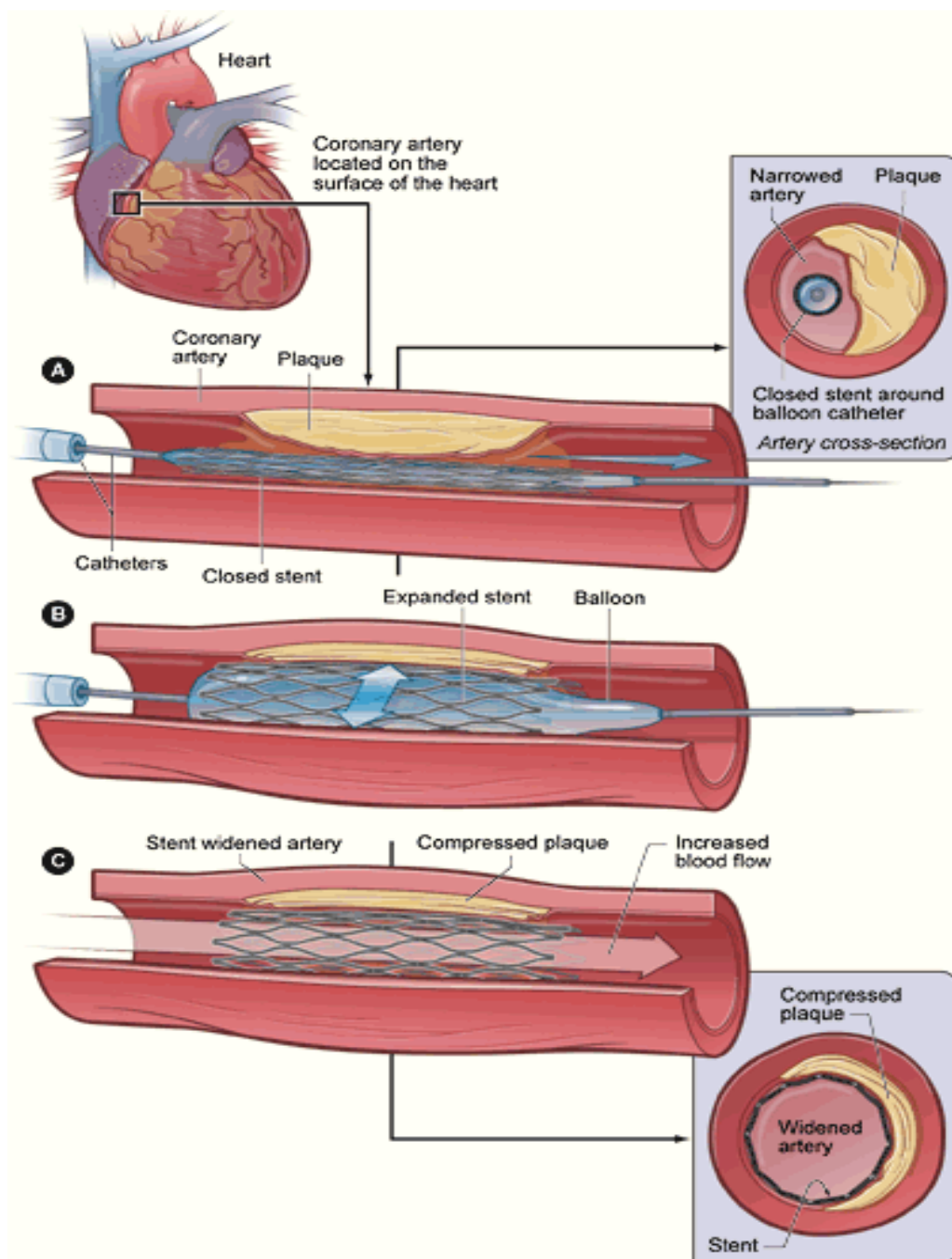


Figure 12. Stent Placement

## 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.

Medical treatments often focus predominantly on the symptoms. 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 are 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.

#### **NEWER DEVELOPMENTS FOR CORONARY STENTS**

##### **1. Intracoronary Radiation( Brachytherapy)**

- Angioplasty of restenosed coronary segment followed by irradiated catheter for several minutes.

##### **2. Drug eluting Intracoronary Stents (FDA approved in 2003)**

- To prevent Restenosis
- Cypher (Johnson & Johnson)
- Endeavor (Medtronic)
- drugs: Paclitaxel
  - Ripamycin
  - Sirolimus

##### **3. Biodegradable stent**

- a. A polymer of poly-L-lactide, polycaprolactone, poly (hydroxybutyrate-hydroxyvalerate), and polyorthoester
- b. withstand up to 1000 mm Hg of crush pressure
  - i. keep its radial strength for 1 month.
- c. The stent was almost completely degraded by 9 months.
- d. optimal vehicle for specific local therapy with drugs or genes

## **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 HDLipoprotein.

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.

However, increasing HDL by any means is not necessarily helpful. For example, the drug torcetrapib is the most effective agent currently known for raising HDL (by up to 60%). However, in clinical trials it also raised deaths by 60%. All studies regarding this drug were halted in December 2006.

The ERASE trial is a newer trial of an HDL booster which has shown promise.

The ASTEROID trial used a high-dose of rosuvastatin—the statin with typically the most potent dose/response correlation track record (both for LDLipoproteins and HDLipoproteins.) 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., *Chlamydia 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 **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 both 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 (see below). 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 Reynold'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 (see below). Additionally, increased peak arterial velocity will augment shear-mediated platelet activation.

#### **Organization of mural thrombi**

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 received 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 (9-10). 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.

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