INTRODUCTION

In cardiac surgery, statins have received Attention with the observation that pretreatment with atorvastatin reduced cytokine release and neutrophil adhesion in patients undergoing Coronary Artery Bypass Grafting (CABG) with Cardiopulmonary Bypass (CPB). Beyond their lipid-lowering actions, statins are known to exert multiple pleiotropic effects including improved endothelial function, plaque stabilization, decrease of inflammatory markers and attenuation of myocardial ischemia-reperfusion injury that can offer direct organ protection and contribute to improved clinical outcome in the early postoperative course. Accumulating evidence from recent trials also suggests that statin use in patients undergoing non-cardiac surgery improves the early postoperative outcome by reducing adverse cardiovascular events and all-cause mortality. (1)

Blood lipid assessments form an essential step in the evaluation of almost every cardiac patient, whether middle-aged or elderly.

Risk factor assessment is integral to the cardiovascular management-of-all-patients, The-widespread, availability, persuasive and substantial clinical database and relative safety of statins have established pharmacological control of lipid as increasingly acceptable strategy. (2)

History

Bruce D. Roth of Ann Arbor, Mich., was honored on 25 March 2003 by the world's largest scientific society for inventing and helping develop the molecule that would become Atorvastatin, the most commonly prescribed drug to lower cholesterol. He received the 2003 ACS Award for Creative Invention from the American Chemical Society at its national meeting in New Orleans. In 1982 it wasn't clear whether lowering plasma cholesterol would have a benefit or that we could do it safely, said Roth. He began work on a class of compounds, originally extracted from fungi that held both promise and challenge in lowering cholesterol averting heart disease and premature death .(1)

The highly complex fungal products, called statins, blocked cholesterol synthesis at a key step. His challenge was to make a molecule that acted the same as statins but was straightforward to assemble. He met that challenge in 1985. Between his discovery and Atorvastatin market debut in 1997, however, were 12 years of more work: first, to make the drug in pure form, then to scale up from laboratory to cost-efficient manufacturing. Only then came the decision to begin human clinical trials. Along the way were entire teams of chemists and others who contributed to Atorvastatin development, he noted. (1)

The trick to his structure was first learning what parts of statins were necessary to work and in what fashion. Then he studied which he could replace with simpler components. The part of Lipitor that anchors the drug in place, for example, went from a highly complicated structure to one that used equally bulky but readily available molecular rings. The drug has since logged more than 36-million patient years of experience and some 400 clinical trials involving more than 80,000 patients to demonstrate its safety and efficacy only till the end of the year 2003. (1)

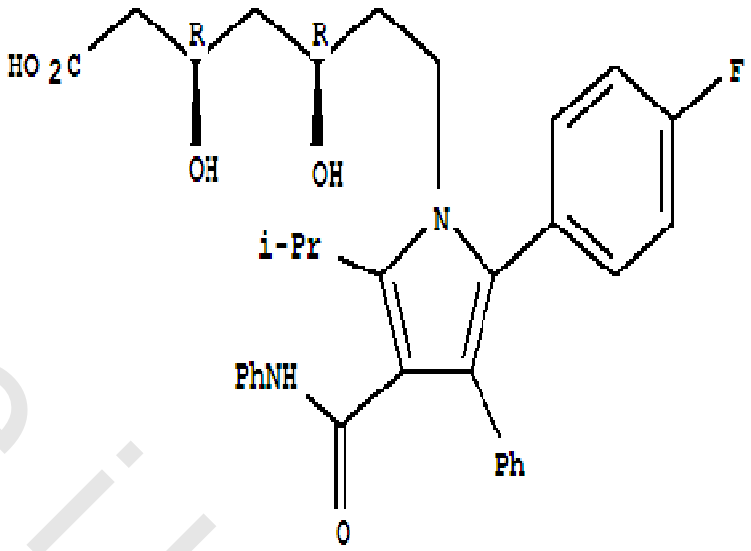

Figure (1): Molecular structure of Atorvastatin.

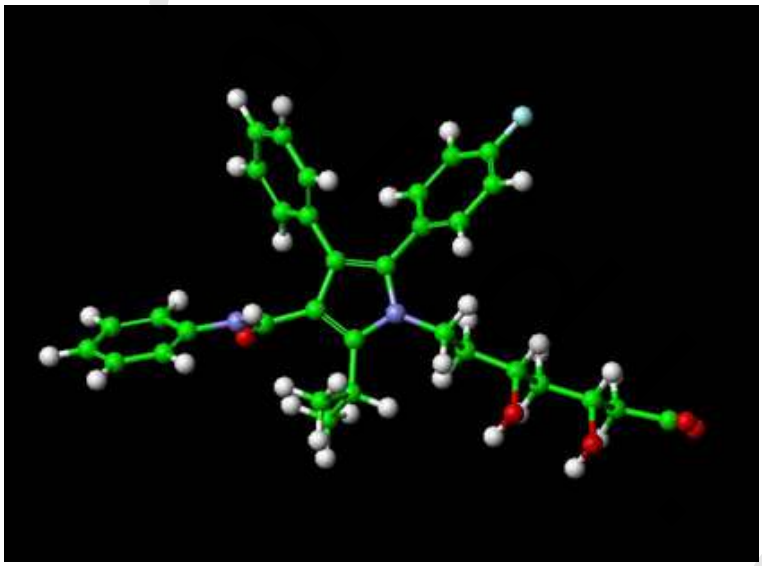

Figure (2): Three dimension Molecular structure of Atorvastatin.

The mechanisms of action of statins:

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase and are the most effective lipid-lowering agents available to clinicians. They exert their action by inhibiting the conversion of 3-hydroxy-3-methylglutaryl coenzyme A into synthesis. In addition to inhibition of mevalonic acid synthesis, statins also decrease the synthesis of other isoprenoid intermediates involved in the cholesterol pathways. The reduction of these intermediate pathways is responsible for the pleiotropic effects of statins that result in clinical benefits which are independent of their lipid-lowering properties. These include improved endothelial function, a reduction in the inflammatory process, and decreased thrombosis and enhanced fibrinolysis. [3]

When a cell is exposed to one of the statins, the function of this enzyme is inhibited and therefore mevalonate and the isoprenoids, it normally creates, are not produced. The alterations in cell function that follow lead to a majority of the effects seen with statin therapy. Many of the results of statin therapy can be reversed when the cells are co incubated with mevalonate, because the downstream products of mevalonate are then replaced [4]. These mechanisms of action of statins are shown in Figure (3)

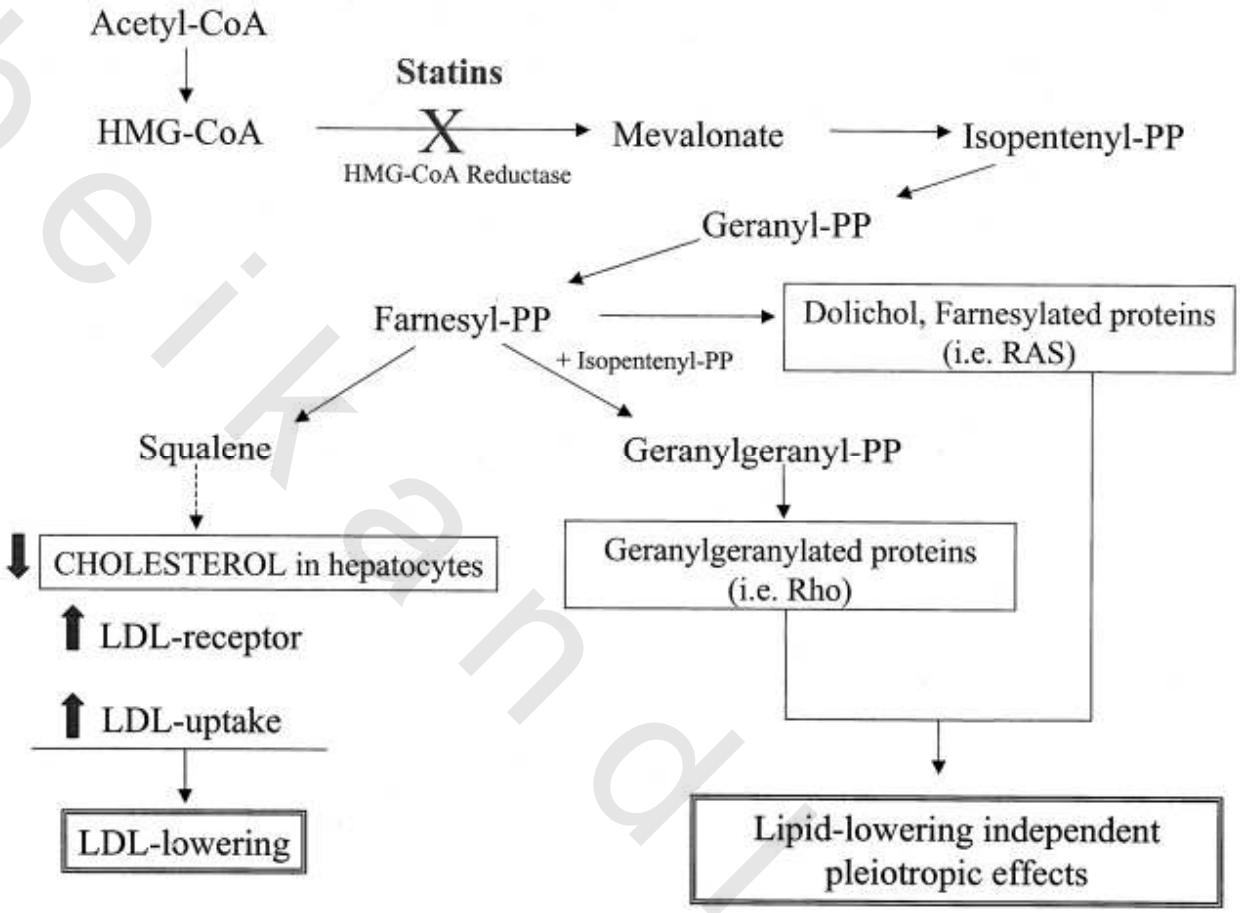

Figure (3): Dual mechanism of action of statins.

Reversible inhibition of 3- hydroxy-3-methylglutaryl (*HMG*)-CoA reductase reduces intracellular mevalonic acid (MVA), which is the precursor of cholesterol and other numerous metabolites (isoprenoids) necessary for relevant cell functions.

The MVA depletion induces the up-regulation of the low-density lipoprotein (*LDL*) receptor expression, mainly in liver cells, which explains most of the LDL cholesterol lowering effect of statins. Conversely, the reduction of specific cellular isoprenoids (geranyl-pyrophosphate, farnesyl pyrophosphate, geranyl geranyl-pyrophosphate) relates to a growing list of antiatherogenic and antithrombotic actions, the so-called "pleiotropic" effects of statins. These include reduction of cholesterol esterification in macrophages, inhibition of smooth muscle cell migration and proliferation, enhancement of nitric oxide and tissue plasminogen activator synthesis, and reduction of endothelin-1 and plasminogen activator inhibitor 1 in endothelial cells, and inhibition of matrix metalloproteinase and tissue factor expression in monocyte. [5]

Pharmacokinetics of statins:

After oral administration, atorvastatin is rapidly absorbed with peak plasma levels occurring within 2 hours .Atorvastatin is about 98% bound to plasma proteins. It is extensively metabolized to hydroxylated and oxidated products. Some of these metabolites are pharmacologically active. Approximately 70% of inhibitory activity of atorvastatin is attributed to these active metabolites .less than 2% of the dose is excreted unchanged in the urine, and the metabolites are eliminated primarily in bile following hepatic and or extra hepatic metabolism. (6)

Indications and contraindications of statins:

Statins are indicated in primary hypercholesterolemia (heterozygous familial and non familial and homozygous familial),as an adjunct to diet to lower plasma levels of cholesterol, LDL and Triglycerides (TG) .Also in cases of mixed hyperlipidemia and hypertriglyceridemia .

Statins are contraindicated in cases of known hypersensitivity to it, active liver disease, unexplained persistent elevations of serum transaminases, pregnancy and lactation.(6)

Side effects

Elevated liver enzymes

Elevation of hepatic transaminases generally occurs in 0.5% to 2.0% of cases, this elevation is dose-dependent. Whether transaminase elevation with statin therapy constitutes true hepato toxicity has not been determined. Progression to liver failure specifically due to statins is exceedingly rare.[7]Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations do not often recur with either re-challenge or selection of another statin. (7) Cholestasis and active liver disease are listed as contraindications to statin use; however, no specific evidence exists showing exacerbation of liver disease by statins. Furthermore, statins have not been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C, and treatment of hyperlipidemia may actually improve transaminase elevations in individuals with fatty liver. (7)

Myopathy

Myopathy is a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life. Myalgia is muscle ache or weakness without creatine kinase (CK) elevation. Myositis is muscle symptoms with increased CK levels. Rhabdomyolysis is muscle symptoms with marked CK elevation (typically greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin). (7)

Statins associated myopathy was in many studies like (PRIMO) Prediction of Muscular Risk in Observational conditions which demonstrated that mild to moderate muscular symptoms with high-dosage statin therapy may be more common and exert a greater impact on everyday lives than previously thought. (8)

Non specific side effects

Cognitive problems

These, too, are widely reported. They include difficulties in concentration, memory impairment and general reduction of cognition. Of real concern is the fact that some cognitive dysfunction can continue when the statin drug is discontinued. [9]

Peripheral neuropathy

Pain and numbness in the extremities like the fingers and toes are also very common. [9]

Other problems

A spectrum of other problems including gastrointestinal side effects, headaches, fatigue (often chronic),elevated blood glucose and tendon problems are linked to statin drug usage. Also listed as adverse effects are pancreatic and sexual problems. [9]

Drug interactions of statins:

Statins have some important drug interactions. The first type of interaction involves the enzymes responsible for the elimination of statins by the liver. Liver enzymes (specifically, the cytochrome P-450 liver enzymes) are responsible for eliminating all statins from the body with the exception of pravastatin and rosuvastatin. Therefore, drugs that block the action of these liver enzymes increase the levels of atorvastatin in the blood and can lead to the development of rhabdomyolysis. Drugs or agents that block these enzymes include: protease (used in treating AIDS), erythromycin, itraconazole, clarithromycin, diltiazem, verapamil and grapefruit juice.

Another important drug interaction occurs between statins and niacin or fibric acids, for example, gemfibrozil , clofibrate , and fenofibrate . Niacin and the fibric acid drugs can cause rhabdomyolysis or liver failure when used alone, and combining them with statins increases the likelihood of rhabdomyolysis or liver failure. Nevertheless, fibric acids and niacin are often used with caution in combination with most statins. Cholestyramine as well as colestipol bind statins in the intestine and reduce their absorption into the body. To prevent this binding within the intestine, statins should be taken one hour before or four hours after cholestyramine or colestipol.Concurrent use of cyclosporines and other immunosuppressive drugs results in increased risk of myopathy also Concurrent use of digoxin with statins increase plasma level of digoxin. [6]

Statins pleiotropic effects

Statins are beneficial both in the primary and secondary prevention of atherosclerotic vascular disease and acute events in a broad spectrum of patient subgroups. However, the observed clinical benefit with statin therapy is much greater than expected through the reduction of cholesterol levels alone. [10]

Clinical and experimental studies suggested that several anti-atherosclerotic effects other than lipid lowering also contribute to the observed benefit of statin therapy. These 'pleiotropic effects' include improvement of endothelial function, antithrombotic actions,

plaque stabilization, reduction of the vascular inflammatory process and anti- oxidation, and many other effects. [10]

Cardiovascular effects

Statins and the Endothelium

The endothelium forms the inner lining of blood vessels and represents a metabolically active system. In addition to its function as a barrier, the endothelium senses and responds to environmental factors and serves as an important organ that regulates the contractile state of blood vessels, blood cell trafficking, and haemostatic balance. [11]

Endothelial dysfunction, as defined by decreased bioavailability of endothelium-derived nitric oxide (eNOS), is one of the earliest manifestations of atherosclerosis.

The anti-atherogenic effects of eNOS include enhancing vascular relaxation and inhibiting platelet aggregation, vascular smooth muscle cell proliferation and leukocyte-endothelial interactions. [11]

Mechanism of action

Statins have been shown to improve endothelial function in patients with hypercholesterolemia and atherosclerosis. This benefit occurs through both cholesterol-dependent and –independent mechanisms.

The cholesterol-dependent mechanism is evident in patients after LDL apheresis, which removes plasma LDL particles physically. These patients show rapid improvement in endothelium-dependent vasomotion through acute reduction in serum cholesterol levels. [12]

The cholesterol- independent mechanism has been linked to the up regulation of eNOS by statins. Statins can up regulate eNOS by several different mechanisms.

First, statins increase the stability of eNOS mRNA, thereby leading to increased eNOS expression.

Another mechanism is through their effects on caveolin-1.which is an integral membrane protein that binds to eNOS and thereby inhibit NO production directly. [12]

Atorvastatin has been shown to reduce caveolin-1abundance leading to restoration of eNOS activity in endothelial cells. [11]

Several studies demonstrated that the effect of statins on the vascular wall, which include improved endothelial function as well as antioxidant and have reported improvement of arterial stiffness by the antioxidant and anti-inflammatory effects of statin therapy in patients with or without hypercholesterolemia. [13]

Preoperative atorvastatin treatment in patients with coronary artery disease increases plasma NO levels before and after reactive hyperemia prior to CABG surgery. [14]

Intensive statins therapy improve the outcome of small diameter vascular prosthesis, atorvastatin treatment (30 mg/d) could accelerate the re-endothelialization process and improve the patency rate in infrarenal abdominal aorta-expanded polytetrafluoroethylene (ePTFE) bypass model. ([15])

Statins and thrombosis:

Hypercholesterolemia is associated with an enhanced thrombotic state and a reduction in fibrinolysis. When patients are treated with statins, an antithrombotic effect and an increase in fibrinolysis occur. Additionally, increased cholesterol levels are associated with increased platelet-dependent thrombin generation, and pravastatin therapy normalizes this thrombin production. **[16]**

Seventy patients with the metabolic syndrome who were not taking antiplatelet agents were assigned consecutively to 1of 6 statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin) or to a no-statin group for 6 weeks. Platelet expression of intact (SPAN12 antibody) and cleaved (WEDE15) PAR-1 thrombin receptors were assessed by flow cytometry at baseline and at weeks 4 and 6 of treatment with an average value of 22% to 37%.[16]

At baseline, no difference was found in receptor expression. However, after 4 weeks of treatment, all statins had significantly inhibited (46% to 55%) the activated epitope of PAR-1 expression. After 6 weeks, inhibition remained.

In conclusion, all statins inhibited the activity of the platelet PAR-1 thrombin receptor, which has a major role in regulating platelet activity and thrombin formation. [17]

Short term administration of atorvastatin in HF patients decreased significantly the plasma concentrations of antithrombin III, protein C and factor V. It is possible that this beneficial effect is exerted by direct action of statins on hepatocyte function or by modulating the host proinflammatory cytokine profile. [18]

In 120 patients with STEMI patients, 80 (67%) received statins while 40 (33%) did not. platelet reactivity was studied on admission and 72 hours later. The investigators concluded that in acute myocardial infarction patients, statins have an early antiplatelet effect, in addition to that afforded by standard antiplatelet therapy, the extent of platelet inhibition was unrelated to patient characteristics, including lipid profile and type of statin administered (lipophylic vs. hydrophilic) . [19]

Statins and myocardium

Cardiac hypertrophy leading to heart failure is a major cause of morbidity and mortality worldwide. Statins, have been shown to inhibit cardiac hypertrophy, increase angiogenesis and myocardial perfusion, decreased myocardial apoptosis, and improvement in endothelial and improve symptoms of heart failure. [20]

In 63 symptomatic, non-ischemic dilated cardiomyopathy patients, those randomized to simvastatin for 14 weeks showed improvements in cardiac function, neurohormonal imbalance and markers of inflammation, compared to placebo. [21]

In a cohort of 551 patients with ischemic and non-ischemic heart failure (LVEF 40% or less), statin use was associated with improved survival without the necessity for urgent heart transplantation. [22]

A retrospective, analysis of all surviving patients from the OPTIMAL study (which compared losartan and captopril), showed that initiation of B-blocker and statin treatment early after MI complicated by heart failure was associated with reduced morbidity and mortality.[23]

Statins and atherosclerosis

Atherosclerosis is a complex inflammatory process that is characterized by the cross-talk between excessive inflammation and lipid accumulation. In the presence of monocytes, macrophages and T-lymphocytes, inflammatory cytokines are secreted and subsequently modify endothelial function, SMC proliferation, collagen degradation, and thrombosis. [13]

The early step in atherogenesis is characterized by an inflammatory response to injury, and involves the recruitment of monocytes to the artery wall, followed by penetration into the subendothelial space. [24]

Simvastatin on Atherosclerosis Progression (ASAP) trial, showed greater reductions in hs-CRP with statins therapy associated with significantly greater decreases in carotid intima media thickness. [25]

The Reversal of Atherosclerosis with Lipitor (REVERSAL) trial has demonstrated the effects of aggressive (atorvastatin 80 mg/d) vs moderate (pravastatin 40 mg/d) lipid lowering therapy on coronary atherosclerosis regression or progression using intravascular ultrasound. Intensive therapy was associated with no progression in atheroma volume whereas progression persisted with moderate therapy [26].

Statins and platelets:

Activated platelets have a critical role in acute coronary syndromes through the release of factors involved in development of platelet recruitment, cell aggregation, and thrombosis. [4]

Two of the factors released by activated platelets, adenosine diphosphate (ADP) and adenosine triphosphate (ATP), induce locomotive activity in neutrophils. Additionally, ADP induces granule release from platelets and increases thromboxane A2 (TxA2) production, which is associated with vasoconstriction. Statins are known to decrease platelet aggregation and decrease TxA2 production. [27]

Prostaglandin F2-like compounds increase platelet activity. These compounds can be formed non enzymatically by free radical attack of arachidonic acid in cell membranes. These free radicals are formed by a process involving oxidation. This is a major point, because patients with atherosclerotic disease have increased oxidant tone. Statins decrease platelet activity by exerting antioxidant effects. [4]

Preoperative control of hypercholesterolemia with simvastatin seems to significantly reduce the incidence of postoperative thrombocytosis.

Unfortunately, these data are not still corroborated by subsequent investigations. Studies on the effects of statins on platelet function provided contrasting results. In some studies, but not in others simvastatin reduced platelet aggregation. Fluvastatin was reported to slightly reduce platelet aggregation, but pravastatin was ineffective. [28]

The magnitude of vessel injury may determine the ability of a statin to prevent the formation of platelet thrombus in vivo. In fact, atorvastatin significantly diminishes platelet deposition on a mildly damaged but not on a severely injured vessel wall. These data suggest that statins may prevent platelet attachment to eroded vessels, reducing the thrombotic risk associated with erosions of the luminal surface. The implications of these findings on CABG patients are evident, at least on a theoretical basis. [29]

Statins and atheroma progression:

The association between hyperlipidemia and aggravation of graft vessel disease has long been recognized. High levels of circulating lipoproteins enhance atheroma formation, at least by increasing the number of SMC- and macrophage-derived foam cells. Conversely, lipid lowering by itself ameliorates the rate and extent of this change. Although the potent hypocholesterolemic effect of statins may explain the inhibitory effect of these drugs on lipid accumulation, some statins also show antioxidant properties, which may reduce LDL oxidation.

Therefore, statins may reduce atheroma development by affecting lipoproteins not only quantitatively but also qualitatively .[30]

Statins and plaque rupture:

Atherogenesis begins with accumulation of low-density lipoprotein (LDL) cholesterol in the endothelial space of blood vessels, followed by its oxidation. After this process, chemotactic factors that attract leukocytes to the vessel wall are released. The monocytes/macrophages drawn to the vessel wall are believed to induce plaque rupture because they produce enzymes, such as matrix metalloproteinases (MMPs), which weaken the plaque's fibrous cap and lead to rupture. In addition to these enzymes, macrophages also produce intimal tissue factor (TF), a potent procoagulant known to induce thrombosis. Statin therapy leads to a reduction in the number of macrophages that interact with atherosclerotic plaque. Fewer macrophages lead to a decrease in MMPs and TF, thereby likely reducing the incidence of plaque rupture. [31]

Pathological studies of acute coronary syndromes have reported that the erosion or rupture of coronary plaque followed by superimposed thrombosis and vasospasm is the principal mechanism that leads to ischemia. Plaque content is a major prognostic factor for plaque stability.

Histologic studies of ruptured plaques reinforce the concept that a plaque with high lipid content is more unstable and prone to rupture. Ruptured lesions contained a soft lipid-rich core, covered by a thin cap of fibrous tissue infiltrated with foam cells. [31]

A hypothesis devised by ***Zhao*** and co-workers proposed that statins increase plaque stability by decreasing the lipid content of vulnerable lipid-rich lesions, which then causes the lesions to regress. Plaque regression was demonstrated by comparing, by means of

magnetic resonance imaging, the carotid arteries of patients treated with statins versus a comparable, untreated group. [32]

Statins strongly intervene in the body's cell metabolism. They therefore have an accordingly wide range of effects on the body, and risks are associated their intake. Statins inhibit the synthesis of cholesterol in the liver. "NO" is released in the blood vessels (see the sections on "oxidative stress"). Statins block cell respiration, obstructing the production of energy in the cell and stimulating the process of aging. They influence growth and differentiation in various cells, which suggests they may influence the development of cancer.

Cholesterol is an extremely important substance for the human body. It is an essential substance for the membranes of all cells in the body. Cholesterol is an effective "radical scavenger" and protects the organism against the destructive attacks of the "superoxide radicals". Cholesterol is the origin of cortisone produced in the body and of all sexual hormones, male and female. 20% of our brain consists of cholesterol; nerve and brain function are dependent on cholesterol. It doesn't sound too good when one hears the body is only to be allowed small portions of this very important substance.

Nearly everyone has heard of "good" ("HDL") and "bad ("LDL") cholesterol. HDL cholesterol protects against oxidative attacks of oxygen radicals. LDL cholesterol is neither "good" nor "bad", it is simply "innocent". "LDL" is not damaging. Only when "LDL" is oxidized by super oxide radicals does it heat up the oxidative fire. Only "ox-LDL" is potentially damaging. To avoid "ox-LDL" accumulating, it makes little sense to demonize "LDL" and cholesterol as a whole. [95]

For example, in the Scandinavian Simvastatin Survival Study (4S) trial, which studied patients with very high levels of low-density lipoprotein cholesterol (LDL-C and known coronary heart disease (CHD), a significant risk reduction was observed with statin treatment. A greater percentage of patients on placebo (28%) experienced a major cardiovascular event than did patients on statin therapy (19%), and the relative risk of a major cardiovascular event in the statin-treated patients was 0.66. On the other hand, those results from 4S also indicate that, over the 5 years of the study, almost 20% of statin-treated patients still had a cardiovascular event. In several major statin trials, significant residual cardiovascular risk remained even after significant reductions in LDL-C had been achieved.

Residual cardiovascular risk is undoubtedly multifactorial, and likely due to a variety of both traditional and emerging risk factors. However, recent evidence suggests the important contribution to cardiovascular risk of lipid parameters beyond LDL-C, such as high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C). For example, Genest et al. reported that although 34% of patients with premature heart disease had LDL-C levels > 160 mg per dL, more than half of the patients with premature heart disease (57%) had low HDL-C levels. Additionally, it has been reported that, in both male and female patients with premature coronary artery disease (CAD), the greatest risk factor is actually low HDL-C levels, though these individuals often possess high TG levels, as well. Although this study had small sample sizes (n = 87 men; n = 15 women), men and women with premature CAD had LDL-C values of approximately 130 mg per dL, which is

near the average LDL-C level in the United States today. Conversely, the study found that TG levels were significantly higher and HDL-C levels were significantly lower in men and women with premature CAD, compared with patients from the Framingham Offspring Study who were free of CHD at baseline.

In addition, a shift in the lipid parameters of patients with CHD has been observed. In past decades, the most frequently seen coronary care unit patient was probably a male cigarette smoker who suffered a myocardial infarction (MI) and who had an LDL-C level near 170 mg per dL. In more recent years, the profile of patients has changed; the average LDL-C level of an MI survivor today is 130 mg per dL, which is similar to the average LDL-C level in individuals without CHD.

Although LDL is recognized as the most important atherogenic lipoprotein, elevations in TG levels can be considered a marker for atherogenic remnant lipoproteins. VLDL-C and other TG-rich lipoproteins are able to enter the artery wall and initiate atherosclerotic processes and aid in foam cell formation just as LDL can. Because VLDL-C is the most readily available measure of atherogenic remnant lipoproteins, it is often combined with LDL-C to improve cardiovascular risk prediction (i.e., VLDL-C + LDL-C = non-HDL-C). When serum TG levels are elevated, the measure called non-HDL-C better represents the concentrations of all atherogenic lipoproteins than does LDL-C. [(18)]

In the previously mentioned PROVE IT-TIMI 22 trial, intensive and normal statin therapy were compared to examine a combination of LDL-C and TG levels on cardiovascular risk in patients with ACS. Participants in the study were randomized to either atorvastatin (80 mg) or pravastatin (40 mg) within days of their cardiac event and then were followed for the next 2 years.

The trial demonstrated that an LDL-C level < 70 mg per dL was associated with a greater degree of CHD event reduction than was an LDL-C level < 100 mg per dL. Further, the relationship between on-treatment levels of TG and LDL-C and the composite end point of CHD events (death, MI, and recurrent ACS) were assessed 30 days after initial presentation. Between the initial day 30 time point and the 2-year follow-up, significantly fewer CHD events occurred in patients who had an LDL-C level < 70 mg per dL than in patients who had an LDL-C level ≥ 70 mg per dL (HR = 0.81; P = 0.015). Similarly, significantly fewer events occurred in patients with a TG level < 150 mg per dL than in those patients with a TG level ≥ 150 mg per dL, as revealed through univariate analysis (HR = 0.73; P < 0.001). Even in multivariate analysis, after adjustment for age, gender, high LDL-C, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment effect, the HR associated with low on-treatment TG (< 150 mg per dL) versus TG ≥ 150 mg per dL was 0.80 (P = 0.025). In univariate analysis, it appeared that for each 10 mg per dL reduction in on-treatment TG, the incidence of CHD events was reduced by 1.8% (P < 0.001). In multivariate analysis, it also appeared that there was a significant effect of TG level on CHD event rate.

A Cox proportional hazards model was used to examine further the relationship between achieved LDL-C and TG at the initial day-30 time point and risk of recurrent CHD events in the PROVE IT-TIMI 22 trial. Compared with referent levels of LDL-C (≥ 70 mg per dL) and TG ≥ 150 mg per dL), lower CHD risk was observed with low on-treatment TG (< 150 mg per dL) and LDL-C (< 70 mg per dL) (HR = 0.72; P = 0.017), with a graded trend observed among patients with LDL-C levels ≥ 70 mg per dL and TG <

150 mg per dL (HR = 0.85; P = 0.180).34 Patients with a TG level < 150 mg per dL, even if they had LDL-C levels > 70 mg per dL, experienced CHD event rates 15.0% lower than those patients who had low LDL-C but high TG. Additionally, when TG levels were < 150 mg per dL, having a lower LDL-C was beneficial compared with higher LDL-C levels; however, in patients with TG levels < 150 mg per dL LDL-C level did not appear to have as large an effect. The benefits conferred through reductions of LDL-C by statin therapy in the PROVE IT-TIMI 22 trial could be modulated by either having a TG level < 150 mg per dL, or having a TG level > 150 mg per dL. Thus, among patients receiving statin therapy after ACS, on-treatment TG level < 150 mg per dL was associated with a lower risk of recurrent CHD events independent of the level of LDL-C. These data support the concept that achieving low levels of both LDL-C and TG may be an important therapeutic strategy in patients after an ACS. [18]

Statins and vasoactive factors:

The propensity of the graft to vasoconstriction may not only reduce lumen diameter and relative blood supply to the myocardium but also determine acute flow changes leading to thrombotic phenomena. A series of in vitro and in vivo studies demonstrate that up-regulation of endothelial NO synthase expression is an action of statins, which is independent, at least in part, from changes in serum cholesterol common pharmacodynamic levels. Importantly, endothelial NO synthase expression declines rapidly after statin withdrawal, suggesting that a continuous administration of the compound is required to preserve endothelial function. [33]

Statins and tissue factor:

Tissue factor (TF) is a potent procoagulant known to induce thrombosis BY generation of thrombin. ***Colli and colleagues*** first demonstrated that fluvastatin and simvastatin, but not pravastatin, decreased TF activity, protein, and mRNA in monocyte-derived human macrophages in culture. Inhibition of TF was shown to be independent on the inhibition of cholesterol biosynthesis as it was observed in the presence of exogenously added cholesterol. [34]

Finally, evidence for an in vivo effect of statins on TF expression in human vessels was recently provided by the ***Atorvastatin and Thrombogenicity of the Carotid Atherosclerotic Plaque (ATROCAP)*** study in patients undergoing bilateral carotid end arterectomy with an average interval time between the first and second carotid end arterectomy of 4 to 6 months. Atorvastatin significantly reduced TF protein and activity as well as macrophage infiltration in atherectomy specimens.

These data strongly suggest that lipophylic statins (atorvastatin, simvastatin, lovastatin), by reducing TF and thus reducing cell-mediated generation of thrombin, are capable of attenuating atherosclerotic plaque thrombogenicity. [35]

Statins and inflammation:

In some aspects, arteriosclerosis may be regarded as a response of the vessel to a diversity of stimuli, with an inflammatory component that includes early leukocyte infiltration and local release of different chemo attractants like monocyte chemo attractant protein- 1 (MCP-1), interleukin-6 (IL-6), and interleukin-8 (IL-8), all of which are known

inflammatory agents. MCP-1 secreted by vascular cells and activated leukocytes, is a chemotactic protein important for drawing leukocytes and granulocytes to the areas in which vascular lesions form. IL-6 is a mediator of the acute-phase response, and exerts a broad range of effects on diverse immune cells. IL-8 regulates the migration of neutrophils and vascular endothelial cells. [36]

The antiinflammatory effects of statins have been noted both in vitro and in vivo. Simvastatin decreased serum concentrations of MCP-1, IL-6, and IL-8 in hypercholesterolemic patients. The drug also was reported to reduce mRNA expression of each of these 3 factors in peripheral blood mononuclear cells which are characteristically elevated in patients with hypercholesterolemia. [36]

Additionally, human umbilical vein endothelial cells, which generally secrete MCP-1, IL-6, and IL-8, demonstrated a decrease in expression for all 3 factors following statin therapy. Statins also have been reported to inhibit nuclear factor kB, which regulates the expression of many cytokines including MCP-1, IL-6, and IL-8. [37]

Basophils are major proinflammatory effector cells. Majlesi and coworkers discovered that cerivastatin and atorvastatin lead to the following:

(1) A decrease in histamine release in a dose-dependent manner by basophils.

(2) Suppression of IL-3-induced differentiation of basophils. [38]

Sparrow and co-workers examined this effect by using simvastatin in a well-established model for inflammation (carrageenan-induced foot pad edema). This model involves a subplantar injection of carrageenan that induces foot pad swelling which is characterized as an acute inflammatory response and marked by an influx of polymorphonuclear leukocytes (PMLs). Inhibition of the edema indicates anti-inflammatory action. When mice are treated with indomethacin, an established antiinflammatory agent, before the injection of carrageenan, foot pad edema was inhibited. Oral administration of simvastatin resulted in a similar effect. [39]

In other studies, simvastatin was also reported to block the influx of PMLs in cardiac muscle after ischemia and reperfusion .[40]

These studies indicate that statins exert antiinflammatory activity acutely (4 hours). This effect is not secondary to a decrease in cholesterol alone, because a reduction in lipids requires several days of treatment. [39]

In this regard, several studies indicate that statins reduce C-reactive protein (CRP), an inflammatory biomarker and an accepted prognostic index of coronary instability.[41]

Clinical data about acute antiinflammatory actions of statins in patients submitted to first elective CABG with cardiopulmonary bypass were reported. In a cohort study, Brull and colleagues compared immediate postoperative variations in plasma interleukin-6 (IL-6) levels between CABG patients who were receiving chronic therapy with statins at the time of surgery and in a group who were not. Although peak IL-6 levels increased many fold after the intervention in both groups, levels were significantly lower in patients receiving statins, a finding that suggests that these drugs may ameliorate acute inflammatory phenomena occurring perioperatively. [42]

Statins and SMC migration and proliferation

Evidence exists that statins may be protective against intimal hyperplasia. In a study by ***Corsini*** and co-workers, lovastatin, fluvastatin, and pravastatin were compared with regard to their effects on the vascular wall. The study showed that the lipophilic fluvastatin, but not the hydrophilic pravastatin, caused a decrease in SMC proliferation. Simvastatin and fluvastatin also inhibited SMC migration. Similarly pravastatin did not inhibit SMC migration. Additionally, lovastatin decreased development of intimal hyperplasia after balloon angioplasty of the femoral artery in hypercholesterolemic rabbits. Another interesting finding was that fluvastatin reduced catheter-induced intimal thickening in the femoral artery puncture site. **(43)**

Recent studies using organ-cultured human saphenous veins show that simvastatin reduces atheroma formation as a result of a combined inhibition of SMC proliferation and migration. The antiproliferative action of statins has been reported consistently on SMC from different species (including humans), both in vitro and in vivo, and with different members of the statin family. (44)

Statins and growth factors and extracellular matrix proteins:

- Platelet-derived growth factor (PDGF) :

Growth and division. Each type of growth factor has a specific receptor it associates with and therefore the protein will stimulate the only cells that express this receptor. Platelet-derived growth factor (PDGF) is categorized as a broad- specificity growth factor because it acts on a range of cells including fibroblasts, SMCs, and neuroglial cells. PDGF play a role in pathogenesis of vascular disease by stimulation of SMC proliferation and migration, which lead to restenosis after revascularization. Simvastatin appears to work through inhibition of PDGF and thus lead to inhibition of both SMC proliferation and migration. **(45)**

− Thrombospondin-1 (TSP-1)

TSP-1 is a transient extracellular matrix glycoprotein and acute phase reactant which is essentially absent in normal vessels, but it accumulates in acutely injured vessels, intimal hyperplasic lesions, and atherosclerotic plaque. On a molecular level, TSP-1 can stimulate SMC migration and proliferation and thus development of intimal hyperplasia, a common cause of vascular reconstructive failure. **(46)**

Riessen and co-workers have reported that lovastatin and simvastatin decrease the expression of TSP-1 mRNA markedly in human vascular SMCs. A decrease in the amount of TSP-1 mRNA in the cell causes a decrease in the concentration of this protein, and subsequently less SMC migration and proliferation. **(47)**

Non Cardiovascular effect

Dementia

Statin treatment has been reported to reduce the risk of dementia, possibly by causing a reduction in amyloid-β peptides in the cerebrospinal fluid and brain and by promoting the activity of the neuroprotective alpha-secretase. [48]

Multiple sclerosis

Cerebrosterol (24S-hydroxycholesterol) is increased in the plasma of subjects with multiple sclerosis. Simvastatin 80 mg/d was recently found to decrease plasma levels of this sterol in hypercholesterolemic subjects.

Atorvastatin was shown to prevent or reverse chronic relapsing paralysis in an animal model of autoimmune encephalomyelitis mimicking multiple sclerosis, and lovastatin had a similar effect in rats. [48]

Osteoporosis

Statin therapy may protect against bone fractures and promote increased bone mineral density and significantly associated with a decreased risk of fracture. [48]

Rheumatoid arthritis

Although there are no trials aimed at studying the pleiotropic effects of statins in this disease, recent small successful trials have indirectly tested the immunomodulatory and anti-inflammatory effects of statins in rheumatoid arthritis and related diseases. Atorvastatin was associated with reduced clinical manifestations and CRP levels in rheumatoid arthritis. [48]

Antiarrhythmic Effect of statins

Satins are hypothesized to have a benefit against arrhythmias; the *antiarrhythmic* actions of statins are related to both anti-atherogenic and non anti atherogenic properties of these drugs, which cardiovascular autonomic activity and ventricular repolarization. [49]

Statins used in patients in DEFINITE (Defibrillators in Non-Ischemic cardiomyopathy Treatment Evaluation) study was associated with a 78% reduction in mortality. This reduction was caused, in part, by a reduction in arrhythmic sudden death. [50]

Statin use was associated with reduced odds of frequent PVCs during and after clinical exercise testing in a manner independent of associations with coronary disease or ischemia. [49]

Statins was significantly associated with a decreased risk of incidence or recurrence of AF in patients in sinus rhythm with a history of previous AF, in those undergoing cardiac surgery, or after acute coronary syndrome. [51]

Pleiotropic actions related to the antiarrhythmic effects of statins

(1) Antiinflammatory properties

- ↓ macrophage number and activation
- ↓ expression of adhesion molecules and leukocyte-endothelial interactions
- ↓ inflammatory cytokine secretion by macrophages
- Switch Th-1 to Th-2 type phenotype in lymphocytes and ↑ anti-inflammatory cytokine production

(2) Stabilization of vulnerable plaques

- ↑ SMC and collagen
- ↓ MMPs in atheroma plaque
- ↓ LDL uptake and oxidation by macrophages

(3) Improvement of endothelial dysfunction

- ↑ NO levels by stabilizing mRNA
- ↑ NO bioavailability
- ↑ expression and activity of NOS3
- ↓ endothelin-1 expression

(4) Antioxidant effects

- ↓ oxidative stress and reactive oxygen species

(5) Cardioprotective effects

- ↓ cardiac and smooth muscle hypertrophy and cardiac fibrosis

(6) Improvement of autonomic function

- ↓ HRV and sympathetic function

(7) Antithrombotic effects

- ↓ platelet activation
- ↓ coagulation factors
- ↓ tissue factor (TF) expression

• ↑ fibrinolytic activity (tPA/PAI-1 ratio)

• ↑ thrombomodulin expression

(8) Effects on cardiac ion channels and transporters

• ↓ Na+-pump and Na+/Ca2+exchanger

• ↓ ICa, L and IKr

• ↓ hKv 1.5, Kv 4.3 and ImK channels

• ↑ KATP channels

Statin therapy reduces stroke incidence:

Clinical trials have demonstrated that statins reduce the incidence of strokes in patients with both normal and elevated cholesterol levels. In the ***CARE*** trial, researchers observed a 32% reduction in strokes or transient ischemic attacks among patients receiving pravastatin. The ***LIPID* study** revealed a 19% reduction in strokes in patients with a wide range of cholesterol levels treated with pravastatin. A meta-analysis of 13 primary and secondary prevention ***LIPID*** trial involving 20,303 patients revealed that treatment with various statins led to a 31% reduction of strokes. The ***HPS*** ,which involved more than 20,000 patients with diabetes and coronary heart disease, demonstrated a 27% reduction in stroke with simvastatin in patients with elevated, normal, and even low LDL-C levels. This benefit was seen in all types of patients, including women, the elderly, and patients with diabetes.

Several studies have examined the potential mechanisms by which statins are protective against cerebrovascular events. Recent studies on mice demonstrated that prophylactic treatment with statins for 2 weeks resulted in 25% to 30% higher cerebral blood flow and 50% smaller cerebral infarct sizes after middle cerebral artery (MCA) occlusion .[52]

Similar results were demonstrated by ***Endres and co-workers*** who showed that the decrease in infarct size was time-dependent, the effect being greater for mice treated for 14 days compared to 3 days. Additionally, this effect was not uniform for all statins, simvastatin conferring a greater protection against stroke than lovastatin. [53] The neuroprotective effects of statins appears to be due to mechanisms that are not related to their cholesterol-lowering properties. The neuroprotective effects of statins are most likely the result of their preservation of endothelial function and their antiinflammatory, antioxidant, and antithrombotic effects. [54]

Effects of statins on clinical events in patients with and without risk for cardiovascular disease:

Many studies reviewed the evidence supporting the use of statins for improving long-term outcomes and reducing ischemic events in patients with and without risk for cardiovascular disease. These studies demonstrate how the potentially beneficial effects of lipid lowering and preserved endothelial function will result in better patient come [3]

Primary prevention trials:

The ***WOSCOPS (West of Scotland Coronary Prevention Study)*** was a clinical trial that examined the effects of lipid lowering in adults who had no history of cardiovascular disease.

In the ***WOSCOPS*** trial, 6,595 men with elevated cholesterol levels without any coronary events were randomized to treatment with pravastatin or placebo and were followed for an average of 5 years. **(55)**

In the WOSCOP trial, LDL-C levels were lowered by 20% to 25%. Significant reductions were noted for risk of nonfatal MI (31%), death from coronary heart disease (33%), and all-cause mortality (22%). WOSCOP trials showed that lipid lowering with statin therapy had a substantial effect on decreasing cardiovascular events in patients who had no prior history of cardiovascular disease

Secondary prevention trials:

Secondary prevention trials were done to determine the effectiveness of statin therapy in patients who had already experienced a coronary event (angina or MI) and in persons who had undergone some type of revascular procedure .

Patients with previous coronary events:

The 4S ***(Scandinavian Simvastatin Survival Study)*** trial followed 4,444 men and women with angina or a previous MI and elevated cholesterol levels for 5.4 years. Patients were randomized to receive either pravastatin or placebo. ***The CARE (Cholesterol and Recurrent Events).*** **(56)** trial followed 4,159 patients who had experienced an MI for 5 years. Patients in this trial were randomized to receive pravastatin or placebo [56]**.**Pravastatin was also used in the ***LIPID (Long-Term intervention with Pravastatin in Ischemic Disease)*** [57] study, which followed 9,014 patients with unstable angina or an acute MI.

In all three trials, total cholesterol and LDL-C levels were reduced by 25% to 35% and the lower lipid levels correlated with improved clinical outcomes. Nonfatal MIs were reduced by 34% in 4S and 24% in the ***LIPID*** and ***CARE*** studies. Deaths from coronary heart disease were reduced by 42% in ***4S***, 24% in ***LIPID***, and 19% in the ***CARE*** trial. Mortality from any etiology was reduced by 30% in 4S, 22% in ***LIPID***, and 8% in ***CARE***

The Medical Research Council British Heart Foundation Heart Protection Study (HPS) [58] was designed to determine whether statins would be of benefit to patients with average-to-low LDL levels who were still at risk for coronary and atherosclerotic-related events due to a history of coronary artery and peripheral vascular disease, stroke, or diabetes. The 20,536 patients were randomized into four groups: simvastatin 40 mg daily, simvastatin 40 mg + vitamin therapy (vitamins E and C and B-carotene), vitamin therapy without any statin, and a placebo group. The average follow up was 5.5 years. Vitamin therapy had no effect in preventing atherosclerotic events. Patients treated with statins had a 24% ($p < 0.00001$) reduction in coronary death and death from other vascular disease, fatal and nonfatal strokes, and the need for revascularization procedures. **(58)**

The ***4S, CARE, LIPID and HPS*** trials demonstrated that statin therapy effectively improves survival and reduces ischemic events in patients with known coronary artery disease

What is coronary artery bypass surgery?

Coronary artery bypass graft surgery (CABG) is a procedure used to treat coronary artery disease in certain circumstances. Coronary artery disease (CAD) is the narrowing of the coronary arteries (the blood vessels that supply oxygen and nutrients to the heart muscle), caused by a buildup of fatty material within the walls of the arteries. This buildup causes the inside of the arteries to become narrowed, limiting the supply of oxygen-rich blood to the heart muscle.

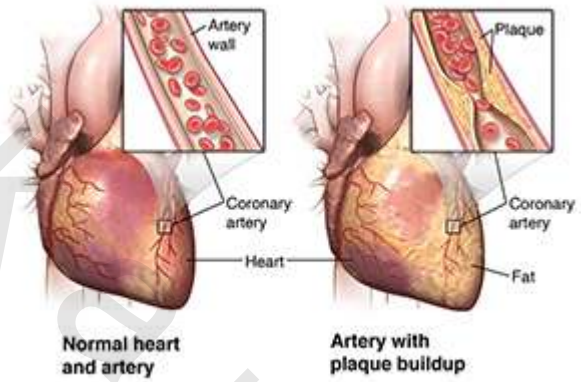

Figure (4): CABG

One way to treat the blocked or narrowed arteries is to bypass the blocked portion of the coronary artery with another piece of blood vessel. Blood vessels, or grafts, used for the bypass procedure may be pieces of a vein taken from the legs or an artery in the chest. At times, an artery from the wrist may also be used. One end of the graft is attached above the blockage and the other end is attached below the blockage. Thus, the blood is rerouted around, or bypasses, the blockage through the new graft to reach the heart muscle. This bypass of the blocked coronary artery can be done by performing coronary artery bypass surgery.

Traditionally, in order to bypass the blocked coronary artery in this manner, the chest is opened in the operating room and the heart is stopped for a time so that the surgeon can perform the bypass. In order to open the chest, the breastbone (sternum) is cut in half and spread apart. Once the heart is exposed, tubes are inserted into the heart so that the blood can be pumped through the body during the surgery by a cardiopulmonary bypass machine (heart-lung machine). The bypass machine is necessary to pump blood while the heart is stopped and kept still in order for the surgeon to perform the bypass operation.

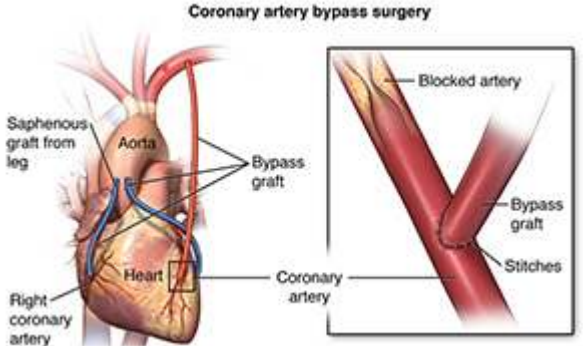

Figure (5): Coronary artery bypass surgery

While the traditional "open heart" procedure is still performed and often preferred in many situations, newer, less invasive techniques have been developed to bypass blocked coronary arteries. "Off-pump" procedures, in which the heart does not have to be stopped, were developed in the 1990's. Other minimally-invasive procedures, such as key-hole surgery (performed through very small incisions) and robotic procedures (performed with the aid of a moving mechanical device), increasingly are being used.

Two other surgical improvements for persons undergoing CABG are endoscopic vein harvesting and endoscopic radial artery harvesting. In both of these procedures surgeons use an endoscope (thin surgical tube with a light and camera on the end) to locate blood vessels that will be used for bypassing the blocked coronary arteries. Veins are generally harvested from the inner thigh and calf areas of the legs, while the radial artery is harvested from the wrist.

Traditional (open) approaches involve making long surgical incisions down the inner thigh and/or calf. Research comparing traditional approaches with endoscopic methods indicates that patients generally have fewer complications, less leg pain, and shorter hospital stays with the endoscopic harvesting methods. Some persons, however, may not be eligible for these methods because of other health conditions.[59]

Statins and prevention of graft disease:

The biology of the vascular conduits obtained for grafting is strongly altered during harvesting, surgical manipulation, and the subsequent exposure to hemodynamic stress. These stimuli elicit a series of changes in the graft that may lead, in certain conditions, to early thrombotic occlusion or to progressive thromboatherosclerotic disease. In addition, the marked systemic changes produced by cardiopulmonary bypass and surgical trauma on inflammation and haemostasis, in addition to the metabolic status of the host (namely hyperglycemia and dyslipidemia), may affect graft prognosis. A series of studies revealed that various of these phenomena may be prevented by statin therapy.

Both the LDL-lowering effect and the direct actions of statins on the arterial wall play a role to prevent early or delayed phenomena leading to recurrence of disease after CABG. [60]

Early changes after CABG and effects of statins:

Endothelial damage occurs in surgically prepared vascular segments and early occlusions after CABG may depend on thrombosis associated with focal endothelial loss. Even though careful vessel harvesting and surgical handling may reduce de endothelialization, critical cell functions are extremely sensitive to injury due to hypoxia, manipulation, or hemodynamic shear stress. Platelet adherence, fibrin deposition, and attachment of neutrophils are enhanced in the graft, and the extrinsic coagulation cascade is activated by tissue factor (TF) expressed in the exposed subendothelium. Several antithrombotic endothelial properties are attenuated such as the release of tissue plasminogen activator, prostacyclin, and nitric oxide (NO). In addition, postoperative thrombocytosis occurs in a significant number of the patients undergoing CABG with cardiopulmonary bypass. Some of these early changes may be favorably affected by statins **(61)**

Statin therapy in the revascularized patient:

The Post-Coronary Artery Bypass Graft (Post-CABG) trial was designed to determine whether statin therapy could delay or prevent the progression of atherosclerotic disease in vein grafts and thereby reduce ischemic events. This multicenter trial included 1,351 patients who were 1 to 11 years from the time of their CABG. Men in the study had to have at least two patent, but not necessarily disease-free saphenous vein grafts; women had to have at least one such graft. Baseline LDL-C levels were 130 to 175 mg/dL. Patients were randomized to receive either aggressive treatment with lovastatin 80 mg/day with a target LDL-C of less than 85 mg/dL or moderate treatment using 40 mg/day with a target LDL-C of 135 mg/dL.

The primary end point was the mean per-patient percentage of grafts with significant progression of atherosclerotic lesions in saphenous vein grafts (at least 0.6 mm change). Secondary end points included new graft occlusion; the incidence of myocardial infarctions; and the need for repeat revascularization (CABG or PTCA). Angiograms were repeated in all patients at an average of 4.3 years from entry into the study.

Furthermore, the beneficial effects of aggressive lipid lowering continued after 7.5 years. Patients who had received aggressive lipid lowering with LDL-C levels of 100 mg/dL or lower had a 30% reduction in revascularization procedures ($p = 0.006$) and a 24% reduction in the composite end point of cardiovascular death, stroke, need for revascularization, and death from any cause ($p = 0.001$). The Post-CABG trial showed the importance of not just lipid lowering, but aggressive treatment to achieve LDL-C levels of 100 mg/dL or less in revascularized patients. The angiographic benefits of decreased progression of atherosclerotic disease, increased vein graft diameter, and improved patency translated into a reduction of clinical events and improved survival that persisted 3 years after the study was completed. This study showed that the benefits of lipid lowering are extended not only to patients at risk for cardiovascular events but also to those who have had supposedly "curative" revascularization procedures. **(62)**

The beneficial effects of statin therapy in the CABG patient was also documented in two other smaller, single-center trials, which involved preoperative statin therapy. ***Christenson*** evaluated the effect of using simvastatin for 4 weeks before CABG and for 1 year after surgery on the incidence of arteriosclerosis graft disease. Repeat angiography

was performed 1 year after surgery. Patients treated with statins had a lower MI ($p = 0.03$) and vein graft occlusion ($p = 0.02$). Furthermore, similar to the Post-CABG trial, statin therapy prevented the development of new lesions in patent vein grafts. [63]

Dotani and co-workers examined the effect of statin therapy in a retrospective study involving patients receiving statin therapy before their CABG. Preoperative statin therapy was associated with a significant reduction in the composite end point of death, MI, and unstable angina 1 year after CABG ($p = 0.006$). Unstable angina was reduced from 11% to 3% with statin therapy ($p = 0.02$). Statin treatment also reduced the incidence of arrhythmias .[64]

Statin therapy may enhance myocardial protection during coronary revascularization:

The favorable effects of statins on endothelial function, inflammation, and fibrinolysis attract the attention to the possible role of statins in enhancing myocardial protection and decreasing ischemic damage during coronary revascularization. Twenty pigs underwent isolated coronary occlusion for 90 minutes, followed by 45 minutes of cardioplegic arrest and 180 minutes of reperfusion. Ten animals received atorvastatin (40 mg qd) for 21 days before surgical intervention .The other group of pigs received no statins. During the 90 minute period of coronary occlusion, statin-treated animals received fewer cardioversions for ventricular tachycardia and fibrillation. This is similar to studies in patients with implantable defibrillators which showed that patients receiving statins have a 40% reduction in the incidence of ventricular tachycardia or fibrillation. [65]

It is postulated that the beneficial effects of statins are due to their reduction of superoxide free radicals and free fatty acids which contribute to sarcoplasmic injury, intracellular calcium overload, and alterations in transmembrane ion channels which affect ventricular conduction and excitability

Statin-treated animals also had higher wall motion scores, lower infarct size, and better preservation of coronary endothelial vasomotor function.

These beneficial effects occurred in the absence of changes in serum cholesterol or LDL-C levels, suggesting that these beneficial effects of statins were the result of pleiotropic properties. [65]

The favorable effects of statin pretreatment before coronary revascularization was also observed by ***Chan and co-workers*** in a retrospective study involving 5,052 patients undergoing PTCA. Patients receiving statin therapy before their PTCA had a significant reduction in mortality that persisted for up to 6 months. [66]

Similar results were noted by ***Walter and co-workers***, who found that the initiation of statin therapy immediately after stent insertion significantly, improved 6-month clinical outcomes in patients with unstable angina. Furthermore, they found that patients with elevated C-reactive protein levels during stent implementation had a decreased risk for major cardiac events if they received statin therapy. This result provides further evidence that statins may decrease ischemic events because of their role in decreasing the inflammatory response. [67]

These studies suggest that statins may also have an important role in decreasing ischemic damage during coronary revascularization. They may also confer additional protection for patients undergoing CABG surgery irrespective of their baseline cholesterol and LDL-C levels**.**

Statin therapy as an alternative to revascularization:

The previously mentioned trials clearly demonstrated that statin therapy has a role in the coronary patient who has already had an ischemic event or undergone a revascularization procedure. But can statin therapy also be used as an alternative to revascularization procedures in patients with stable coronary artery disease? ***The AVERT (Atorvastatin versus Revascularization Treatment)*** study was undertaken to assess whether aggressive lipid-lowering therapy could be used as an alternative to percutaneous catheter therapy in patients with stable coronary artery disease.

The AVERT trial showed that aggressive statin therapy may be used in patients with stable coronary disease as an alternative to PTCA. It also suggested that statins may not only prevent the progression of atherosclerotic changes in vein grafts, but may also have a protective effect on native coronary vessels with obstructive lesions. **(68)**

Late changes after CABG and effects of statins:

After the first month and throughout the first postoperative year, intimal hyperplasia represents the major histologic change in the graft. A combination of conditions promotes smooth muscle cell (SMC) proliferation. These include:

(1) Transient attenuation of endothelial antiproliferative signals (NO, transforming growth factor-ß, prostacyclin, and adenosine).

(2) Release of growth factors from adhering platelets and non-occlusive thrombi (platelet-derived growth factor).

(3) Up-regulation of vein graft receptors for growth factors (basic fibroblast growth factor).

The stimulus for SMC proliferation and migration in vivo is degradation of the basement membrane. In this hyper plastic period and thereafter, lipoprotein-derived cholesterol esters accumulate in the vessel wall. Lipid accumulation occurs initially into smooth muscle and macrophage-derived foam cells and then extracellular, progressively developing a mature atheromatous plaque, indistinguishable from the typical lesions found in native arteries Statins may influence various of the steps involved in this process. (31)

Statins and non-cardiac vascular surgery:

Statin therapy may also play an important role in decreasing ischemic events in patients undergoing non cardiac vascular surgery. To evaluate the effect of statin use and perioperative mortality, ***Poldermans and co-workers*** performed a case-controlled study among 2,816 patients who underwent vascular surgical procedures. Patients who received a statin were less likely to have a cardiovascular mortality after their vascular surgery procedure .(***69)***

The effects of pretreatment with statins following non cardiac vascular surgery was also studied by ***Durazzo and co-workers*** in a prospective, randomized, double-blind trial involving atorvastatin (20 mg/d) 30 days before surgery. The incidence of cardiovascular events (death, MI, unstable angina, and stroke) was significantly less (p = 0.022) in patients treated with atorvastatin during the 6-month follow-up. [(70)]