

CHAPTER 3

THERAPEUTIC STRATEGIES FOR ATHEROSCLEROTIC PLAQUE

- Plaque Regression
- Plaque Stabilization
- Statins
- Other Drugs

- Complications and outcome of ASO coronary plaque are the result of:
 1. Plaque growth, progression and subsequent encroaching on coronary lumen.
 2. Plaque destabilization, tear or rupture with subsequent coronary thrombus formation and coronary artery occlusion.

- The goals of therapy are therefore:
 1. Induce regression or at least prevent progression of plaque.
 2. Stabilization or passivate the vulnerable plaque and make it less prone to rupture.

PLAQUE REGRESSION

Mechanisms

- Depletion of plaque lipid.
- Depletion of connective tissue.
- Lysis of thrombi.

Proof

Atherosclerotic plaque regression was demonstrated by:

- Coronary angiography- Computer assisted quantified coronary angiography.
 - § There is improvement in stenosis 1-2% in lipid lowering intervention groups and approximately a 3% progression of stenosis in control group (metanalysis). This takes 2-4 years of lipid lowering therapy.

- Magnetic resonance imaging (MRI)
 - § Statin therapy induced regression of carotid and aortic atherosclerotic plaques as seen in sequential MRI of hyperlipidemic patients (Fig 28).
 - § Significant reduction in plaque size observed with simvastatin after 12 months of therapy. Maximal plaque shrinkage was achieved before increase in lumen dimensions.

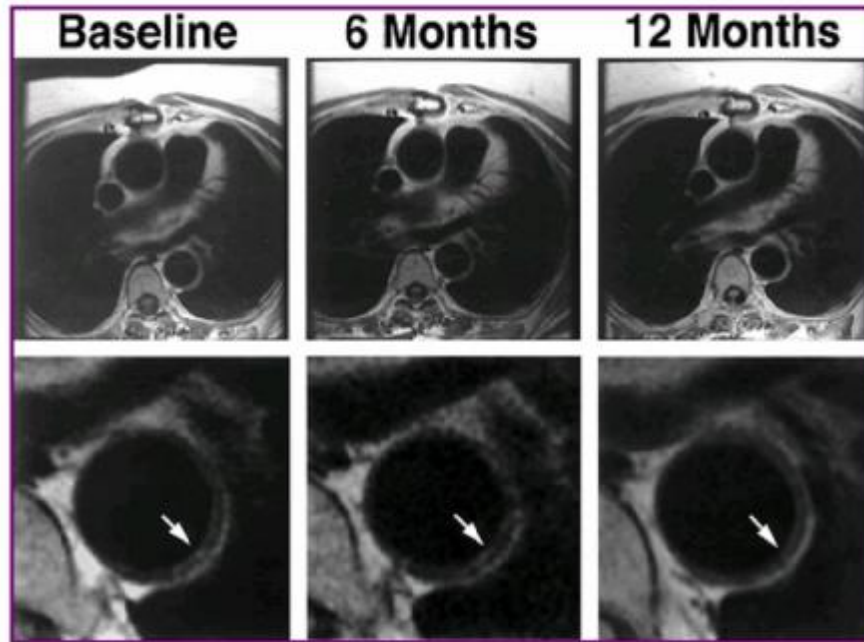


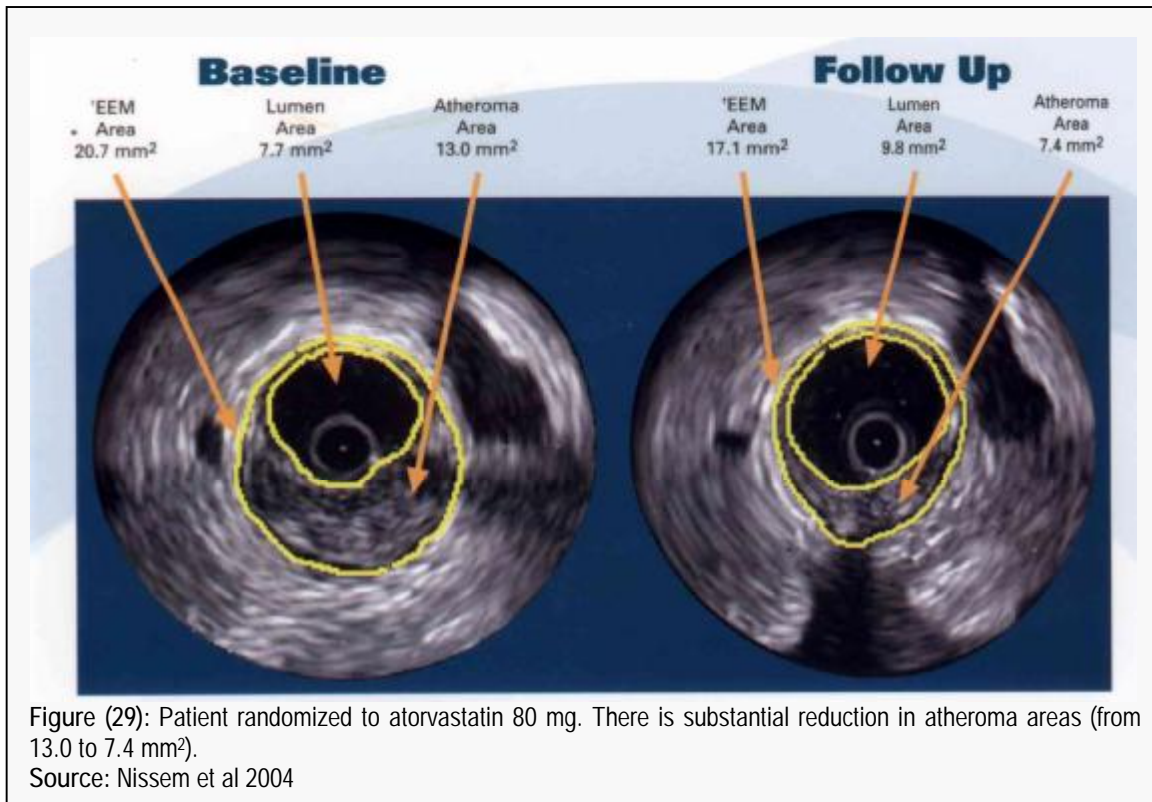
Figure (28): Sequential MR imaging of aortic atherosclerotic plaque after statin therapy in a hyperlipidemic patient. Statin induced regression of plaque after 12 months of therapy.
Source: Corti et al. Circulation. 2001.

- Intravenous ultrasound (IVUS)

- § Aggressive lipid lowering with statins (atorvastatin) caused substantial regression in atherosclerotic disease burden (Fig 29).

Approaches

- Life style:
 - Diet: reduction in intake of saturated fat and cholesterol. Increase fiber intake.
 - Weight reduction.
 - Exercise.
- Lipid lowering:
 - Intensive lipid lowering by a variety of drug interventions retards the progression of atherosclerotic plaques and in a subset of patients, leads to their regression or reduced the formation of new lesions.



PLAQUE STABILIZATION

Approaches to achieve Plaque Stabilization

1. *Change plaque structure*
 - a. Lipid core:
 - Smaller lipid core.
 - Harder and less soft core. Change the soft cholesterol esters to the more solid cholesterol crystals.
 - b. Fibrous cap: increase thickness and collagen content.
2. *Attenuate inflammatory reaction*
 - Decrease macrophages and T-lymphocytes (Macrophages are the principal source of MMP enzymes that digest the collagen matrix and produce erosion and thinning of fibrous cap).
3. *Improve endothelial function*
 - Improve vasomotor tone and decrease coronary vasoconstriction.
 - Decrease inflammatory and prothrombotic reaction.
4. *Decrease wall stress*
 - Reduction in circumferential stress resulting from the increased vasomotor tone of the vessel.
 - Reduction in direct stress resulting from perpendicular pressure on the fibrous cap.
 - Both can be achieved by lowering of blood pressure and decrease in sympathetic vasoconstriction.

5. Attenuate the procoagulant and prothrombotic state.

- Drugs that help in plaque stabilization include**
- Statins
 - Beta-adrenergic blockers
 - ACE-Inhibitors
 - Aspirin
 - Anticoagulants
 - Antibiotics

**Mechanism of Action of Drugs Used for
Plaque Stabilization / Passivation**

	Lipid core	Inflammation	Endothelium	Thrombosis	Wall stress
ACE-I	-	++	++	+	+
Statins	++	++	++	+	-
B-Block	-	-	+/-	-	++
ASA	-	++	-	+	-
Anticoag	-	- / +	-	++	-
Antibiotics	-	++	-	-	-

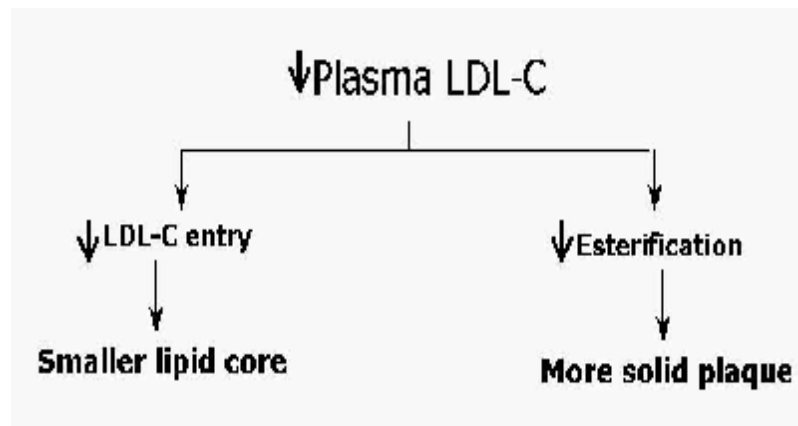
- : no effect +: mild or modest effect ++: significant effect

DRUGS

STATINS

- Statins are possibly the best available pharmacologic approach for plaque stabilization: They achieve this goal through both:
 - Aggressive lipid lowering.
 - Non-lipid mechanisms.
- Statins stabilize ASO plaque through:
 1. Reduction in lipid core.
 2. Change in lipid composition of core- decrease in cholesterol esters which are soft to crystalline cholesterol which is more firm and solid.

A small, solid and firm lipid core will tolerate wall stress and is less prone to disruption. Decrease in plasma LDL-C will decrease its rate of entry to the vessel wall and decrease its chance for esterification.



3. Antiinflammatory action:

- § Reduction in plasma LDL-C will decrease risks of LDL-C modification and oxidation. Modified LDL is a highly inflammatory and cytotoxic agent (Fig 30).
- § Direct anti-inflammatory action of statins will decrease macrophages and T-cells activity. Inflammatory cells are responsible for MMP and other proteolytic enzymes generation which digest the extracellular matrix proteins and cause erosion and thinning of the fibrous cap.
Statins increase collagen production and decrease collagen degradation. These actions increase fibrous cap thickness.
- § A significant increase in plaque hyperechogenicity as determined by IVUS was observed within six months to one year of statin (atorvastatin) therapy. Hyperechogenic plaques are rich in dense fibrous tissue (Fig 31).

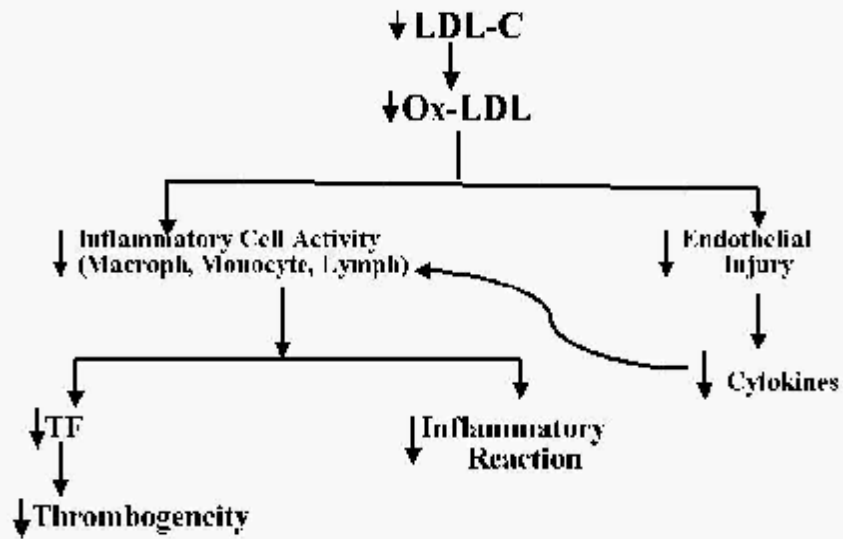


Figure (30): Actions of Statins

Anti-inflammatory, anti anti thrombotic effects of statins. Reduction in LDL-cholesterol with decrease the chance of oxidation. A reduced ox-LDL level has beneficial effects regarding reduction in endothelial injury and in inflammatory cell (monocytes, macrophages and lymphocyte) activity. These effects will attenuate the inflammatory reaction and tissue factor (TF) production.

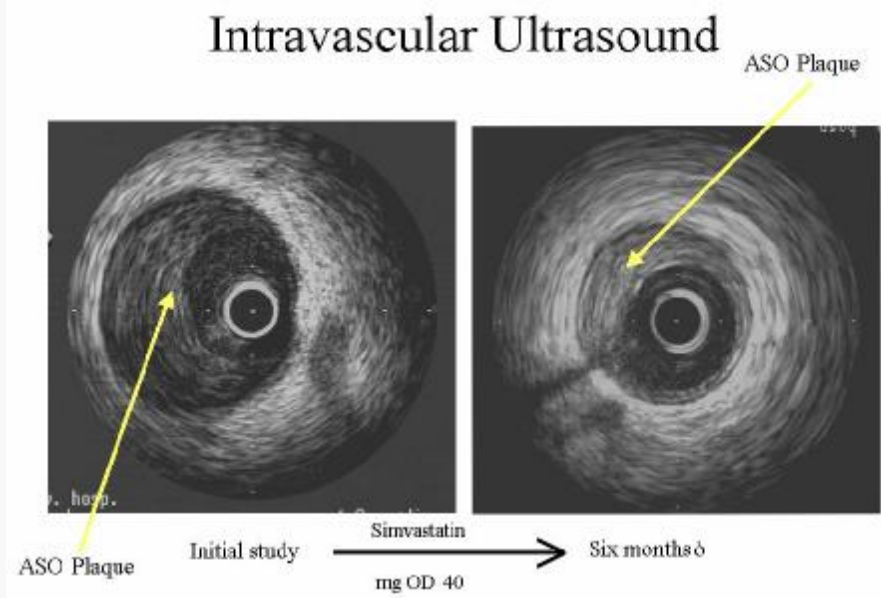


Figure (31): IVUS recording of a large atherosclerotic plaque in coronary artery. Statin therapy for six months led to reduction in plaque size and increased echogenicity indicative of fibrous tissue formation and decrease in the echolucent lipid material. Findings are suggestive of plaque stabilization.

4. Improvement in endothelial function:

§ There is improvement of endothelial function with cholesterol lowering (fig 32).

Improvement has been demonstrated within 2-4 weeks of initiation of therapy.

Effects include:

§ Reduction in oxidative stress and increased NO generation.

§ Potentiate anti-inflammatory and antithrombotic actions.

§ Improve vasodilation and elimination of myocardial ischemia.

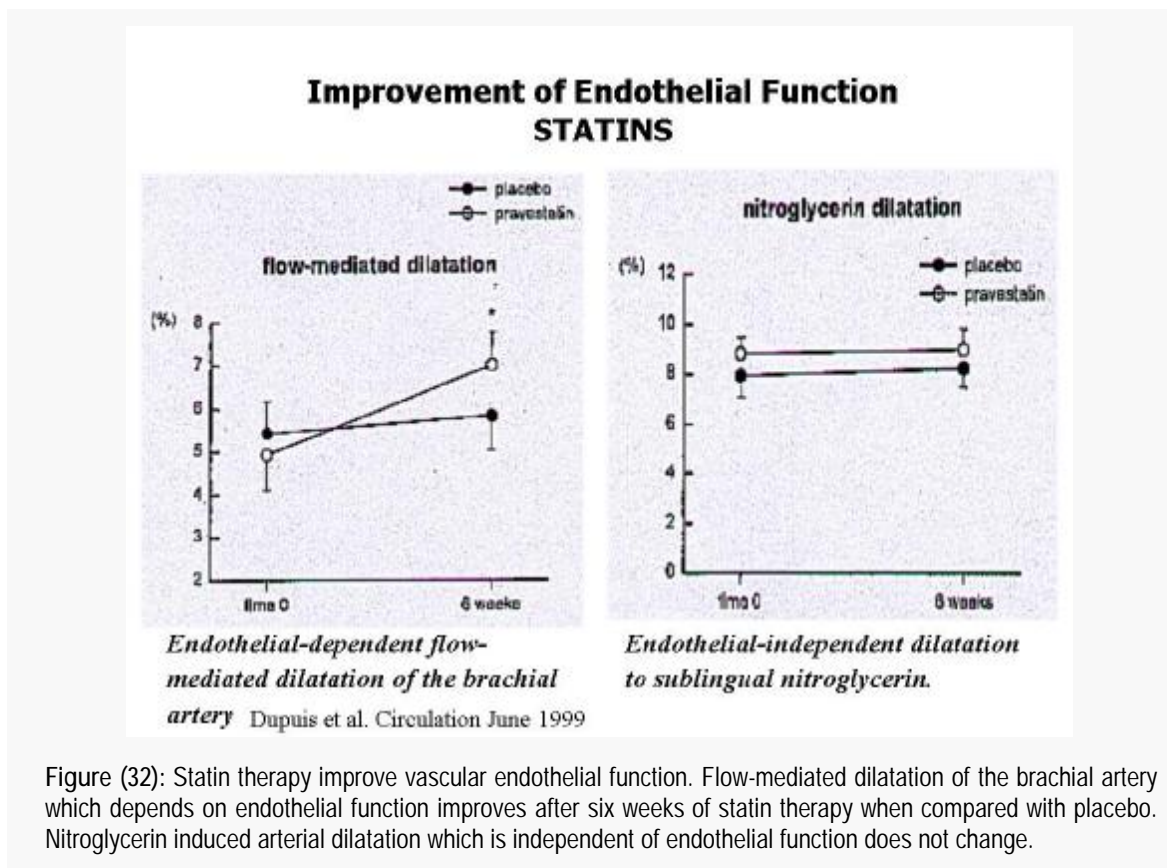


Figure (32): Statin therapy improve vascular endothelial function. Flow-mediated dilatation of the brachial artery which depends on endothelial function improves after six weeks of statin therapy when compared with placebo. Nitroglycerin induced arterial dilatation which is independent of endothelial function does not change.

5. Antithrombotic actions

§ Hypercholesterolemia is associated with blood hypercoagulability and increased platelet activation and TF generation.

§ Lipid lowering decrease TF expression, platelet activity and improve endogenous fibrinolysis.

Beta Adrenergic Blockers

Stabilize ASO plaque chiefly through reduction in blood pressure, wall stress and sympathetic activation.

ACE-Inhibitors

Stabilize plaques through the following mechanisms:

1. Attenuate plaque inflammation.
ACE-I decrease inflammatory markers: IL-6, MCP-1, CRP and NF- κ B.
2. Improve endothelial function.
3. Decrease wall stress by blood pressure reduction.
4. Decrease plaque thrombogenicity:
ACE-I decrease:
 - PAI-I: a physiologic inhibitor of fibrinolysis.
 - Plasma fibrinogen.
 - Tissue factor.
 - Platelet activation and aggregation.

Aspirin

It has both anti-inflammatory and antithrombotic properties.

Anticoagulants

- Decrease plaque thrombogenicity.
- Attenuate the systemic procoagulant state.
- Favour fibrin thrombi prevention.
- Have a mild anti-inflammatory action.

Antibiotics

- Infection with *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Helicobacter pylori*, Cytomegalovirus and *Mycoplasma pneumoniae* is involved in the development of ASO plaques.
- Antibiotics may have a possible role in attenuating the inflammatory reaction at ASO plaque and improving stabilization.
(See the chapter on systemic milieu).