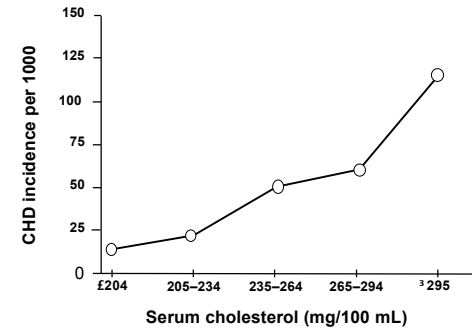


Lipidforstyrrelser og aterosklerose

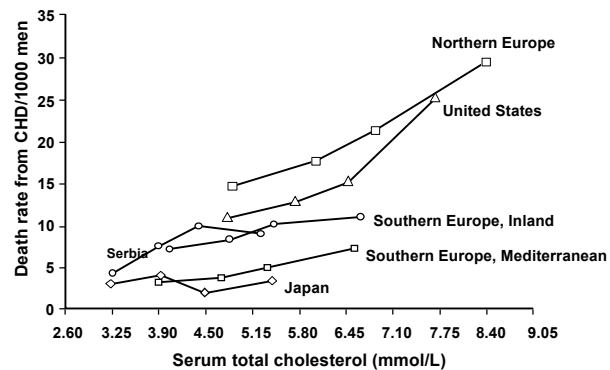
FRM3020 A.C. Rustan

Relationship Between Cholesterol and CHD Risk: The Framingham Study



(Adapted from Castelli WP, 1984)

Relationship of Serum Cholesterol to Mortality: Seven Countries Study



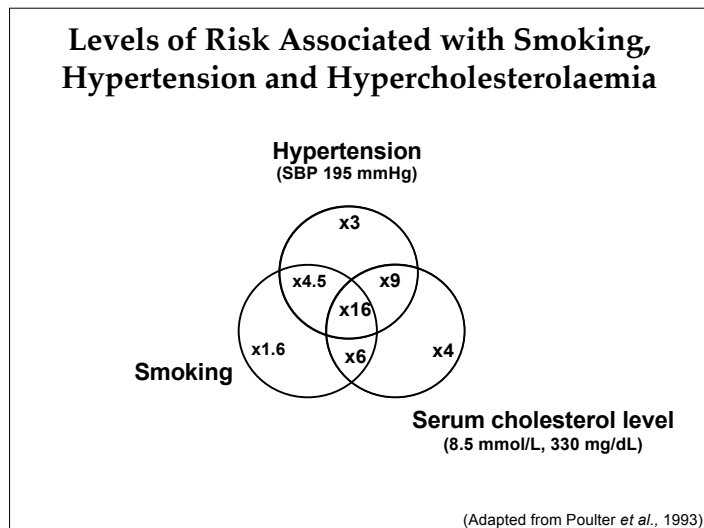
(Adapted from Verschuren *et al.*, 1995)

Cholesterol — A Modifiable Risk Factor?

- In the USA:
 - 97 million people have total cholesterol 5.2 mM
 - 38 million people have total cholesterol 6.2 mM
- 10% reduction in total cholesterol results in:
 - 15% reduction in CHD mortality ($p < 0.001$)
 - 11% reduction in total mortality ($p < 0.001$).
- LDL cholesterol is the primary target to prevent CHD.
- Intensity of intervention depends on total CV risk.

Risikofaktorer for hjerte-karsykdommer		
Upåvirkelige forhold	Levevaner & livsstil	Tilstander
Alder	Kosthold	Hyperlipidemi
Kjønn	Fettmengde	Kolesterol
Arv	Fett-type	LDL/HDL-kolesterol
	Salt	Triglyserider
	Fiber	Trombose risiko
	Fysisk aktivitet	Diabetes mellitus
	Stress	Hypertensjon
	Røyking	Overvekt

Risikogrupper		
Pasienter (uansett alder/kjønn) med	Øvrige tilstander med høy risiko	Familiær disposisjon
Etablert koronarsykdom (CHD)	Hypertensjon	Foreldre, søsken og/eller barn med
Annen aterosklerotisk sykdom	Røyking	tidlig debut av CHD eller annen aterosklerotisk sykdom (< 65 år)
Diabetes mellitus type 2	Overvekt	Forekomst hos foreldre og/eller søsken av uttalt
	Kronisk nyresykdom	hyperkolesterolemi (> 8,0 mmol/L)



Hyperlipidemi

Synet på legemiddelbehandling av hyperlipidemi har endret seg. Man fokuserer nå i mindre grad på nivået av blodlipider. Selv pasienter med kolesterolnivåer i referanseområdet, og under det, kan profitere på å benytte lipidsenkende legemidler. Noe av effekten går på å bremse avleiringene av ateromatøse plakk, men også stabilisering av allerede dannede plakk er viktig. Enkelte legemidler kan muligens også indusere en rekke metabolske forandringer i endotel med bl.a. nedsatt trombogenisitet som resultat.

En ny erkjennelse er at kolesterolreduksjon ikke bare forebygger koronar hjertesykdom, men også perifer karsykdom og hjerneslag.

Hyperlipidemi

Primær hyperlipidemi er hovedsakelig arvelig betinget, men også nært forbundet med livsstil, spesielt diettvaner.

Blant de sekundære årsakene finner man diabetes, thyreoidealidelser, nyre- og leversykdommer. Høyt alkoholforbruk øker triglyseridnivået, som normaliseres ved redusert forbruk.

Classification of Dyslipidaemias Fredrickson (WHO) Classification

Phenotype	Lipoprotein elevated	Serum cholesterol	Serum triglyceride	Atherogenicity	Prevalence
I	Chylomicrons	Normal to ↑	↑↑↑↑↑	None seen	Rare
Ila	LDL	↑↑	Normal	+++	Common
Ilb	LDL and VLDL	↑↑	↑↑	+++	Common
III	IDL	↑↑	↑↑↑	+++	Intermediate
IV	VLDL	Normal to ↑	↑↑	+	Common
V	VLDL and chylomicrons	Normal to ↑	↑↑↑↑	+	Rare

LDL – low-density lipoprotein
IDL – intermediate-density lipoprotein
VLDL – very low-density lipoprotein.
High-density lipoprotein (HDL) cholesterol levels are not considered in the Fredrickson classification.

(Adapted from Yeshurun *et al.*, 1995)

Lipidendringer hos pasienter med diabetes

Type 1 Type 2

	Dårlig kontroll	God kontroll	Dårlig kontroll	God kontroll
Total kolesterol	↑	Normal	↑	Normal
LDL kolesterol	Normal ↑	Normal	↑	Normal
Triglyserider	↑	Normal	↑↑	↑
HDL kolesterol	↓	↑ Normal	↓	↓

Behandlingsmål = ønsket nivå (generelt og ved diabetes)

- Total kolesterol < 5.0 mmol/L
- Total/HDL ratio < 4.0
- LDL-kolesterol < 3.0 mmol/L (lavere hos diabetikere < 2.6 mmol/L)
- Triglyserider < 2.0 mmol/L (< 2.4)
- HDL-kolesterol > 1.0 mmol/L (> 1.15)

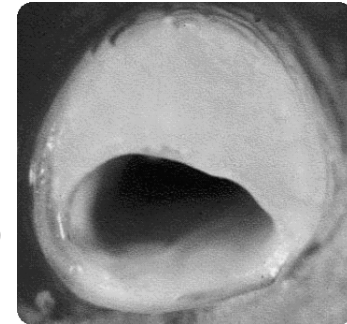
Aterosklerose

Aterosklerose - kliniske manifestasjoner

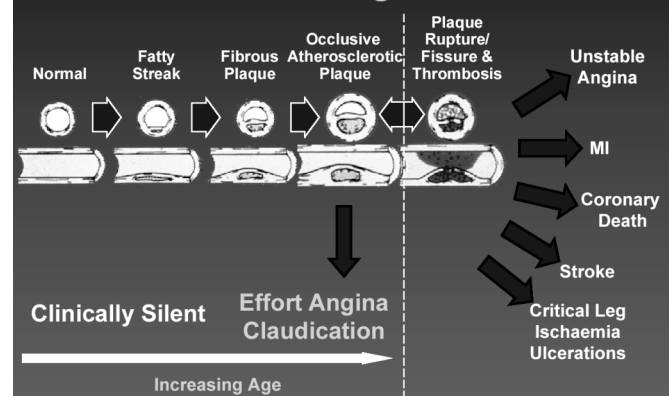
- **Hjerte-kar sykdom**
 - stabil angina
 - ustabil angina
 - akutt hjerteinfarkt
- **Cerebrovaskulær sykdom**
 - slag
- **Perifer arteriesykdom**
 - intermittent claudication
 - amputasjon

Hva er aterosklerose ?

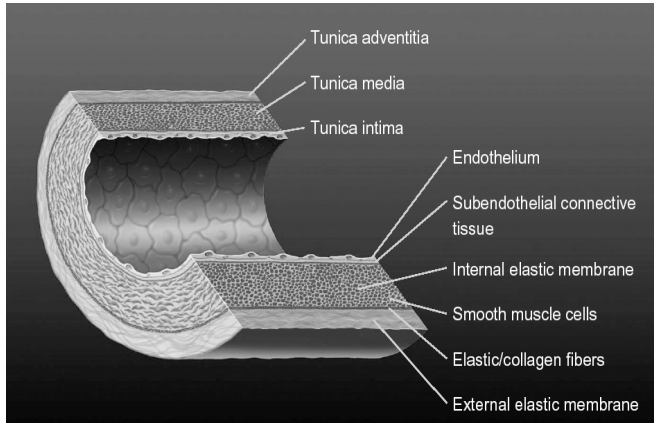
- **Athere** - myk
 - lipider
 - ustabil
- **Skleros** - hard
 - kollagen, glatte muskelceller (SMC)
 - ufarlig



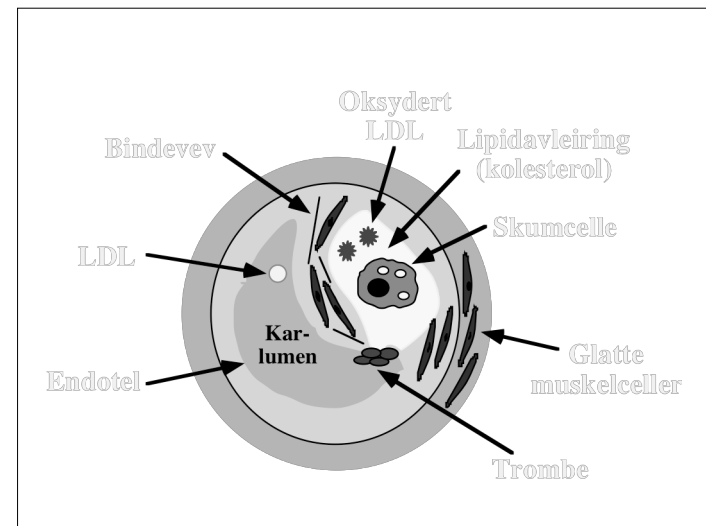
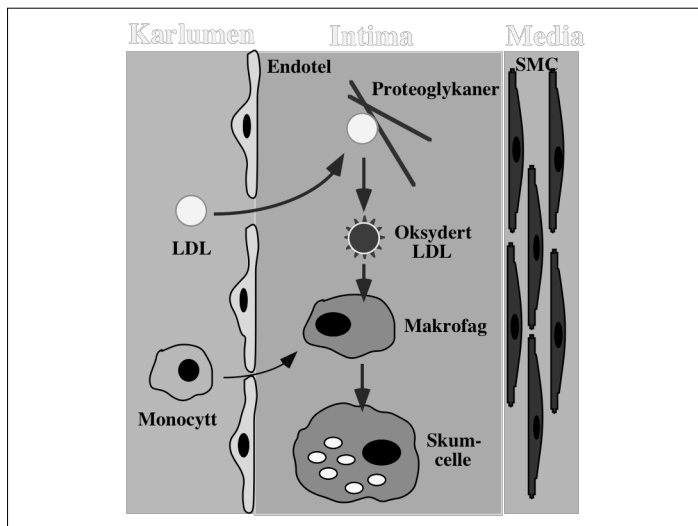
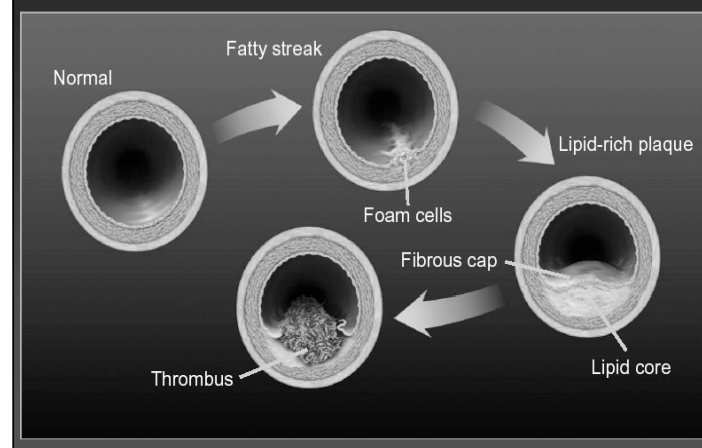
Atherosclerosis: A Progressive Process



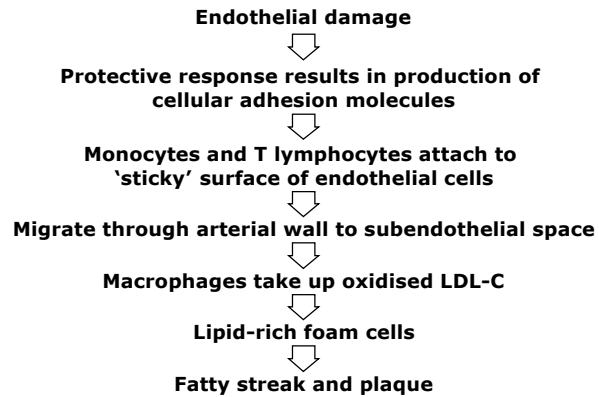
Normal Arterial Wall



Stadier i utvikling av aterosklerose



Pathogenesis of Atherosclerotic Plaques



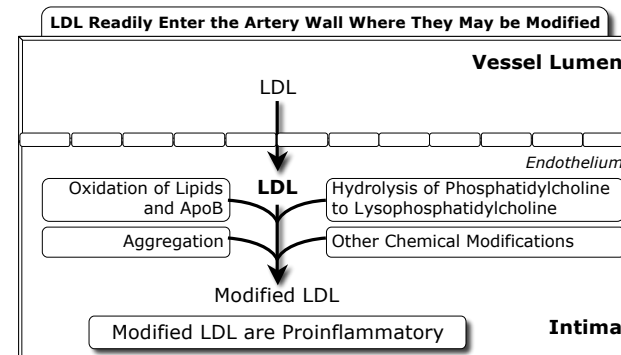
Stabilitet og ruptur av plakk

- **Plakkets sammensetning**
 - Kjerne
 - Kapsel
- **Inflamasjon**
 - Monocytter/makrofager
 - Oksydert LDL
 - Cytokiner/vekstfaktorer
- **"Ytre faktorer"**
 - Hemodynamiske forhold
 - Trombogene faktorer



Lipoproteinenes rolle

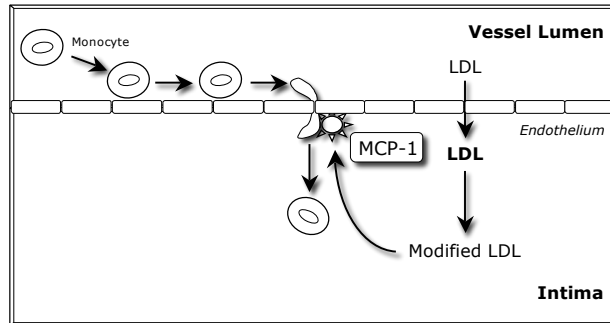
Role of LDL in Atherosclerosis



Steinberg D et al. *N Engl J Med* 1989;320:915-924.

Lipids Online

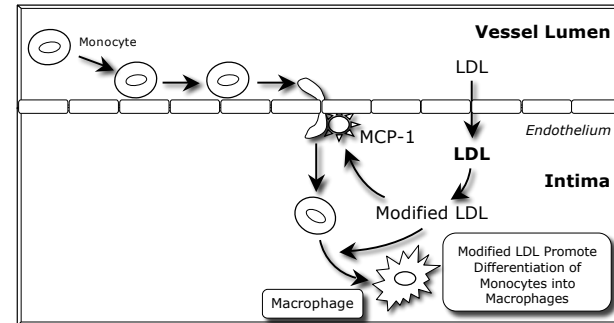
Role of LDL in Atherosclerosis



Navab M et al. *J Clin Invest* 1991;88:2039-2046.

Lipids Online

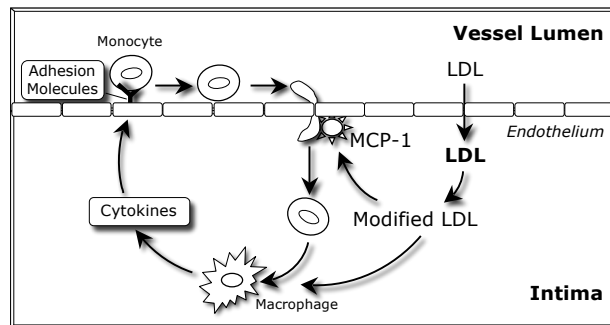
Role of LDL in Atherosclerosis



Steinberg D et al. *N Engl J Med* 1989;320:915-924.

Lipids Online

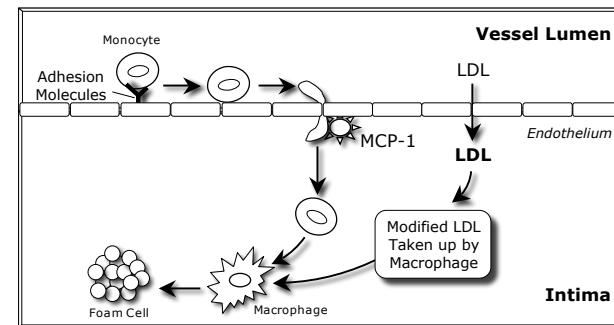
Role of LDL in Atherosclerosis



Nathan CF. *J Clin Invest* 1987;79:319-326.

Lipids Online

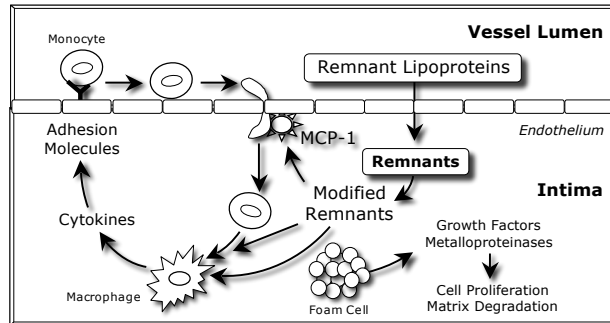
Role of LDL in Atherosclerosis



Steinberg D et al. *N Engl J Med* 1989;320:915-924.

Lipids Online

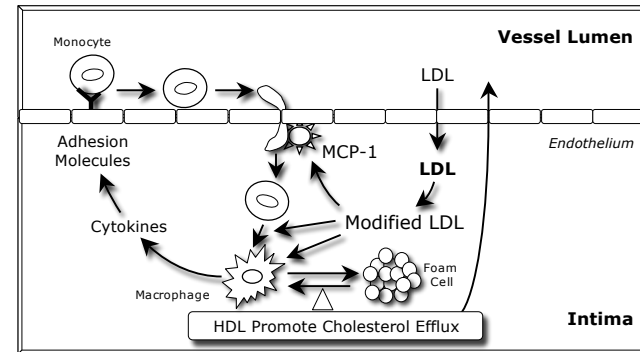
Role of remnant lipoproteins in Atherosclerosis



Doi H et al. *Circulation* 2000;102:670-676.

Lipids Online

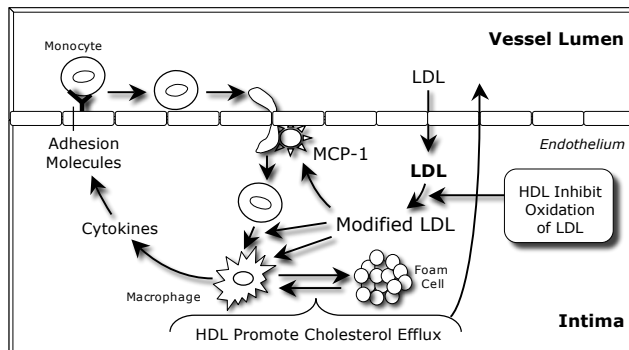
HDL Prevent Foam Cell Formation



Miyazaki A et al. *Biochim Biophys Acta* 1992;1126:73-80.

Lipids Online

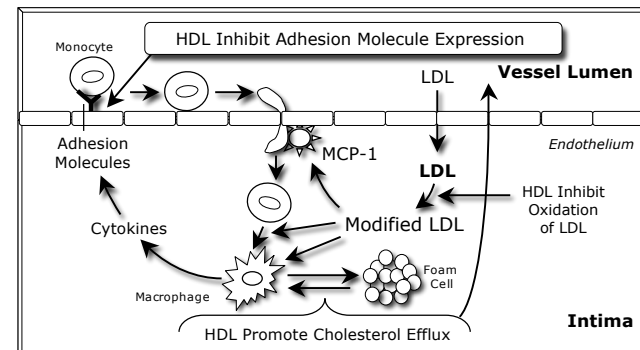
HDL Inhibits Oxidative Modification of LDL



Mackness MI et al. *Biochem J* 1993;294:829-834.

Lipids Online

HDL Inhibits Expression of Adhesion Molecules



Cockerill GW et al. *Arterioscler Thromb Vasc Biol* 1995;15:1987-1994.

Lipids Online

Potential Mechanisms of Accelerated Atherogenesis in Diabetes

- Insulin resistance
- Abnormalities in apolipoprotein and lipoprotein particle distribution
- Accumulation of advanced glycosylation end-products in plasma and arterial wall
- Glycooxidation and oxidation of lipoproteins
- Procoagulant state
- Hormone-, growth-factor-, and cytokine-enhanced SMC proliferation and foam cell formation

SMC=smooth muscle cell