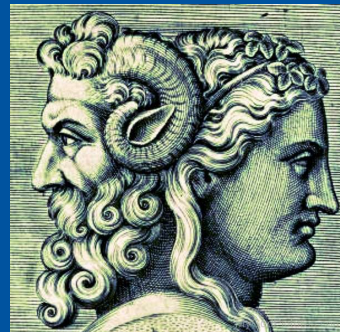


Dyslipidemie (of beter: “Lipids, lipoproteins and metabolism”)

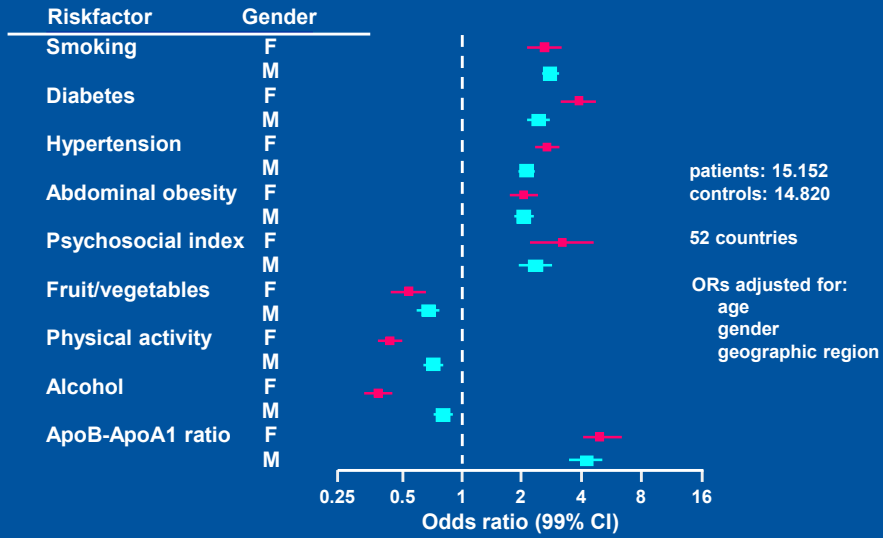
F.L.J. Visseren
28 maart 2023
NVHVV - CNE



“.... Cholesterol is a Janusfaced molecule. The very property that makes it useful in cell membranes, namely its absolute insolubility in water, also makes it lethal. “



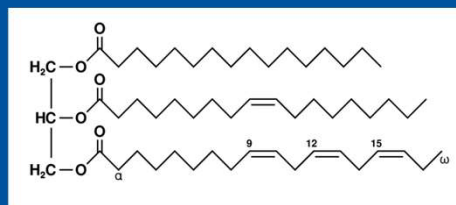
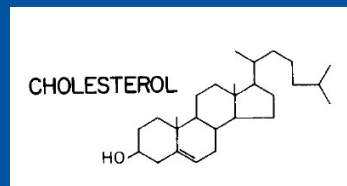
Most important risk factors for MI (INTERHEART study)



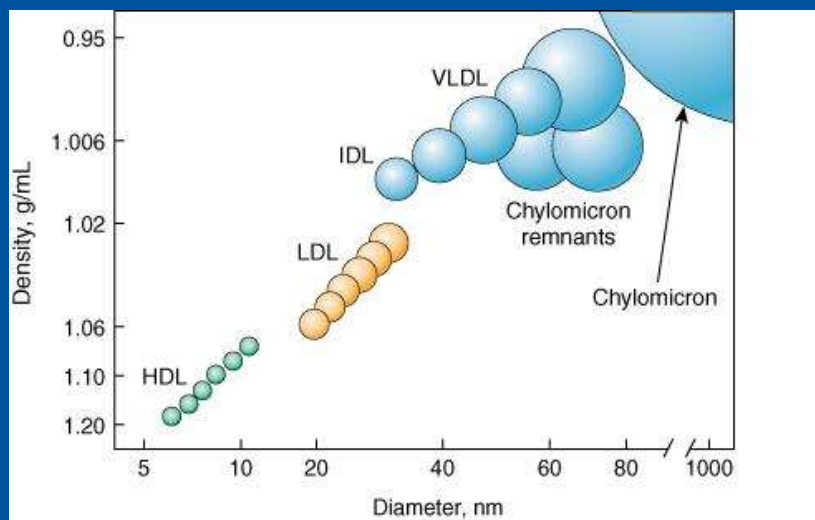
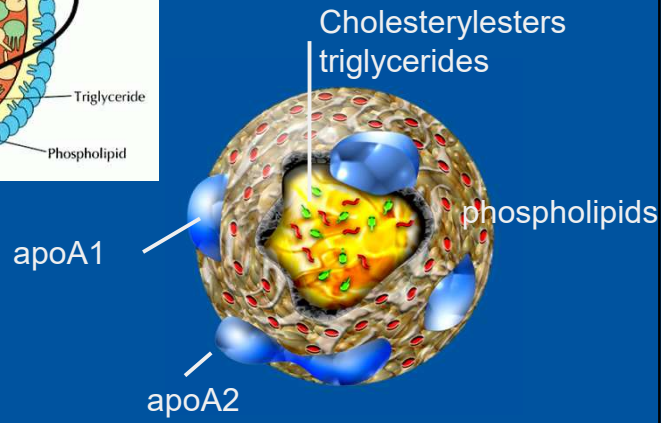
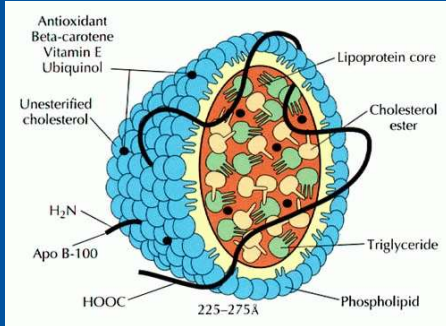
Yusuf S et al. Lancet. 2004;364:937-52.

Lipids

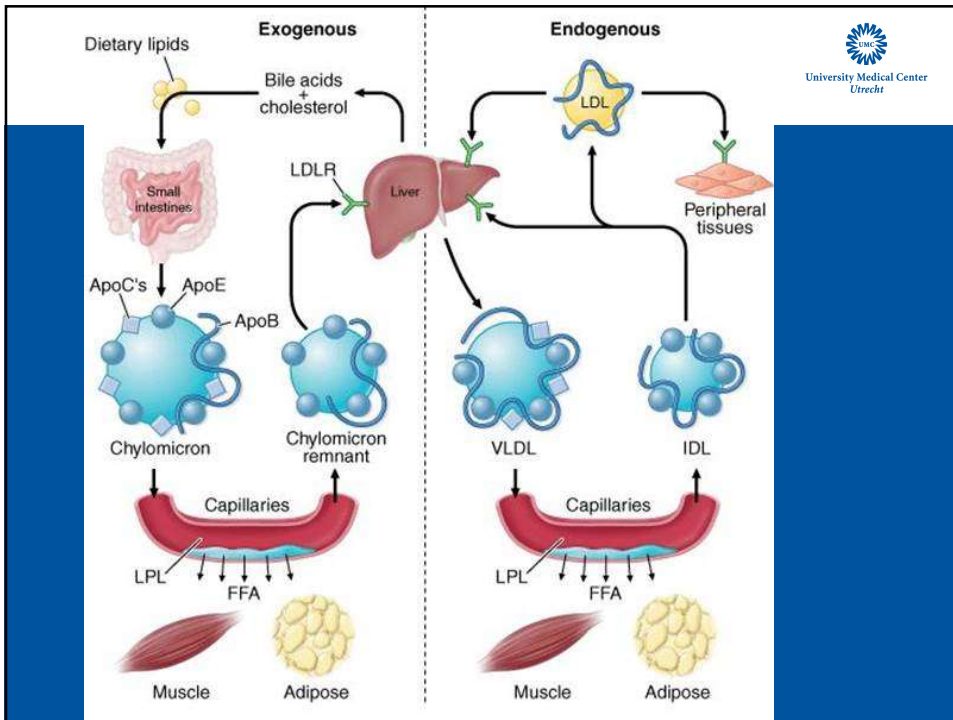
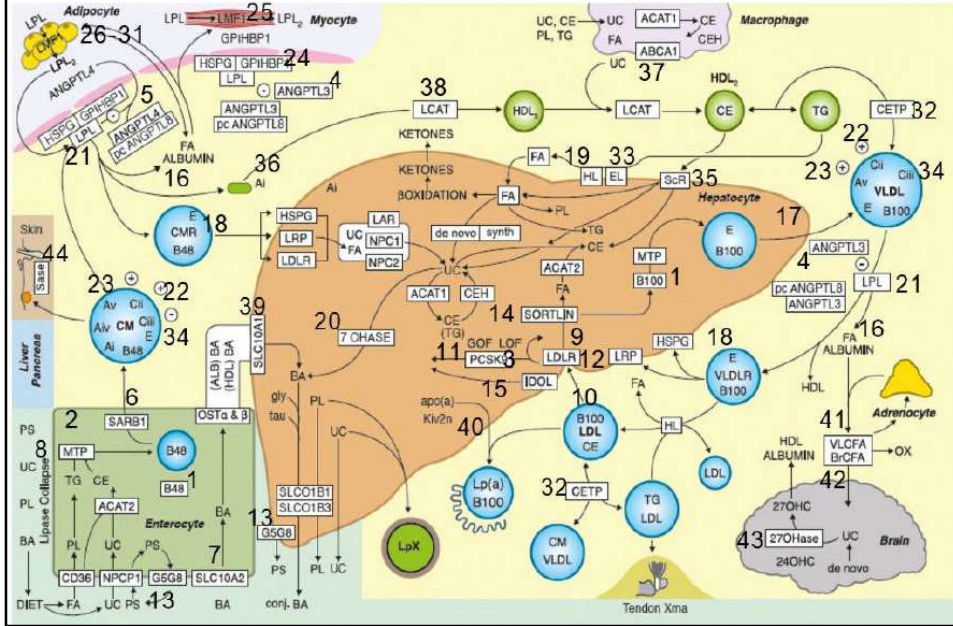
- Cholesterol
- Triglyceride



Het draait om lipoproteinen



Hoe denkt een internist over cholesterol?

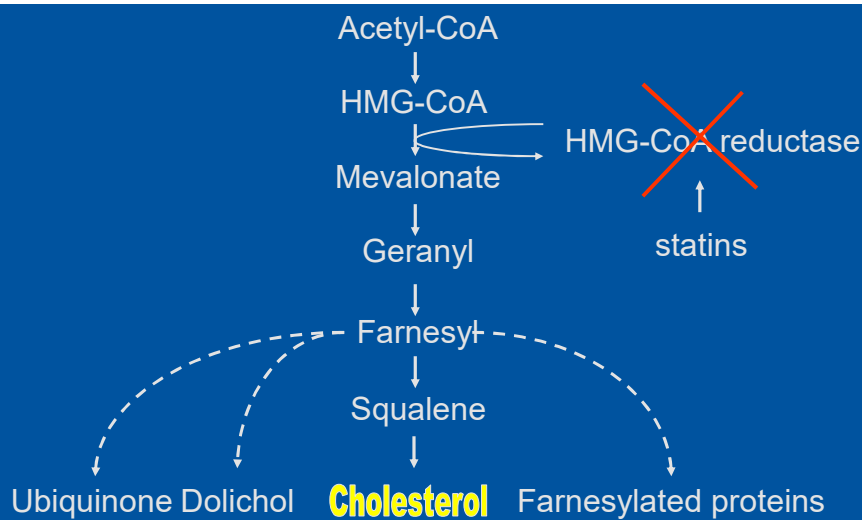


Why do we need cholesterol and lipoproteins?



- Component of cell membranes
 - *Physical and biological properties*
 - *Myelin structure*
- Synthesis of steroid hormones
 - *Cortisol*
 - *Aldosteron*
 - *Sex hormones: estrogen, testosterone*
- Synthesis of bile acids
 - *Formation of bile*
 - *Digestion of fatty foods*
- Transport of fat-soluble vitamins

Mevalonate pathway



Goldstein et al., Nature 1990

Stel een diagnose!!!



Hypercholesterolemie of
hypertensie is geen diagnose!!

Hoofdpijn is ook geen diagnose!

Lipids



LDL-cholesterol

The LDL particle is the most
abundant atherogenic lipoprotein

Friedewald formule (Clin Chem 1972;18:499-502):

$$\text{LDL-c} = \text{TC} - \text{HDL-c} - (0,45 \times \text{TG})$$

INVITED COMMENTARY

Fasting for Lipid Testing

Is It Worth the Trouble?

EDITORIAL

Should We Fast Before We Measure Our Lipids?

Arch Intern Med 2012;172:1705-1706

Arch Intern Med 2012;172:1710-1712

Differentialdiagnosis of hypercholesterolemia (elevated LDL-c)



- Familial Hypercholesterolemia (FH) **DLCN criteria**
- Hypothyroidism **TSH en vrij T4**
- Nefrotic syndrome **albumine/creat in urine**
- Liverfunction abnormalities **Laat maar zitten**
- Polygenic hypercholesterolemia

Stel een diagnose!!!



- cholesterol ziekte: behandel de ziekte
- cholesterol als risicofactor: behandel het risico

FH: Experiment of nature

Familial hypercholesterolemia (FH)

- *Mutation in LDL receptor*
- *Autosomal dominant (1:250)*
- *High plasma LDL levels*
- *High risk of coronary heart disease*
- *Fat deposits (xanthomata) on tendons*



Lancet 362:717, 2003



NEJM 341:490,1999

Familial Hypercholesterolemia



arcus lipoides



Xanthelasma

Familial Hypercholesterolemia




Frans Hals, 1633.
Nat Art Gallery, Washington DC, USA

Familial Hypercholesterolemia




Leonardo da Vinci, 1507.
Louvre, Parijs

Medicine


 **The Nobel Prize in Physiology or Medicine 1985**

University Medical Center Utrecht

"for their discoveries concerning the regulation of cholesterol metabolism"



Michael S. Brown



Joseph L. Goldstein

A RECEPTOR-MEDIATED PATHWAY FOR CHOLESTEROL HOMEOSTASIS

Nobel lecture, 9 December, 1985

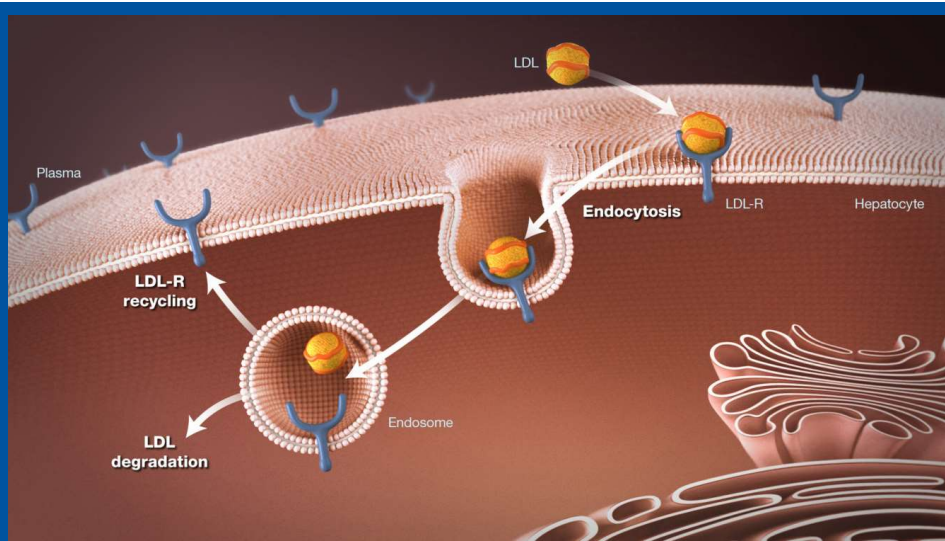
by
MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

Department of Molecular Genetics, University of Texas Health Science Center, Southwestern Medical School, 5323 Harry Hines Blvd. Dallas, Texas, U.S.A.

nobelprize.org

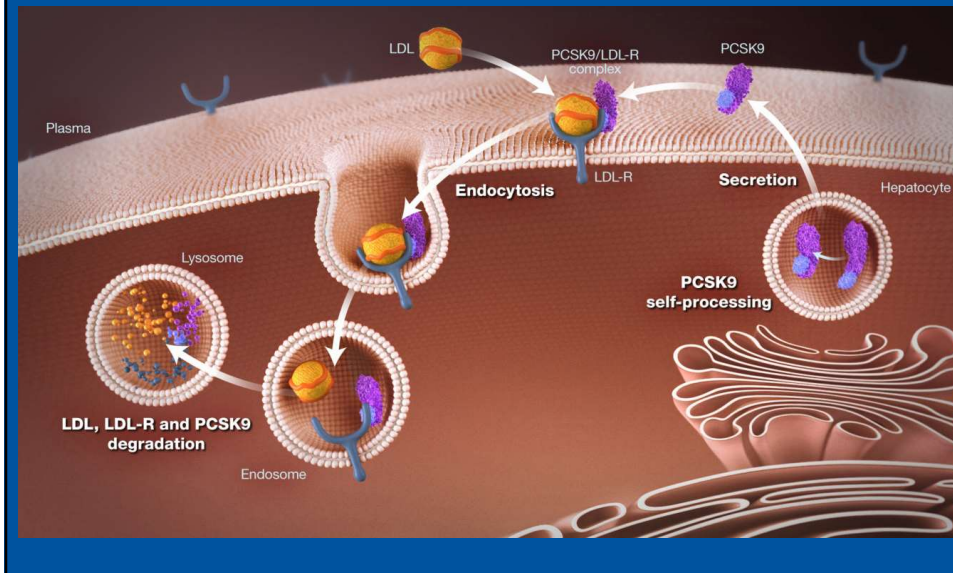
Hepatic LDL-R play a key role in regulating plasma LDL-c levels

University Medical Center Utrecht

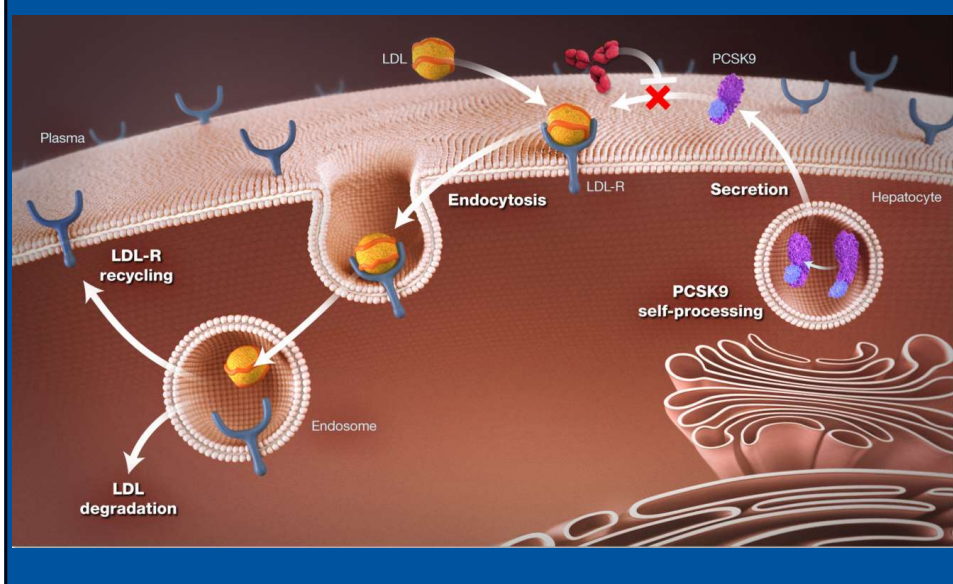


The diagram illustrates the cellular mechanism of LDL regulation in a hepatocyte. LDL particles, shown as orange spheres, are present in the plasma. They bind to LDL receptors (LDL-R) on the cell surface. This binding triggers endocytosis, where the membrane pinches off to form a vesicle containing both the LDL particle and the receptor. Inside the cell, the vesicle matures into an endosome. In the endosome, the LDL particle is degraded, releasing cholesterol. Simultaneously, the LDL-R receptors are recycled back to the cell surface, ready to bind more LDL particles. The diagram also shows the internal structure of the hepatocyte, including the endoplasmic reticulum.

PCSK9 regulates the surface expression of hepatic LDL-Rs

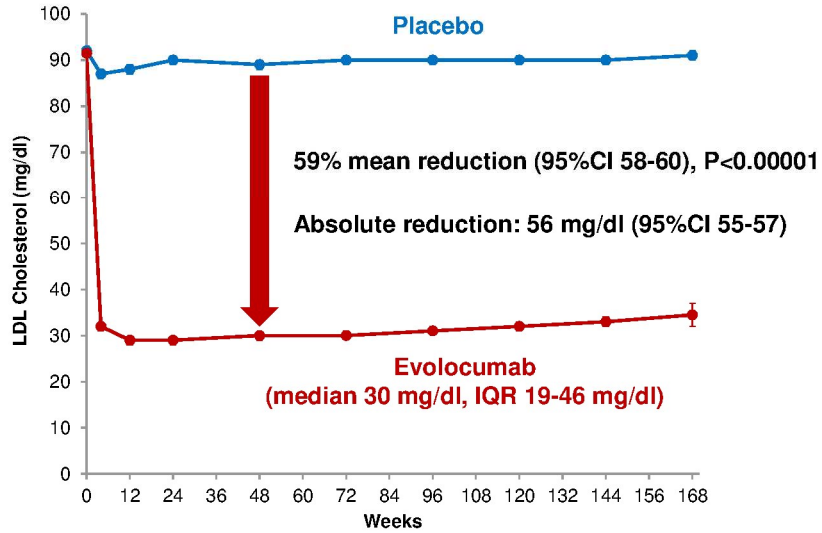
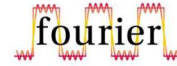


Anti-PCSK9 monoclonal antibodies block PCSK9/LDL-R interaction and may lower LDL-C





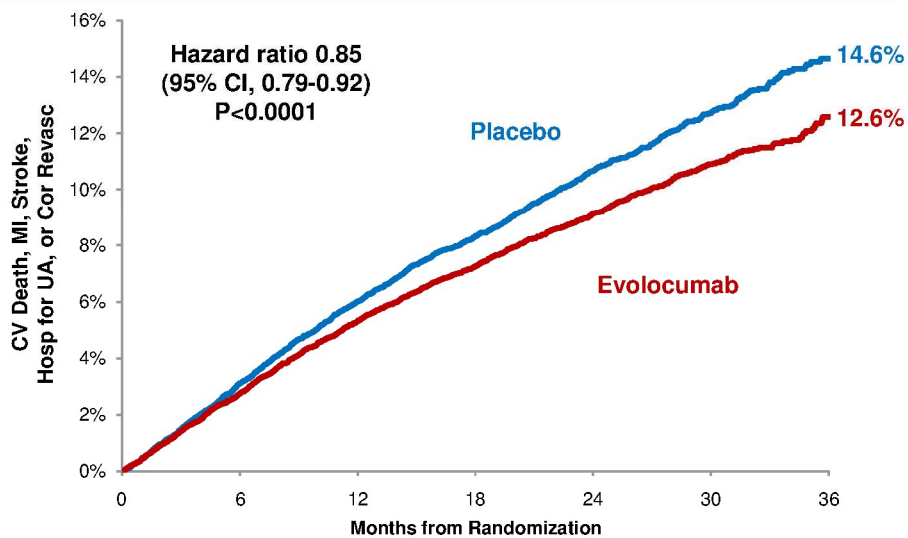
LDL Cholesterol



NEJM 2017;376:1713-1722

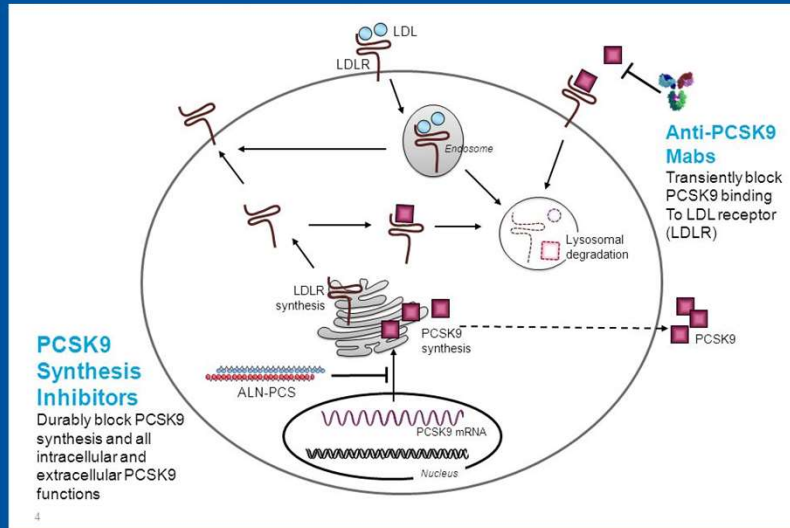


Primary Endpoint



NEJM 2017;376:1713-1722

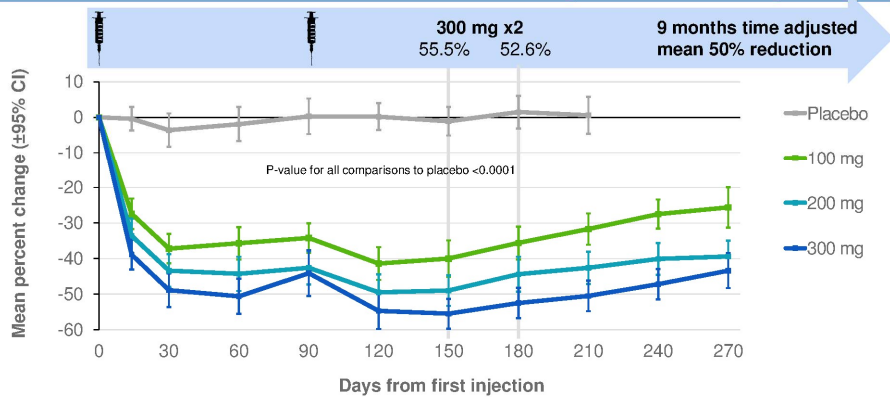
PCSK9 inhibition by RNAi



NEJM 2017;376:41-51.

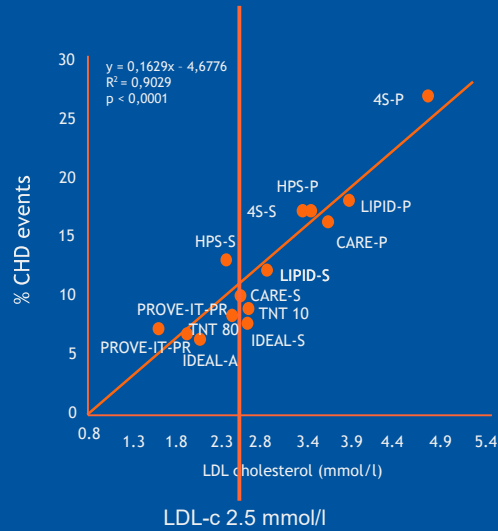
ORION trial

Efficacy: Two dose starting regimen
Robust, sustained LDL-C reductions – optimal start regimen



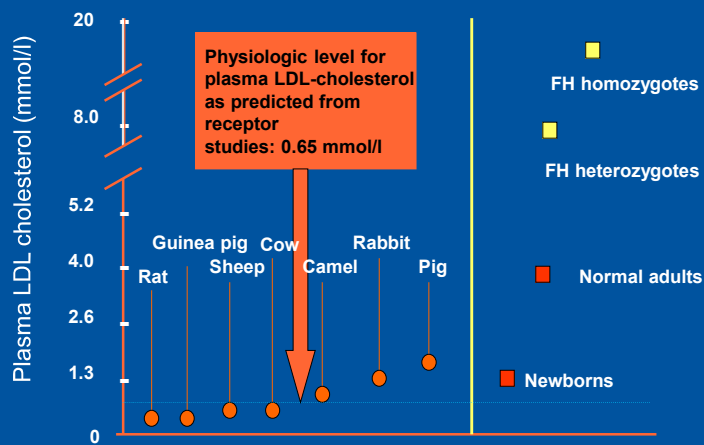
NEJM 2017;376:1713-1722

Wat is the optimal LDL-c treatment goal?



Adapted from O'Keefe, Jr. et al. JACC 2004;11:2142-2146

"Normal" LDL-cholesterol



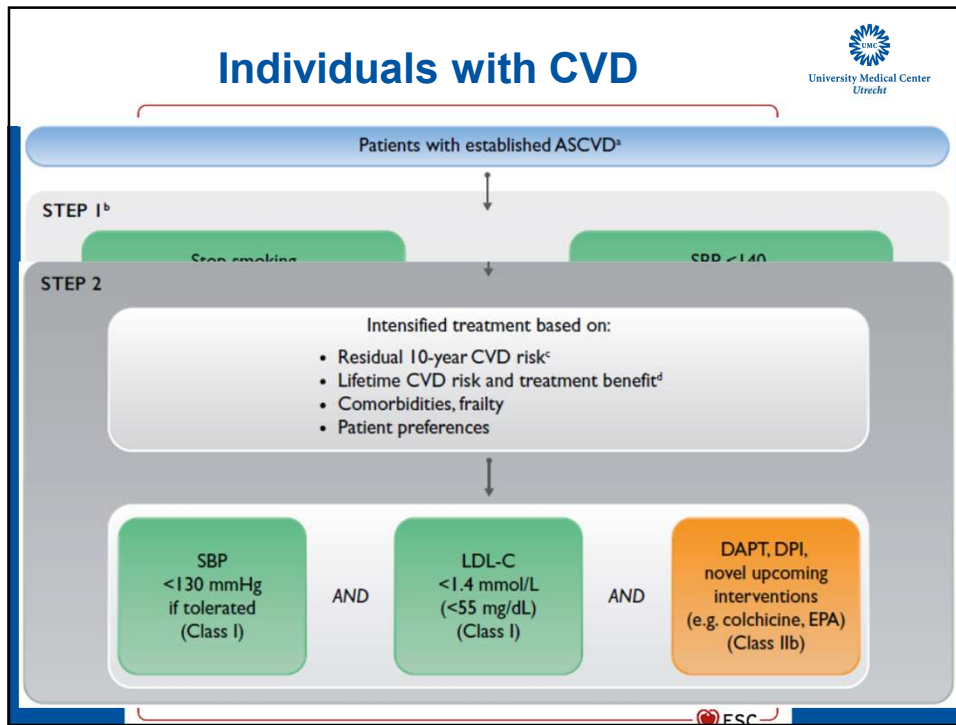
Vrij naar Goldstein en Brown "The Metabolic basis of Inherited Disease"

Individual 10-year CV risk (SCORE risk table)

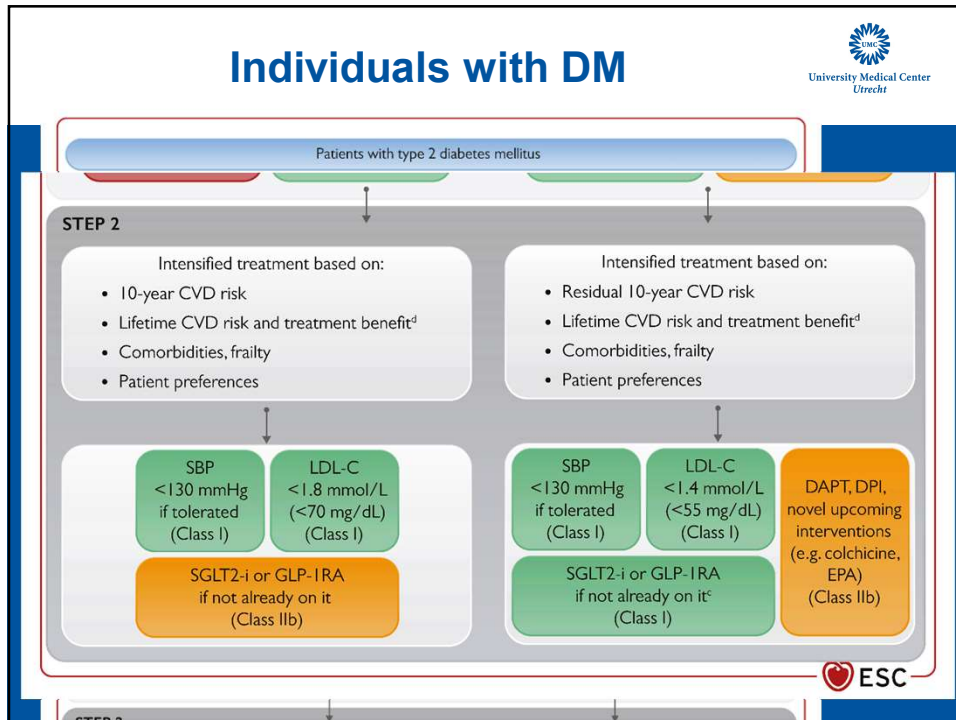


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Individuals with CVD



Individuals with DM



Instead of treatment goals, estimation of lifetime treatment benefit to guide treatment



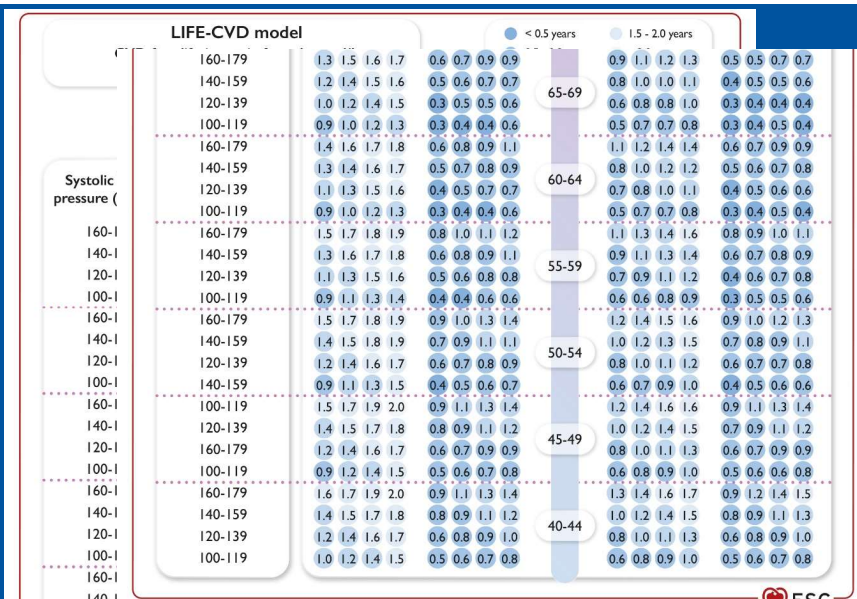
Treatment threshold/goal LDL-c <2,6, <1,8 (<1,4) mmol/l

Calculate lifetime benefit of lipid-lowering treatment

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Instead of treatment goals, estimation of lifetime treatment benefit to guide treatment



Treatment options for LDL-c lowering



Statins (simva, prava, fluva, atorva, rosuva)
Ezetimibe
PCSK9-mab of si-RNA (evo, ali, inclisiran)
Fibrates (bezafibraat)

Statins: safe, super effective, super cheap

Ezetimibe: safe, moderate effective, super cheap

PCSK9-i: safe, super effective, super expensive

Fibrates: few indications, specialized clinics

Statine-geassocieerde klachten



- Komt voor, maar is vrij zeldzaam (2-4%?)
- Stoppen statine, herstarten (evt. lagere dosis, andere statine)
- Indien aanhoudende klachten, laagst verdraagbare dosis statine in combi met eze, evt PCSK9-i

