Universitair Medisch Centrum
Utrecht

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

F.L.J. Visseren

17 mei 2022

NVHVV - CNE

University Medical Center
Utrecht

Vascular Medicine Utrecht

University Medical Center
Utrecht

"Cholesterol is the most highly decorated small molecule in biology. Thirteen Nobel Prizes have been awarded to scientists who devoted major parts of their careers to cholesterol. Ever since it was first isolated from gallstones in 1784, almost exactly 200 years ago, cholesterol has exerted a hypnotic fascination for scientists from the most diverse domains of science and medicine….. "

"…. 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. "

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"…. 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)

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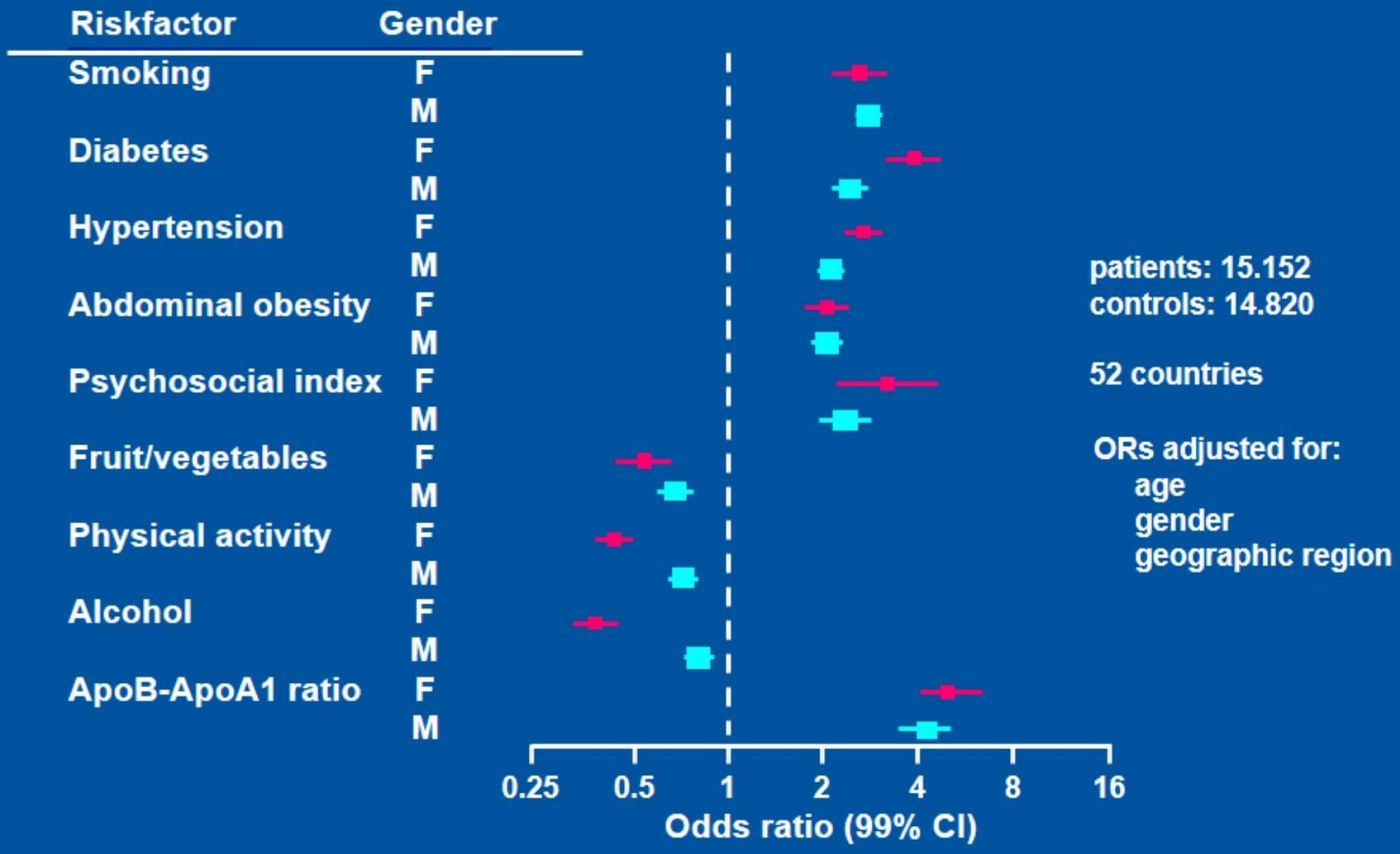

Yusuf S et al. Lancet. 2004;364:937-52.

Lipids

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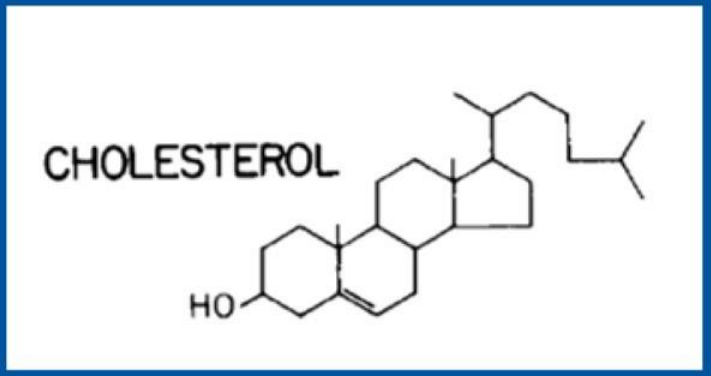
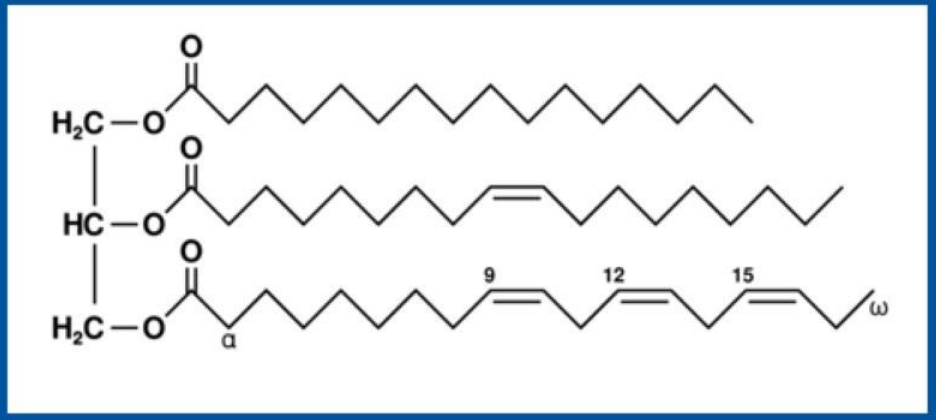
- Cholesterol
- Triglyceride





Het draait om lipoproteinen

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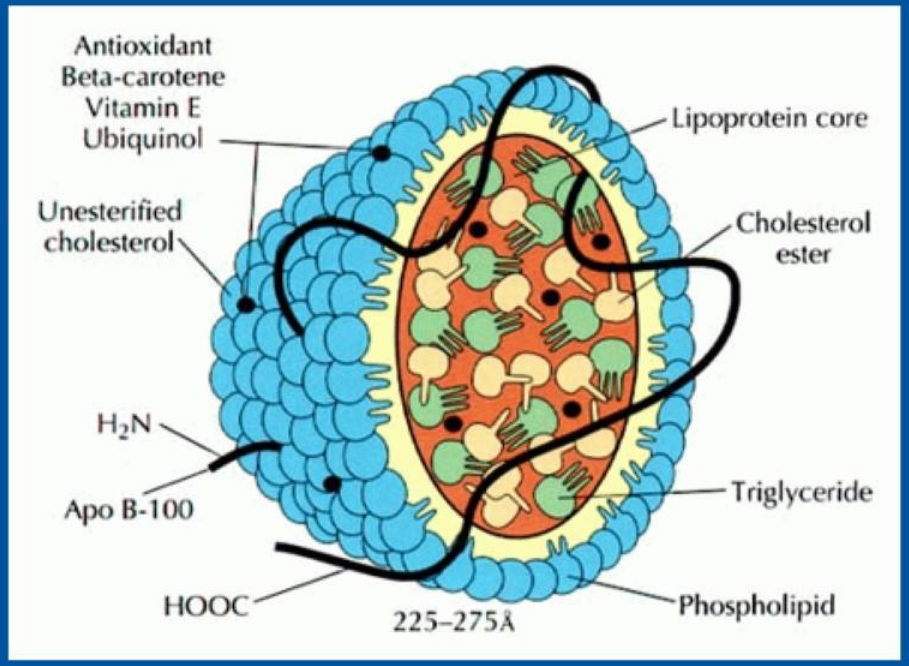

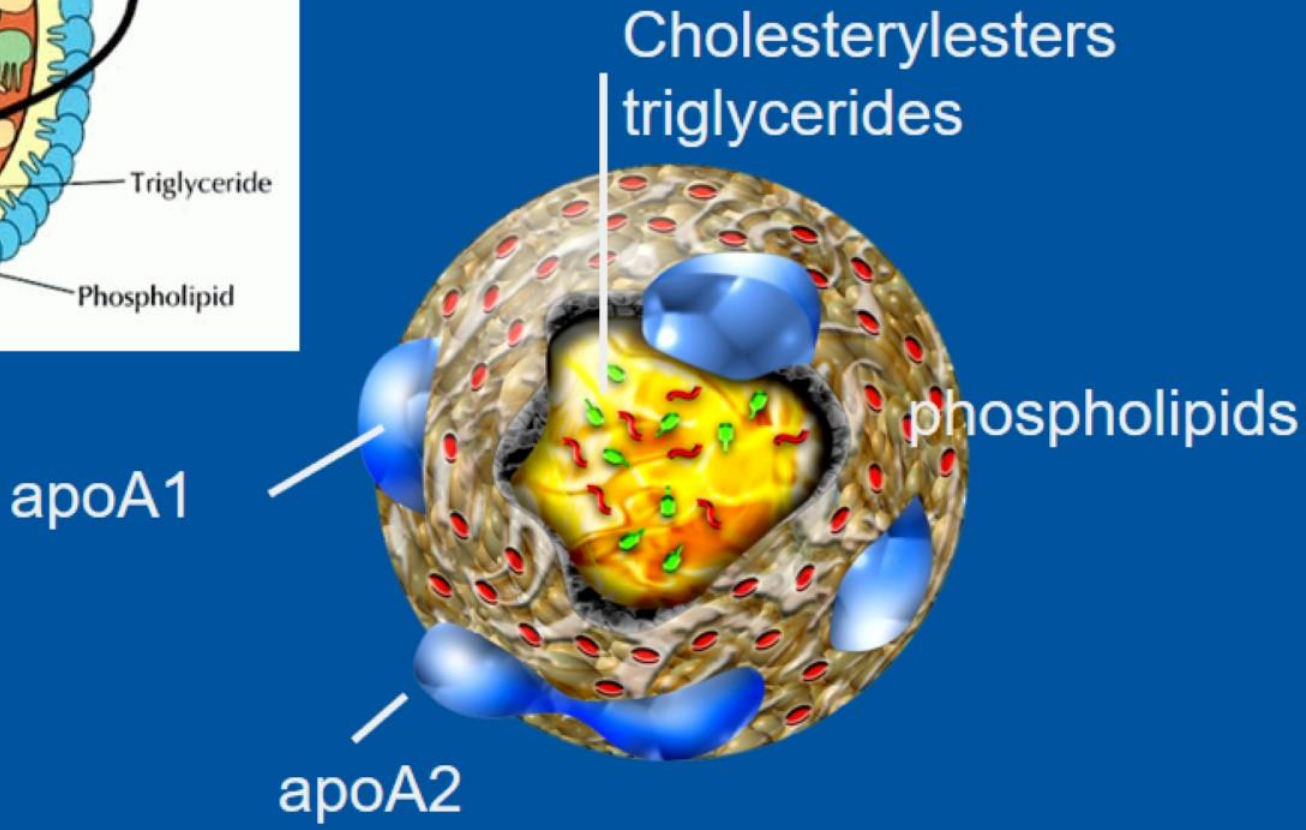

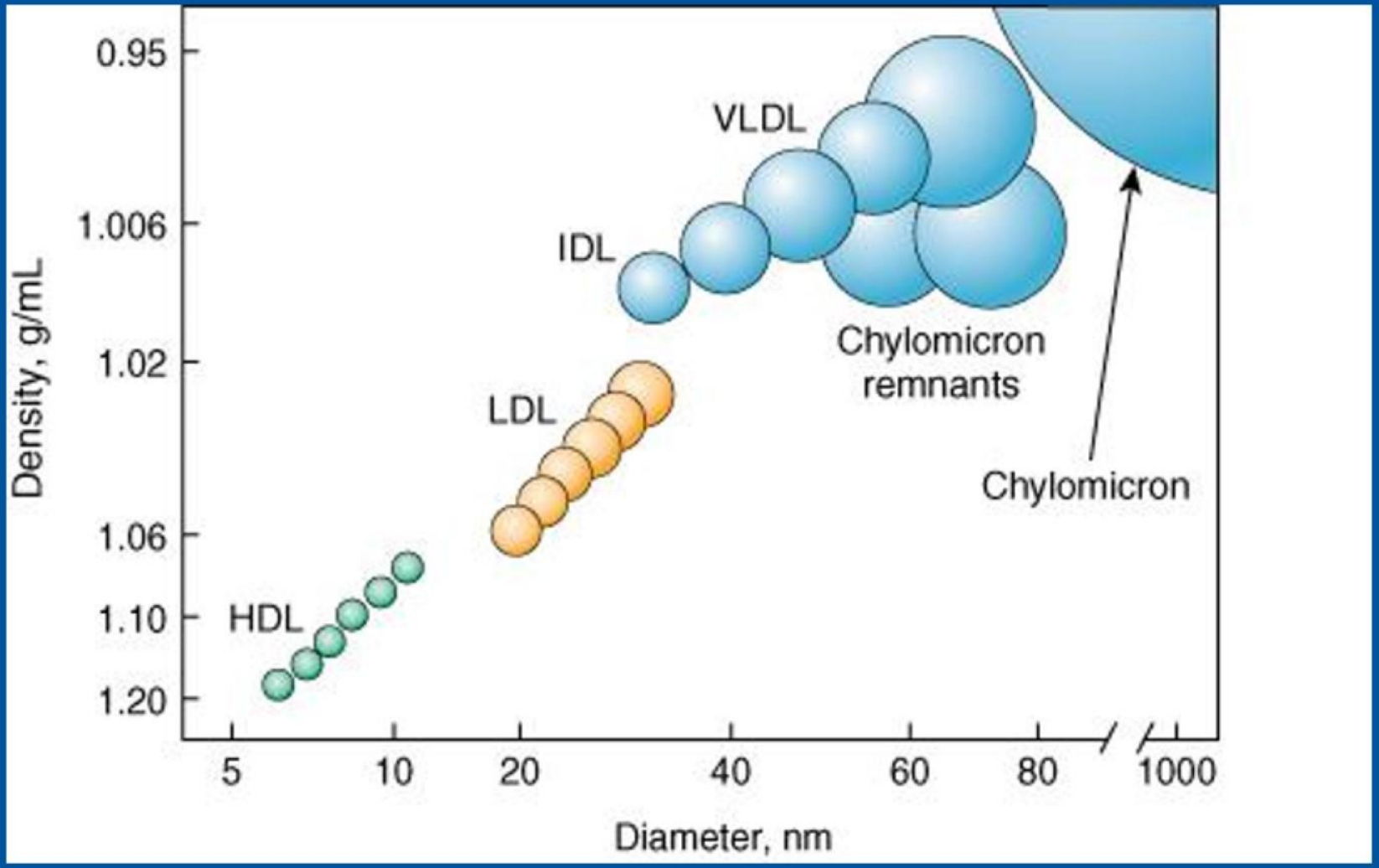
0.95
1.006
1.02
1.06
1.10
1.20
Density, g/mL
VLDL
IDL
LDL
HDL
Chylomicron
remnants
Chylomicron
5
10
20
40
60
80
1000
Diameter, nm

Hoe denkt een internist over cholesterol?

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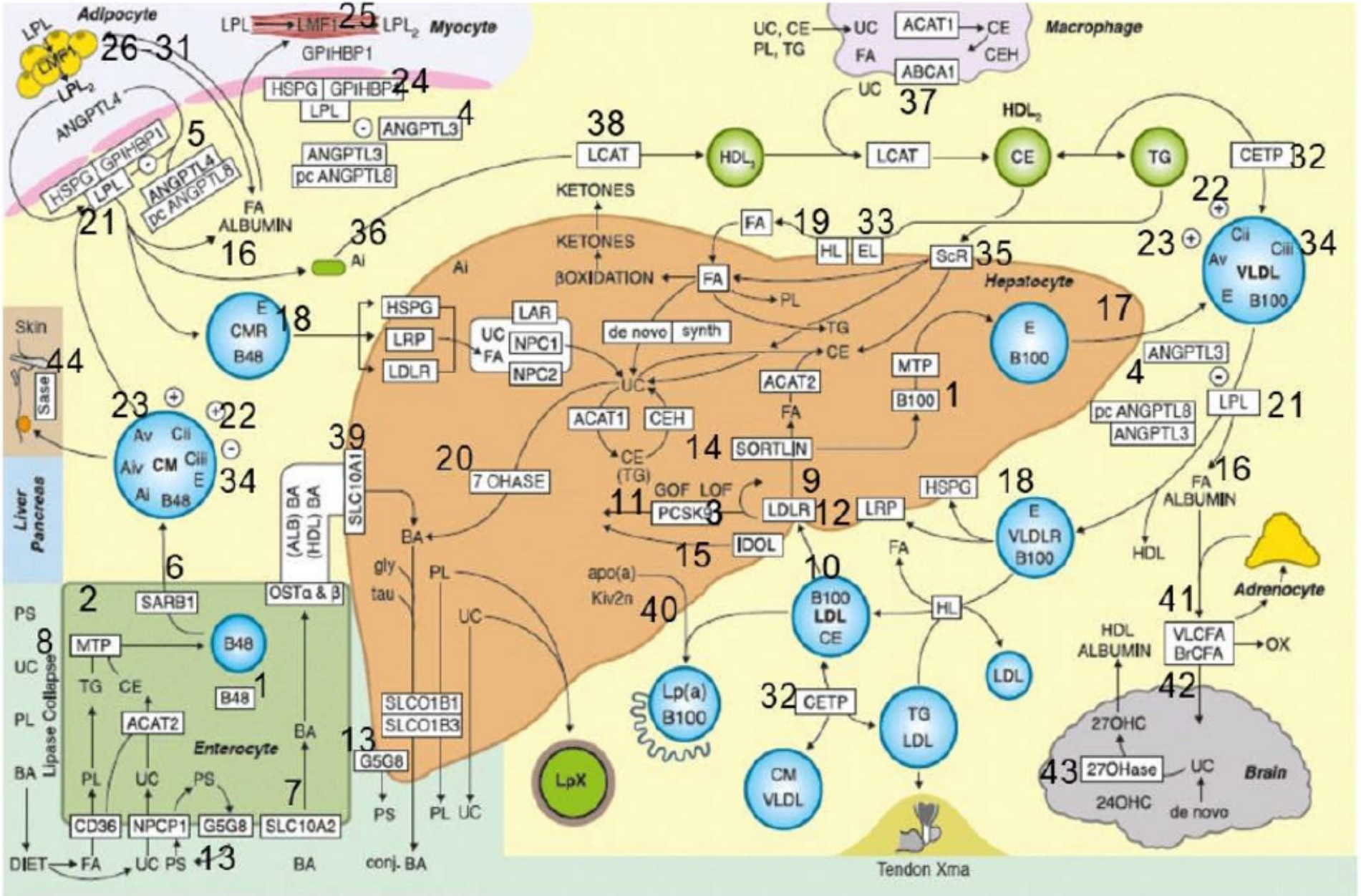

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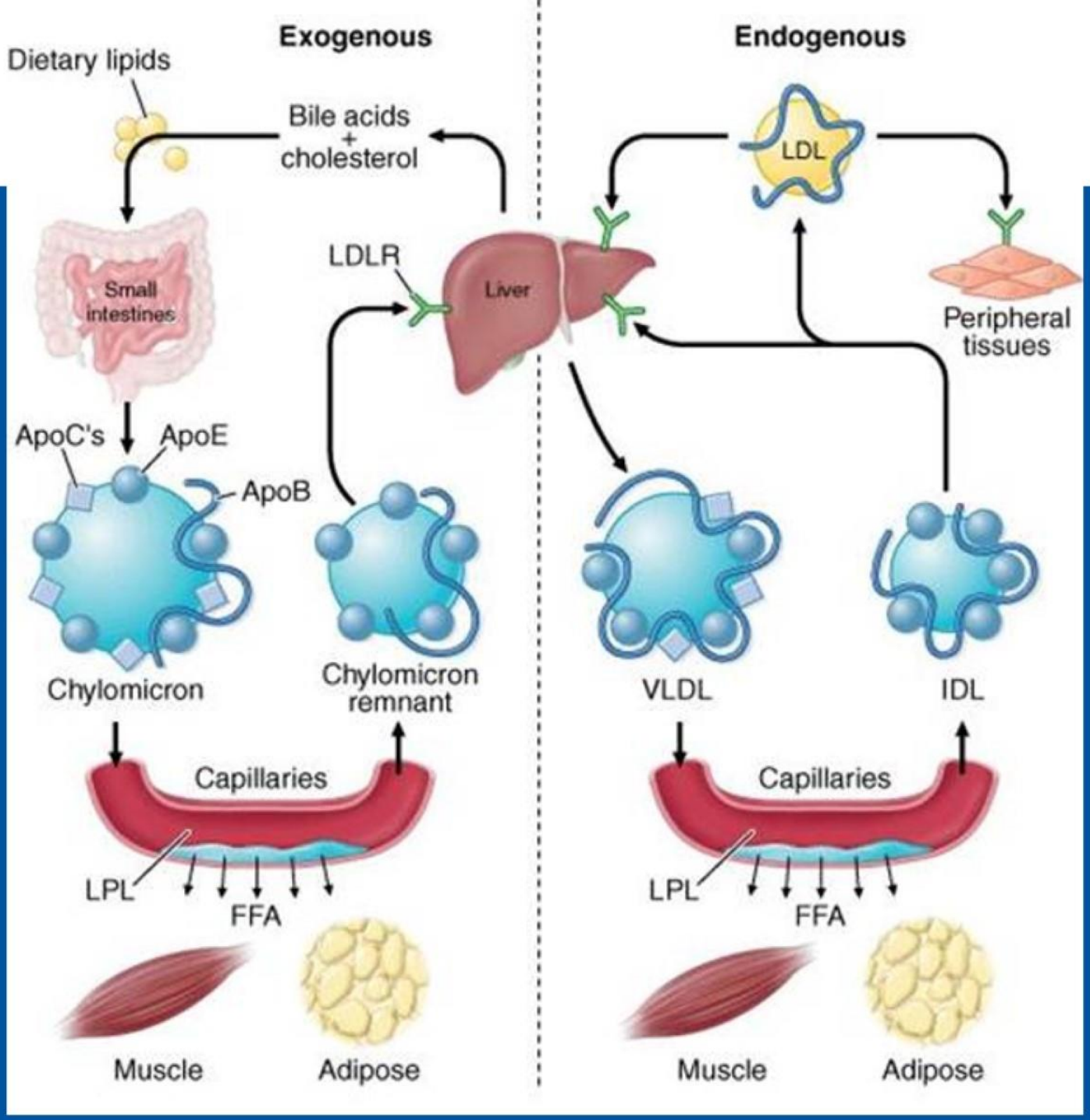

Why do we need cholesterol and lipoproteins?

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

Mevalonate pathway

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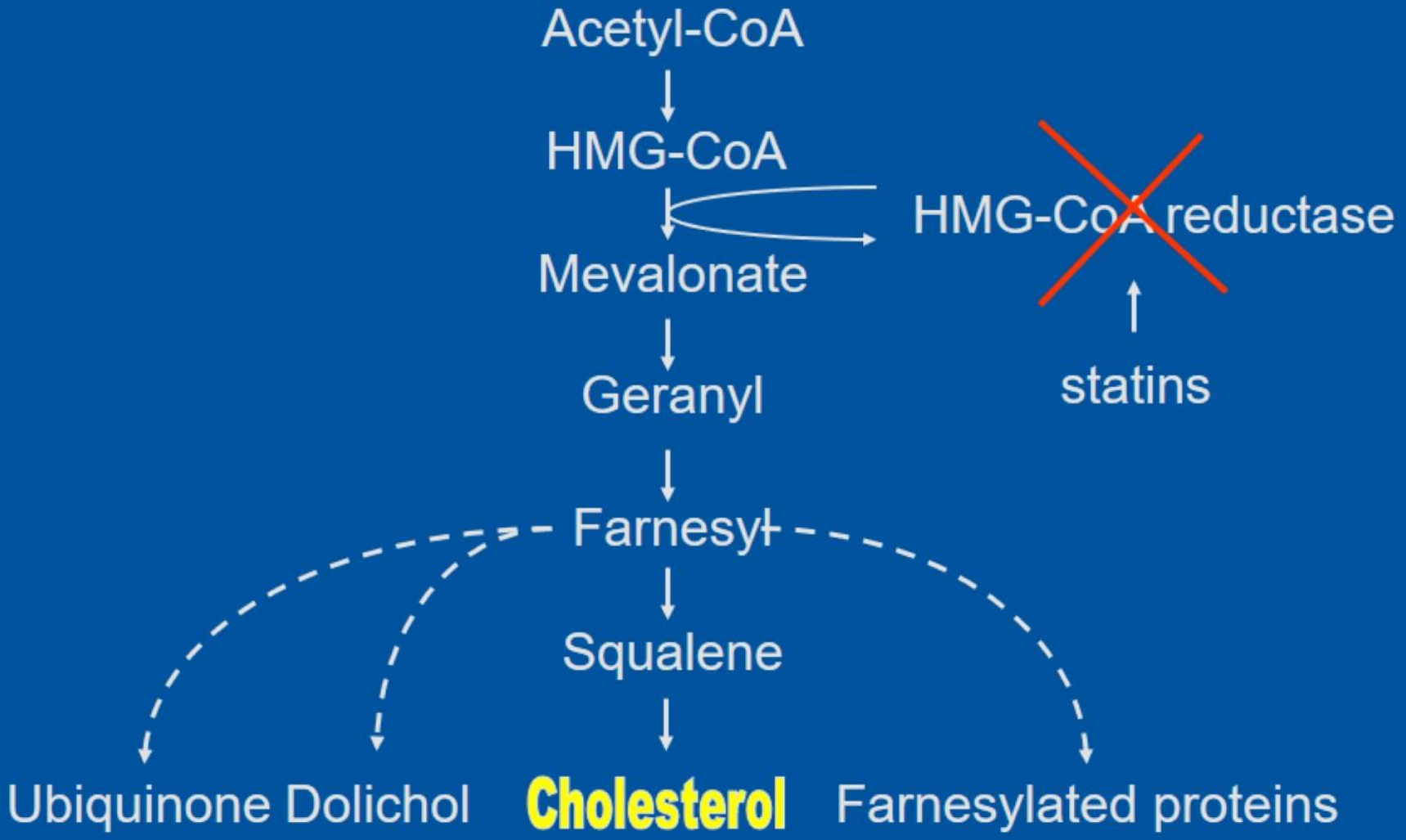

Goldstein et al., Nature 1990

Stel een diagnose!!!

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Hypercholesterolemie of hypertensie is geen diagnose!!

Hoofdpijn is ook geen diagnose!

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LDL-cholesterol

The LDL particle is the most abundant atherogenic lipoprotein

Lipiden

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

LDL-c = TC – HDL-c – (0,45 x TG)

Total cholesterol is niet bruikbaar in de praktijk

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LDL-c
HDL-c
VLDL-c

Total cholesterol

Nuchter meten is meestal niet nodig

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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)

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- 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!!!

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

FH: Experiment of nature

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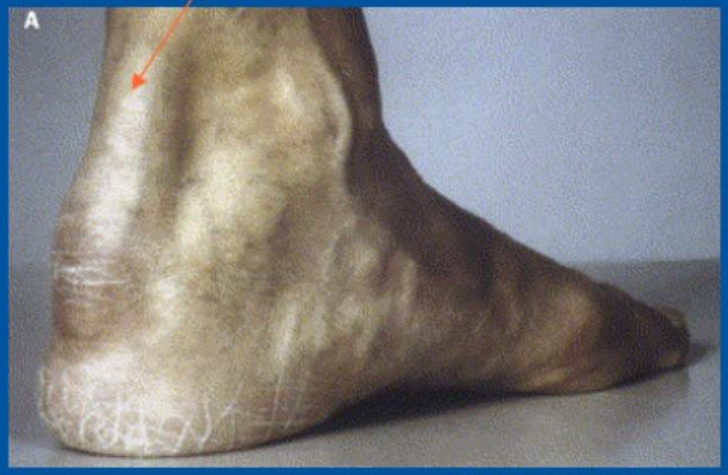
Familial hypercholesterolemia (FH)

- *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

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arcus lipoides

Xanthelasma

Familial Hypercholesterolemia

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Frans Hals, 1633.

Nat Art Gallery, Washington DC, USA

Familial Hypercholesterolemia

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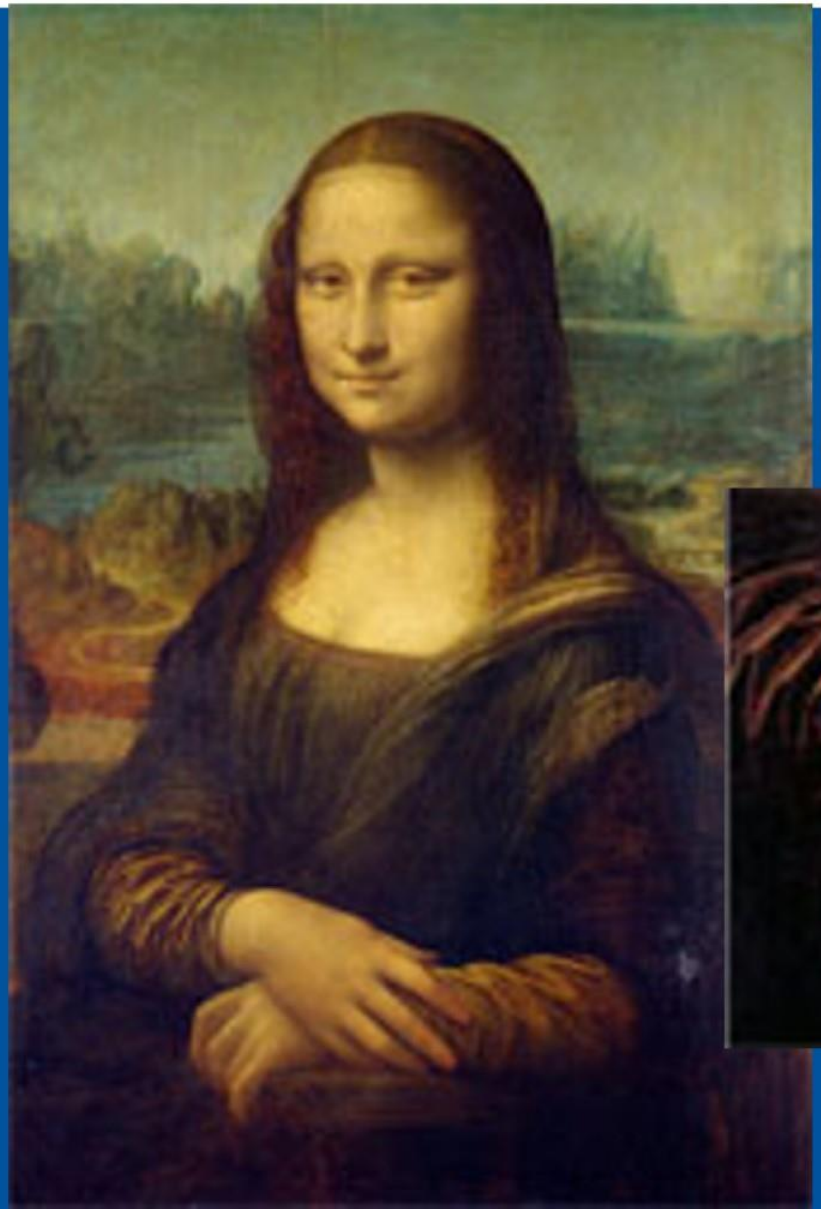

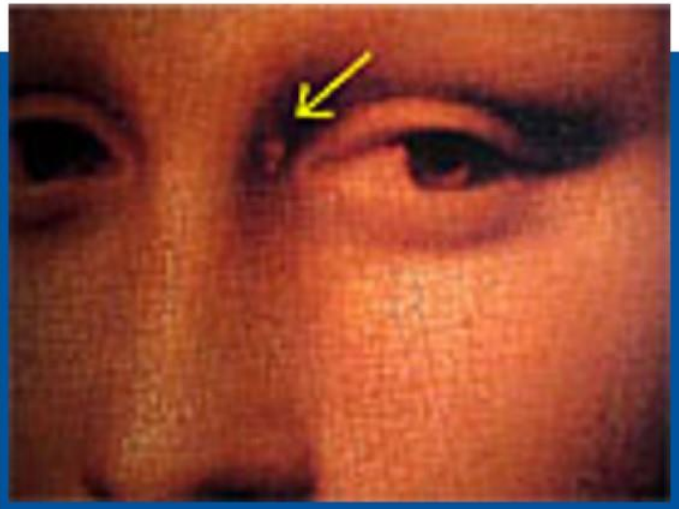

Leonardo da Vinci, 1507.
Louvre, Parijs

The Nobel Prize in Physiology or Medicine 1985

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"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

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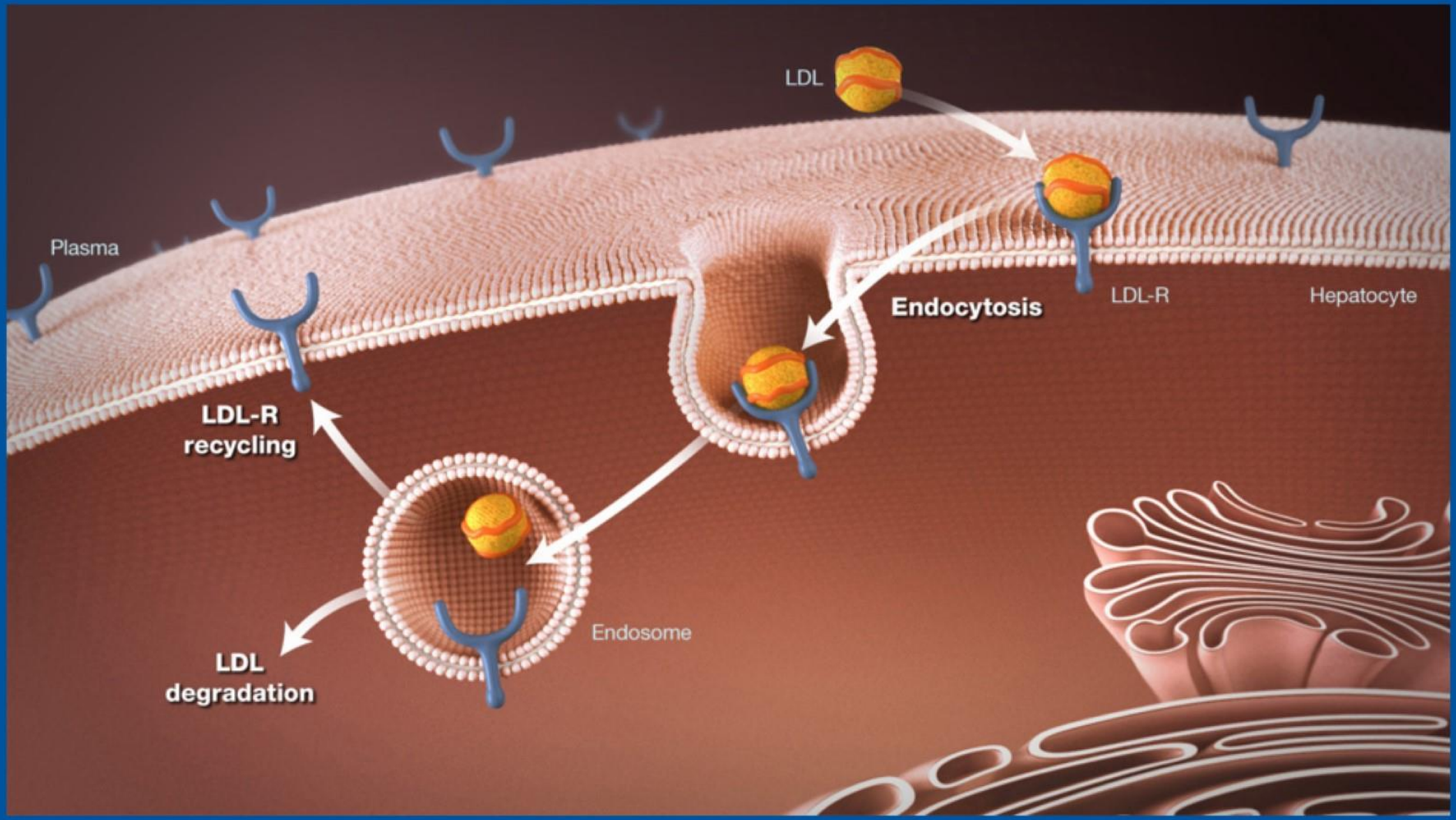

Genetic analyses FH

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- LDL-receptor gene
- apoB gene
- PCSK9 gene

PCSK9; a scientific and clinical fairytale

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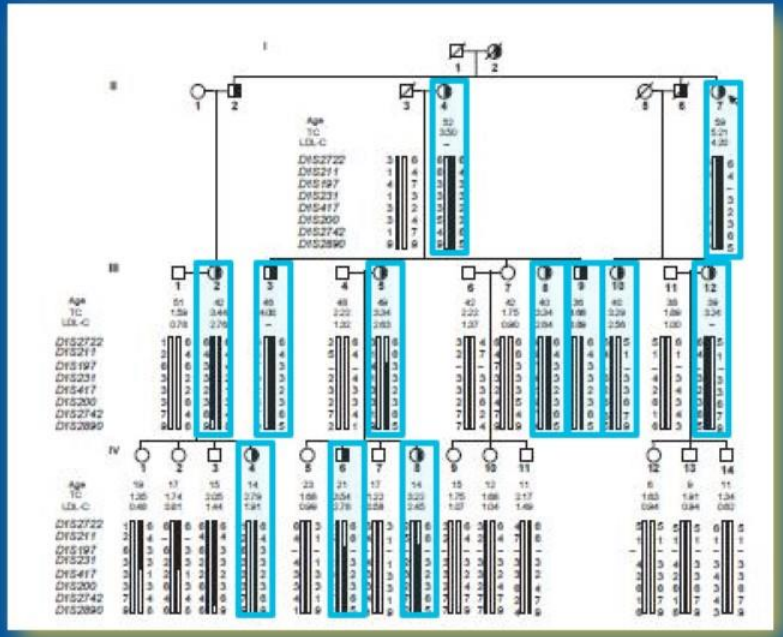
Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes *LDLR* (encoding low-density lipoprotein receptor) or *APOB* (encoding apolipoprotein B). We mapped a third locus associated with ADH, *HCHOLA3* at 1p32, and now report two mutations in the gene *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. *PCSK9* encodes



Affected family members with:

- Total cholesterol >90th percentile
- Tendon xanthomas
- CHD, early MI, Stroke

Nat Genet 2003;34:154-156

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Admirer

Catherine Boileau

ESC Barcelona 2017

PCSK9 regulates the surface expression of hepatic LDL-Rs

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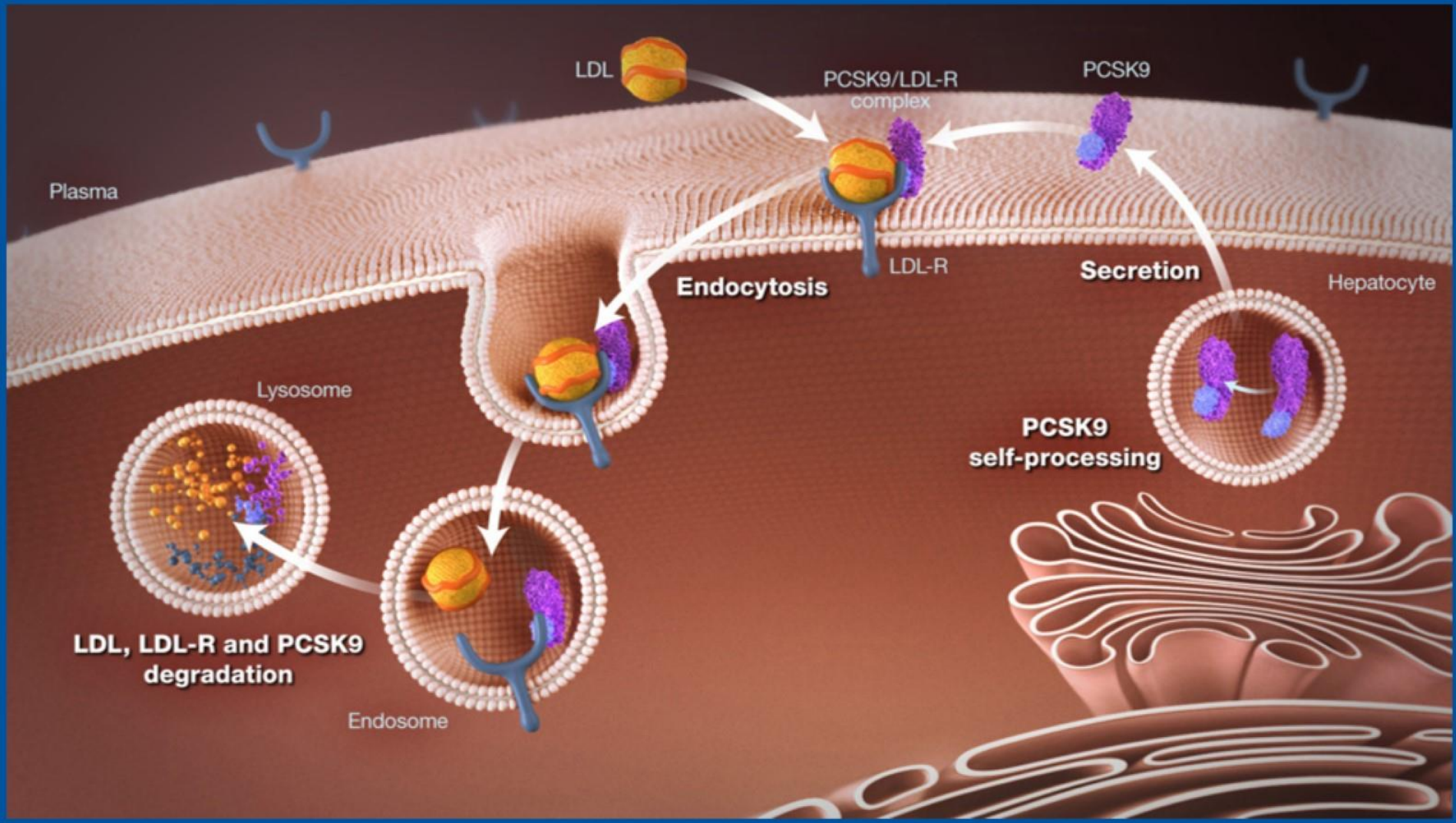

Anti-PCSK9 monoclonal antibodies block PCSK9/LDL-R interaction and may lower LDL-C

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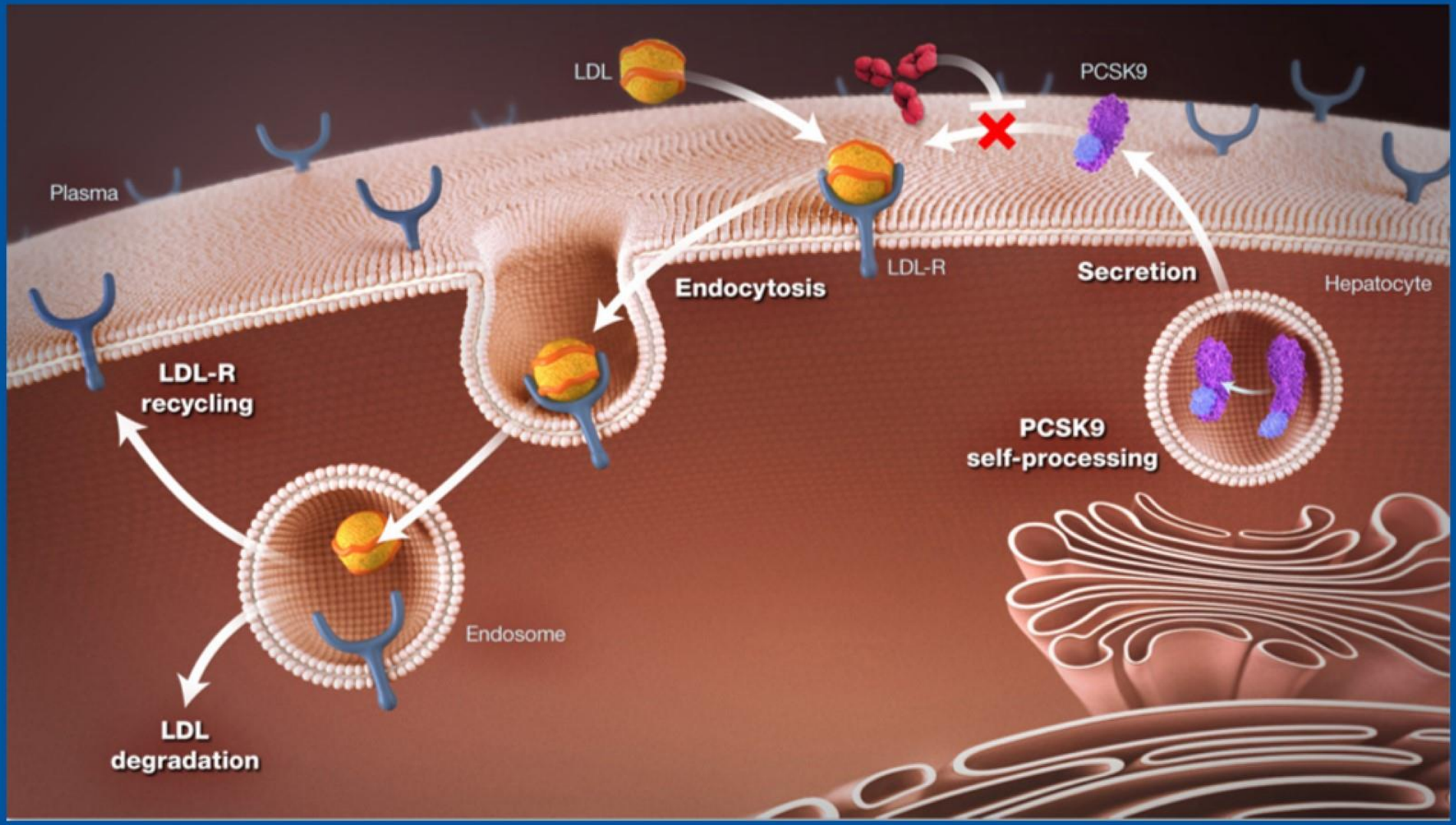
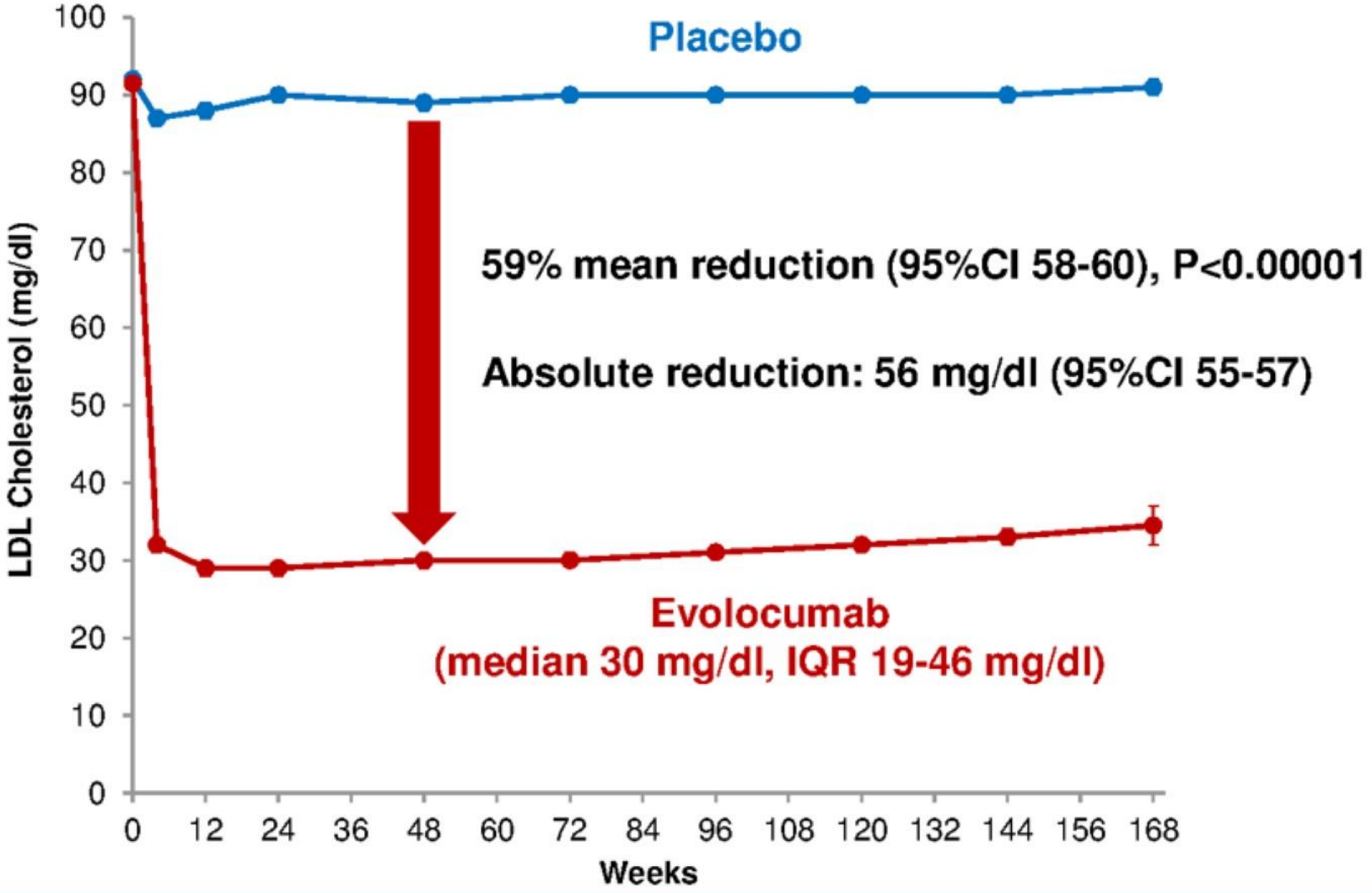
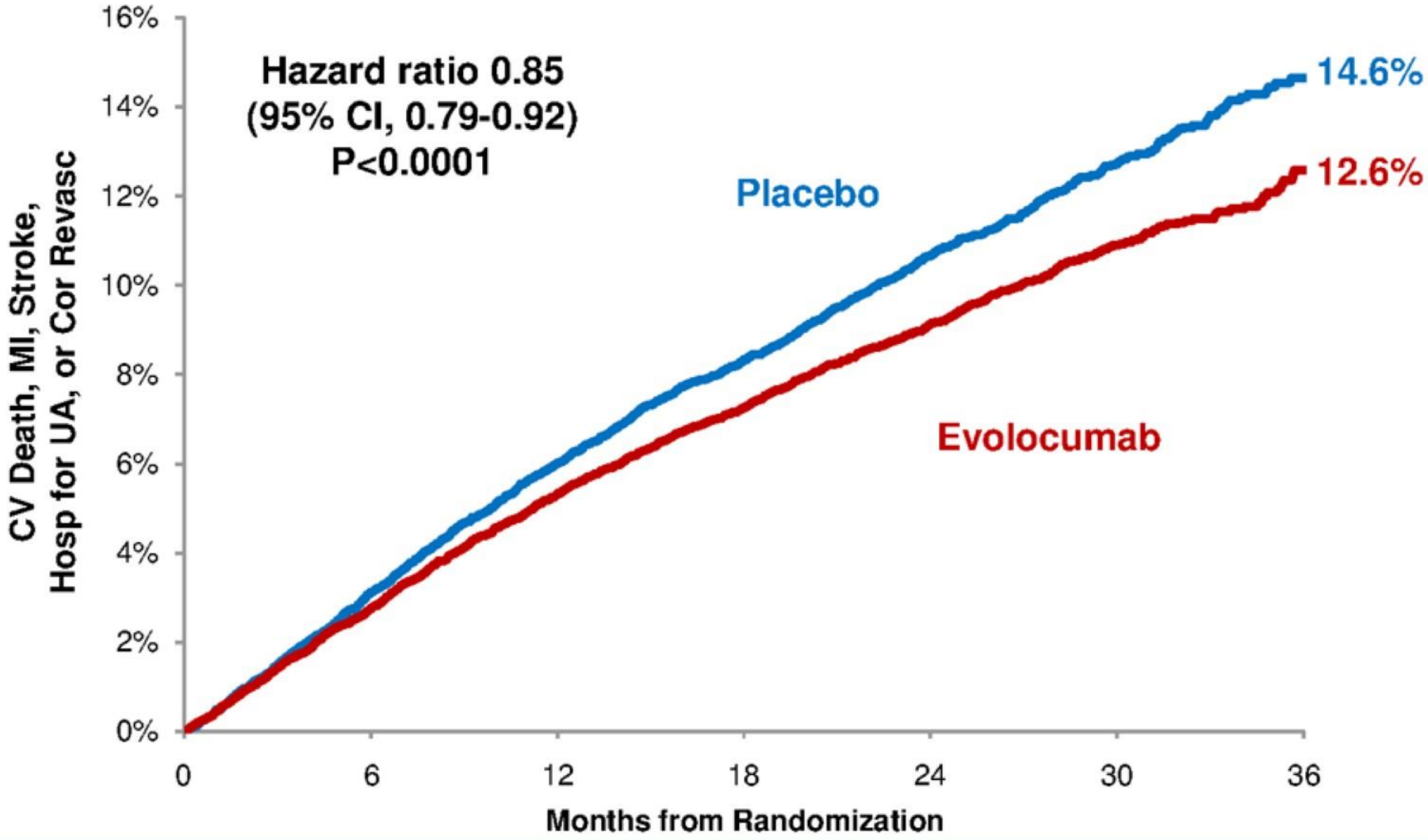


LDL Cholesterol



Primary Endpoint



NEJM 2017;376:1713-1722

PCSK9 inhibition by RNAi

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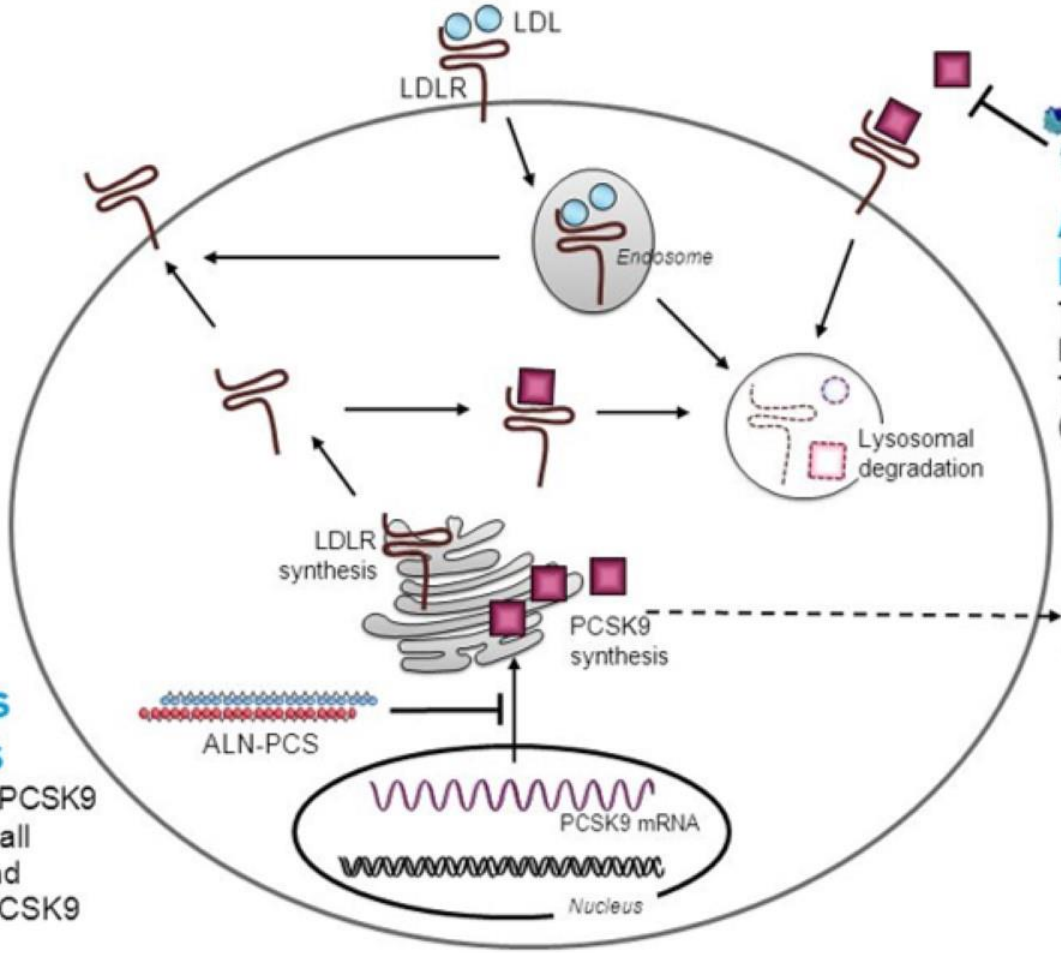

Anti-PCSK9 Mabs

Transiently block PCSK9 binding To LDL receptor (LDLR)

PCSK9 Synthesis Inhibitors

Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

4

NEJM 2017;376:41-51.

ORION trial

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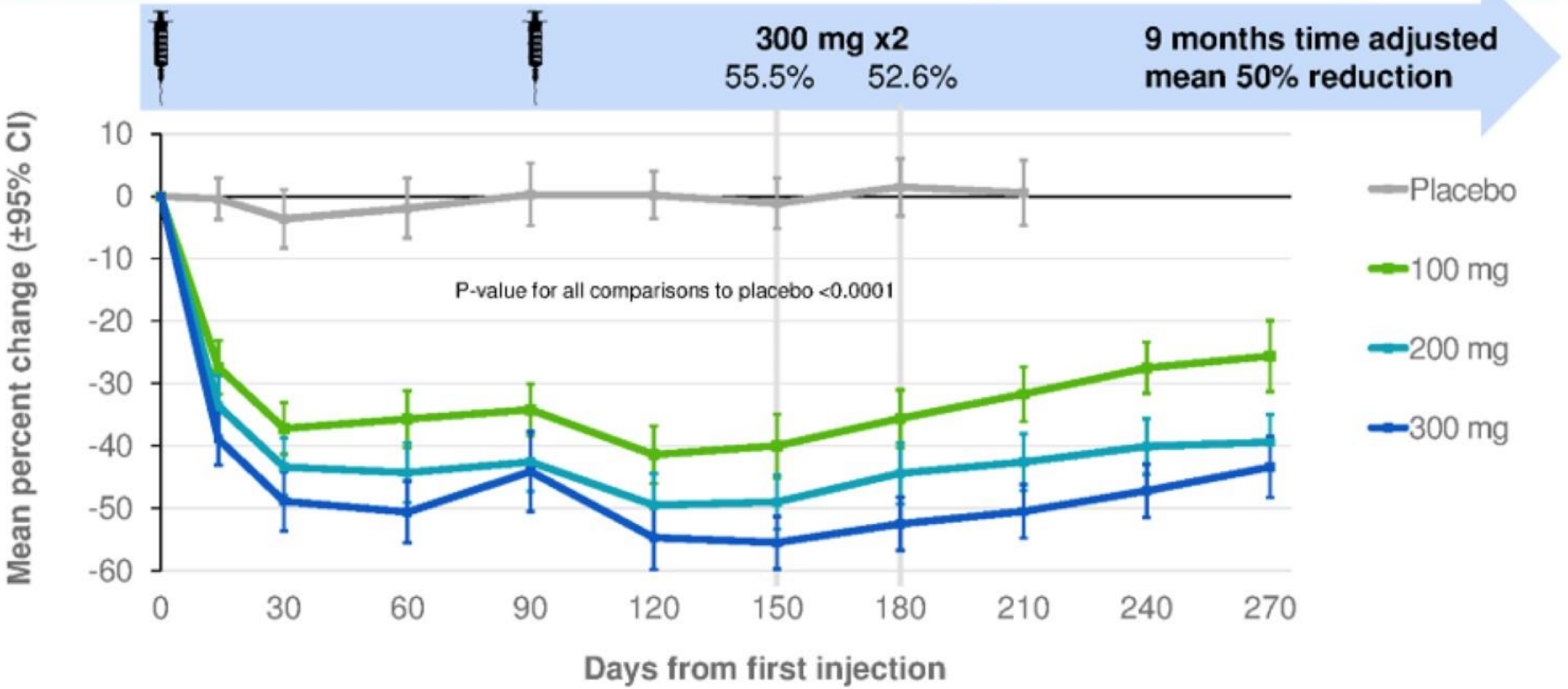
Efficacy: Two dose starting regimen

Robust, sustained LDL-C reductions – optimal start regimen



NEJM 2017;376:1713-1722

Wat is the optimal LDL-c treatment goal?

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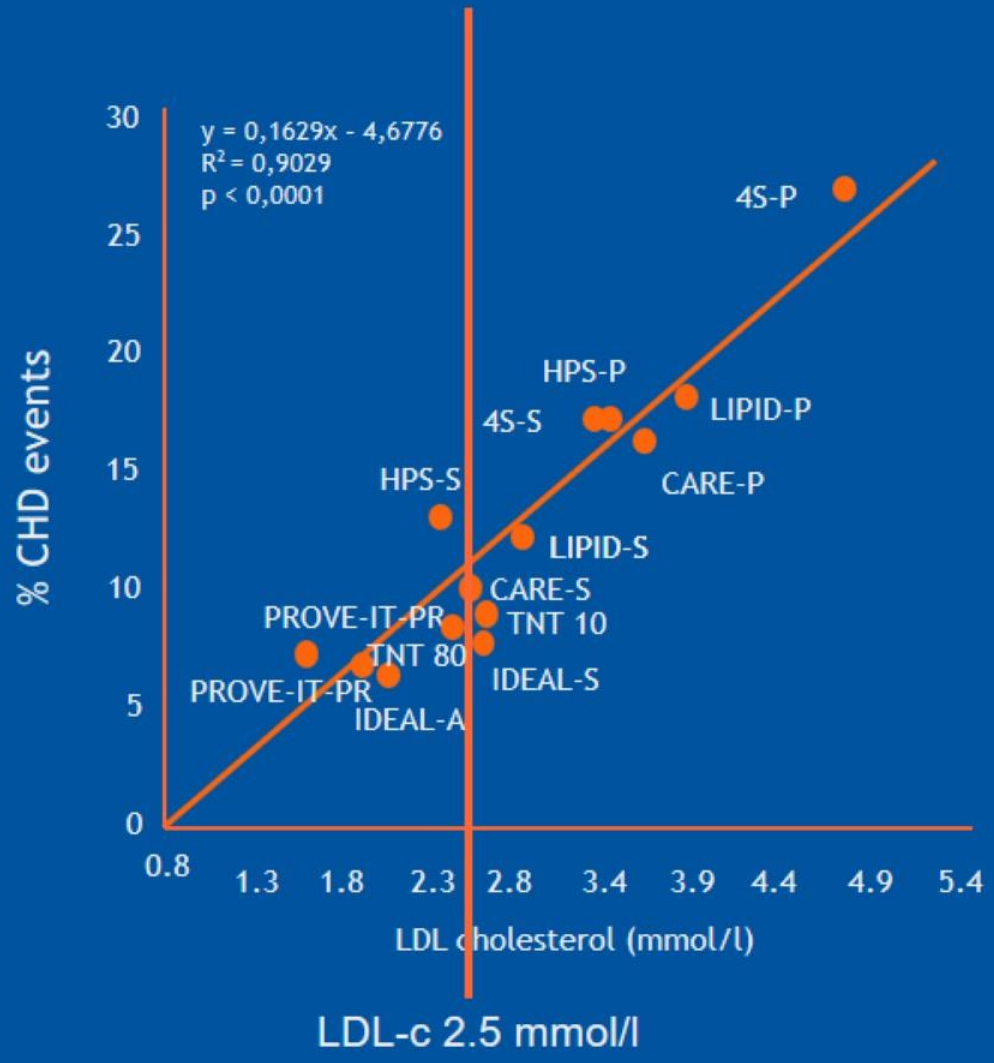

Adapted from O'Keefe, Jr. et al. JACC 2004;11:2142-2146

“Normal” LDL-cholesterol

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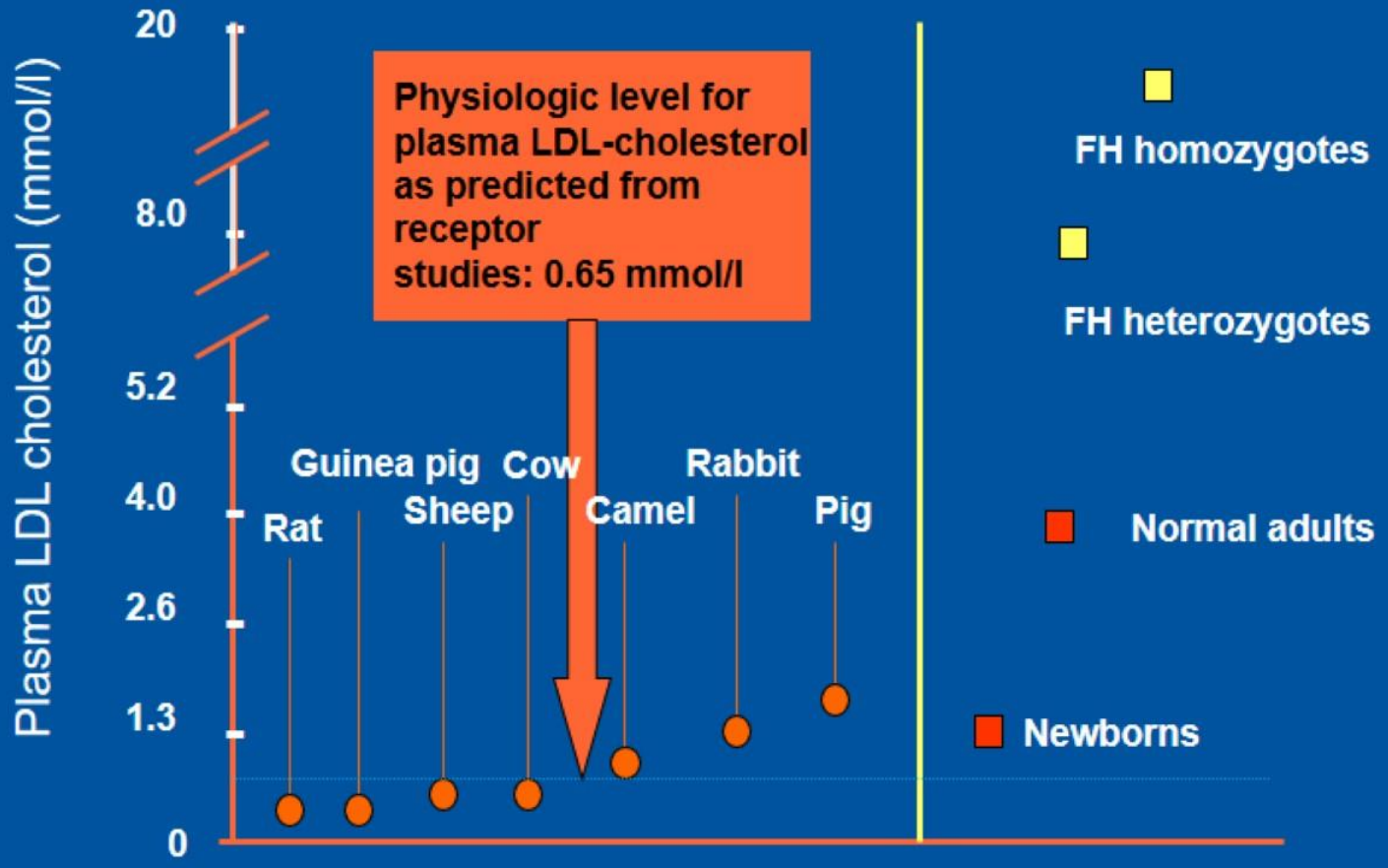

Vrij naar Goldstein en Brown "The Metabolic basis of Inherited Disease"

Individual 10-year CV risk (SCORE risk table)

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Individuals without CVD or DM

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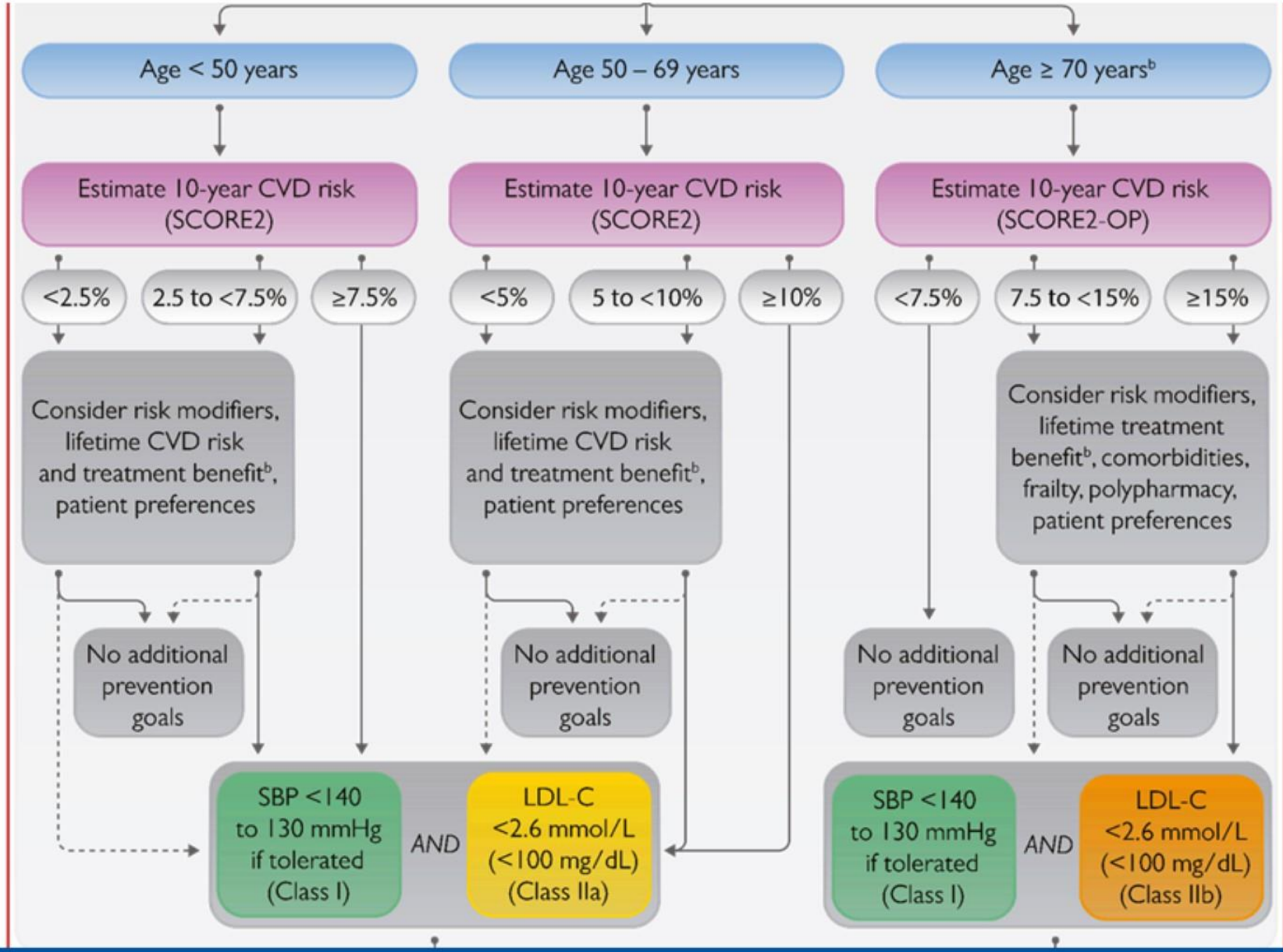

Individuals with CVD

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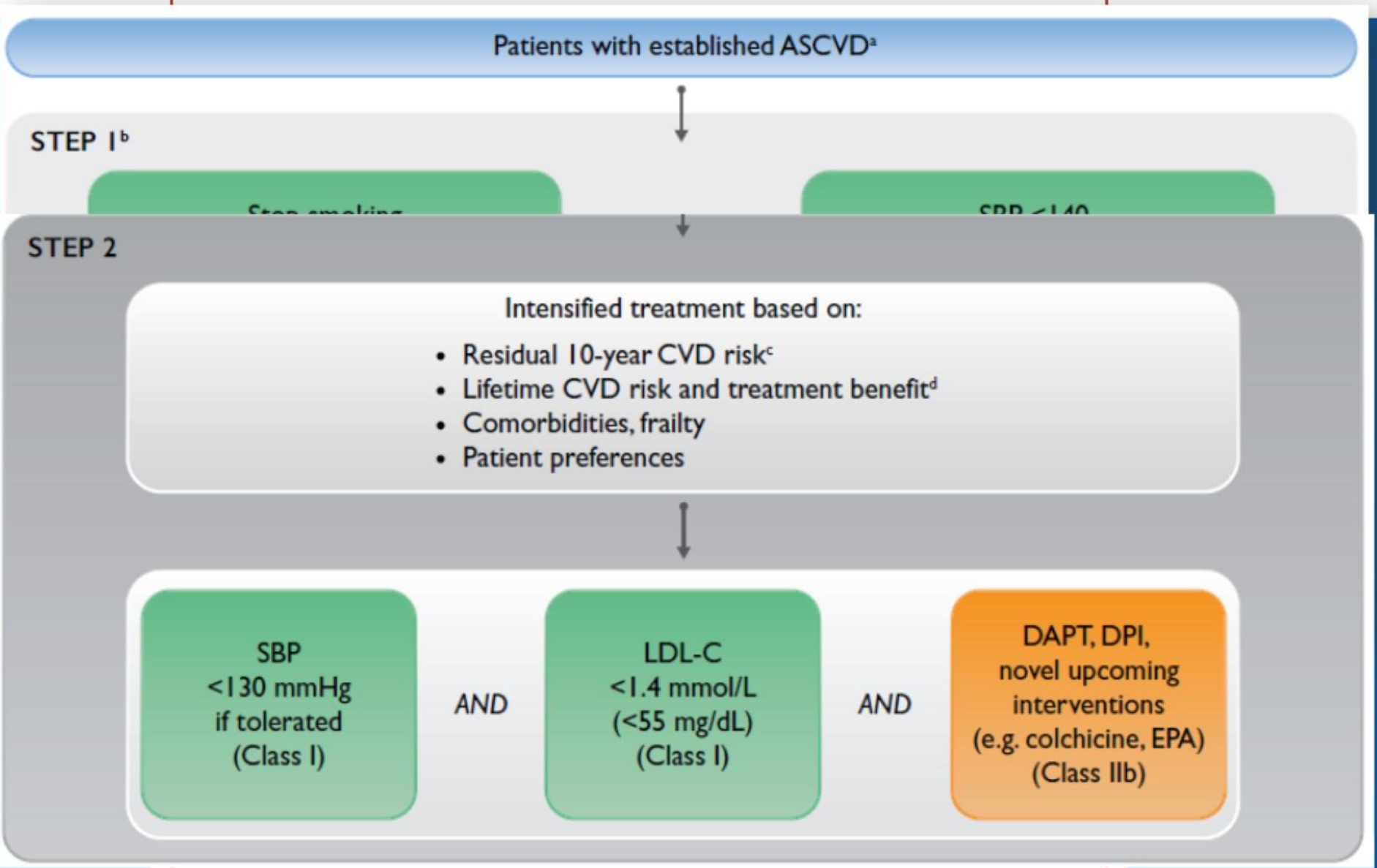

Individuals with DM

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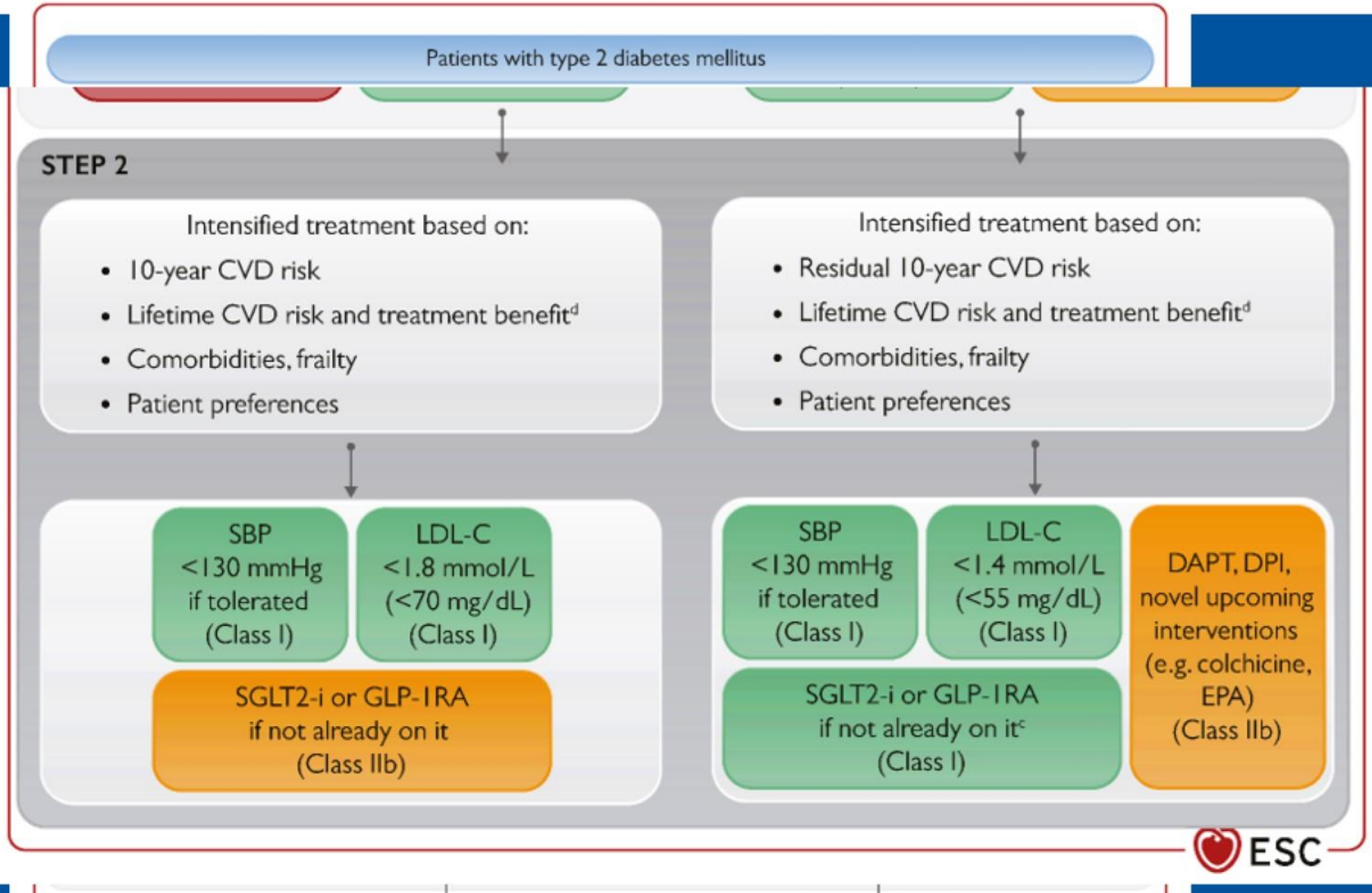

Instead of treatment goals, estimation of lifetime treatment benefit to guide treatment

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

Calculate lifetime benefit of lipid-lowering treatment

U-Prevent

you are in control

www.U-Prevent.com

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

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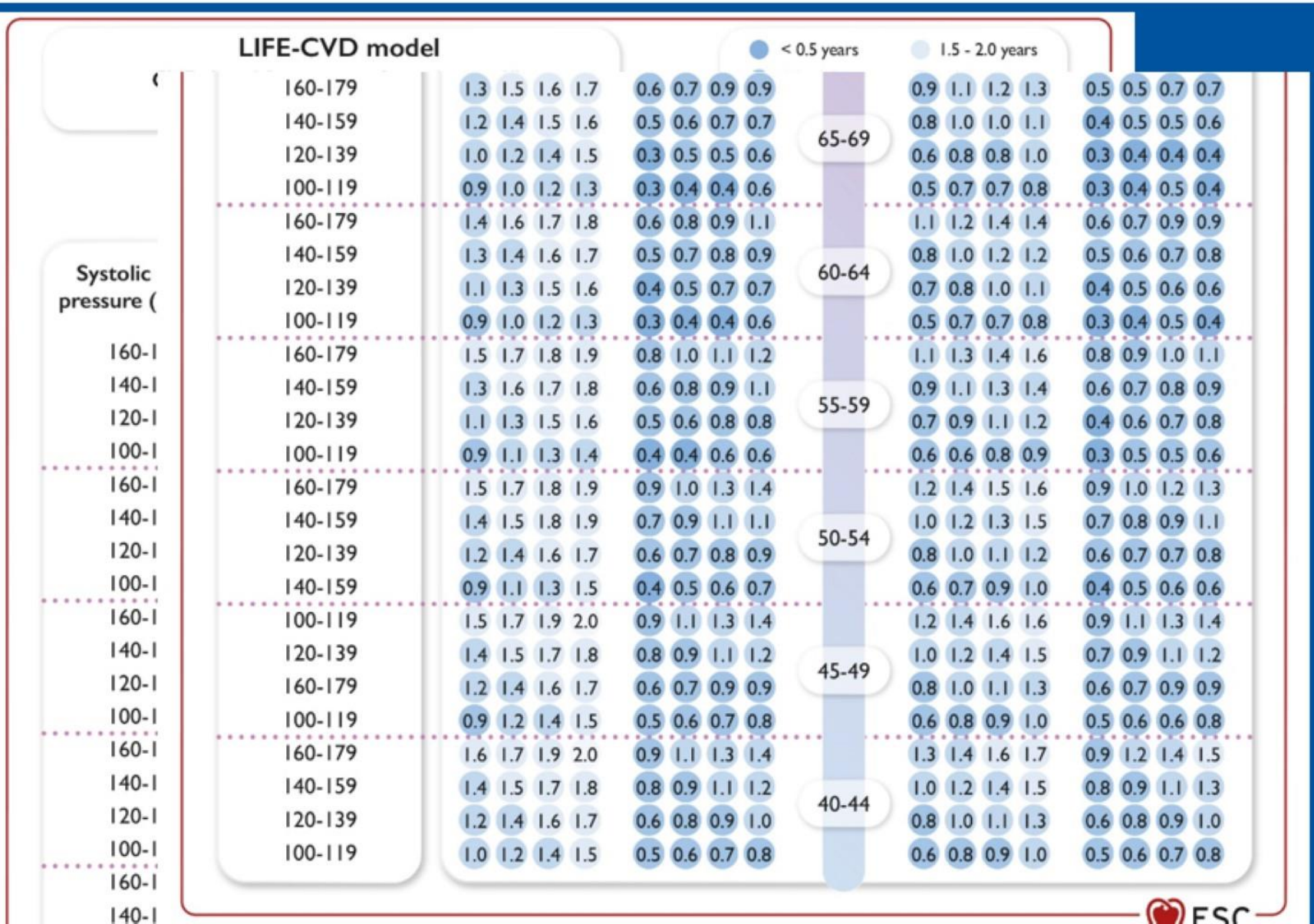

Treatment options for LDL-c lowering

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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

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- 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

En wat dan met HDL-c en triglyceriden?

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- laag HDL-c is een risico-indicator. Geen behandeldoel. Bij hele lage HDL-c (<0,6 mmol/l bij mannen, <0,7 mmol/l bij vrouwen) in combi met normale TG verdere analyse

- Verhoogde triglyceriden: nuchter meten. Vetbeperkt dieet. Bij hele hoge triglyceriden (>10 mmol/l) verdere analyse


Vascular Medicine Utrecht