

Grand Rounds

Rigshospitalet



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rigshospitalet.dk/grandrounds



Grand Round om arveligt forhøjet kolesterol - Familiær Hyperkolesterolæmi

Oplægsholdere:

- Professor, overlæge, dr. med. Anne Tybjærg-Hansen, Afd. for Klinisk Biokemi, Rigshospitalet
- Klin. forskningslektor, afdelingslæge, ph.d. Stefan Stender, Afd. for Klinisk Biokemi, Rigshospitalet
- Professor, PhD Albert Wiegman, Dept. Pediatrics, Amsterdam University Medical Center, Holland

Paneldiskussion: Overlæge, ph.d. Emil Daniel Bartels, Afd. for Klinisk Biokemi, Rigshospitalet (ordstyrer); Ledende overlæge, ph.d. Kristian Korsgaard Thomsen, Hjertemedicinsk Afdeling, Sydvestjysk Sygehus, Esbjerg; Overlæge, ph.d. Helle Lynge Kanstrup, Hjertemedicinsk Afd., Aarhus Universitetshospital; Cheflæge, ph.d. Birgitte Rode Diness, Afd. for Genetik, Rigshospitalet.

Hvad er arveligt forhøjet kolesterol – Familiær Hyperkolesterolæmi (FH)?

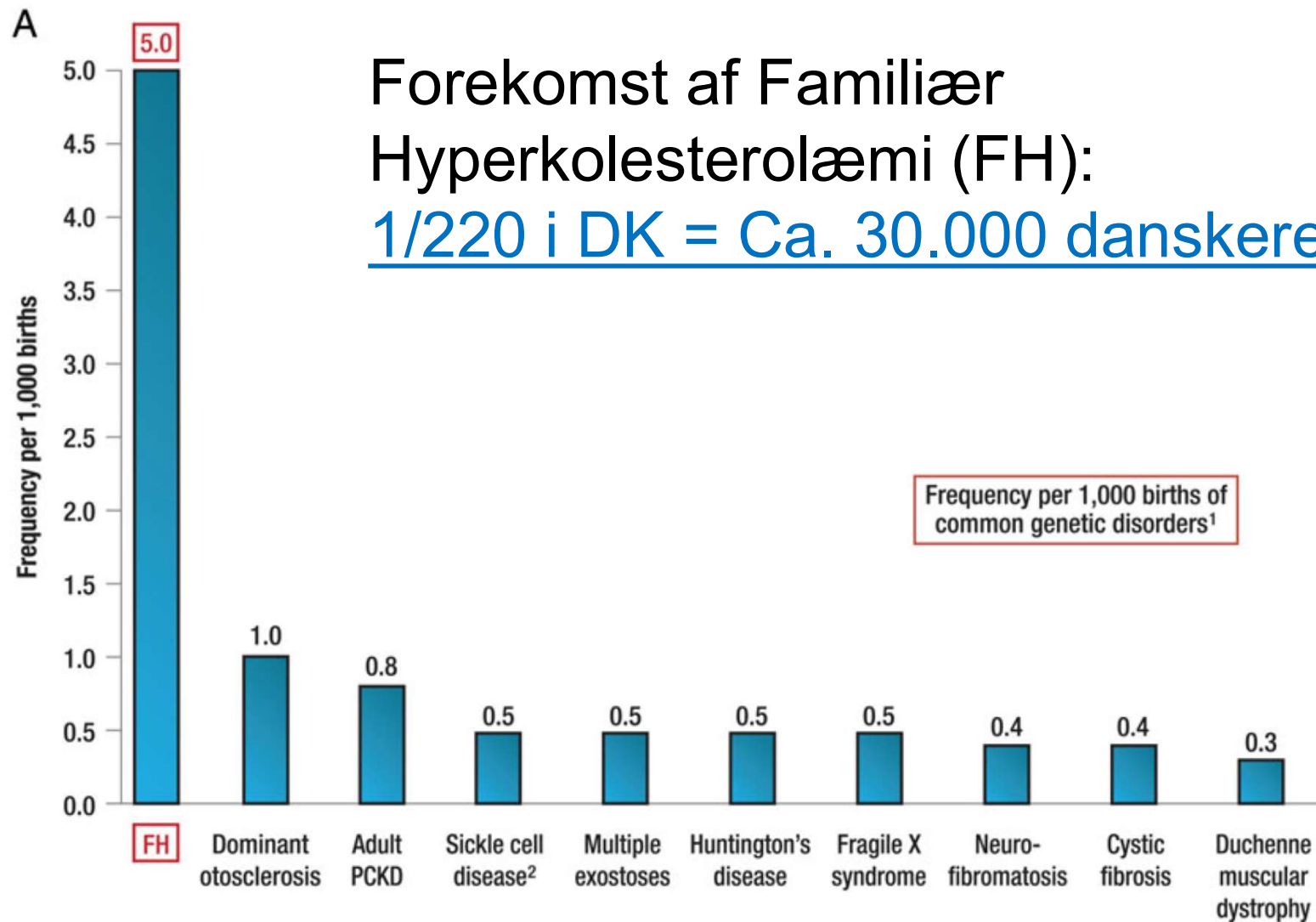
Fakta om Familiær Hyperkolesterolæmi

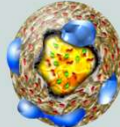
- Risiko for tidlig blodprop i hjertet
- Risiko for tidlig død
- Årsagen er velkendt
- Nemt at diagnosticere og behandle

MEN

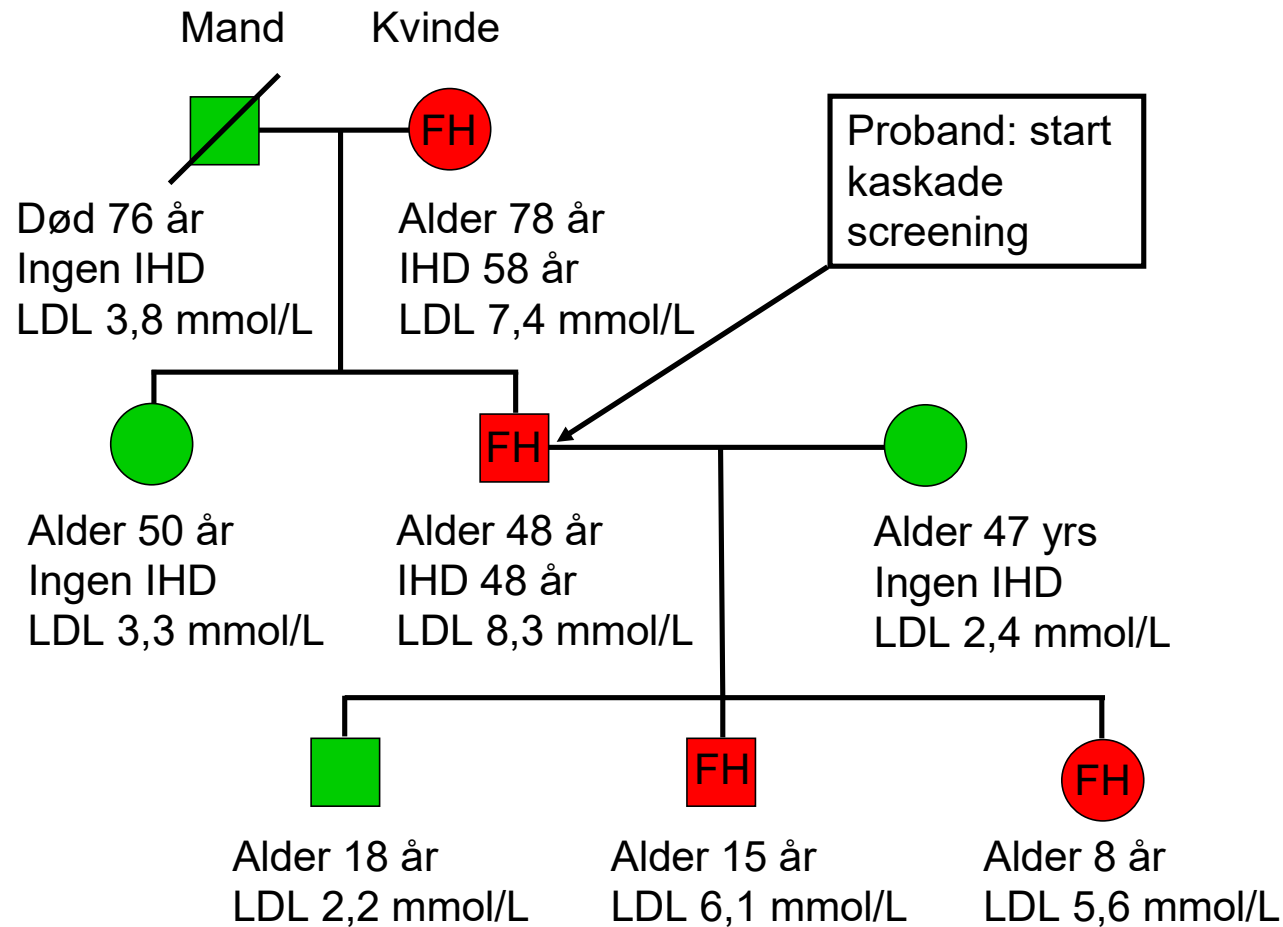
- Underdiagnosticeret og underbehandlet

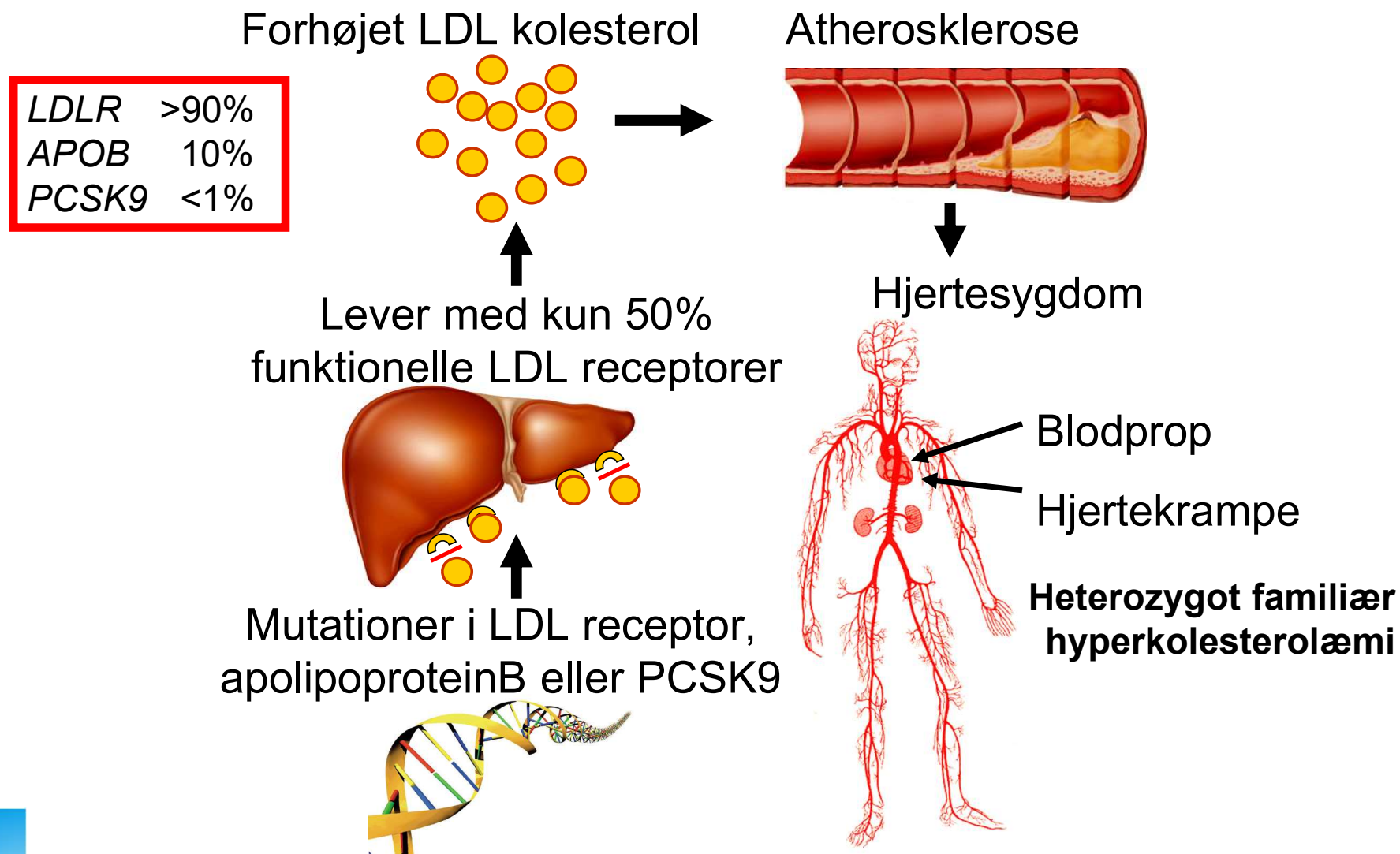
Forekomst af Familiær Hyperkolesterolæmi (FH): 1/220 i DK = Ca. 30.000 danskere



Feature	DUTCH FH CRITERIA		Score
Family history			
First-degree relative with known premature coronary and/or vascular disease (men <55 years, females <60 years) OR First-degree relative with known LDL-C above the 95th percentile for age and sex			1
First-degree relative with tendinous xanthomata and/or arcus comealis OR Children aged less than 18 years with LDL-C above the 95th percentile for age and sex			2
Clinical history			
Premature coronary artery disease (men <55 years, females < 60 years)			2
Premature cerebral or peripheral vascular disease (men <55 years, females <60 years)			1
Physical examination			
Tendinous xanthomata			6
Arcus comealis prior to age 45 years			4
LDL-C (mmol/L)			
– 8.5 or higher			8
– 6.5 to 8.4			5
– 5.0 to 6.4			3
– 4.0 to 4.9			1
DNA analysis: functional mutation in the LDLR, APOB or PCSK9 gene			8
Stratification of familial hypercholesterolaemia (FH), as determined by total score using the Dutch Lipid Clinic Network Criteria:			
• Definite FH = total score greater than 8 • Probable FH = total score between 6 and 8 • Possible FH = total score between 3 and 5 • Unlikely FH = total score of less than 3			

Stamtræ FH



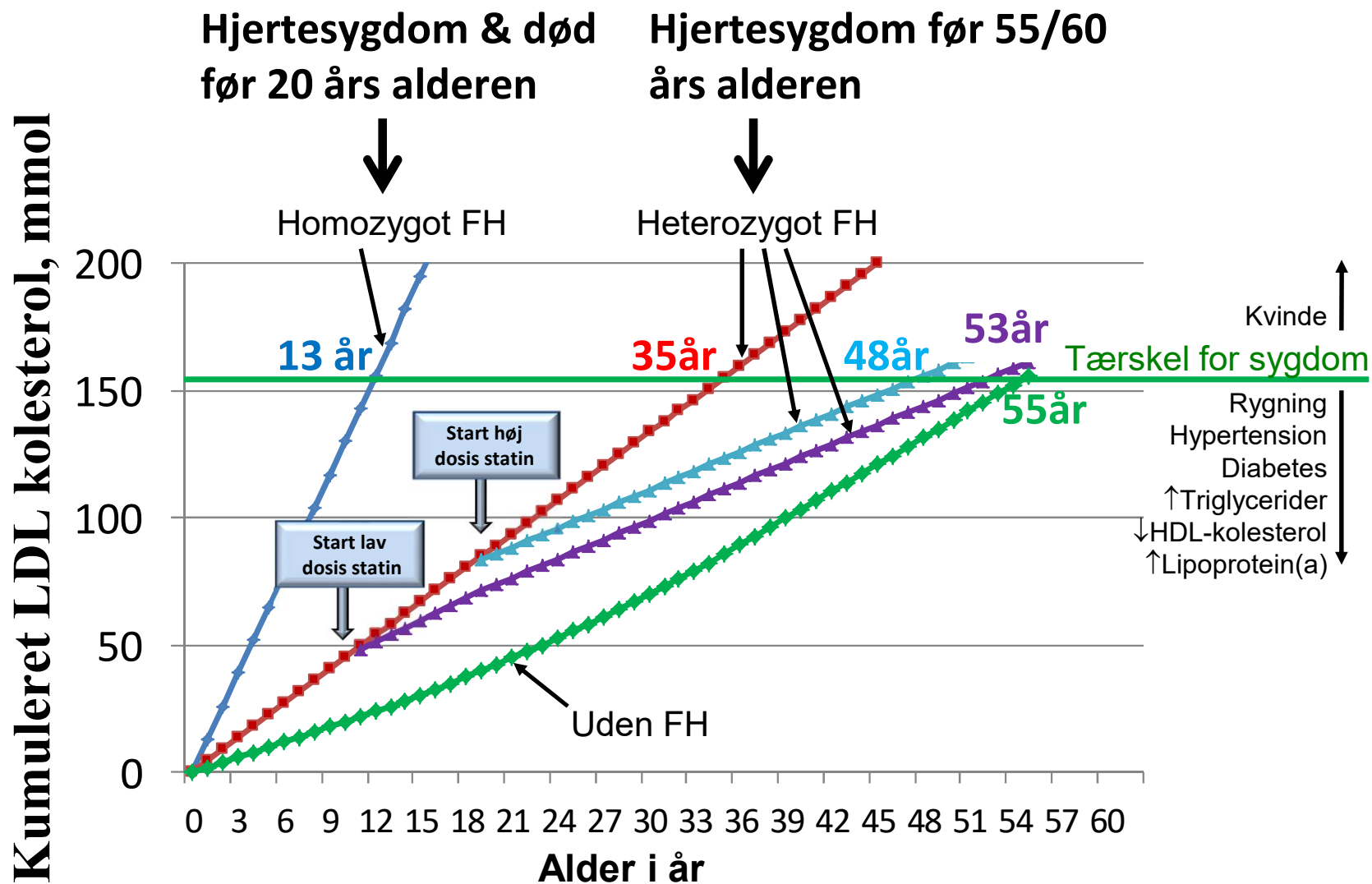


Senexanthomer hos barn med homozygot FH



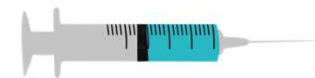
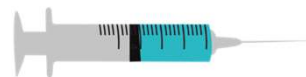
Ubehandlet LDL kolesterol = 23 mmol/L

Behandling – hvornår og hvordan?



Behandling udover kostvejledning og livsstilsfaktorer

- Statiner
- Ezetimibe
- Galdesyrebindere
- PCSK9 hæmmere
- Lomitapid (homozygote)
- ANGPTL3 hæmmere (homozygote)
- Lipoprotein apherese (homozygote)



Status i DK – opsporing, behandling

FH-indsats sammenlignet med lande, vi normalt sammenligner os med



Holland
71% FH
fundet
Organiseret



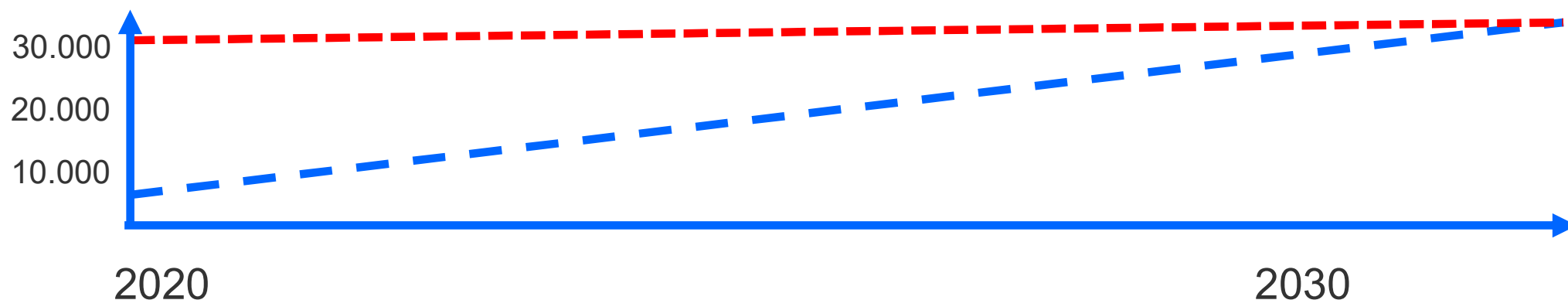
Norge
43% FH
fundet
Organiseret



Danmark
4% FH
fundet
Uorganiseret

Ville en opsporingsgrad for kræft eller diabetes på 4% være OK?

Databasen for Familiær Hyperkolesterolæmi



- Genetisk test ved mistanke om FH
- Lp(a) test ved mistanke om FH
- Medicinsk behandling for LDL-C
- LDL-C behandlingsmål nået

2023

90%

84%

84%

60%

Standard

>70%

>80%

>90%

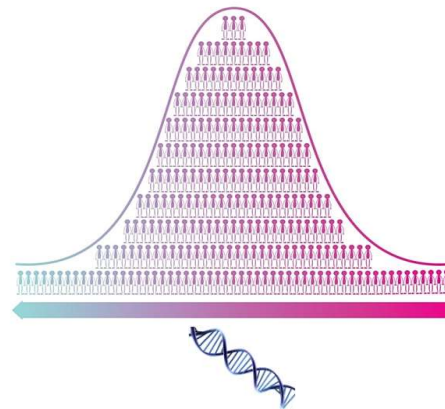
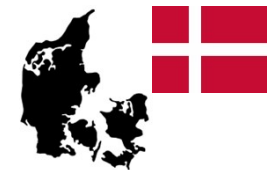
>60%

Regionernes kliniske kvalitetsudviklingsprogram

Brug af forskningsdata i diagnostikken af FH

1. Befolkningsundersøgelser med genomdata som 'opslagsværk'

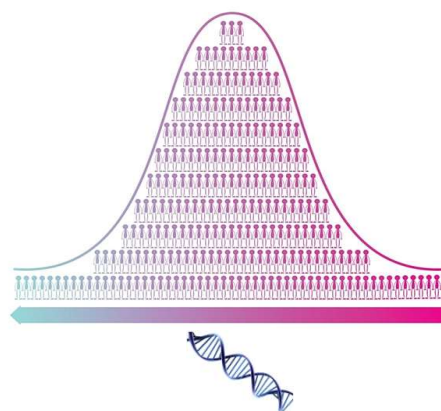
2. Polygene risikoscores



Brug af forskningsdata i diagnostikken af FH

1. Befolkningsundersøgelser med genomdata som 'opslagsværk'

2. Polygene risikoscores



UK Biobank



- 500.000 personer
- Genomdata på alle
- Kolesterol målt på alle
- Adgang for alle forskere

The screenshot shows the UK Biobank website with the following elements:

- Navigation Bar:** Includes links for "Researcher log in", "Participant log in", and "Contact us". Below this are links for "Enable your research", "Explore your participation", and "Learn more about UK Biobank".
- Header:** The "uk biobank" logo is on the left.
- Main Content Area:**
 - Top Section:** "The world's most important health research database". It describes the database as a uniquely powerful biomedical database accessible globally by approved researchers. It includes buttons for "About our data" and "About us".
 - Below Main Section:** Three promotional tiles:
 - "Change in how to access data" with a circular diagram.
 - "UK Biobank Conference: register today" with a photo of a panel discussion.
 - "YOUR GENETICS, EVERYBODY'S HEALTH" with a graphic of a DNA helix and the text "Annual Newsletter 2023/24".
 - Bottom Section:**
 - What is UK Biobank?** A text block explaining that UK Biobank is a large-scale biomedical database and research resource containing de-identified genetic, lifestyle and health information and biological samples from half a million UK participants. It also states that the dataset is globally accessible to approved researchers.
 - Video Player:** A video titled "What is UK Biobank?" with a play button icon.

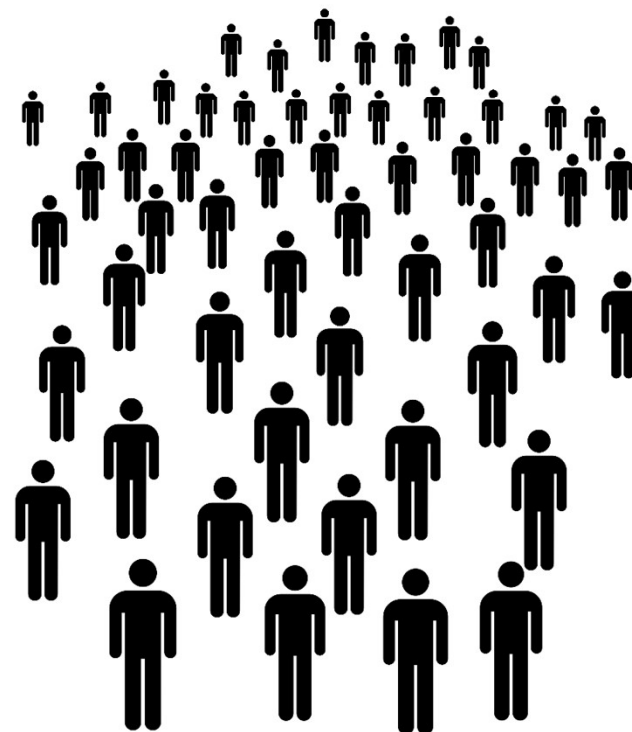
<https://www.ukbiobank.ac.uk/>

Patient med højt
kolesterol



Ukendt
genetisk
variant

Hyppighed:
1 ud af 50.000



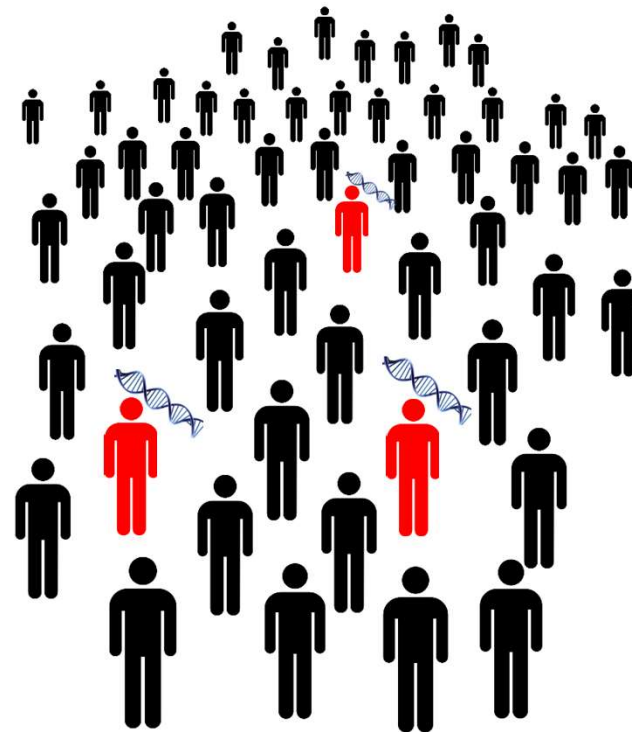
N = 500.000

Patient med højt
kolesterol



Ukendt
genetisk
variant

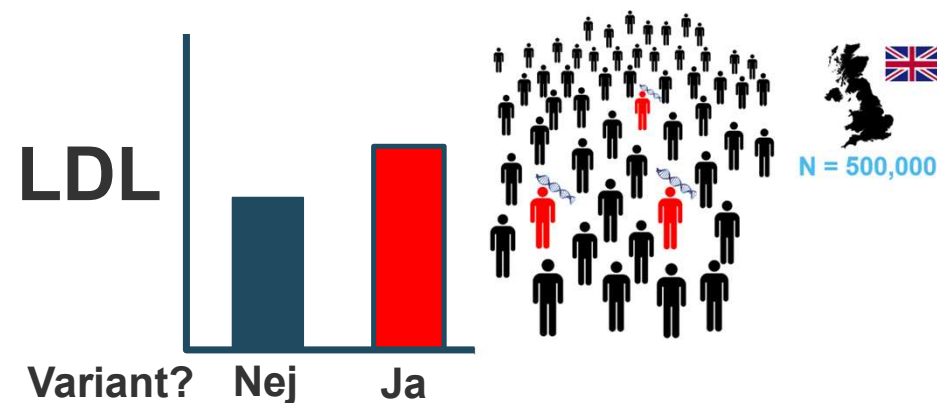
Hyppighed:
1 ud af 50.000



N = 500.000

Eksempel fra 2023

- 60-årig mand med højt kolesterol
- Sjælden genetisk variant af uvis effekt
- UK Biobank: 41 bærere af varianten

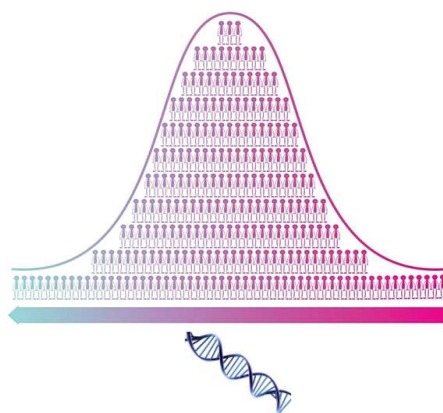


I UK Biobank er der 41 heterozygote bærere af varianten (allelfrekvens 8×10^{-5}), og disse har i gennemsnit ca. 0.5 mmol/L højere LDL kolesterol end ikke-bærere ($p=0.007$, kilde: genebass.org).

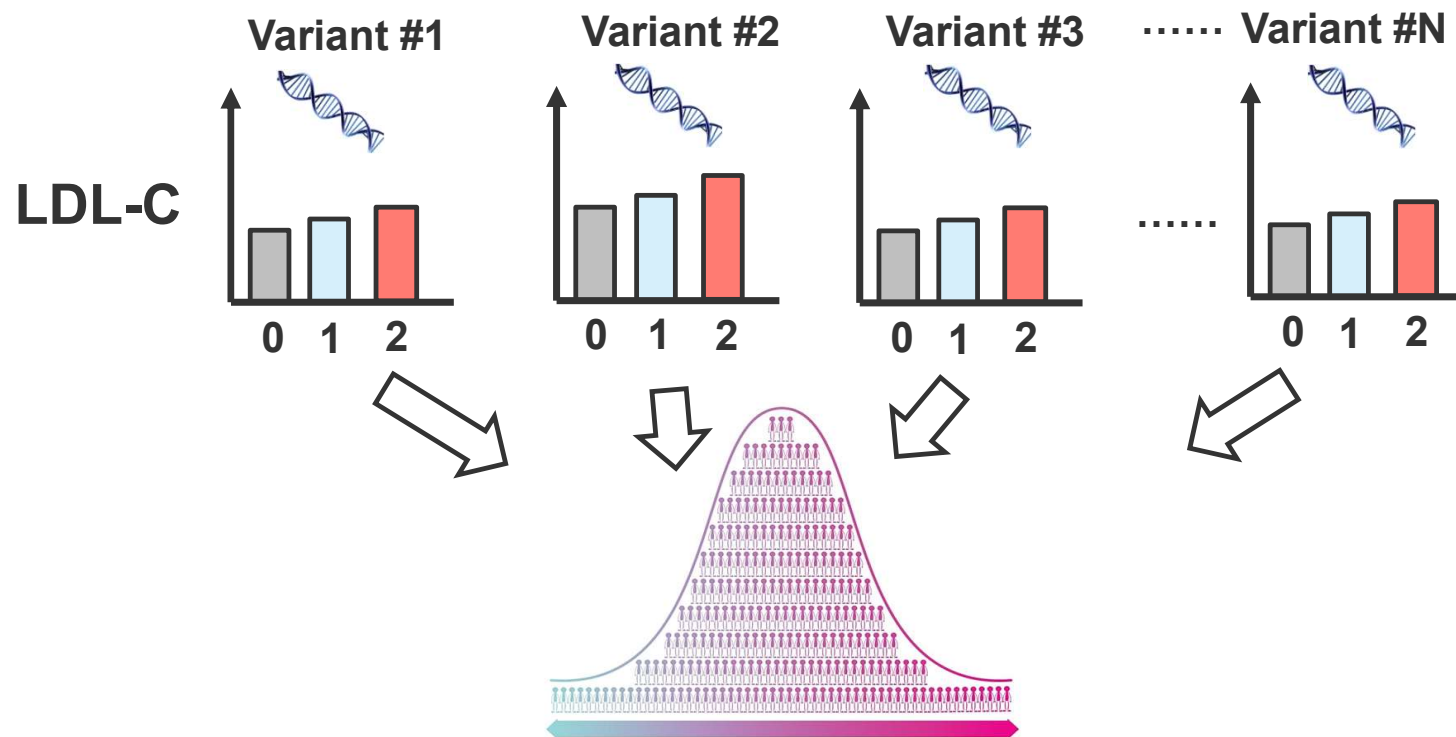
Brug af forskningsdata i diagnostikken af FH

1. Befolkningsundersøgelser med genomdata som 'opslagsværk'

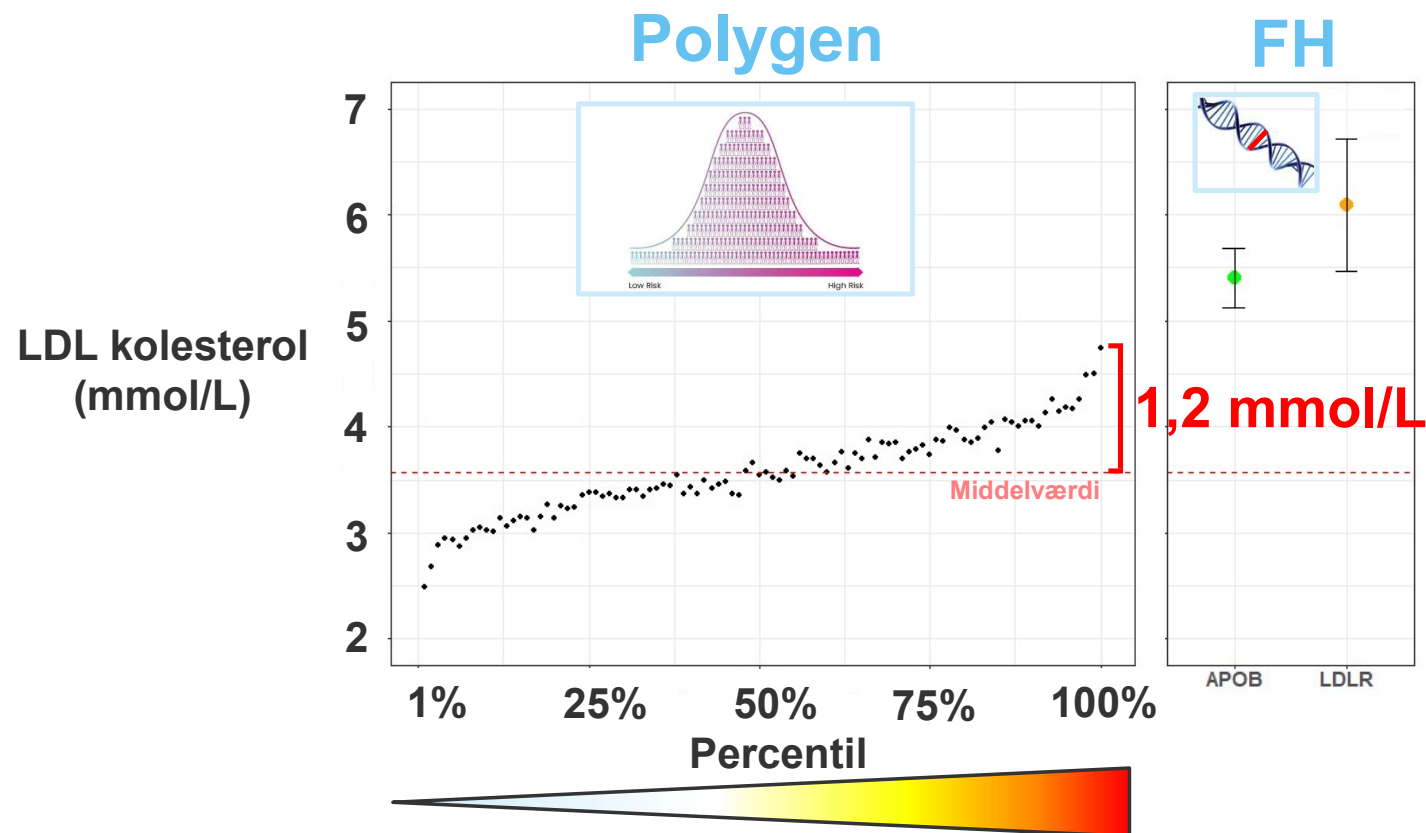
2. Polygene risikoscores



Polygen risk score (PRS)



Genetisk effekt på LDL kolesterol



Herlev-Østerbro Undersøgelsen

N = 21.475



Eyrich TM, et al. *Atherosclerosis* 2024

Implementering af polygen risikoscore i svar work in progress



Sundhedsplatformen

Rigshospitalet MedTek Huset

MedTek / Digitale Løsninger / KB Genetik - Udviklet af MedTek-huset

KB Genetik - Udviklet af MedTek-huset

Optimering af arbejdsgange styrker sikkerheden i svarafgivelsen

I Sektion for molekylærgenetisk diagnostik, Afdeling for Klinisk Biokemi har der igennem flere år været ønske om og behov for et system som supplement til LABKA, hvor prøver kan registreres og følges i laboratoriet, og hvor man kan udfærdige svar, der sendes direkte til Sundhedsplatformen (SP).

Hovedudfordringen med det "gamle" system var, at det var papirbaseret, og med mange manuelle arbejdsgange. Der var mange indtastninger og registreringer af f.eks. prøve-numre, CPR-numre og analyseresultater, hvor der var risiko for tastefejl. Det gav en del utilsigtede hændelser, som vi selvfølgelig gerne ville eliminere.

Ingen af de tilgængelige standardløsninger matchede vores behov, og derfor opstod ideen om et lokalt udviklet system.

MEDTEK-huset udviklede derfor systemet KB Genetik

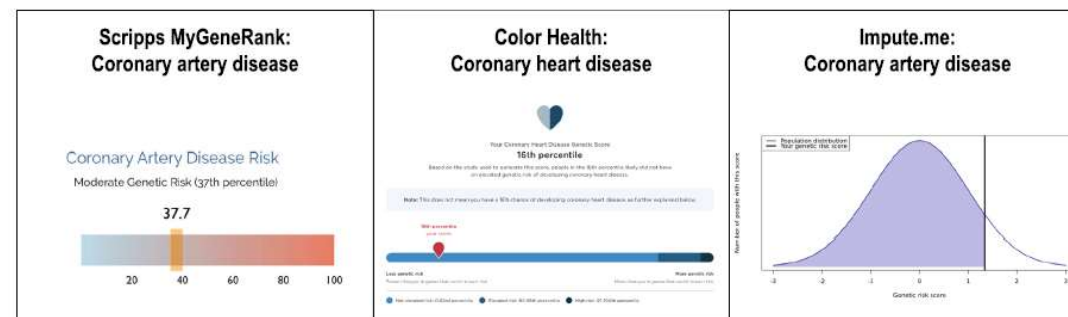
Implementeringen af KB Genetik har ført til bedre overblik over prøveflow i sektionen og hurtigere svar til gavn for klinikere og patienter. Faktisk har vi skåret 75 pct. af vores svartid, så det er en klar forbedring. Systemet trækker samtidigt oplysninger fra LABKA om patient-ID, prøve-ID, prøvetagningsstidspunkt og rekurrent, så disse oplysninger ikke længere skal indtastes og kontrolleres manuelt for svarafgivelse. Dette styrker sikkerheden i svarafgivelsen, og vi oplever ikke utilsigtede hændelser, som følge af tastefejl.

Hvordan skal en polygen risikoscore rapporteres?

- **Simpelt**
- **Visuelt**
- **Beskrivelse af begrænsninger**
- **Link til uddybende forklaring**



Eksempler fra verden



Familial Hypercholesterolemia in children

Disclosures:

Chair Steering Cie Inclisiran HoFH & HeFH children: - Novartis

Member Safety Board Lomitapide HoFH children: - Chiesi

Research grant trials children with FH/high Lp(a): - Amgen, Esperion,
Merck, Novartis, Regeneron, Sanofi, Silence Therap., Ultragenyx

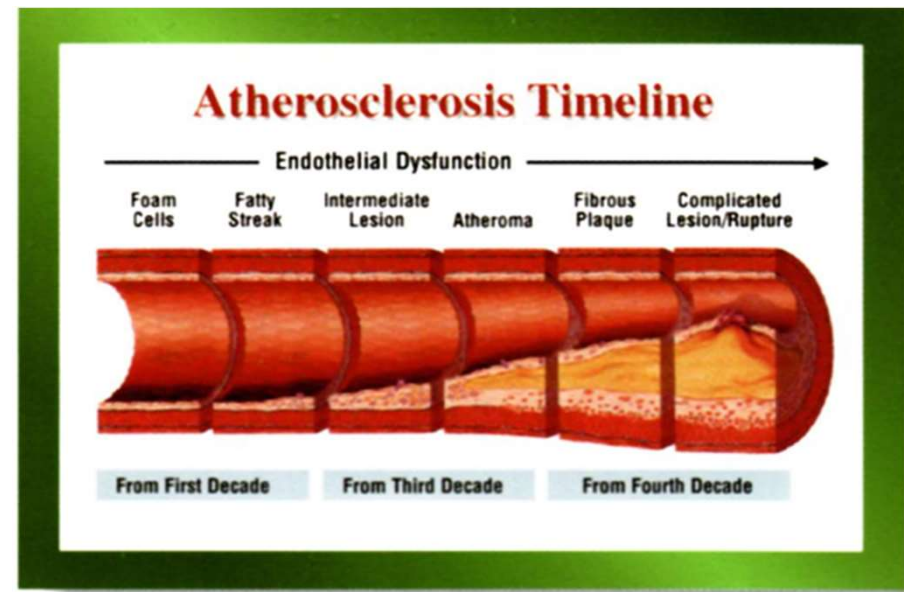
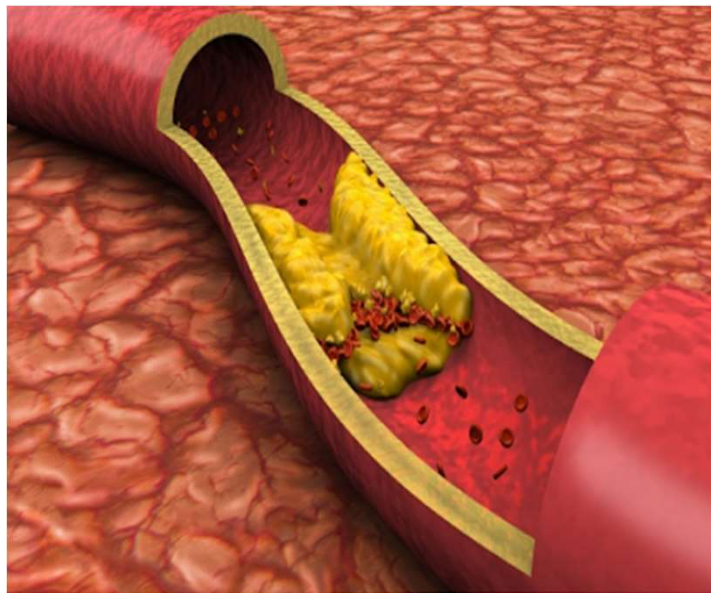
Albert Wiegman MD, PhD, FESC

Amsterdam UMC

26th September 2024



Cholesterol and Cardiovascular Diseases (CVD)



Current guidelines:

In children with homozygous FH, start lipid lowering treatment from diagnosis onwards.

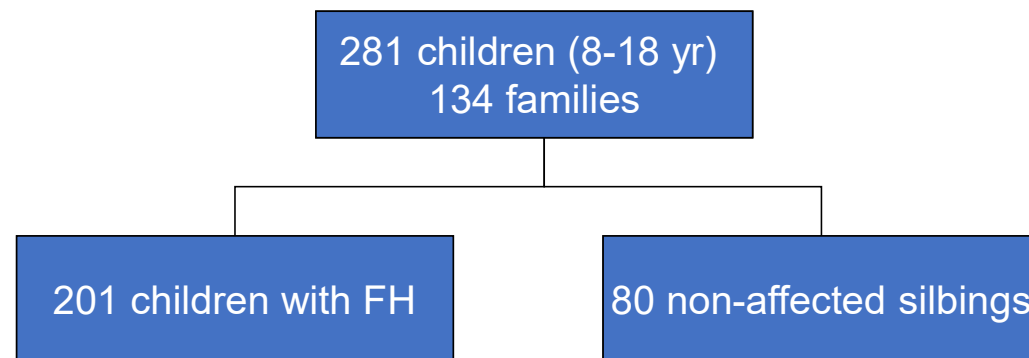
In children with heterozygous FH, start lipid lowering treatment from 8 years onwards.

Three times 'surprises' in the young: First time

In 2003/2004:

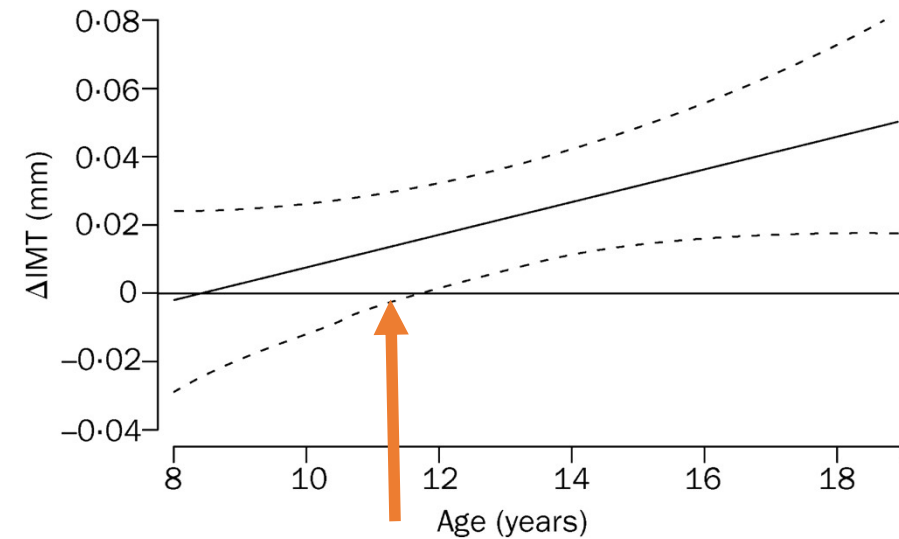
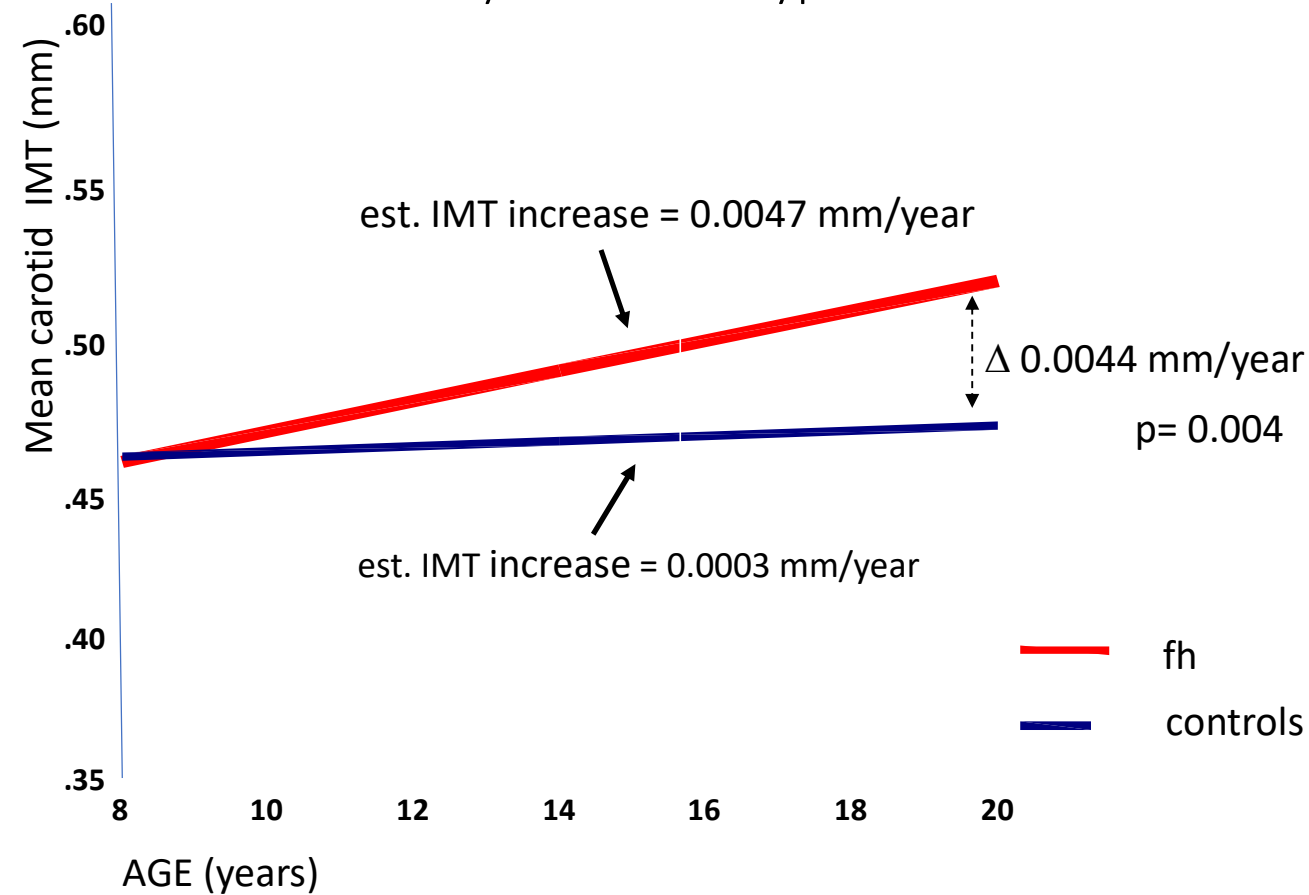
- Fat is already visible at a young age, shown by measuring cIMT

Carotid artery intima-media thickness in childhood:
study in familial hypercholesterolemia heterozygotes and their siblings

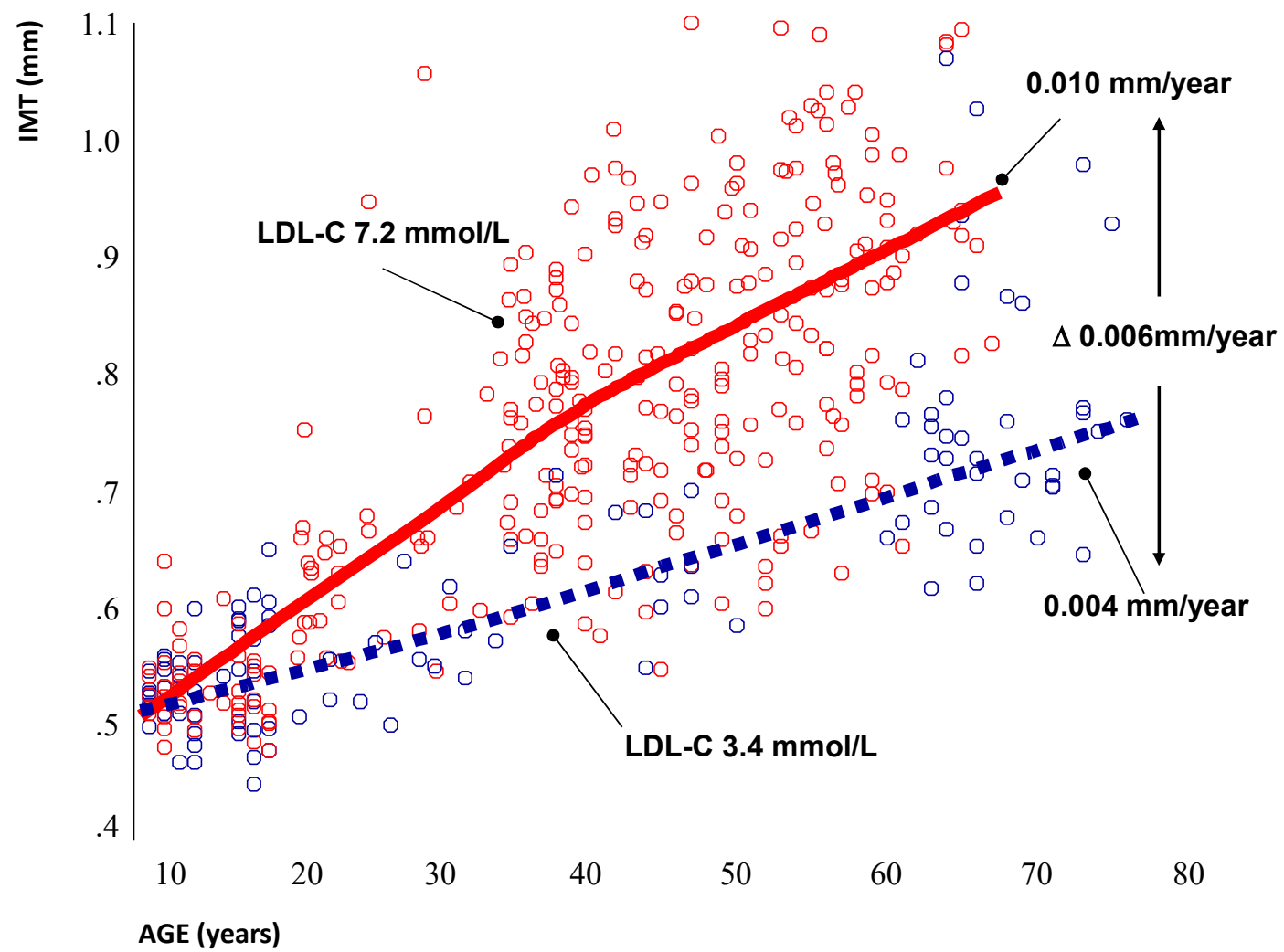


Wiegman et al, *Lancet* 2004;363:369-70

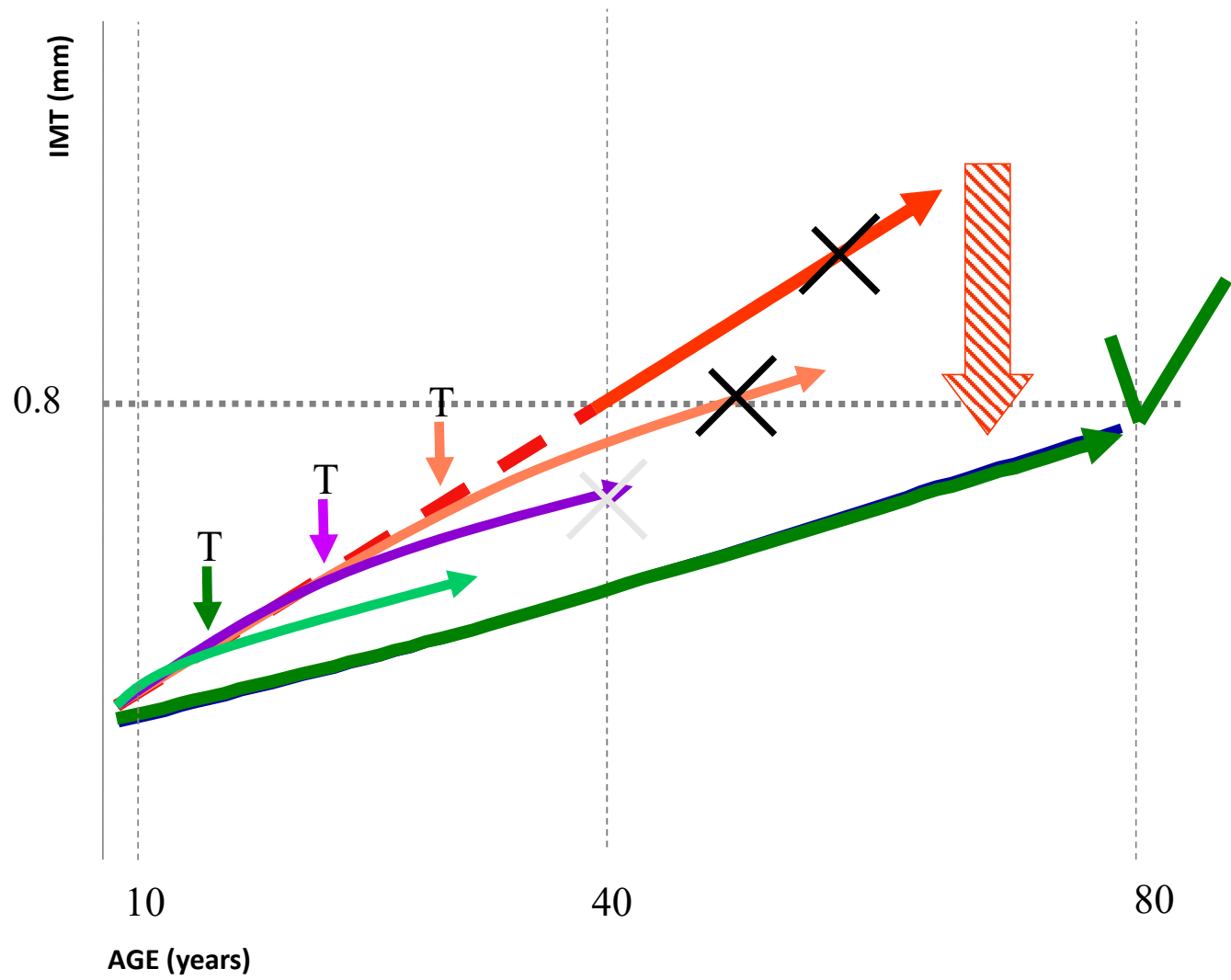
Carotid artery intima-media thickness (cIMT) in childhood: study in familial hypercholesterolemia heterozygotes and their siblings



Significant difference between FH and sibs

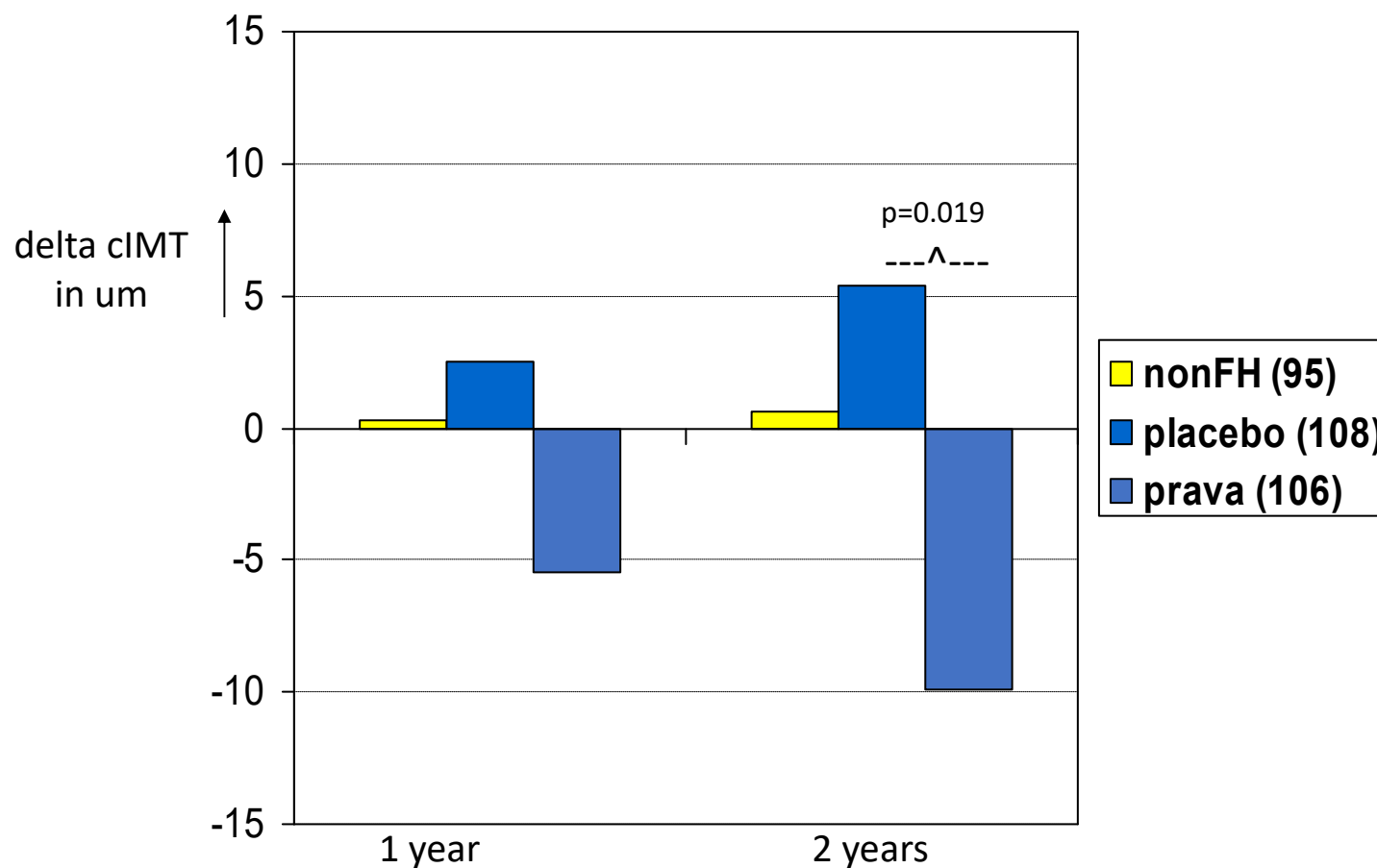


De Groot et al. *Circulation* 2004;109(S):III33-8

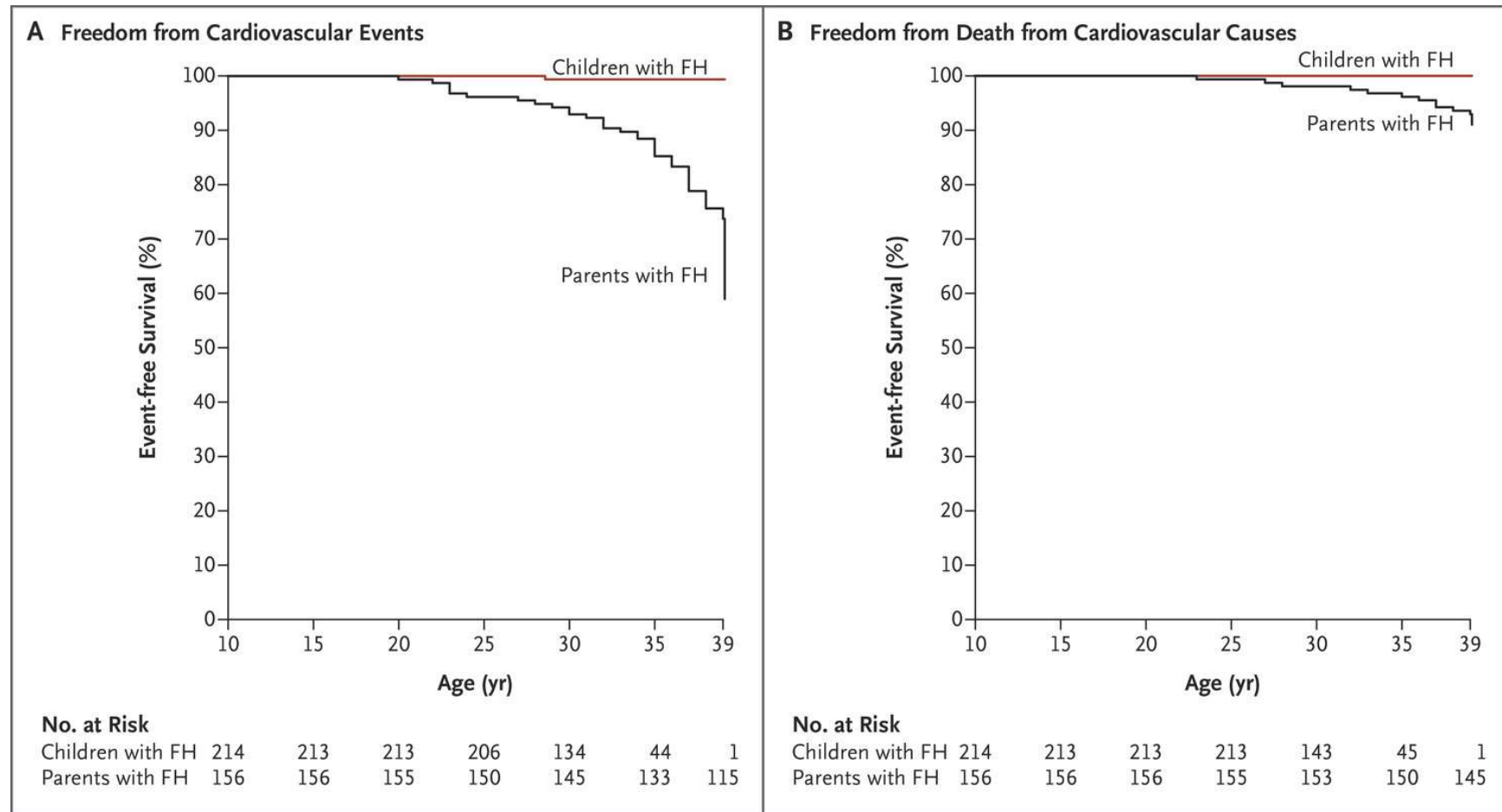


De Groot et al, *Circulation* 2004; 109(S):III33-8

Two year RCT: Efficacy of pravastatin therapy in children with familial hypercholesterolemia (8-18 yrs) by cIMT



20 years follow-up of children and parents with heFH



Kaplan–Meier curve for children with FH who began statin therapy at mean age 13 and their affected parents for whom statins were available at mean age 32

Luirink et al, *N Engl J Med* 2019;381:1547-56

Three times 'surprises' in the young: Second time

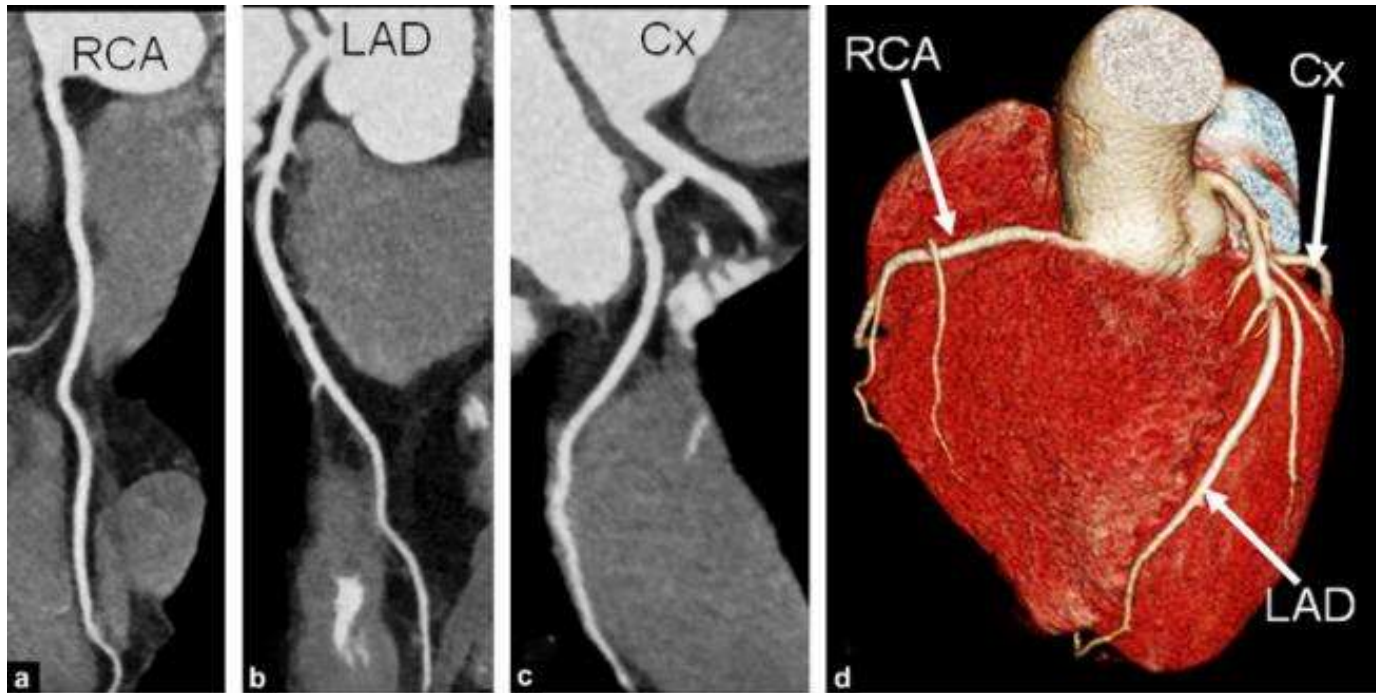
In 2003/2004:

- Fat is already visible at a young age, shown by measuring cIMT
- And can come out of the vessel wall!

In 2021:

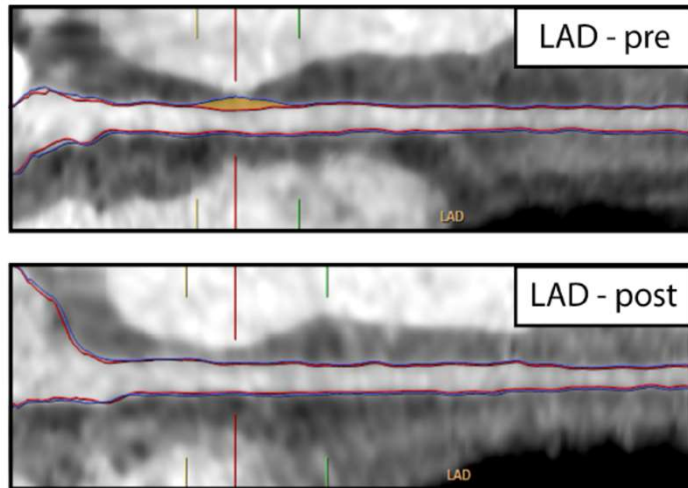
- Even in homozygous FH

Quantative plaque analysis/analysis stenosis

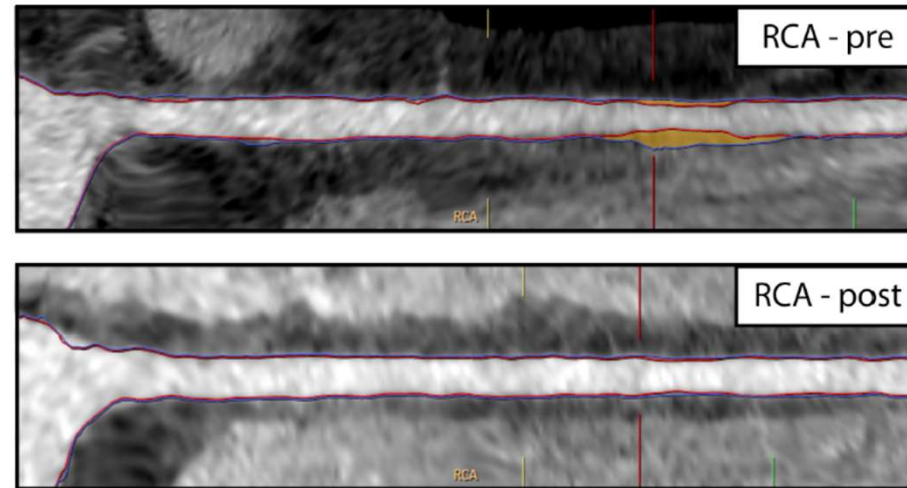


Evinacumab in adolescents with homozygous FH

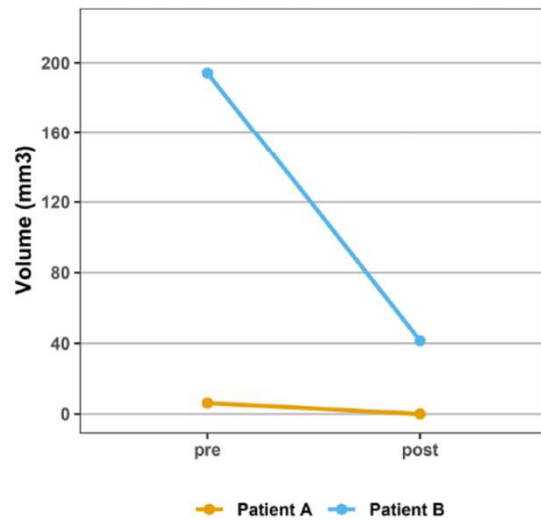
A Patient A: coronary plaque regression 12 yrs



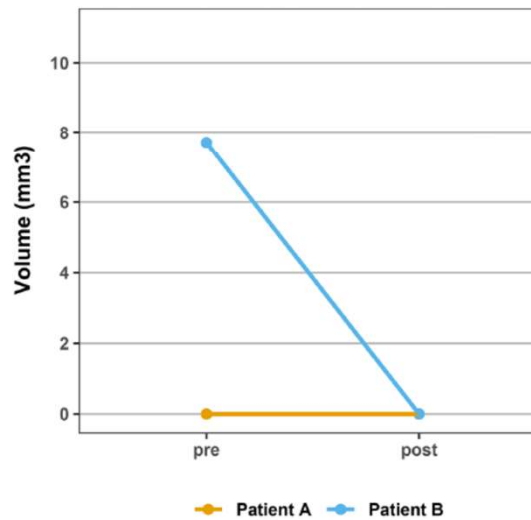
B Patient B: coronary plaque regression 17 yrs



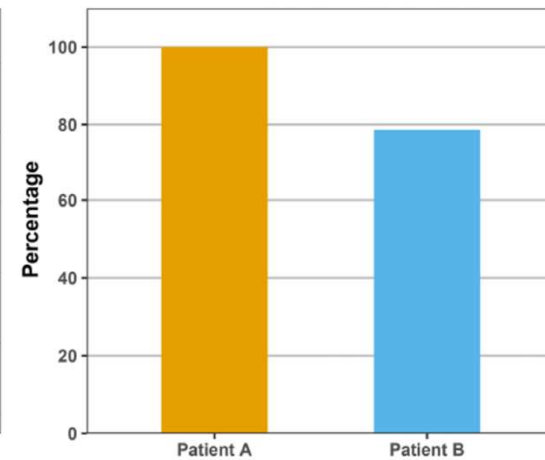
C Total Plaque Volume



D Total Low-Attenuation Plaque Volume

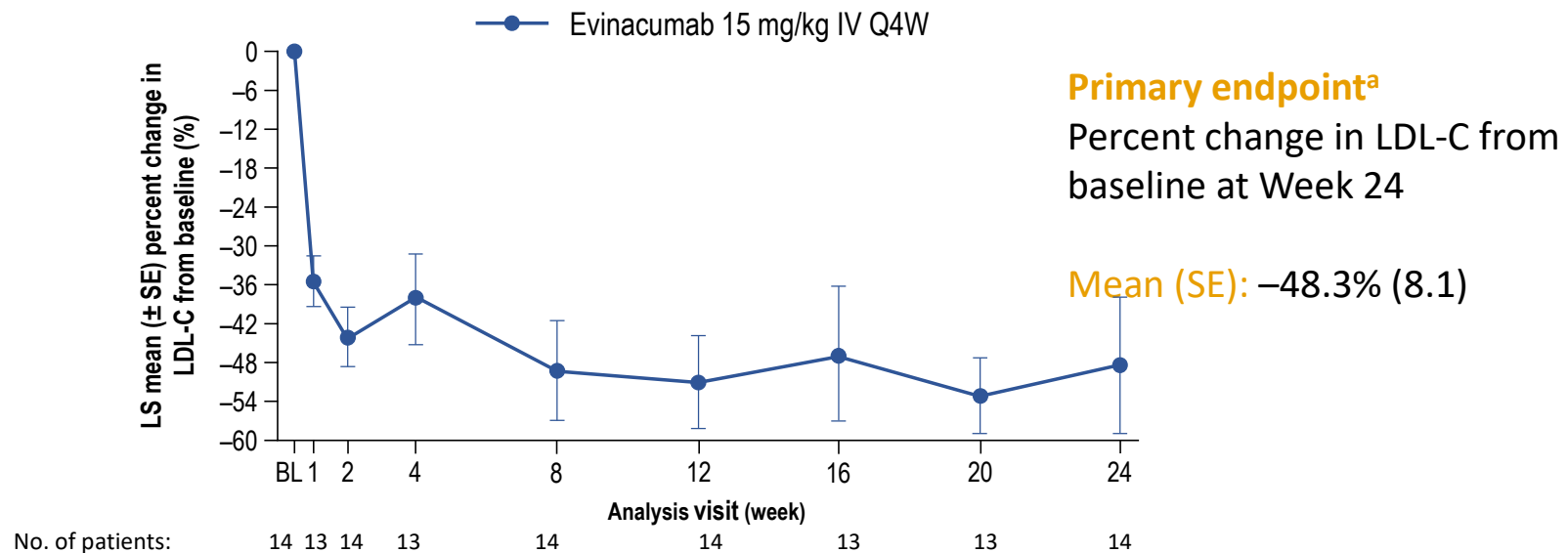


E Total Plaque Volume reduction



Reeskamp et al, *Atherosclerosis* 2021;327:13-7

Efficacy and Safety of Evinacumab in Paediatric Patients 5-11 years old with Homozygous FH



^aRaw data shown as there was no missing data at the primary efficacy timepoint (24 weeks).
BL, baseline; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LS, least squares, Q4W, every 4 weeks; SE, standard error.

Wiegman et al, *Circulation* 2024;149:343-53

Three times 'surprises' in the young: Third time

In 2003/2004:

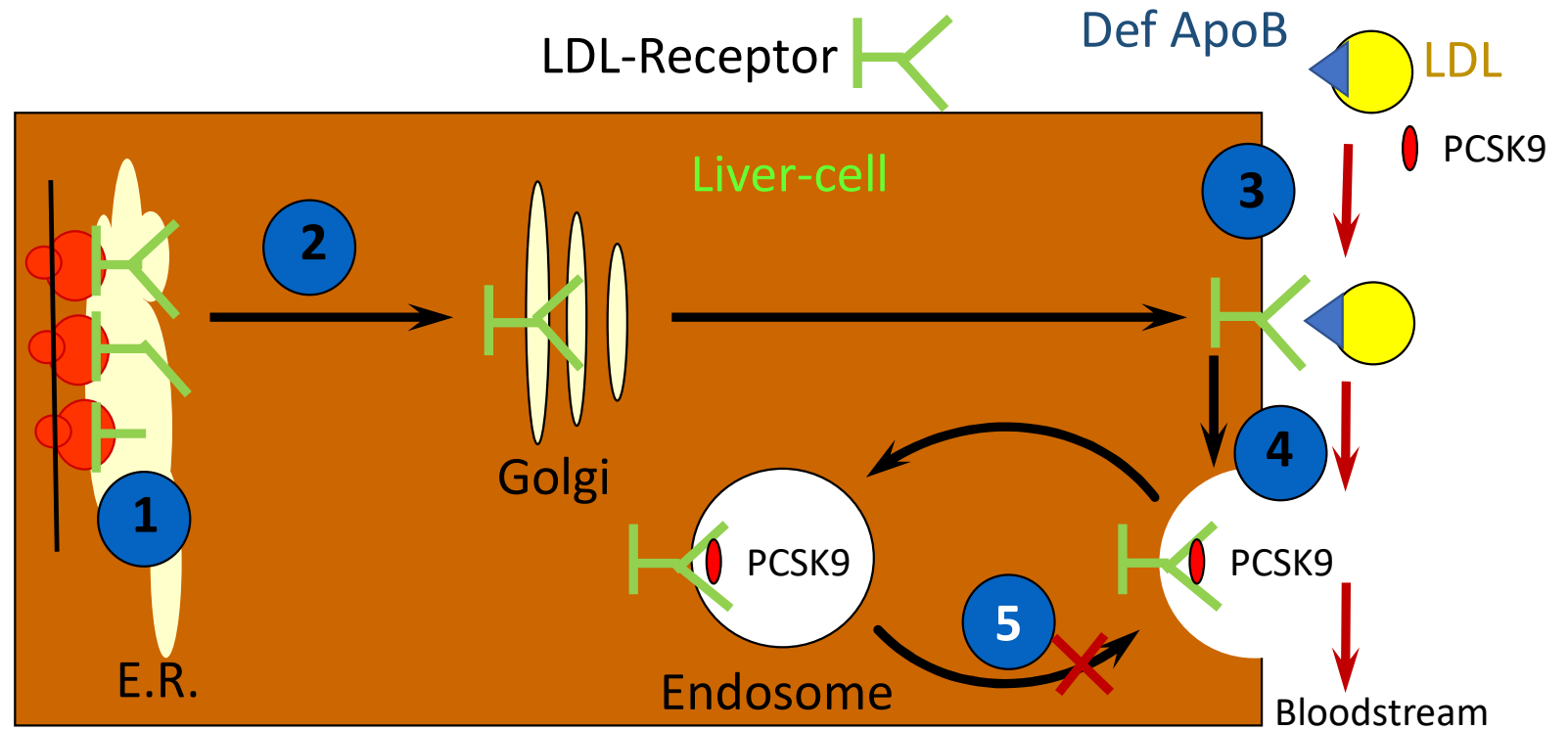
- Fat is already visible at young age, shown by measuring cIMT
- And can come out of the vessel wall!

In 2021:

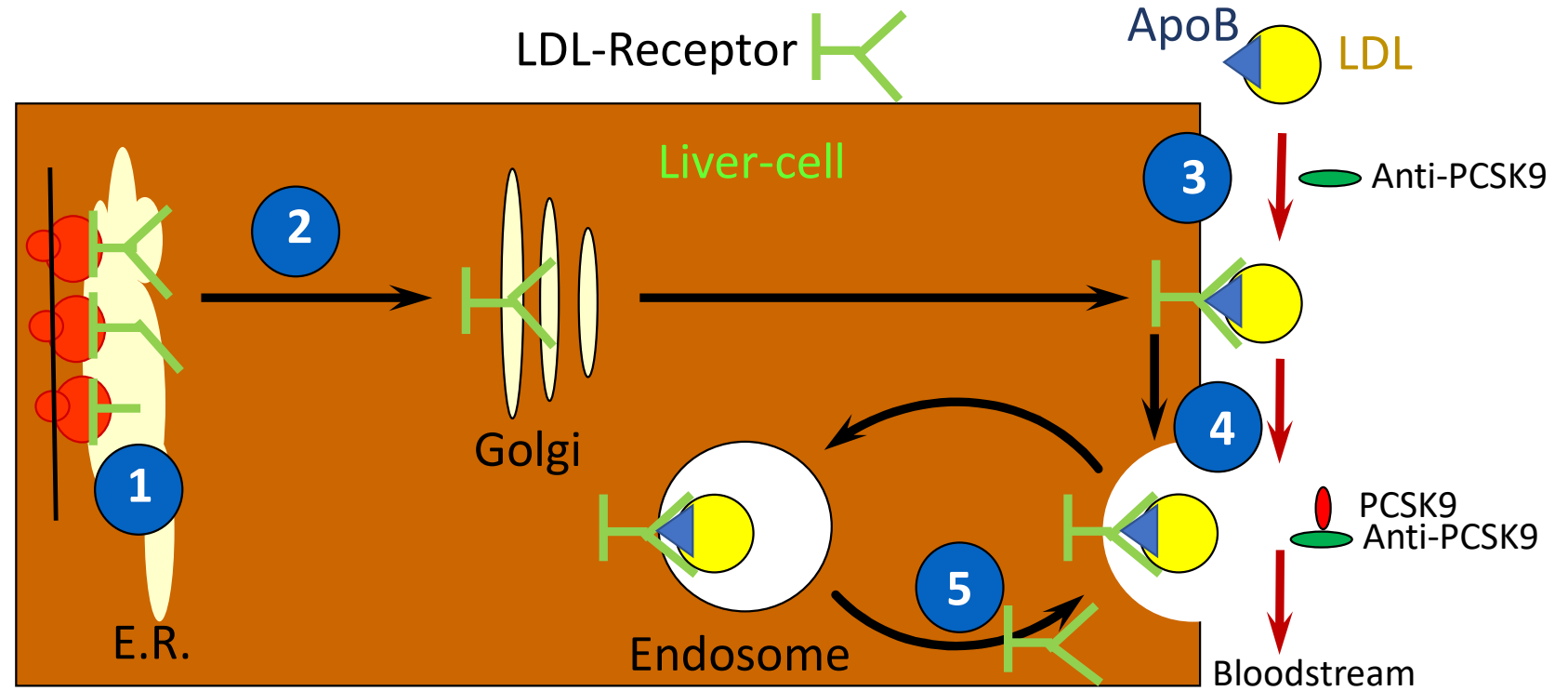
- Even in homozygous FH plaques can disappear
- If not calcified

In 2022:

- On top of statins, anti-PCSK9

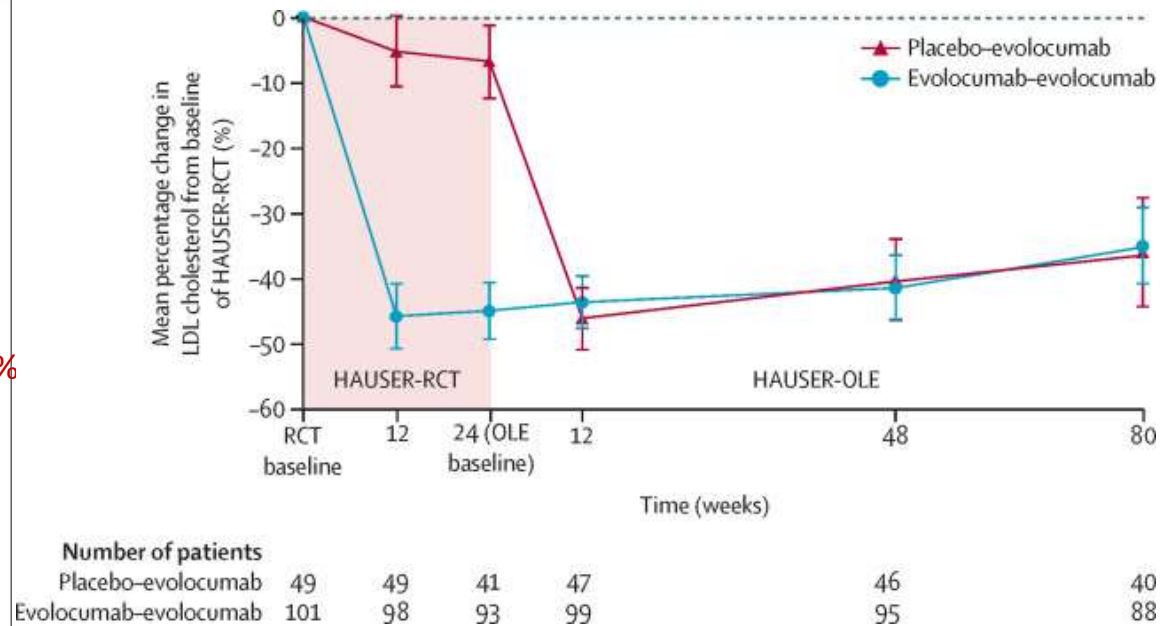
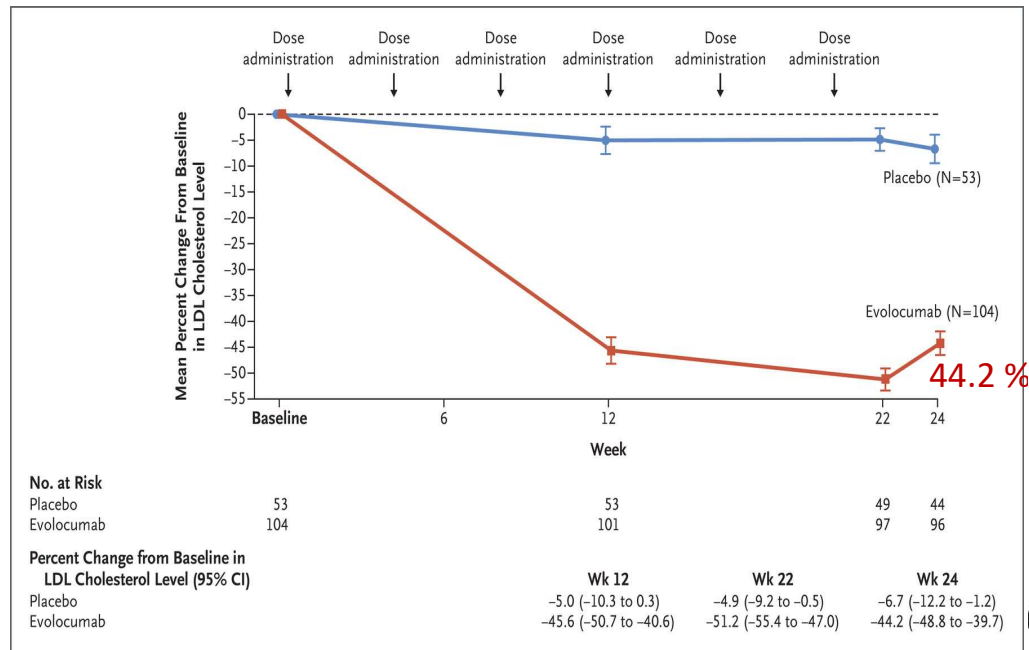


Mutation class	Synthesis	Transport	Binding	Clustering	Recycling
1	X				
2		X			
3			X		
4				X	
PCSK9					X



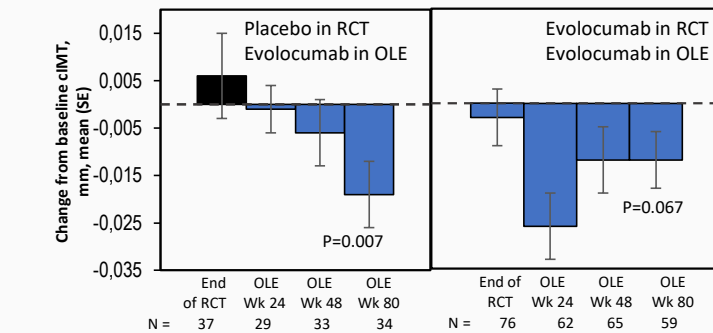
Mutation class	Synthesis	Transport	Binding	Clustering	Recycling
1	X				
2		X			
3			X		
4				X	
5					X

Evolocumab in Pediatric (10-18 yrs) Heterozygous FH Patients (24 wks HAUSER-RCT) (80 wks HAUSER-OLE)



104 received evolocumab, 53 received placebo, all on top of statins

Evolocumab Treatment Reduces Carotid IMT in Paediatric Patients with HeFH on Background Statin Therapy



Mean change from baseline in cIMT

– summary score across visits

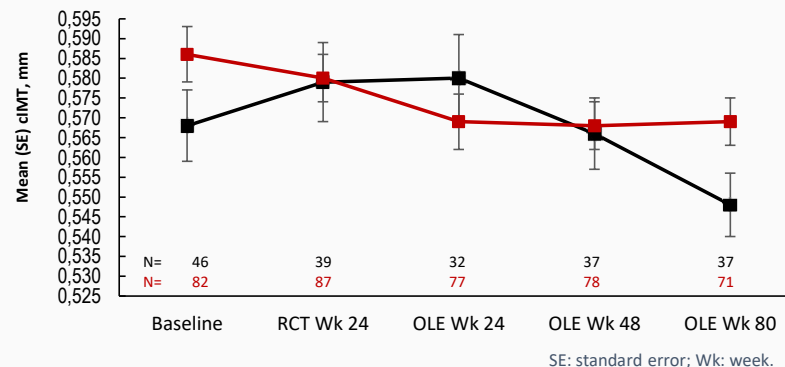
- Placebo (Statin + Placebo)
- Evolocumab (Statin + Evolocumab)

Across all patients who received evolocumab in the OLE, cIMT decreased from Day 1 to Wk 80 (p=0.034).

Mean cIMT –

summary score across visits

- Placebo in RCT / Evolocumab in OLE
- Evolocumab in RCT/Evolocumab in OLE



Three times 'surprises' in the young: Third time

In 2003/2004:

- Fat is already visible at young age, shown by measuring cIMT
- And can come out of the vessel wall!

In 2021:

- Even in homozygous FH plaques can disappear
- If not calcified

In 2022:

- On top of statins, anti-PCSK9 shows cIMT regression

We have to detect FH as early as possible

- Do we find them early enough?
- No, not at all!

Global perspective of Familial Hypercholesterolaemia:
a cross-sectional study from the EAS FH Studies Collaboration (FHSC)

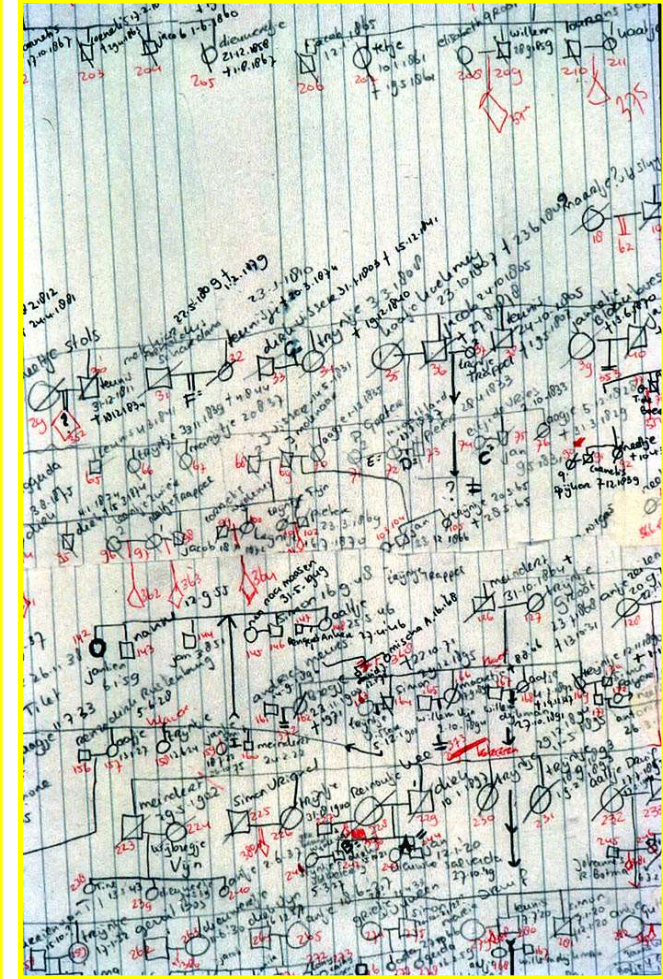
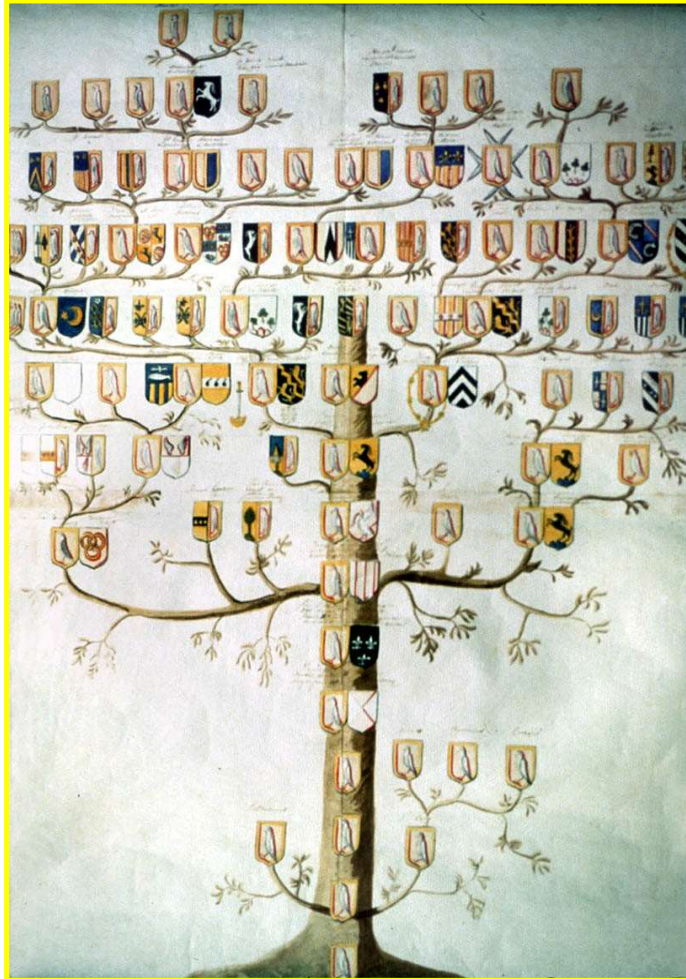
Study in 42,167 adults from 56 countries, with following conclusions:

- a. FH is diagnosed late: median age 44!!!
- b. Guideline LDL-C is infrequently achieved with single-drug therapy.

EAS, European Atherosclerosis Society; FH, Familial Hypercholesterolaemia; SC, Studies Collaboration; LDL, low density lipoprotein

EAS FHSC, *Lancet* 2021;398:1713-25

Genetic Field Work



A Nationwide Case-Finding Program for Familial Hypercholesterolemia in the Netherlands: ~ 13.000 Children

After a pathogenic mutation was known in the family,
1,810 children served as index cases

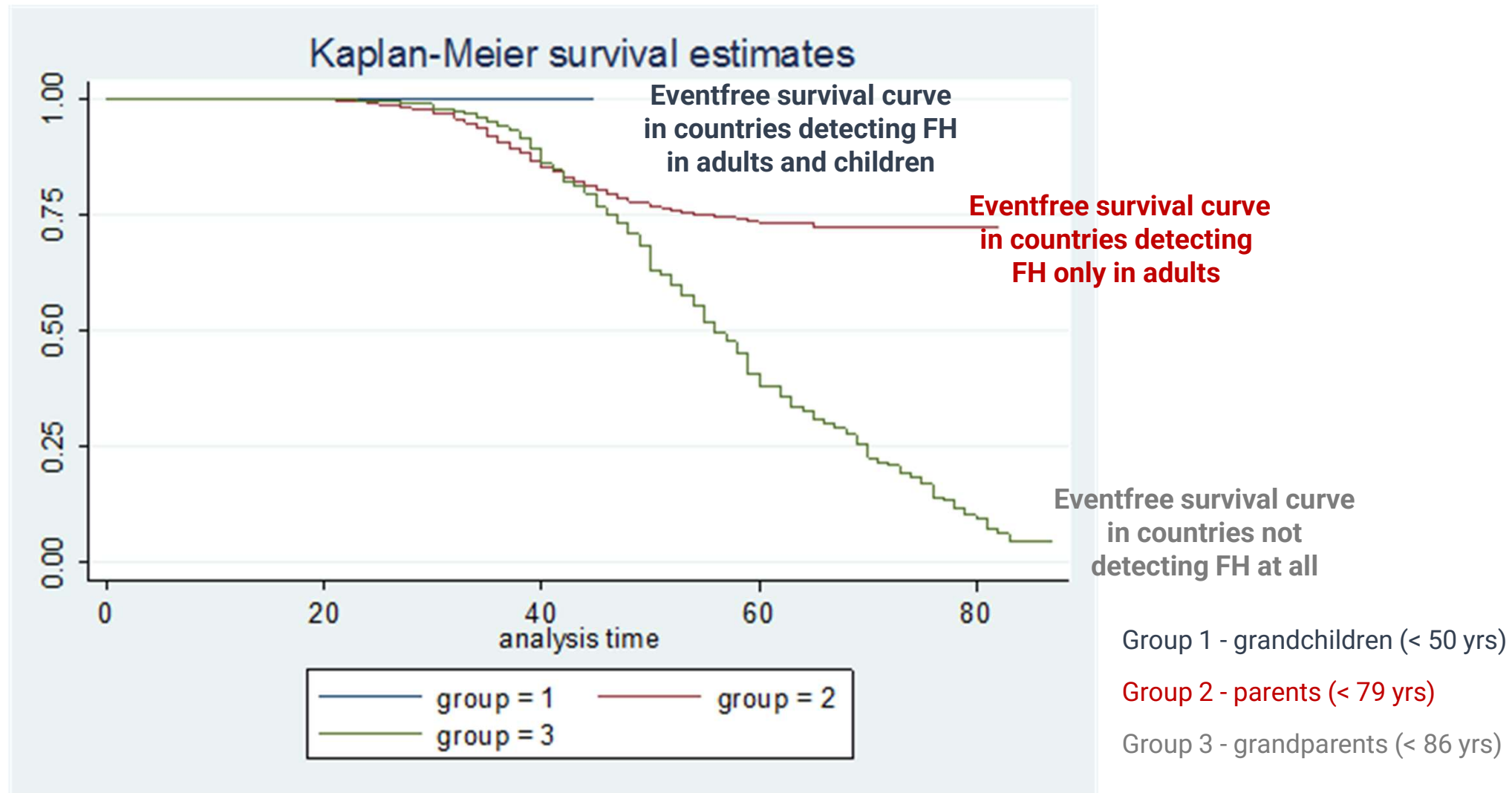
11,070 children were cascade screened nationwide, of whom
5,457 were identified as mutation positive and
5,613 as mutation negative

Return of Investment for detection and treatment program of FH
in children was: € 8.37

Premature cardiovascular disease (CVD) in 2308 first degree relative in 32 years

Period	Number of parents	N parent prem CVD	%	Mean age CVD	Deceased to CVD	%	Mean age death	Mean age visit
1989 - 2000	769	265	34.4	38.2	91	11.8	40.6	41.1
2001 - 2009	770	178	23.1	38.1	42	5.4	41.1	42.0
2010 - 2021	769	125	16.3	39.0	25	3.3	45.4	41.9

Early FH detection saves lives!



n=1517 grandparents, parents and grandchildren

Wiegman et al, To be published 2024

Take home message:

1. It is all about package-years!
2. Fat can come out of the vessel wall, calcium can't!
3. So, the younger the better!
4. Even if calcium is already in the wall, new fat can be removed!

Vigtige pointer fra dagen – Familiær Hyperkolesterolæmi

- **FH er underdiagnosticeret og derfor underbehandlet**
- **Tidlig opsporing og behandling er essentiel**
- **Større fokus på henvisning fra primærsektoren og på familieopsporing**

Grand Rounds

Rigshospitalet

Paneldebat



Grand Rounds

Rigshospitalet

Paneldebat

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Grand Rounds

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Tak for i dag

