EAS Consensus Paper

Familial Hypercholesterolaemia in Children and Adolescents: Identifying and Treating Early to Prevent Premature Heart Disease

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REVIEW

Prevention

Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment

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Key points about Familial Hypercholesterolaemia (FH)

- One of the most common genetic disorders, affecting 1:200 to 1:250 people
- Inherited in an autosomal dominant manner
- Disabling at a young age and shortens life expectancy.

- Consider Homozygous FH if:

  - LDL-C levels >13 mmol/L (500 mg/dL)
  - Tendon xanthomas in the hands and Achilles tendons
  - Evidence of premature cardiovascular disease, aortic valve disease

- A psychological challenge for families because of the inherited nature of the disorder, the lack of early symptoms in HeFH, and the need for long term lifestyle changes and pharmacologic therapy.

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What is familial hypercholesterolaemia?

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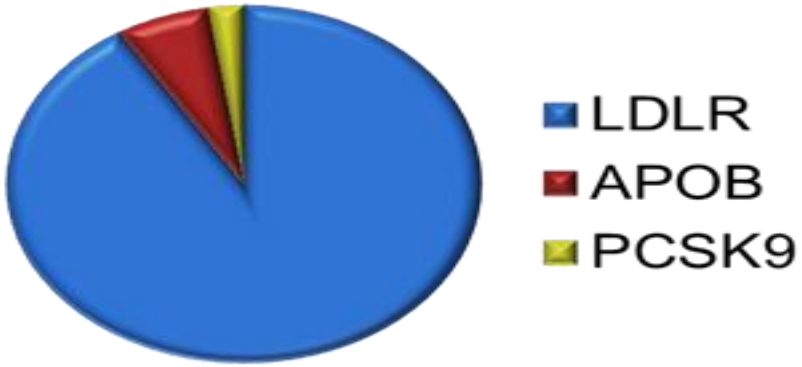
About FH

FH is an autosomal dominant disorder

- The most common FH-causing mutations are in the gene coding for the LDL receptor (*LDLR*). There are >1500 documented mutations in the *LDLR* gene.
- Less common mutations involve *APOB* and *PCSK9*



- Rarely, mutations in *LDLRAP1* lead to recessive FH

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FH and atherosclerosis

- FH is an asymptomatic condition . Accumulation of LDL-C in the plasma results in accelerated atherogenesis. If undiagnosed, this leads to premature coronary events, typically in early middle age

- The relative risk for a fatal coronary event in a young adult with FH aged 20-39 years is 80-100 fold greater than age-matched controls

- In general, the severity of atherosclerosis is proportional to the extent and duration of elevated LDL-C – the "Cholesterol -Year- Score"

Schmidt HH et al. Am J Cardiol 1996;77:575-80

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How common is familial hypercholesterolaemia?

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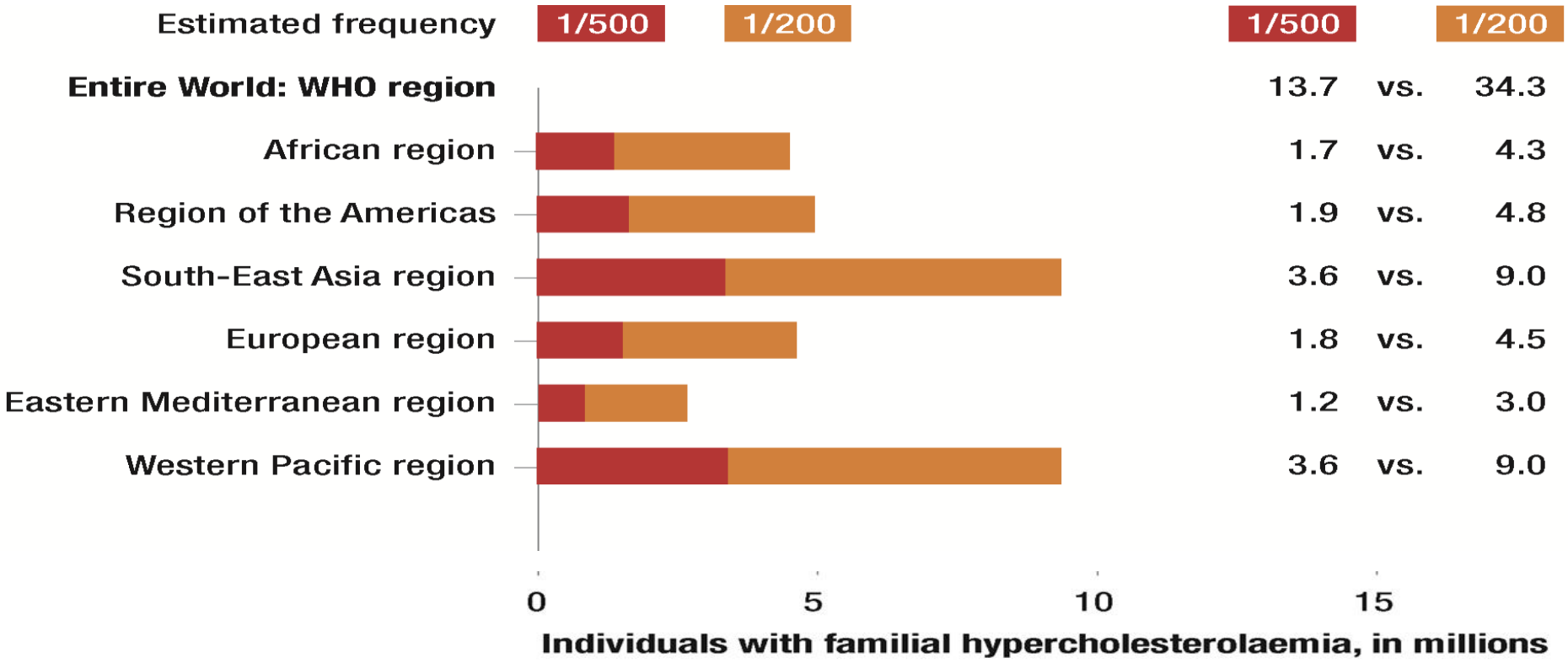
FH Prevalence

- Heterozygous FH affects about 1 in 200-250 people
- World-wide nearly 35 million people have FH



Nordestgaard BG et al. Eur Heart J 2013;34:3478-90a.

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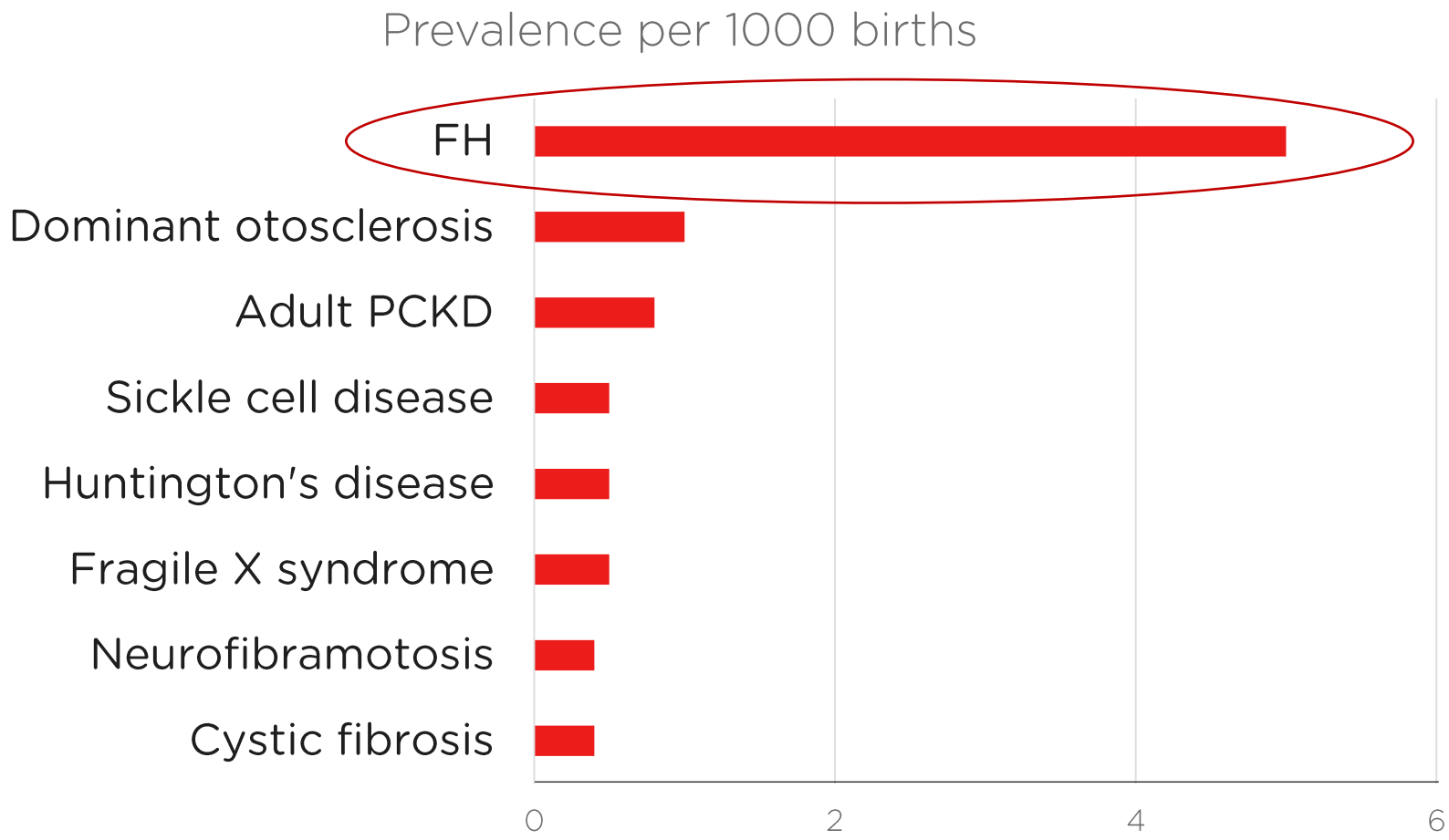
FH Prevalence

- FH affects about 5 in every 1,000 births
- Worldwide one baby is born with FH each minute



Wiegman A et al. Eur Heart J 2015 Epub ahead of print

Why we need to identify and treat FH early

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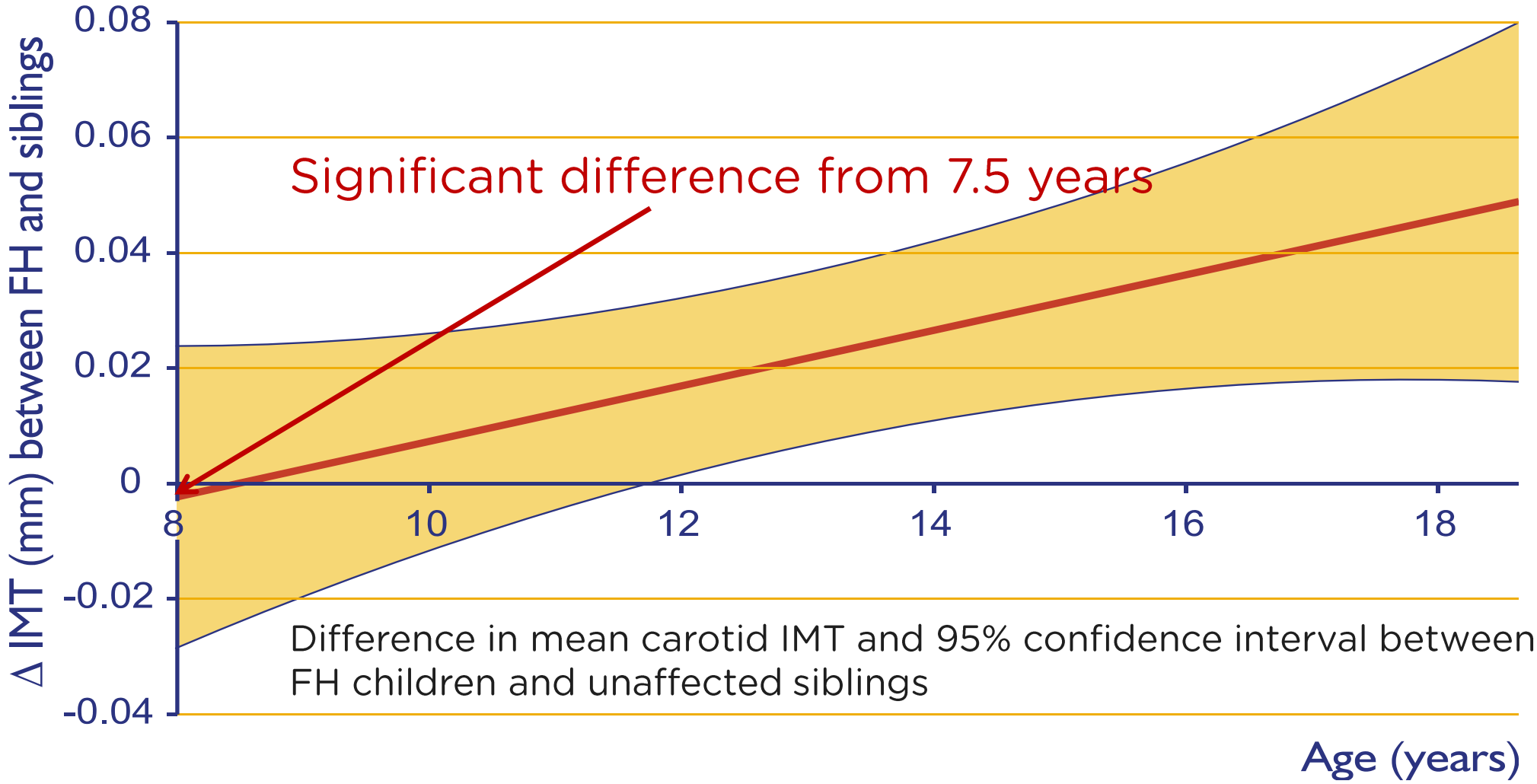
Carotid IMT: A marker of early atherogenesis in FH children



KustersDM et al. Circ Res 2014;114:307–310

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Early detection is critical

- Early detection of FH and early initiation of lifestyle and pharmacological treatment is imperative to reduce the life-long burden of elevated LDL-C levels

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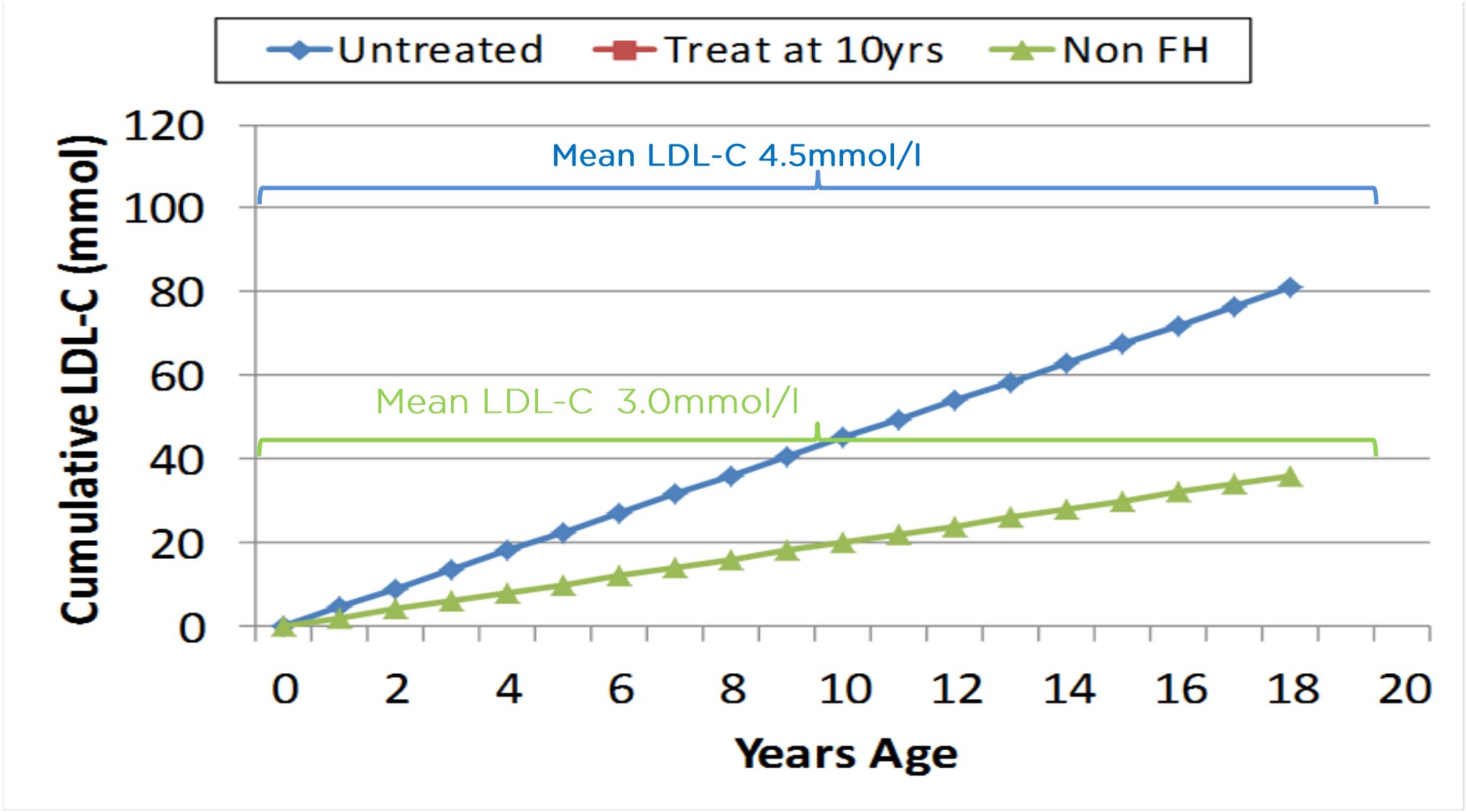
LDL-C burden in untreated FH children



Adapted from Vuorio A et al. Atherosclerosis 2013;226:315–20.

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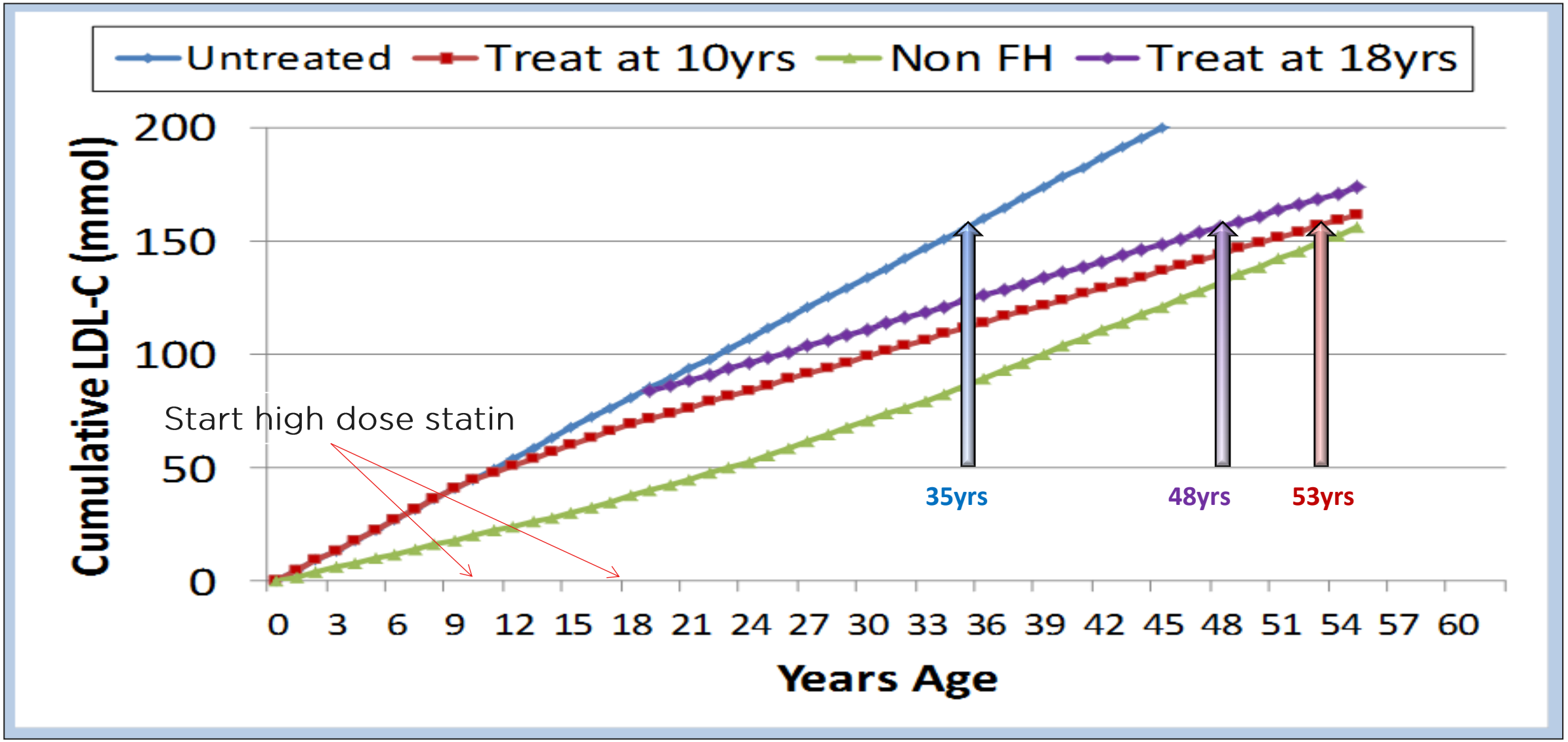
Early statin treatment delays LDL-C burden



Adapted from Vuorio A et al. Atherosclerosis 2013;226:315–20 based on data from Starr B et al. Clin Chem Lab Med 2008;46:791–803.

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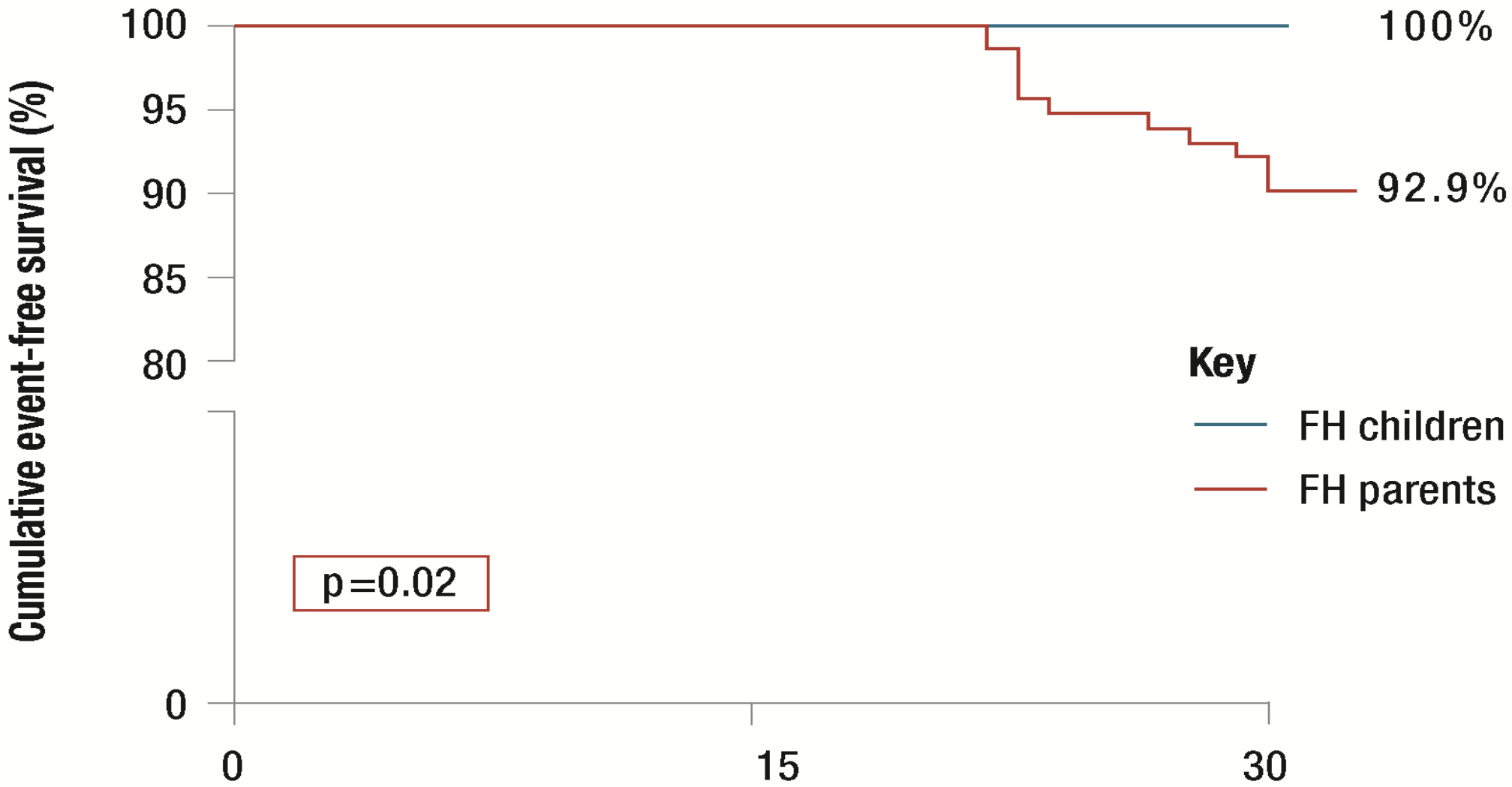
Impact of early statin treatment on event-free survival



Braamskamp MJ et al. Circulation 2013;128:A17837

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How to diagnose FH in children

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Family History + Hypercholesterolemia = FH in Children*

- Cholesterol testing should be used to make a phenotypic diagnosis
  - 5 mmol/L (190 mg/dL), 2 successive occasions over 3 months
  - 4 mmol/L (160 mg/dL) AND family history of premature CVD ± baseline high cholesterol in one parent
  - 3.5 mmol/L (130 mgdL) AND positive genetic diagnosis in the family
- Rule out secondary causes (thyroid, liver or renal dysfunction, concomitant medication, obesity)
- Genetic testing confirms the diagnosis (after parental testing)

*FH Foundation

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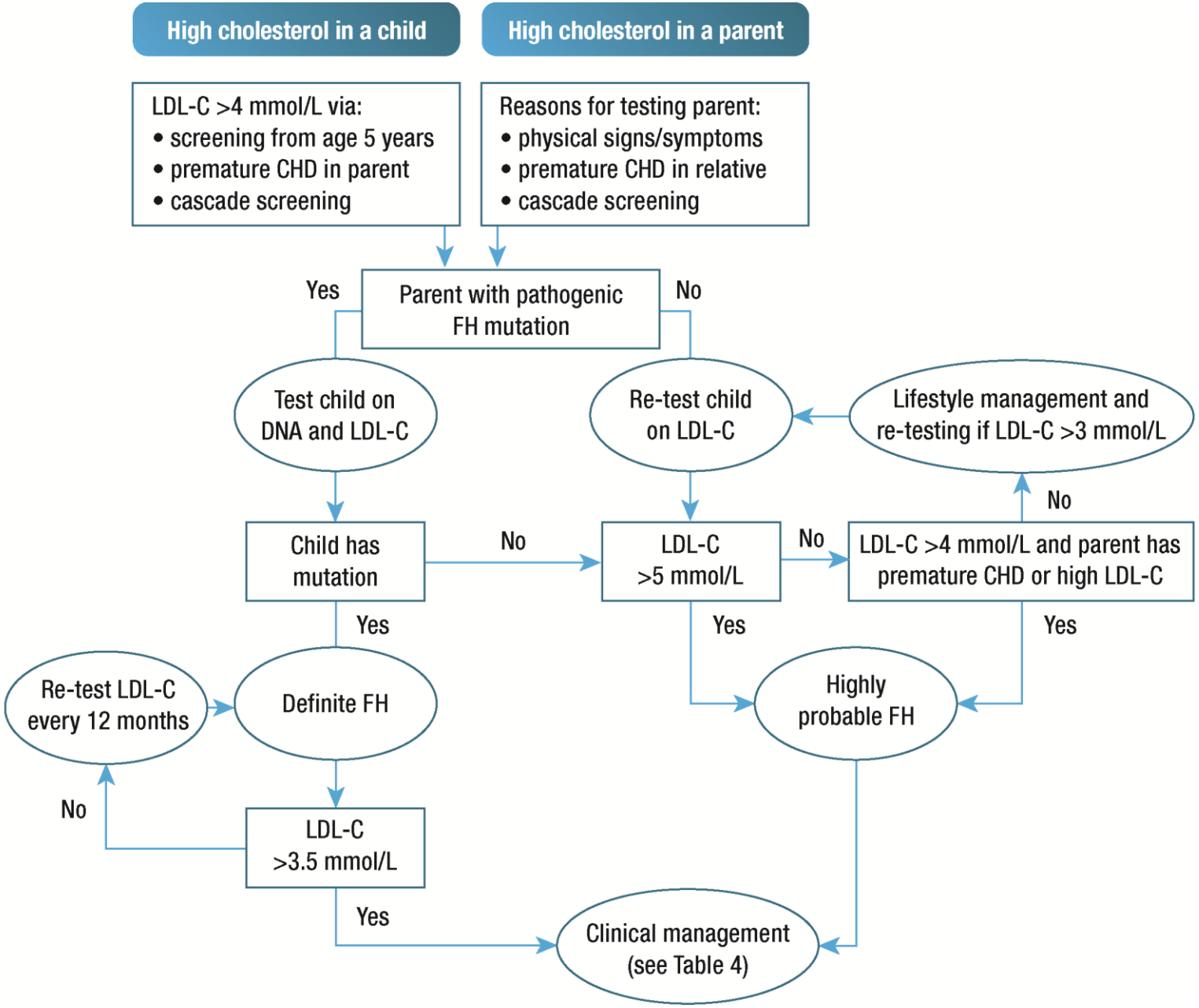
Diagnostic algorithm for FH in children & adolescents



Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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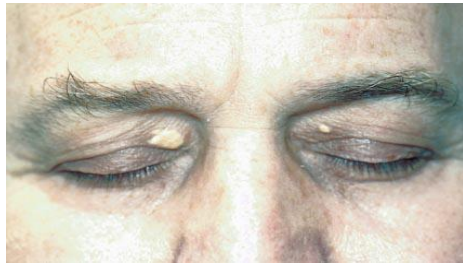
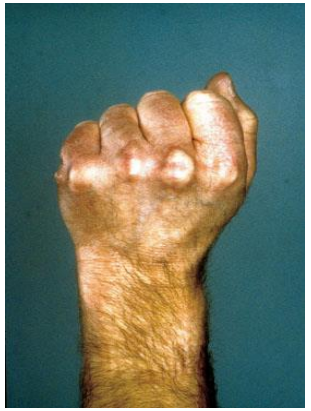
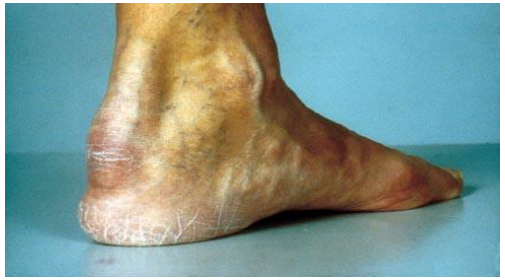
Consider Homozygous FH

Clinical evidence of:



- Premature cardiovascular disease
- Corneal Arcus
- Xanthelasma
- Tendon xanthomas in the hands and Achilles tendons





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The importance of FH screening

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Screening for FH in children and adolescents

- Despite the importance of early detection, FH remains under-diagnosed
- Cascade screening of families is the most cost-effective strategy to increase FH diagnosis and treatment.
- A genotypic strategy is recommended if DNA testing is available.
- If DNA testing is not available, a phenotypic strategy based on country, age and gender-specific low-density lipoprotein cholesterol (LDL-C) levels should be used

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Screening for FH in children & adolescents

- Suspected heterozygous FH: Screen from age 5 years
- **Suspected homozygous FH: Screen if clinically suspected (both parents affected or xanthoma present) as early as possible**
- Age at screening should be similar for boys and girls

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Treating FH children

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Diet and risk factor control

- Assess cardiovascular risk factors including lipoprotein (a)
- No smoking
- Encourage exercise
- Diet
  <30% of calories from fat
  <7% of calories from saturated fat
  <200mg cholesterol/day
  appropriate energy for normal growth and sufficient in micronutrients

Early initiation of lifestyle is essential for ensuring long-term adherence.

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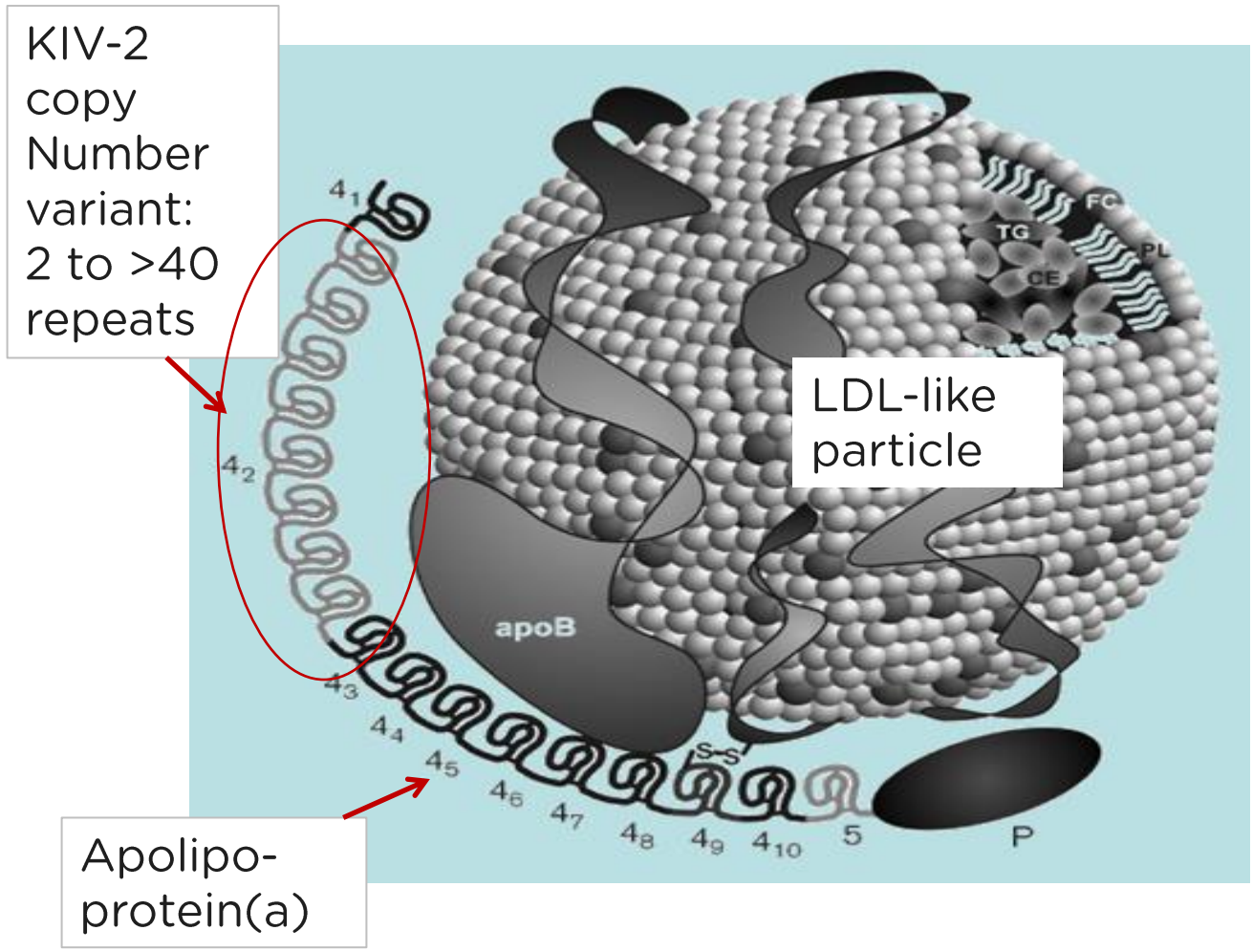
Risk factors: What is lipoprotein(a)?



- An LDL-like plasma lipoprotein BUT with an additional protein, apolipoprotein(a)
- Apo(a) comprises a series of loop structures called kringles. Kringle IV type 2 has from 2 to >40 copies

- Elevated Lp(a) ->50 mg/dL (80th percentile) is a cardiovascular risk factor
- FH is associated with elevated Lp(a)

Koschinsky et al. Cur Opin Lipidol 2004;15:167-174; Nordestgaard BG et al. Eur Heart J 2010;31;2844-53

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When to start a statin?

Heterozygous FH:

- Generally, at age 8-10 years (depending on local prescribing information)
- Earlier if considered at very high risk
  - family history of very premature coronary artery disease (30s-40s)
  - diabetes
  - organ transplantation
  - multiple coronary risk factors
- Stronger statins may need to be introduced after puberty in the case of severe mutations

Homozygous FH: At diagnosis

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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LDL-C Targets in children with FH

8–10 years:
Aim for 50% reduction in LDL-C from pre-treatment level

≥10 years:
<3.5 mmol/L (130 mg/dL) especially if there are additional cardiovascular risk factors, including elevated lipoprotein(a)

Adding ezetimibe or a bile-acid sequestrant may be needed to attain LDL-C goal

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Homozygous FH

- Children with homozygous FH should be referred to and cared for at a specialised centre

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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Monitoring FH children

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Monitoring treatment in FH children & adolescents

- Monitor weight, growth, physical and sexual development, and well-being
- Measure hepatic aminotransferases at least every 3 months if there is a history of liver disease. Monitor more frequently if levels increase >3-fold x ULN.
- Measure plasma CK levels if musculoskeletal symptoms are reported.
- Measure fasting plasma glucose and/or random HbA1c every 6 months in children on higher doses of statins who are obese or have impaired glucose tolerance.

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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Safety: liver & muscle

	FH n=194	Sibling n=83	*P* Value
Aspartate aminotransferase – IU/l			
Median (IQR)	25.0 (22.0-30.0)	26.0 (22.0-30.0)	0.44
> 3x ULN – no. (%)	1 (0.5%)	1 (1.1%)	0.55
Alanine aminotransferase – IU/l			
Median (IQR)	18.0 (13.0-25.0)	17.0 (13.0-24.0)	0.63
> 3x ULN – no. (%)	1 (0.5%)	0 (0.0%)	0.51
Creatine kinase – IU/l			
Median (IQR)	101.0 (72-150)	101.0 (82.0-161.0)	0.28
> 10x ULN – no. (%)	0 (0.0%)	2 (2.1%)	0.03

Kusters DM et al. JAMA 2014;312:1055–1057

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Safety: growth/development

- Growth

	FH n=194	Sibling n=83	*P* Value
Height – m	1.74 ± 0.1	1.76 ± 0.09	0.27
Weight – kg	74.2 ± 14.8	73.8 ± 12.9	0.82
Body-mass index	24.4 ± 4.8	23.9 ± 3.9	0.36

- Menarche: 13.1 vs 13.2 years, *P*=0.72

Kusters DM et al. JAMA 2014;312:1055–1057

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Special issues: adherence

- Check adherence if heterozygous FH children fail to achieve LDL-C targets with combination lipid-lowering treatment.

- Consider referral of non-adherent patients to a dedicated, multidisciplinary clinic

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Special issues in adolescent girls with FH

Contraception

- Preferred contraceptive measures: low oestrogen oral agents, intra-uterine devices and barrier methods
- Monitor lipids after starting oral contraceptives

Pregnancy

- Counselling is recommended for all women considering pregnancy due to the risk for FH
- Statins should be discontinued: Bile-acid resins are the only safe agents for use in pregnancy and breast-feeding

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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Better education about FH a priority

Norwegian Registry data

- 118 FH patients, treated with statin from age 8-10 years in trials
- 72% (48 of 67 consented) continued on statin
- Only 9% participants had LDL-C ≤ 2.5 mmol/L

Implications

- Statins are severely underused in young adult FH patients.
- Better education of patients and frequent (yearly) consultations therefore seem warranted.

Langlet G et al. EAS Congress Glasgow 2015 [poster]

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Conclusions

- World-wide, one baby is born with FH every minute
- Identifying and treating children with FH is the key to gaining decades of healthy normal life and making premature coronary heart disease history
- Better awareness and education are essential to achieving this

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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About lipoprotein(a)

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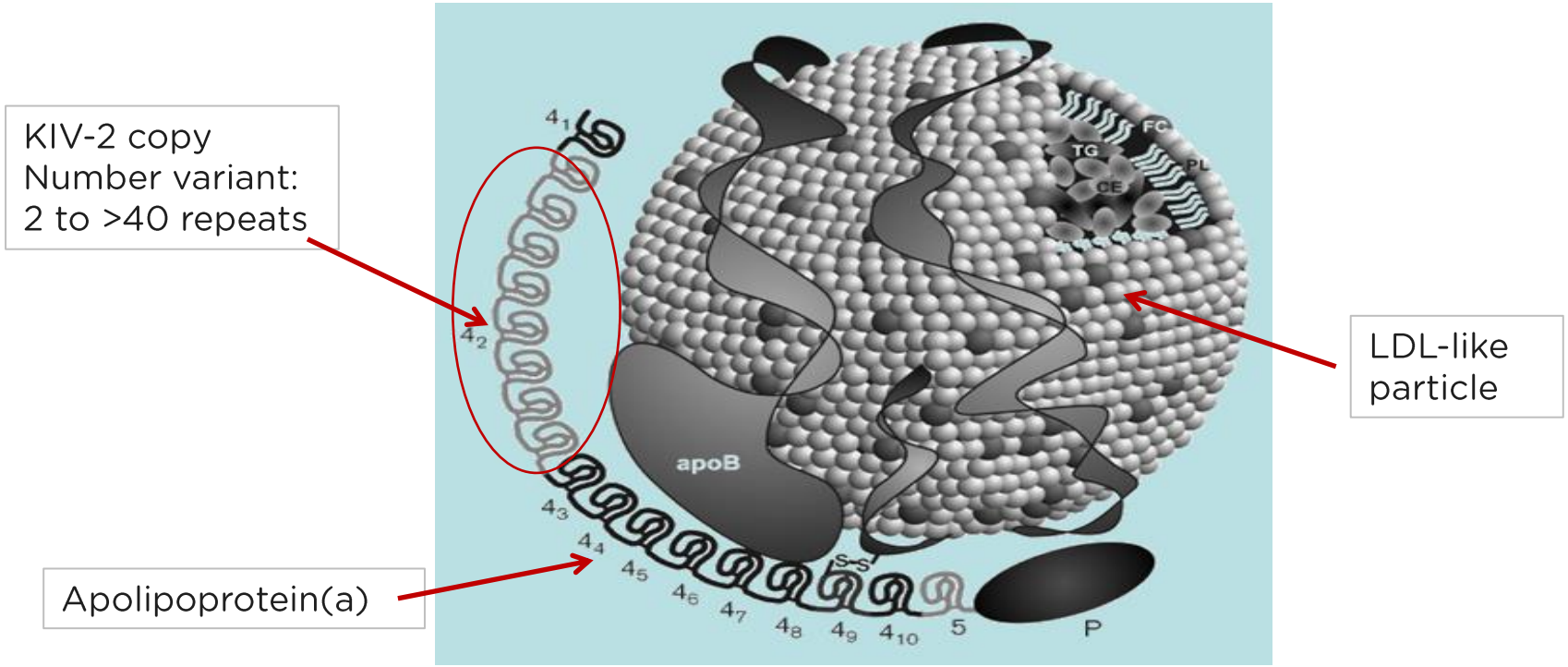
What is lipoprotein(a)?

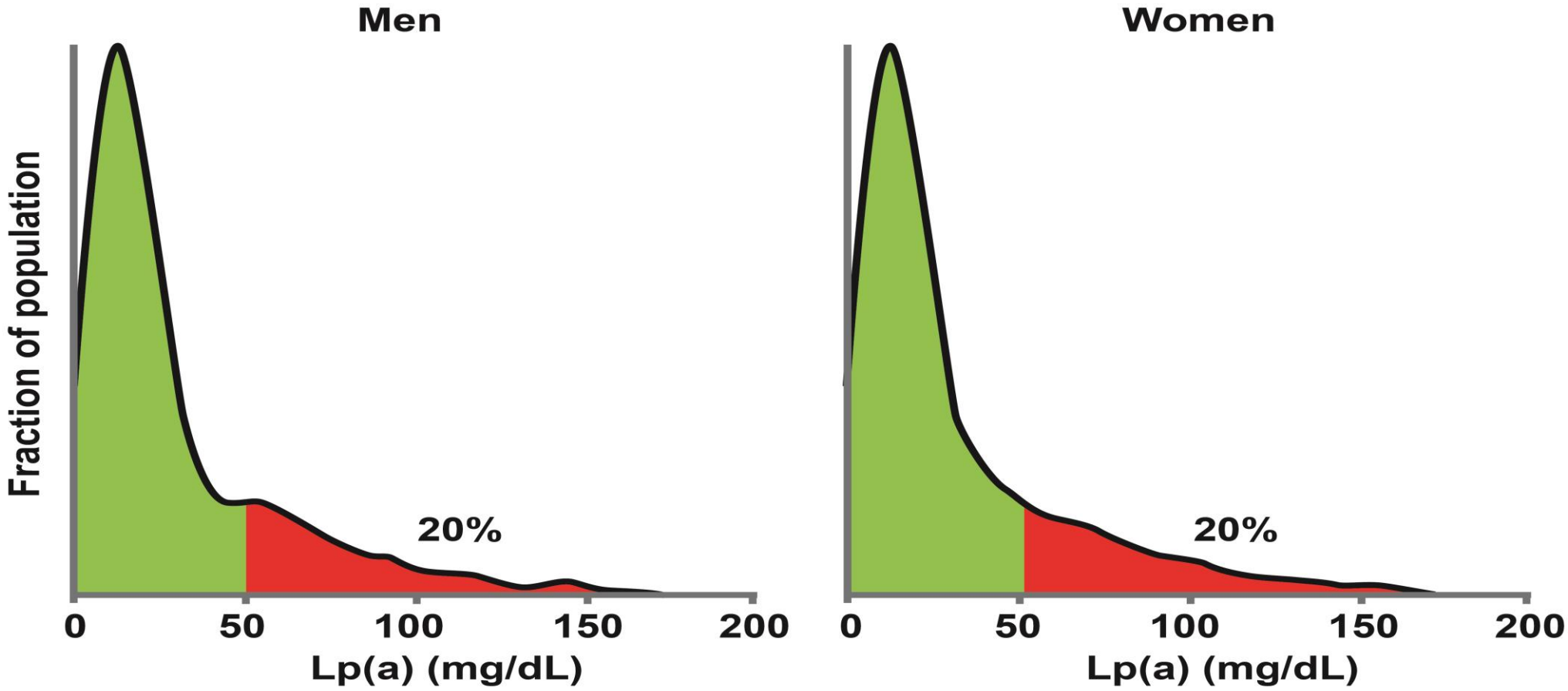
- An LDL-like cholesterol-rich particle which differs from LDL as it contains an additional protein, apolipoprotein(a).
- Apo(a) comprises a series of loop structures called kringles. Kringle IV type 2 has from 2 to >40 copies



Koschinsky et al. Cur Opin Lipidol 2004;15:167-174

Plasma Lp(a) levels in general population

20% have plasma Lp(a) levels >50 mg/dL



Nordestgaard BG et al. Eur Heart J 2010;31:2844-53

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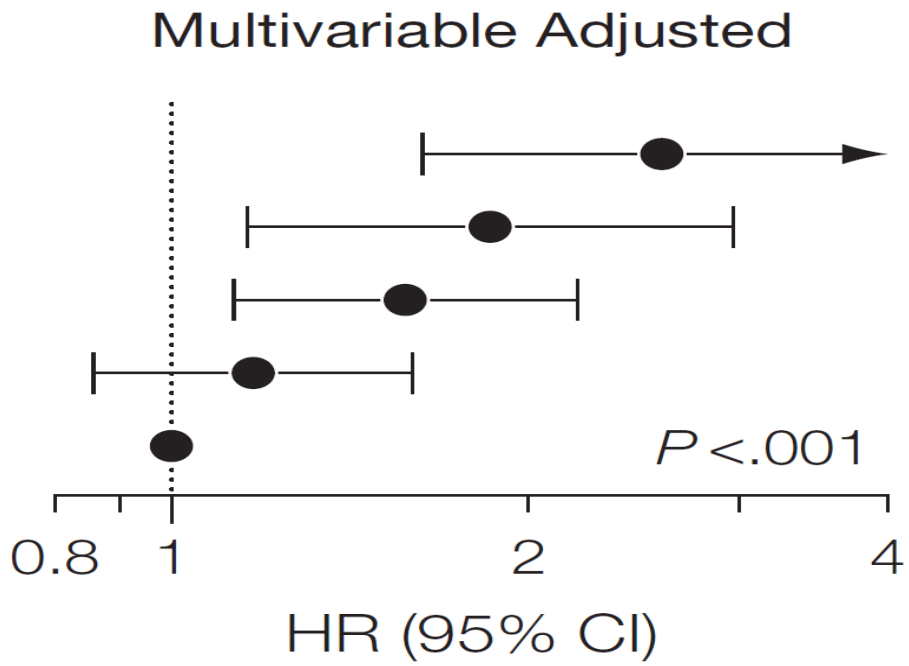
Lp(a) and cardiovascular risk: Epidemiological evidence

- Copenhagen General Population Study:
- people with Lp(a) > 50 mg/dL had 2-3-fold increased risk for MI

Lipoprotein(a)	
Percentile	mg/dL
>95th	>117
90th-95th	77-117
67th-89th	30-76
22nd-66th	5-29
<22nd [Reference]	<5



Kamstrup et al. JAMA 2009; 301: 2331-9, Nordestgaard BG et al. Eur Heart J 2010;31:2844-53

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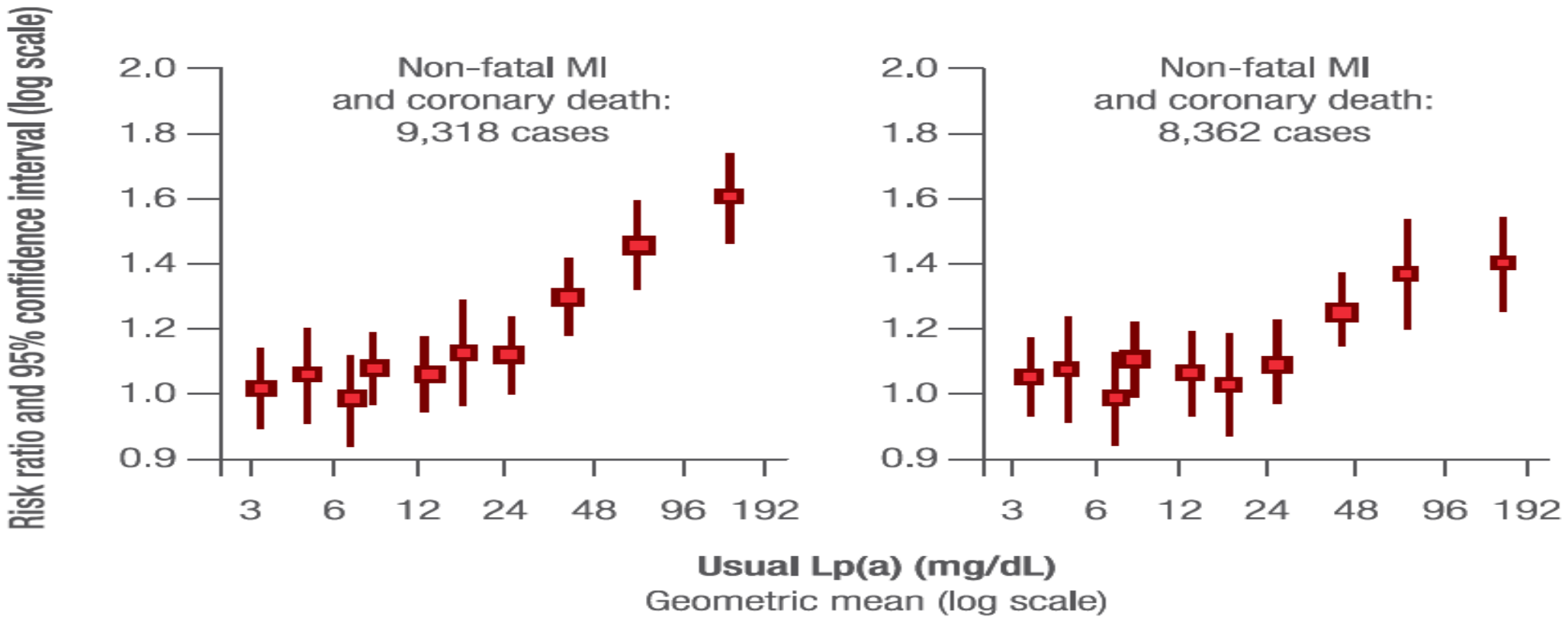
Lp(a) and cardiovascular risk: Epidemiological evidence

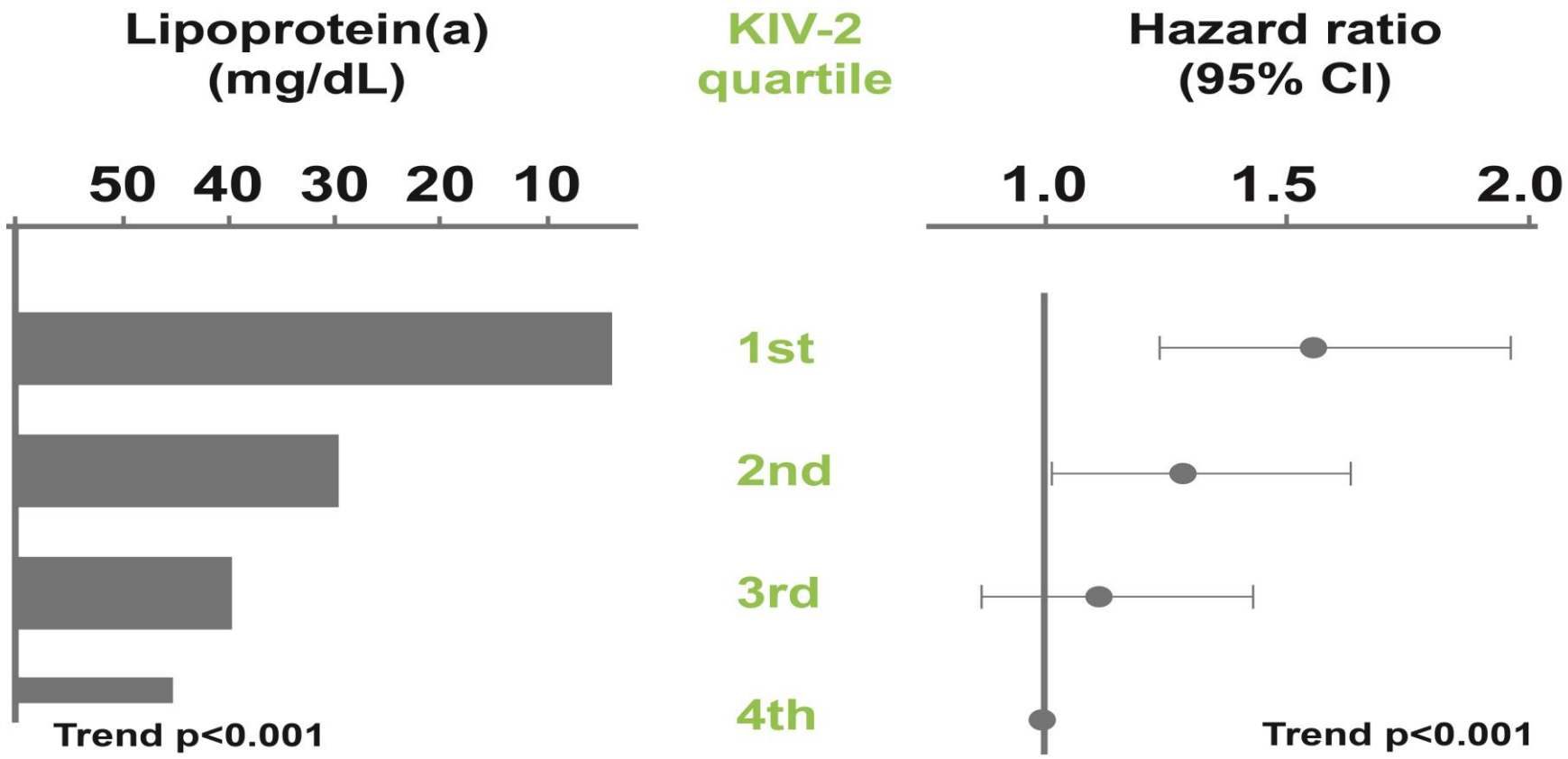
- Emerging Risk Factors Collaboration:
  Each 1 standard deviation increase in Lp(a) increased CHD risk by 13%



Erqou S et al. JAMA 2009;302:412-23

Lp(a) and cardiovascular risk: Genetic evidence

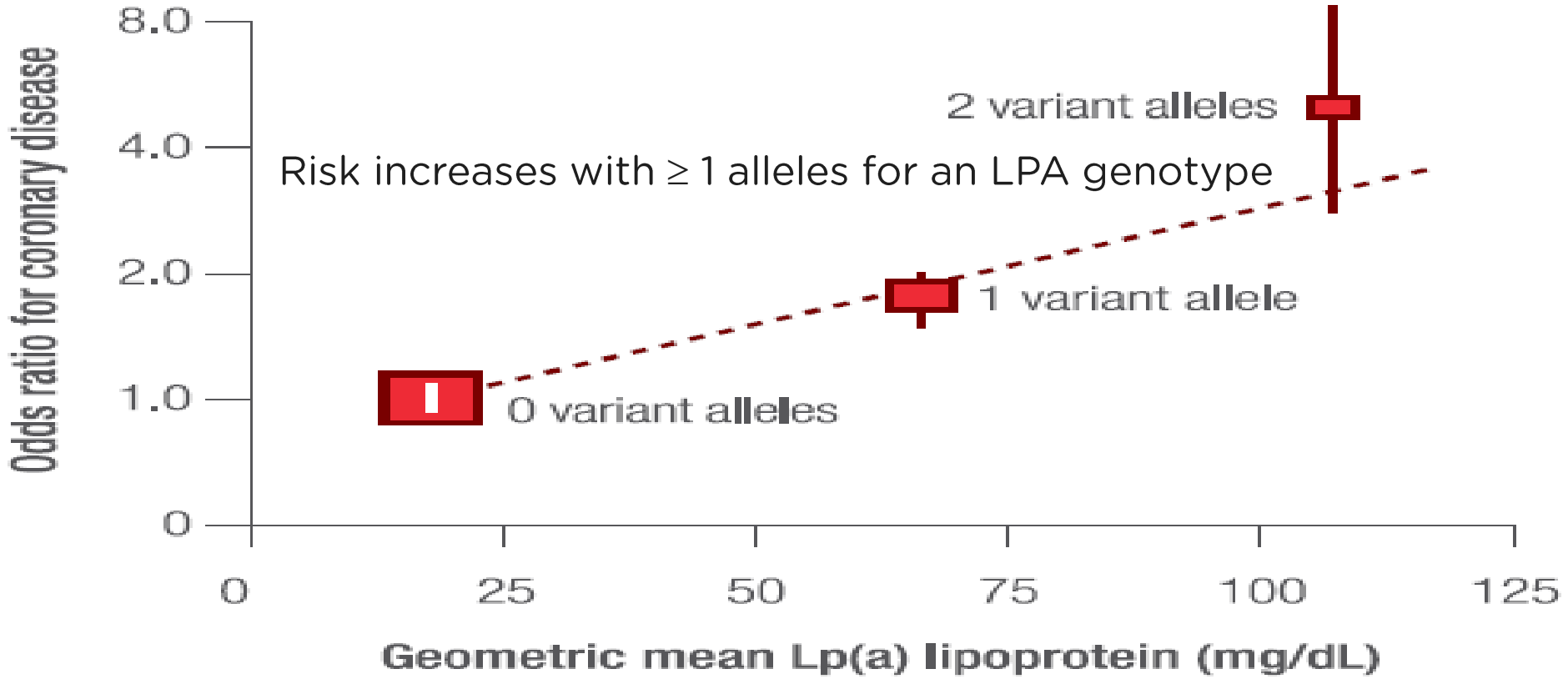
- Decreasing quartiles of kringle IV type 2 repeats were associated with increasing plasma Lp(a) levels and increased MI risk



Kamstrup PR et al. JAMA 2009;301:2331-9

Lp(a) and cardiovascular risk: Genetic evidence

- Plasma Lp(a) levels and CHD risk increases with ≥1 variant alleles of the *LPA* gene



Clarke R et al. NEJM 2009; 361:2518-28

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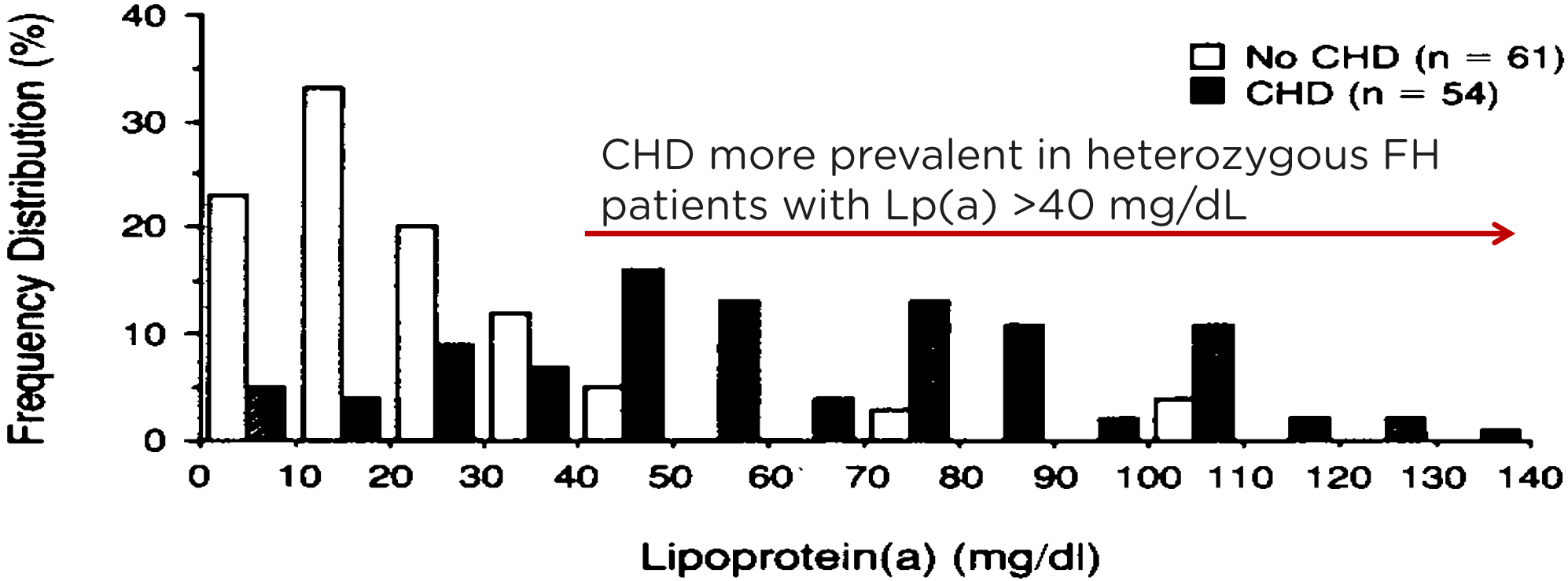
Lp(a) and FH

- CHD more prevalent in heterozygous FH patients with Lp(a) >40 mg/dL
- Frequency of variant *LPA* allele ~2.5-fold higher in FH patients with CHD than in those without



Seed M et al NEJM 1990;322:1494-9

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Lp(a) and FH

- Retrospective cohort study of 2400 patients with heterozygous FH
- Lp(a) >30 mg/dL was associated with 1.5-fold increase in CVD risk

	Univariate			Multivariate ($n = 1956$)		
	RR	95% CI	*P* value	RR	95% CI	*P* value
Male gender	2.95	2.54–3.43	<0.0001	2.82	2.37–3.36	<0.0001
Smoking (time dependent + lag effect)	1.79	1.55–2.08	<0.0001	1.67	1.40–1.99	<0.0001
Hypertension (time dependent)	1.42	1.15–1.75	0.001	1.36	1.06–1.75	0.02
Diabetes (time dependent)	1.96	1.28–3.01	0.002	2.19	1.36–3.54	0.001
BMI (kg m^{-2})	1.03	1.01–1.05	0.01	–	–	–
HDL risk (males <0.9 mmol L^{-1}; females <1.1 mmol L^{-1})	1.36	1.15–1.62	0.0004	1.37	1.15–1.63	0.0004
Triglycerides (mmol L^{-1})	1.12	1.05–1.20	0.001	–	–	–
Lp(a) risk (>300 mg L^{-1})	1.46	1.23–1.73	<0.0001	1.50	1.20–1.79	0.0001[a]
Homocysteine risk (>15 μmol L^{-1})	1.57	1.24–1.99	0.0002	–	–	–

[a] $n = 1698$.

Jansen AC et al. J Intern Med 2004;256:482-90

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More information:

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CURRENT OPINION

Lipoprotein(a) as a cardiovascular risk factor: current status

Børge G. Nordestgaard[1*], M. John Chapman[2], Kausik Ray[3], Jan Borén[4], Felicita Andreotti[5], Gerald F. Watts[6], Henry Ginsberg[7], Pierre Amarenco[8], Alberico Catapano[9], Olivier S. Descamps[10], Edward Fisher[11], Petri T. Kovanen[12], Jan Albert Kuivenhoven[13], Philippe Lesnik[2], Luis Masana[14], Zeljko Reiner[15], Marja-Riitta Taskinen[16], Lale Tokgözoglu[17], and Anne Tybjærg-Hansen[18], for the European Atherosclerosis Society Consensus Panel[†]

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