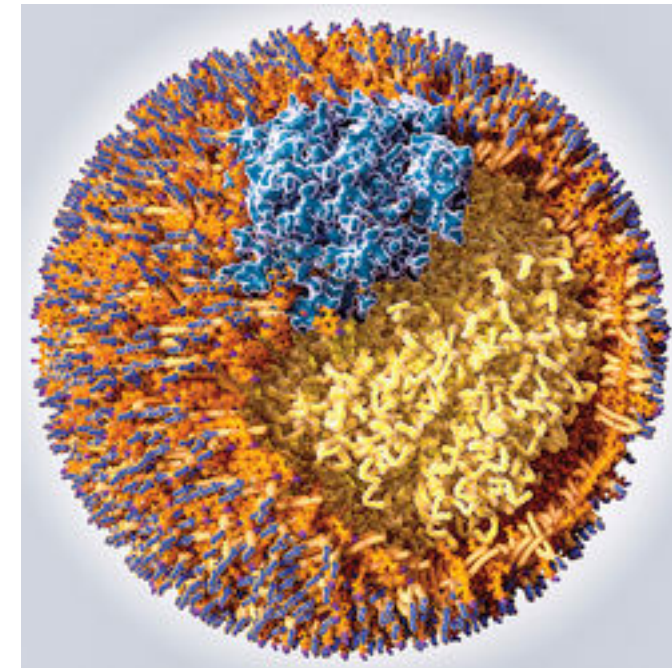
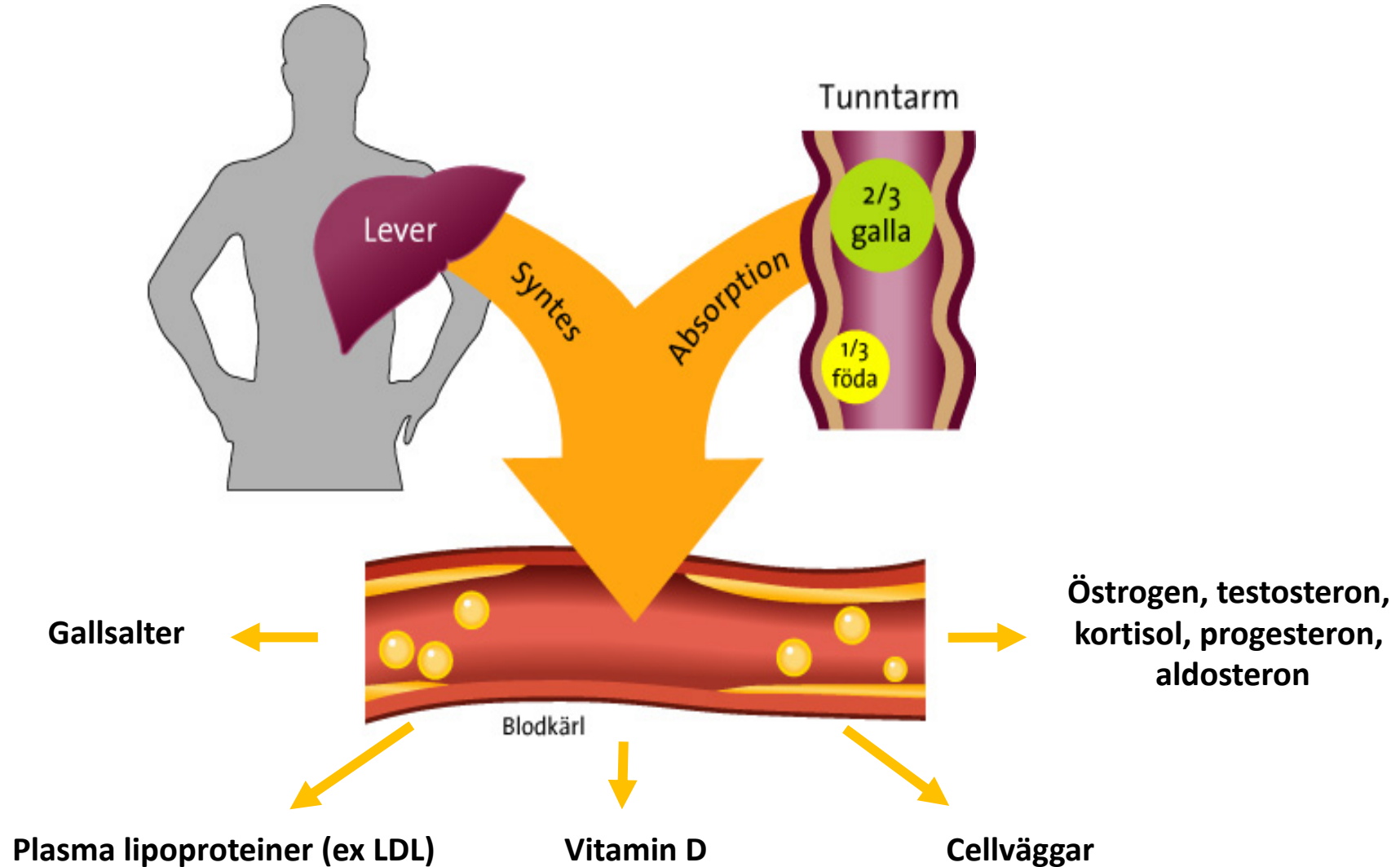


Statin i högdos eller kombination med icke statin.
När ska vi använda PCSK9-hämmare?

Emil Hagström
Akademiska sjukhuset

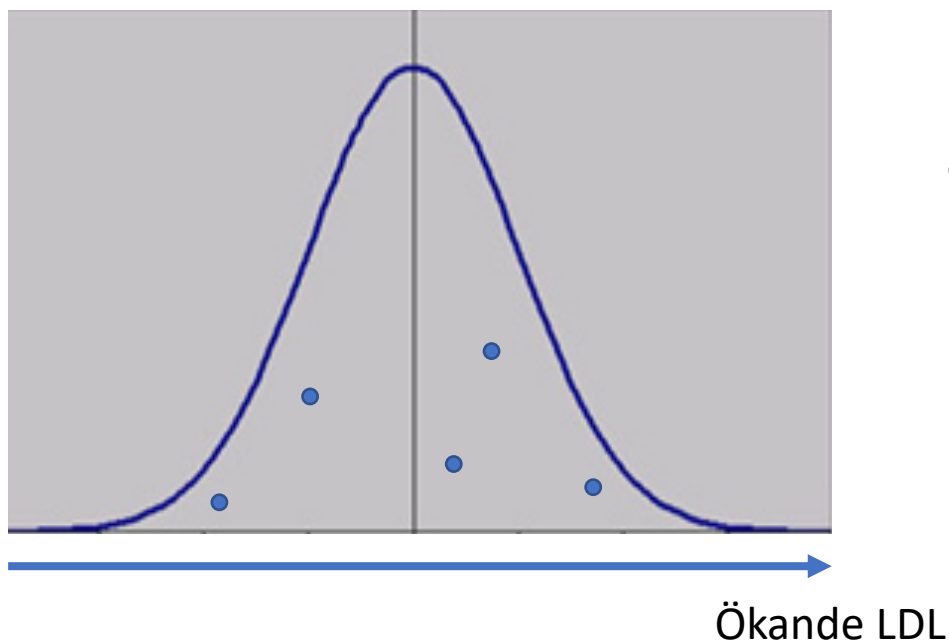


Två källor till kolesterol



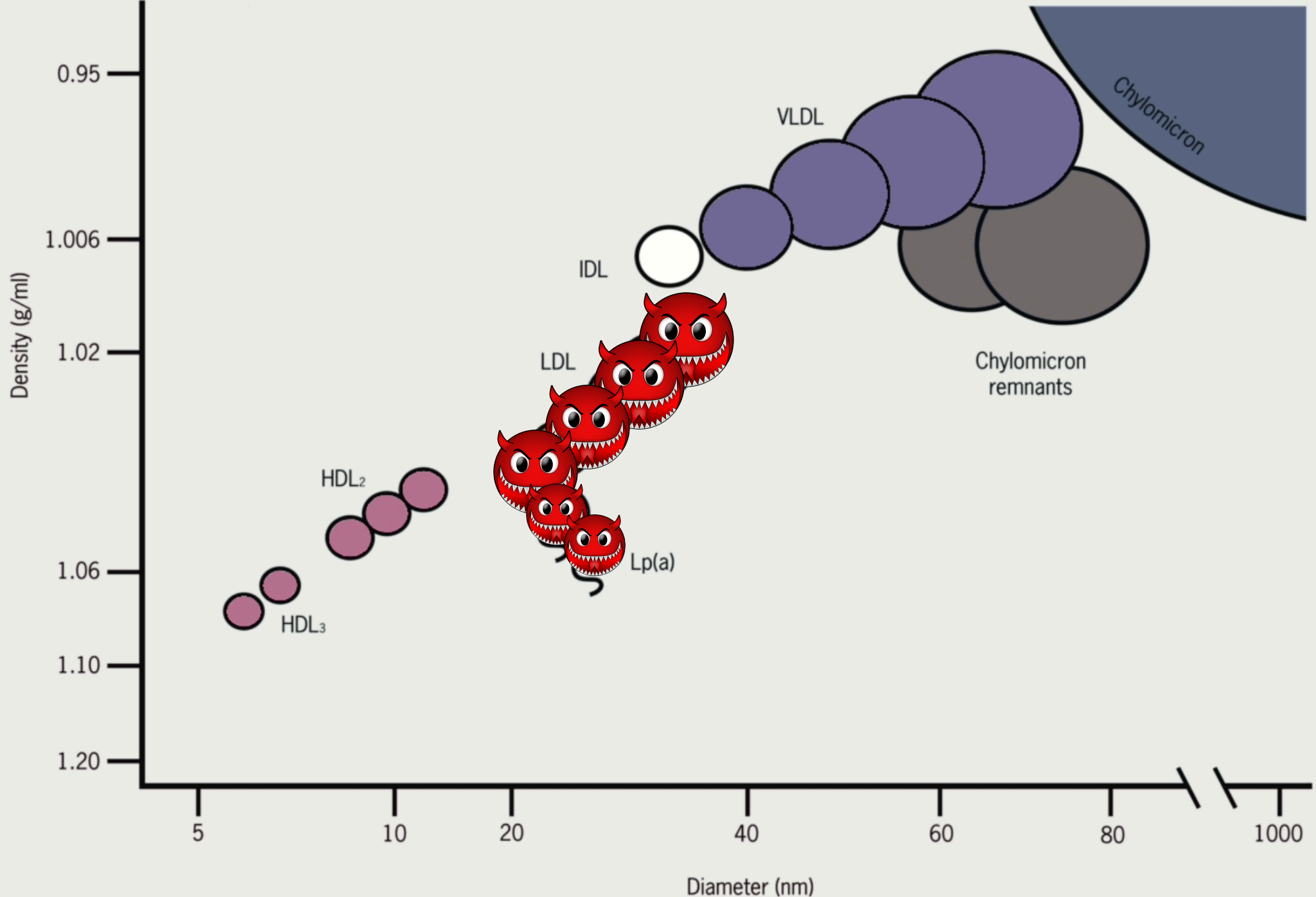
Kolesterol, livsstil och ärftlighet

Plasma LDL-kolesterol

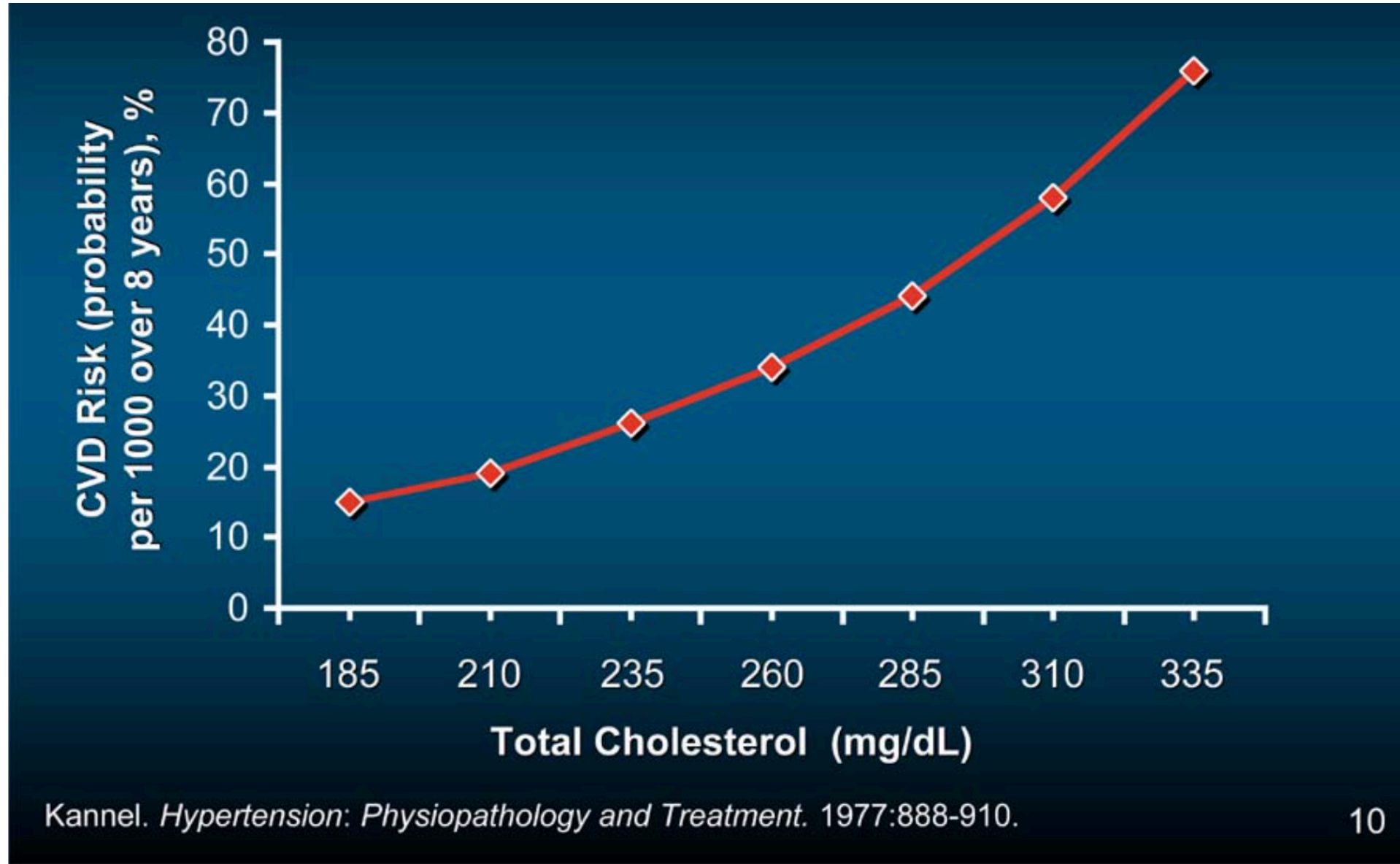


Plasma LDL-kolesterol i befolkningen är normalfördelad och varierar med ca faktor tre.

Ca 50% bestäms av gener och 50% av miljö/livsstil.



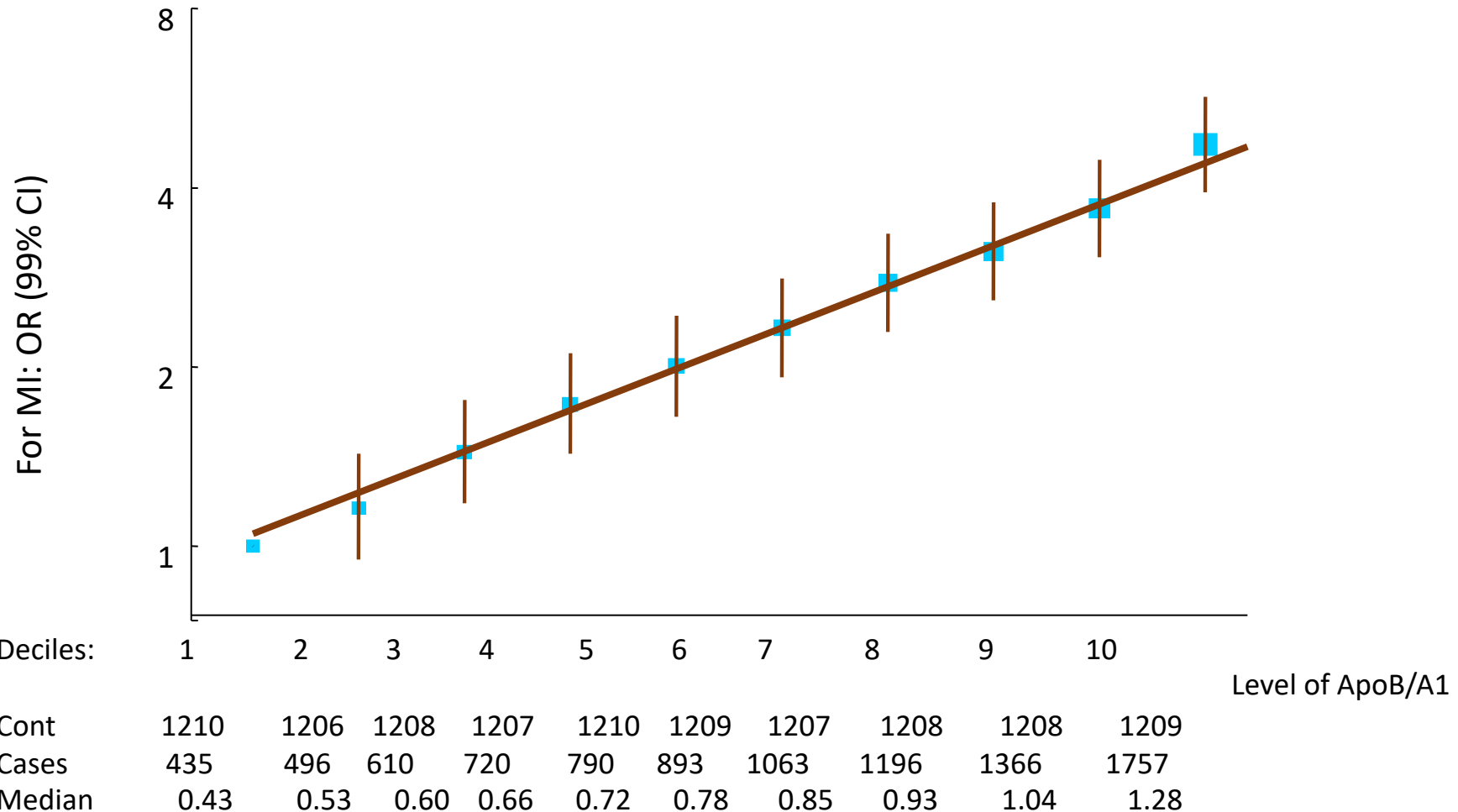
Primärprevention: ökande kolesterol och risk



Framingham

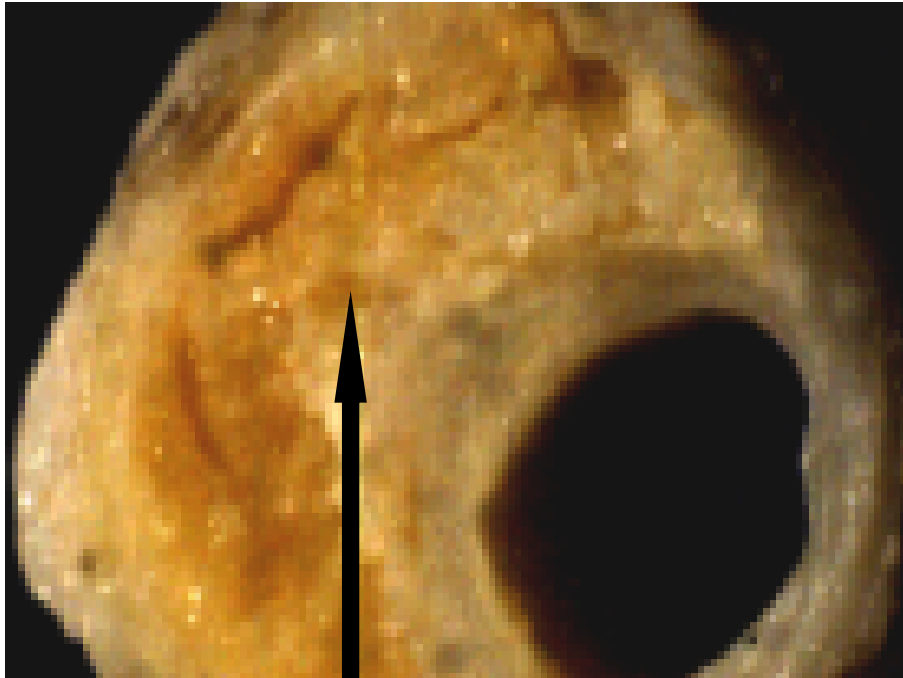
Kolesterol (ApoB/A1) och odds för hjärtinfarkt

N = 27.098, 52 länder



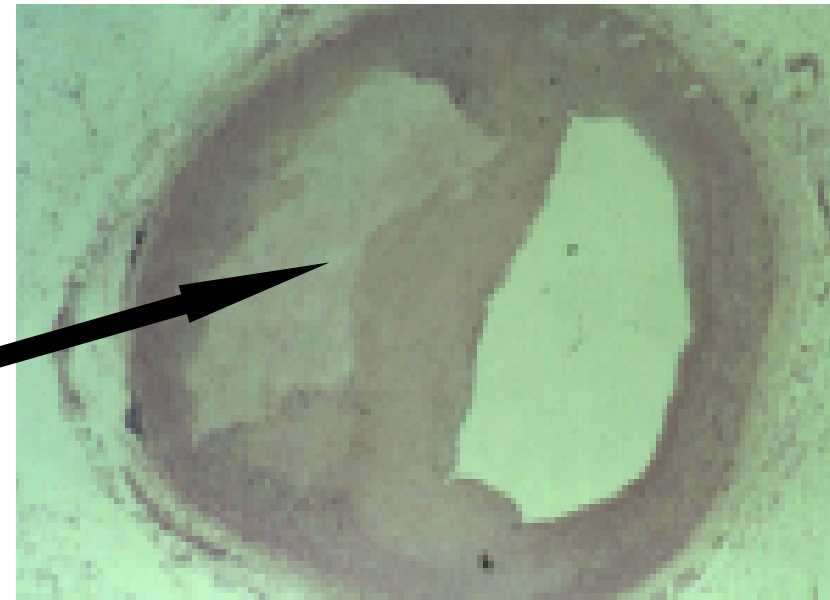
INTERHEART

Ateroskleros

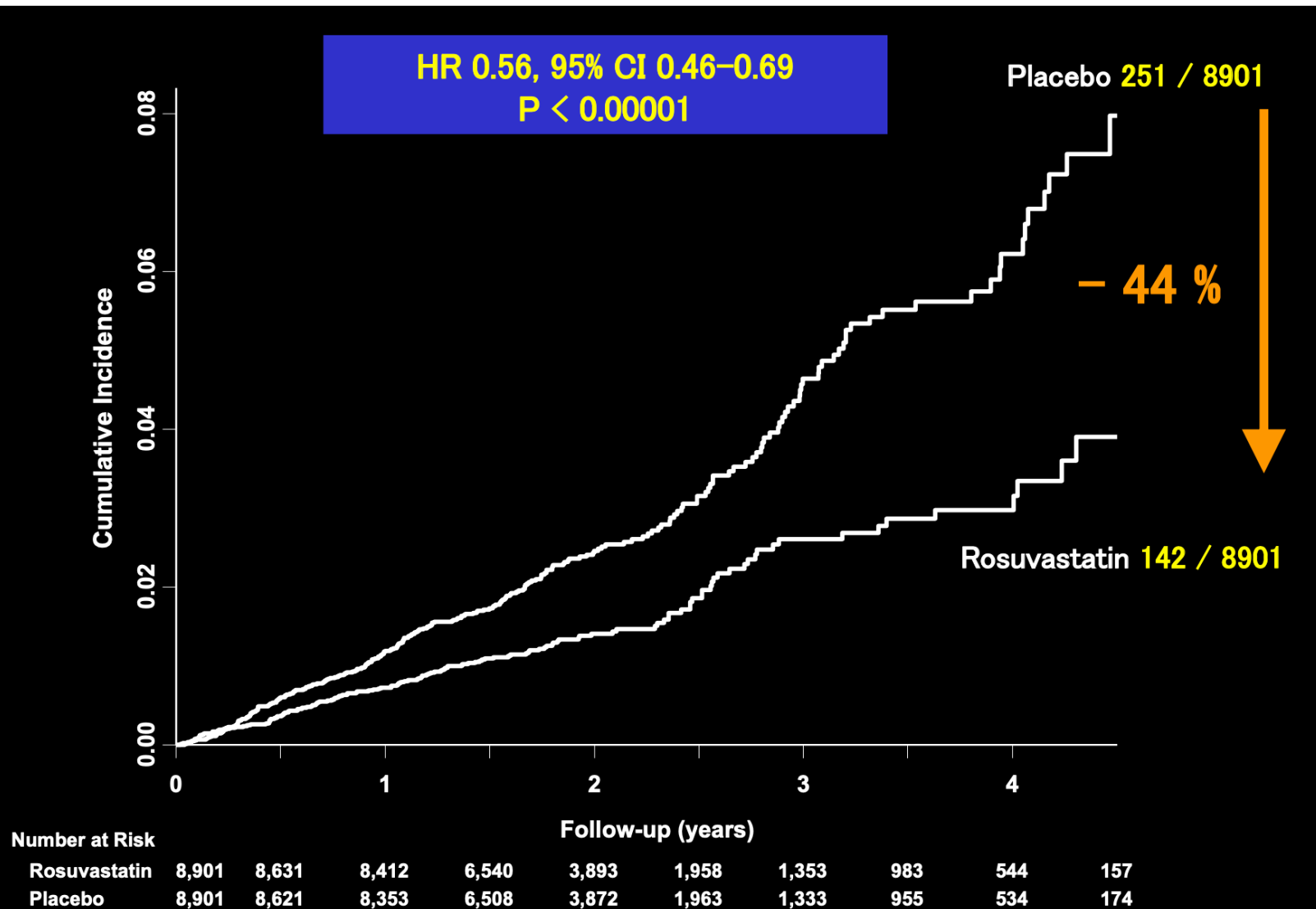


Kolesterolinlagring

Kolesterolinlagring, inflammation,
fibros, oxidation, nekros



Sänkning av LDL med statin ger minskad risk primärpreventivt



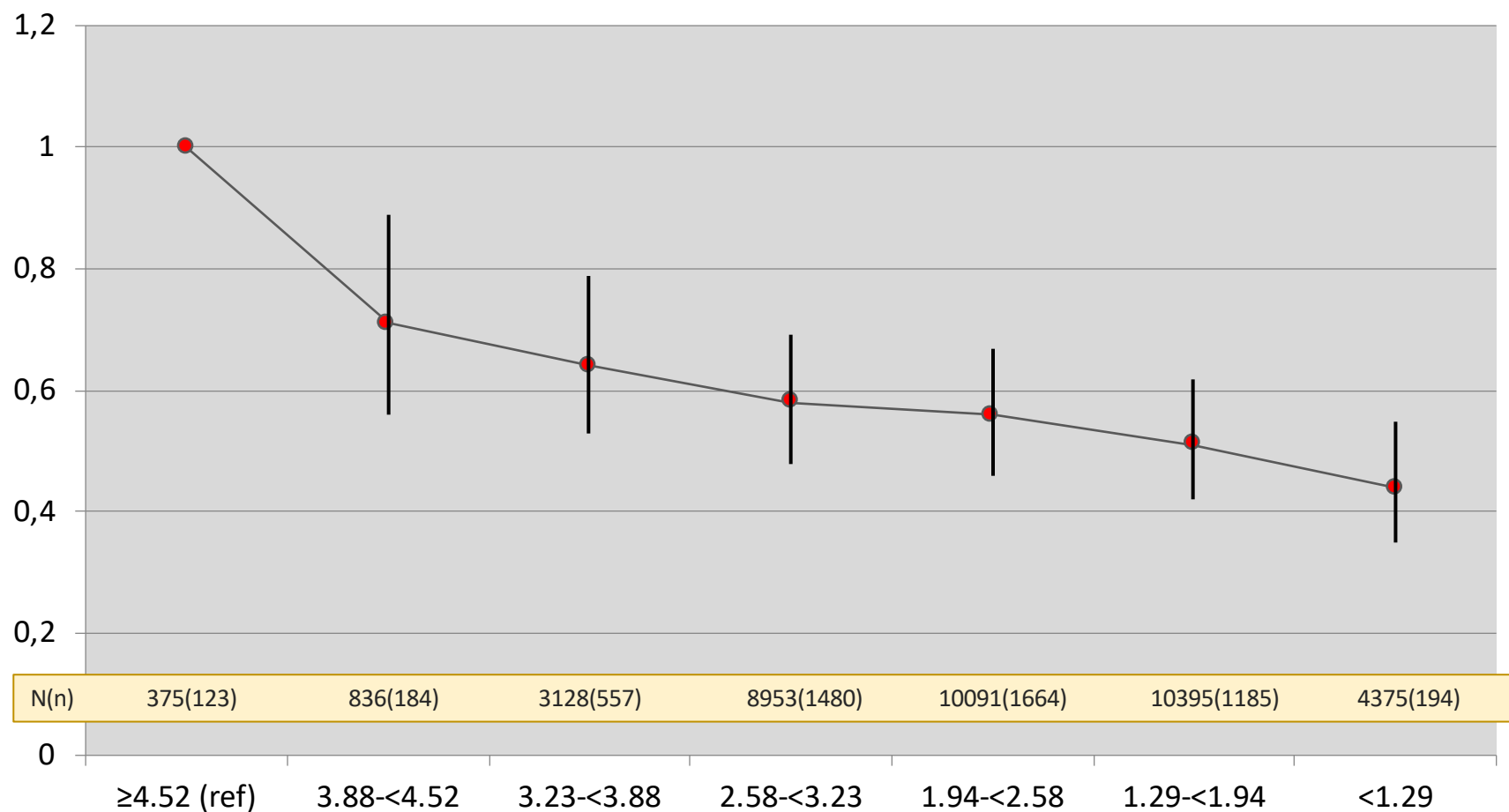
Jupiter. N: 17.802.

Rosuvastatin till hjärtkärlfriska.

Primary endpoint: MI, stroke, revask/IAP, CV death.

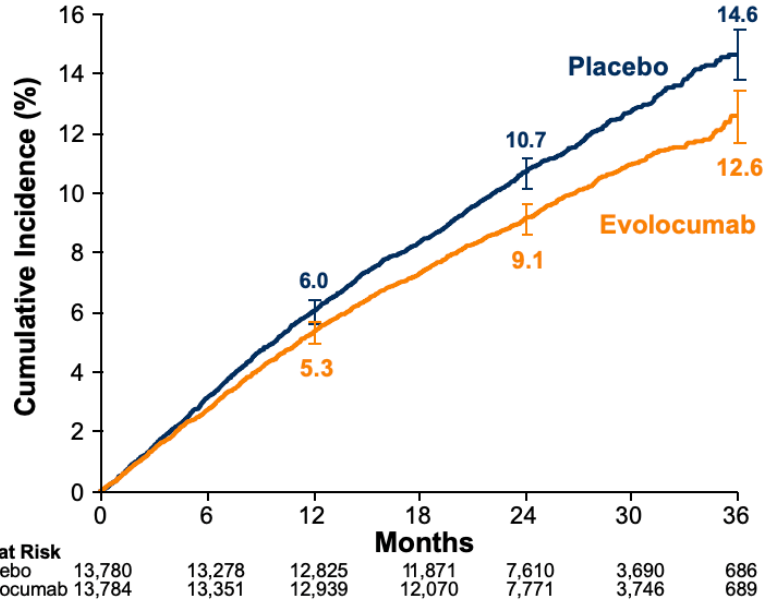
Ridker 2008.

Sänkning av LDL med statiner ger minskad risk sekundärpreventivt



Boekholdt SM. Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events - A Meta-Analysis of Statin Trials. JACC 2014;64(5);485-94

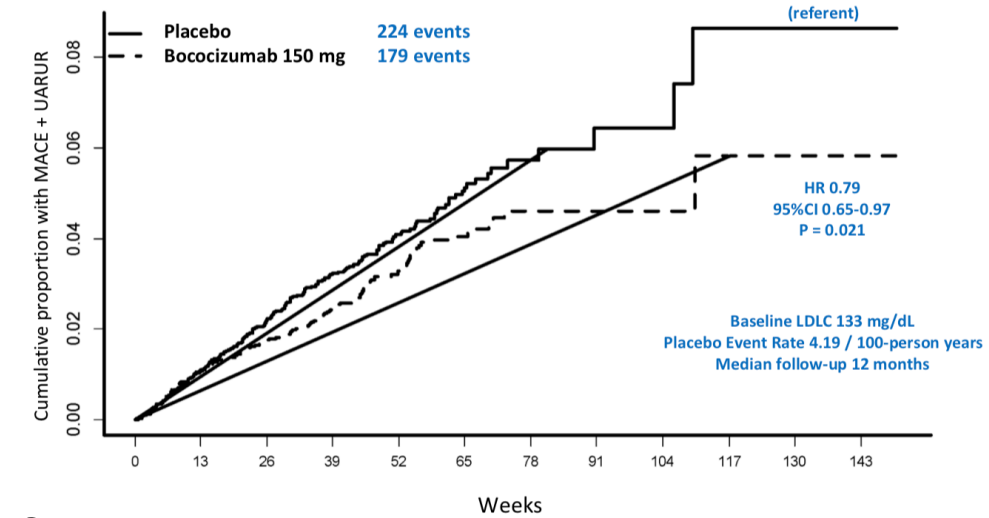
N: 38153



Sekundärprevention:

- PCSK9-hämning
- Ezetimib

The SPIRE-2 Cardiovascular Outcomes Trial: Baseline LDLC \geq 100 mg/dL Primary Pre-Specified Endpoint*

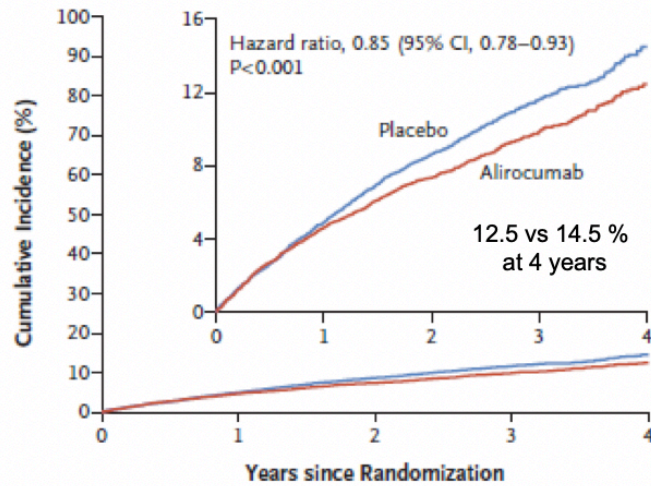


HR 0.85 (95% CI 0.79 to 0.92); P < 0.001

SPIRE-2

*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

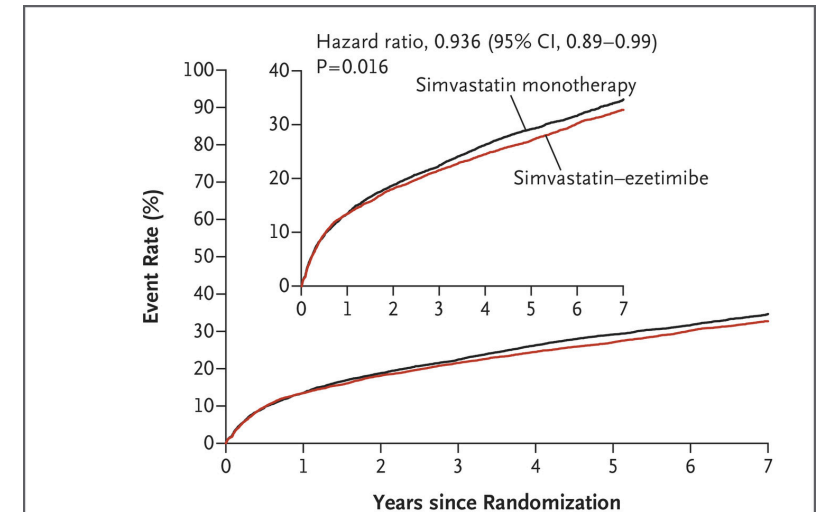
Ridker et al, NEJM 2017;376:1527-1539



No. at Risk	0	1	2	3	4
Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

Primary endpoint: composite of CHD death, non-fatal MI, ischaemic stroke or unstable angina requiring hospitalisation

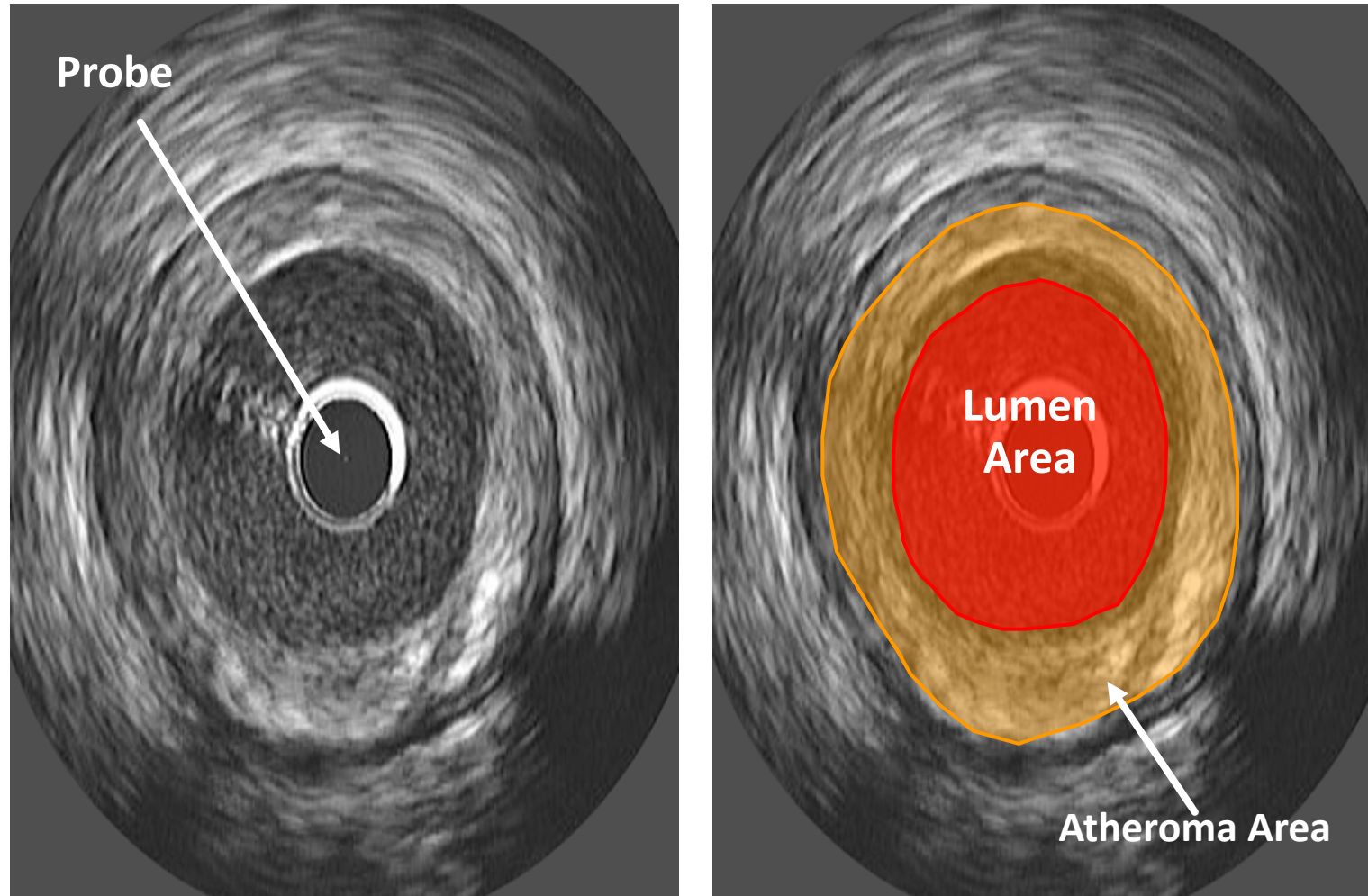
N Engl J Med. 2018 Nov 7. doi: 10.1056/NEJMoa1801174. [Epub ahead of print]



No. at Risk	0	1	2	3	4	5	6	7
Simvastatin-ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

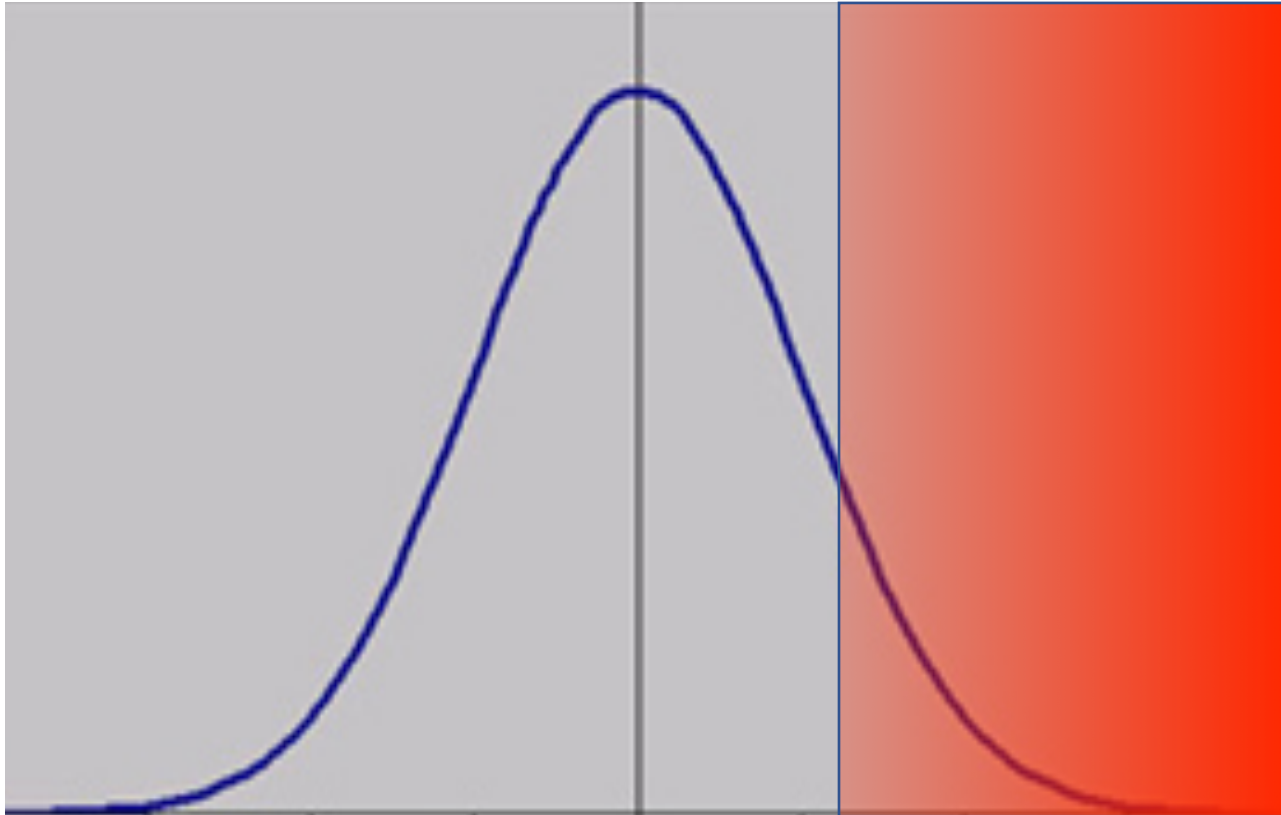
IMPROVE-IT

Minskad aterosklerotisk börda vid behandling med PCSK9-hämning mätt via intravaskulärt (kranskärl) ultraljud



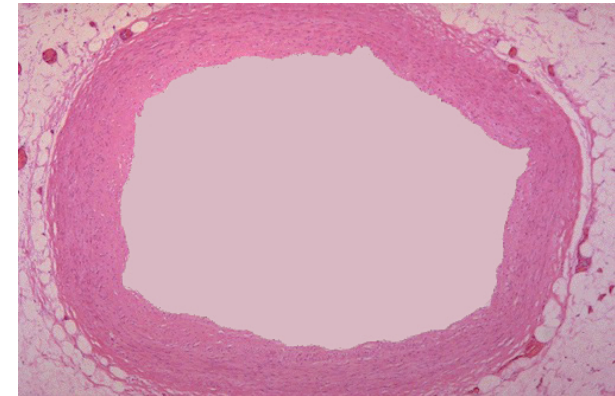
GLAGOV
Evolocumab

Riskbedömning

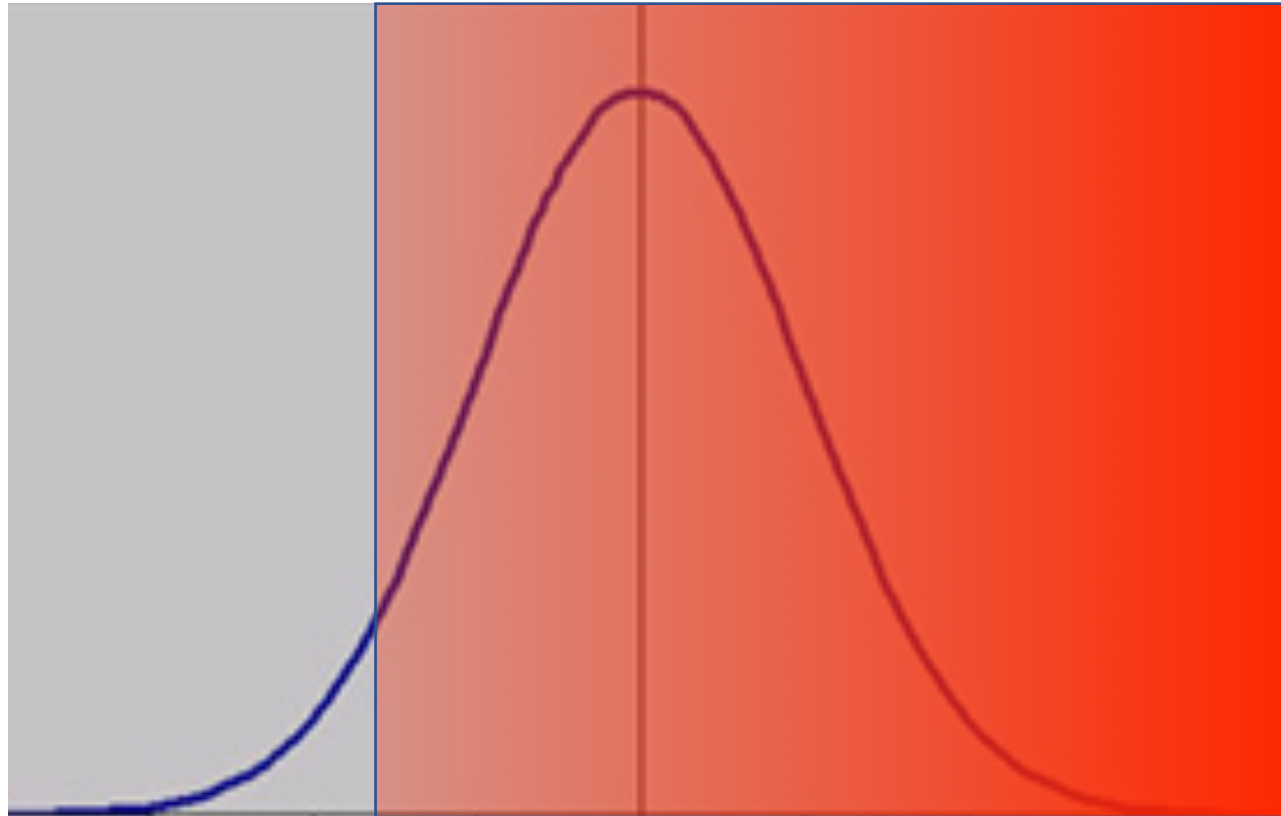


LDL-distribution i befolkningen

Frisk, ung

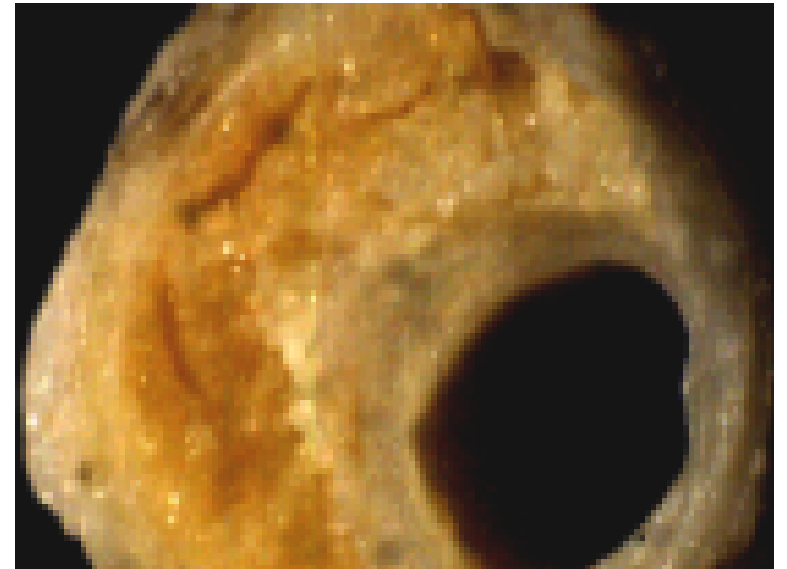


Riskbedömning

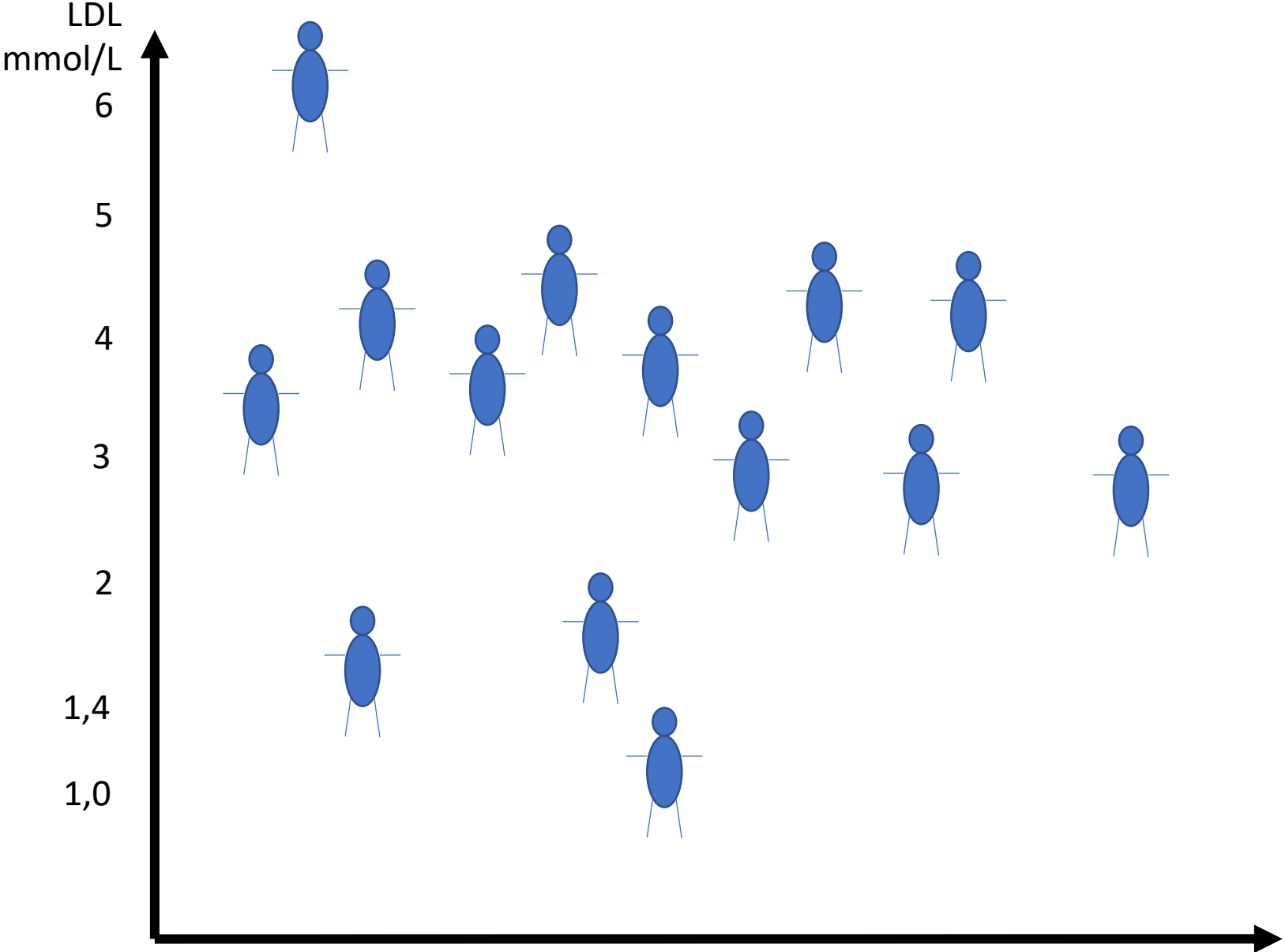


LDL-distribution i befolkningen

Äldre, riskfaktorer,
etablerad kärlsjukdom



Hur ska då alla dessa behandlas?

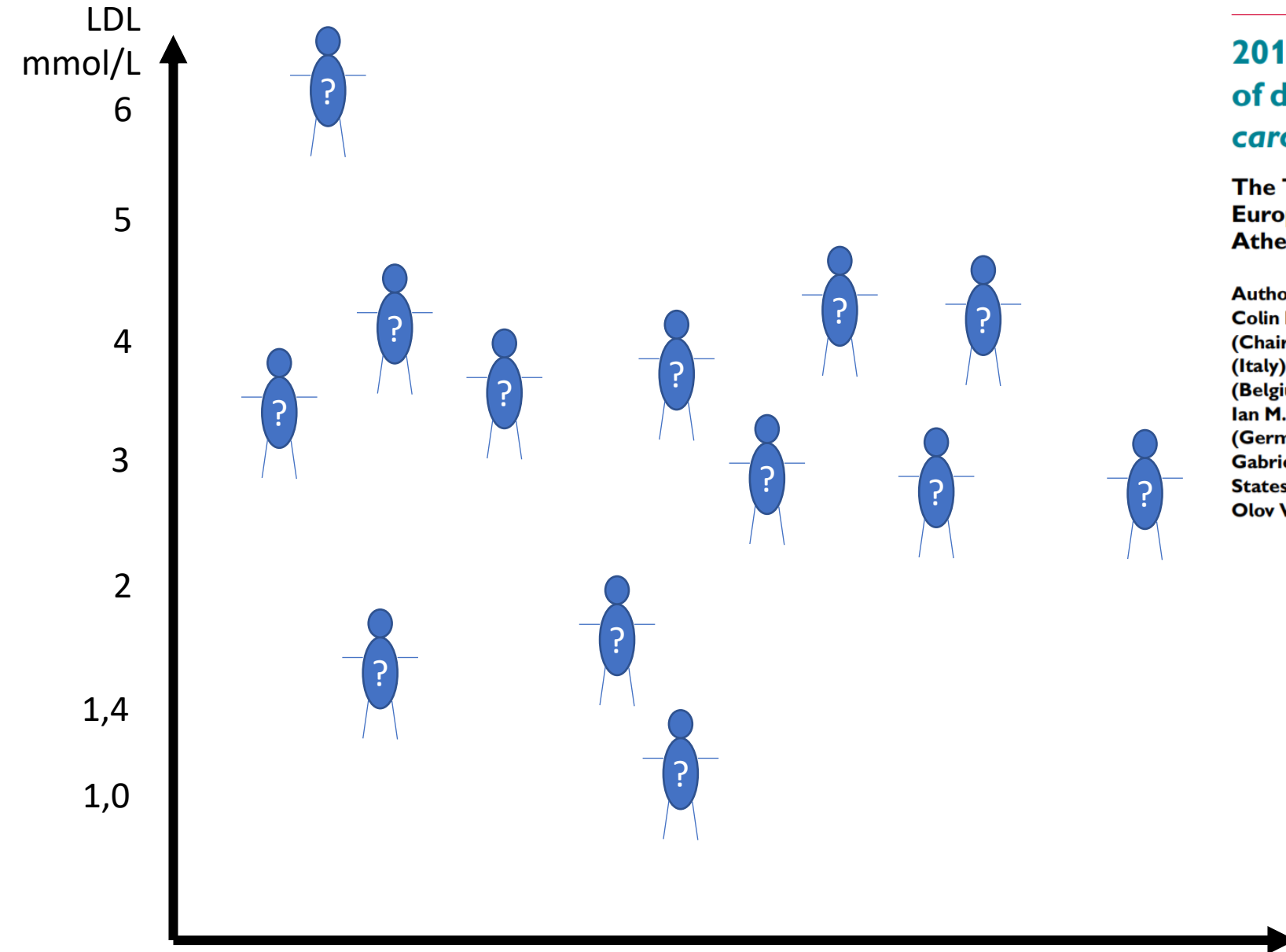


De måste riskkattas individuellt!

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano^{1*} (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula¹ (Italy), Lina Badimon (Spain), M. John Chapman¹ (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi¹ (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen¹ (Finland), Lale Tokgozoglul¹ (Turkey), Olov Wiklund¹ (Sweden)



Very high risk

People with any of the following:

- Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG, and other arterial revascularisation procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (**multivessel coronary disease with two major epicardial arteries having >50% stenosis**), or on carotid ultrasound
- DM with target organ damage,* or at least **three major risk factors**, or **early onset of T1DM of long duration (>20 years)**
- Severe CKD (eGFR <30 mL/min/1.73 m²)
- A calculated SCORE ≥10% for 10-year risk of fatal CVD
- **FH with ASCVD or with another major risk factor**

	Moderate risk	Low risk
factors, in) mg/dL), LDL- or BP	<ul style="list-style-type: none"> • Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk 	<ul style="list-style-type: none"> • Calculated SCORE <1% for 10-year risk of fatal CVD
or major risk et organ 0 years or /min/1.73 10% for 10-	<div style="border: 1px solid black; padding: 10px;"> <ul style="list-style-type: none"> • Betydelsefull/etablerad ateroskleros (ASCVD) • DM med komplikationer • CKD <30 • FH med ateroskleros eller riskfaktor </div>	

High risk

People with:

- Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (> 190 mg/dL), or BP ≥180/110 mmHg
- Patients with FH without other major risk factors**
- Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor**
- Moderate CKD (eGFR 30—59 L/min/1.73 m²)
- A calculated SCORE ≥ 5% and <10% for 10-year risk of fatal CVD

	Moderate risk	Low risk
Risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (> 190 mg/dL), or BP ≥180/110 mmHg, or another major risk factor Target organ damage: eGFR <30 L/min/1.73 m ² or albuminuria ≥30 mg/day or a calculated SCORE ≥10% for 10-year risk of fatal CVD	<ul style="list-style-type: none"> Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors 	<ul style="list-style-type: none"> Calculated SCORE <1% for 10-year risk of fatal CVD
	<ul style="list-style-type: none"> Enstaka kraftigt stegrad riskfaktor (LDL, BT) FH DM utan komplikationer Måttlig CKD 30-59 SCORE 5-<10% 	

Riskkategorier

	Moderate risk	Moderate risk	Low risk
<p>People</p> <ul style="list-style-type: none"> • Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors • Calculated SCORE ≥ 1 % and <5% for 10-year risk of fatal CVD 	<ul style="list-style-type: none"> • Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk 	<ul style="list-style-type: none"> • Calculated SCORE <1% for 10-year risk of fatal CVD 	
<ul style="list-style-type: none"> • Unga DM, <10 år duration, inga riskfaktorer • SCORE 1-<5% 			

*Defined as microalbuminuria, retinopathy, or neuropathy.
 ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography;
 CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
 Adapted from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

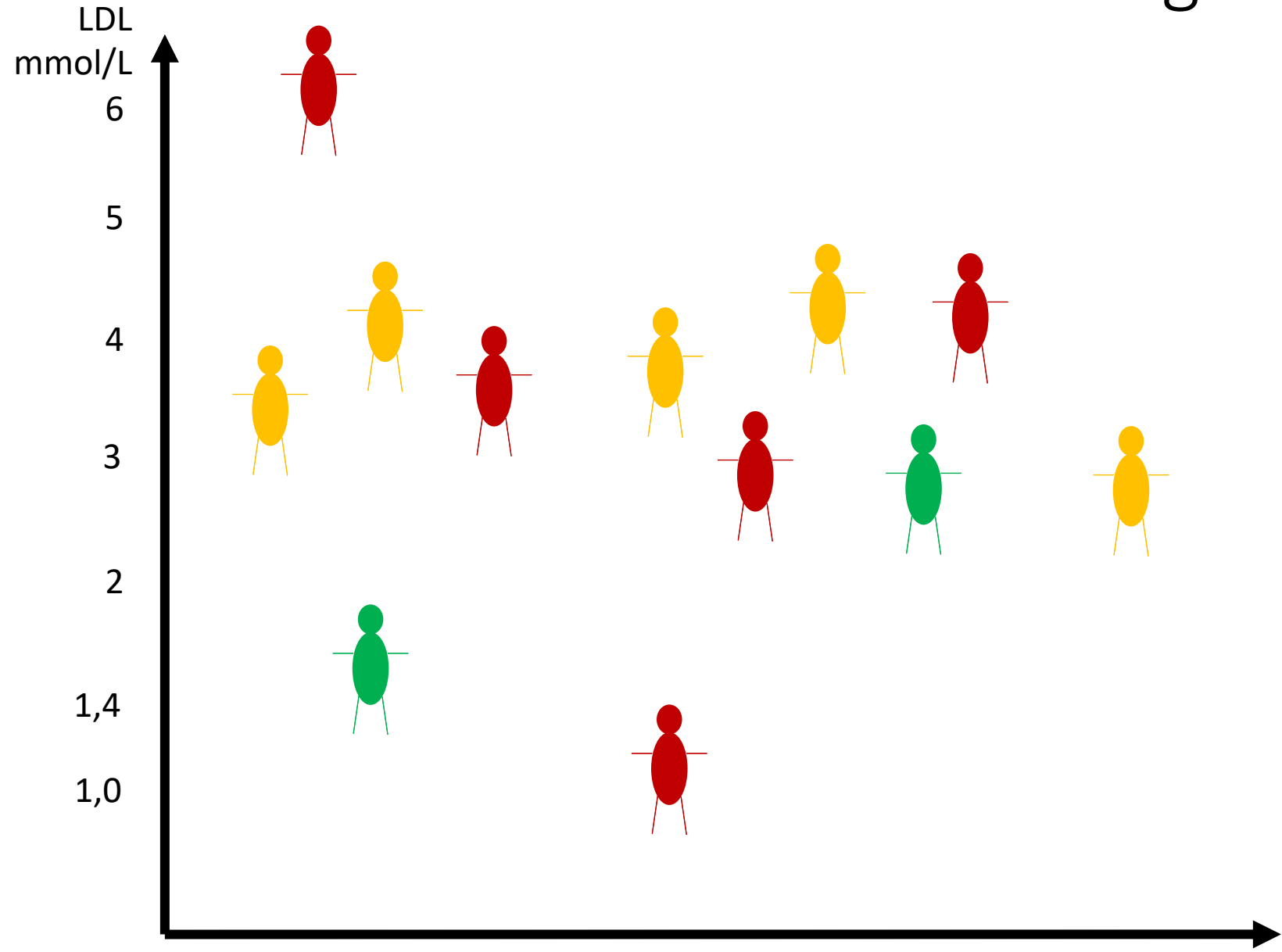
Risikkategorier

	Low risk	High risk	Moderate risk	Low risk
<p>People with atherosclerotic cardiovascular disease</p> <ul style="list-style-type: none"> Documented atherosclerotic cardiovascular disease (MI or stroke, revascularization, peripheral artery disease, or aortic disease) with documented findings of atherosclerosis on imaging DM with target organ damage Severe CKD (eGFR <30 mL/min/1.73 m²) A calculated 10-year risk of fatal CVD ≥ 5% and <10% for 10-year risk of fatal CVD FH with ASCVD 	<ul style="list-style-type: none"> Calculated SCORE <1% for 10-year risk of fatal CVD 	<p>Without other major risk factor</p> <p>Without target organ damage</p> <p>Duration ≥10 years or risk factor</p> <p>eGFR 30–59 L/min/1.73 m²</p> <p>≥ 5% and <10% for 10-year risk of fatal CVD</p>	<ul style="list-style-type: none"> Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factor 	<ul style="list-style-type: none"> Calculated SCORE <1% for 10-year risk of fatal CVD

• SCORE <1%

*Defined as microalbuminuria, retinopathy, or neuropathy.
 ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography;
 CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
 Adapted from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

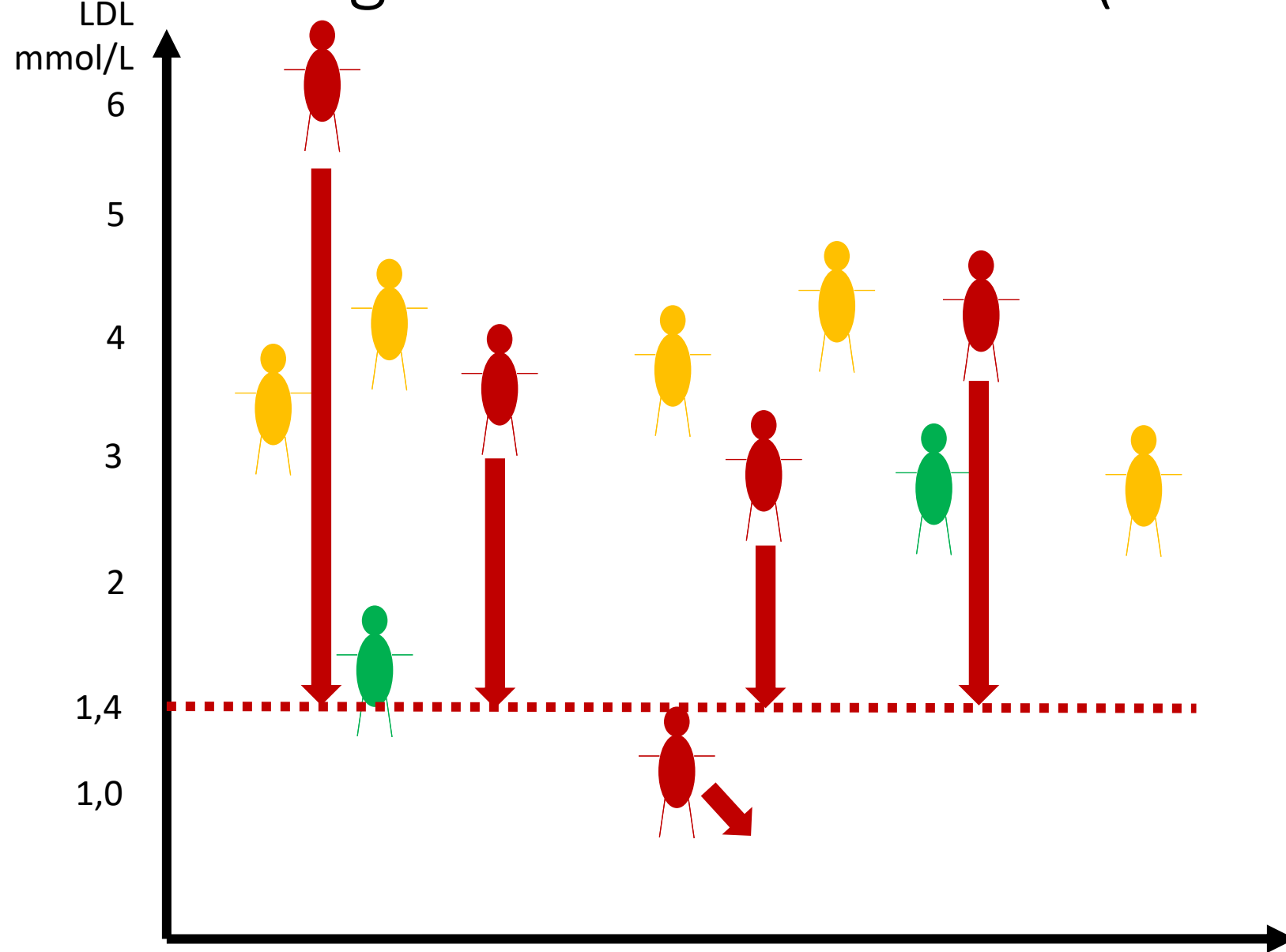
Individbaserad riskstratifiering



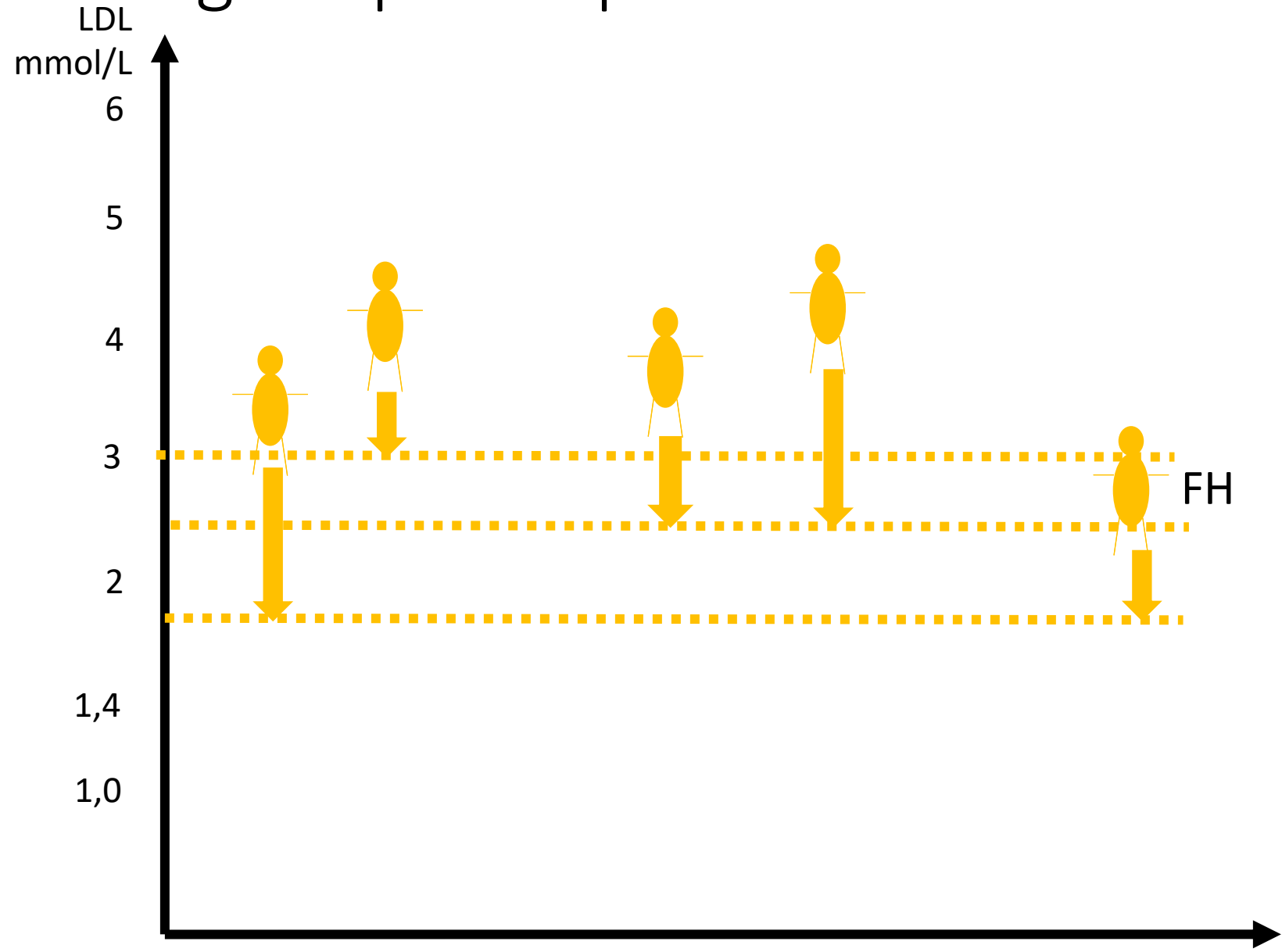
Behandling baseras på: 1, riskstratifiering; 2, LDL-nivå

Total kardiovaskulär risk (SCORE) %		Obehandlade LDL-C-nivåer (mmol/L)					
		<1,4	1,4 - <1,8	1,8 - <2,6	2,6 - <3,0	3,0 - <4,9	≥4,9
PRIMÄR- PREVENTION	<1, låg risk	Livstilsråd	Livstilsråd	Livstilsråd	Livstilsråd	Livstilsintervention, överväg tillägg av läkemedel	Livstilsintervention och samtidig läkemedelsbehandling
	≥1 - <5 eller moderat risk	Livstilsråd	Livstilsråd	Livstilsråd	Livstilsintervention, överväg tillägg av läkemedel	Livstilsintervention, överväg tillägg av läkemedel	Livstilsintervention och samtidig läkemedelsbehandling
	≥5 - <10 eller hög risk	Livstilsråd	Livstilsråd	Livstilsintervention, överväg tillägg av läkemedel	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling
	≥10 eller mycket hög risk pga risktillstånd	Livstilsråd	Livstilsintervention, överväg tillägg av läkemedel	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling
SEKUNDÄR- PREVENTION	Sek.prev. Mycket hög risk	Livstilsintervention, överväg tillägg av läkemedel	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling	Livstilsintervention och samtidig läkemedelsbehandling

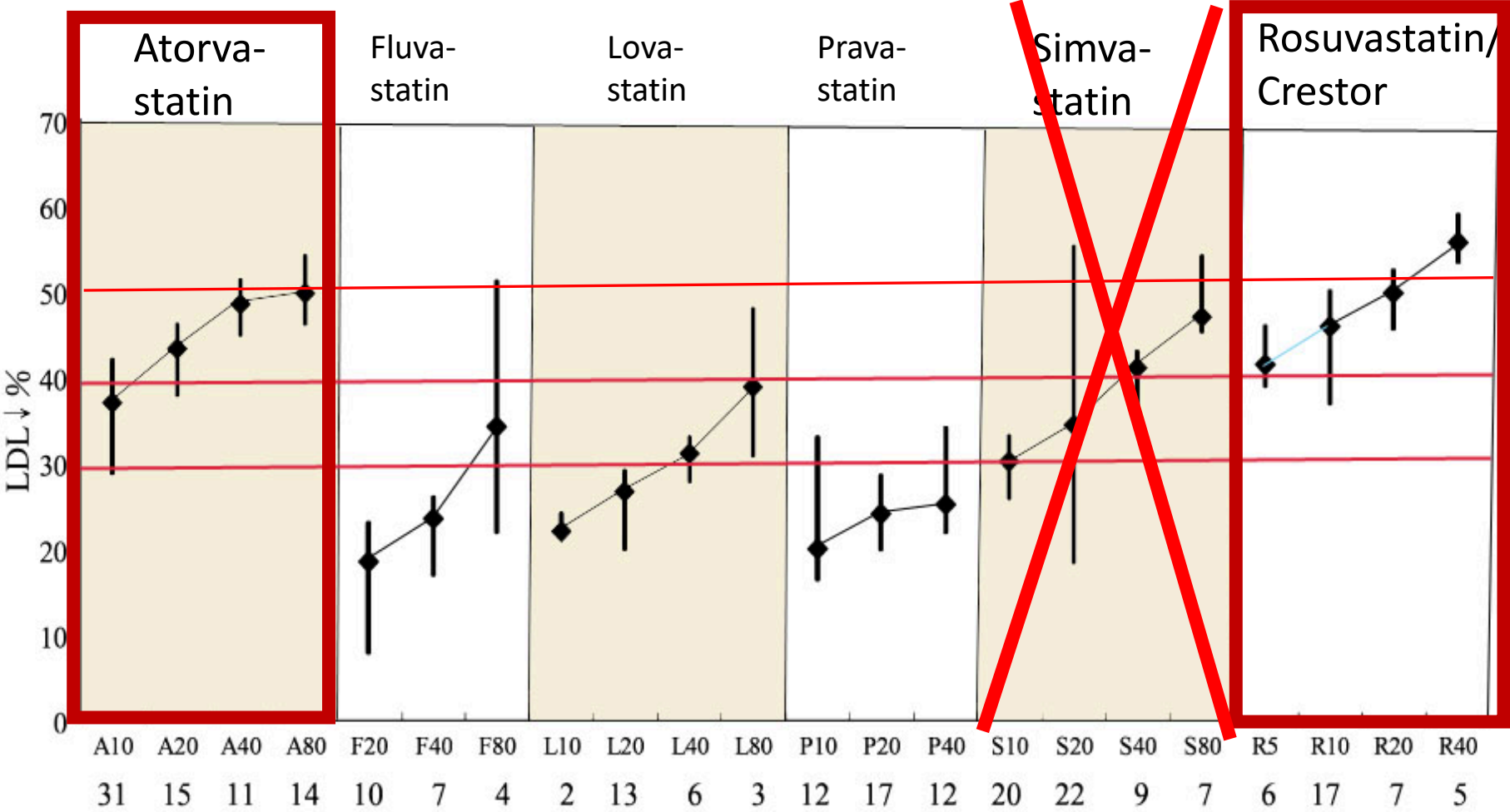
Behandling vid ASCVD? Ett mål. (eller två)



Behandling vid primärprevention? Stratifierat mål.

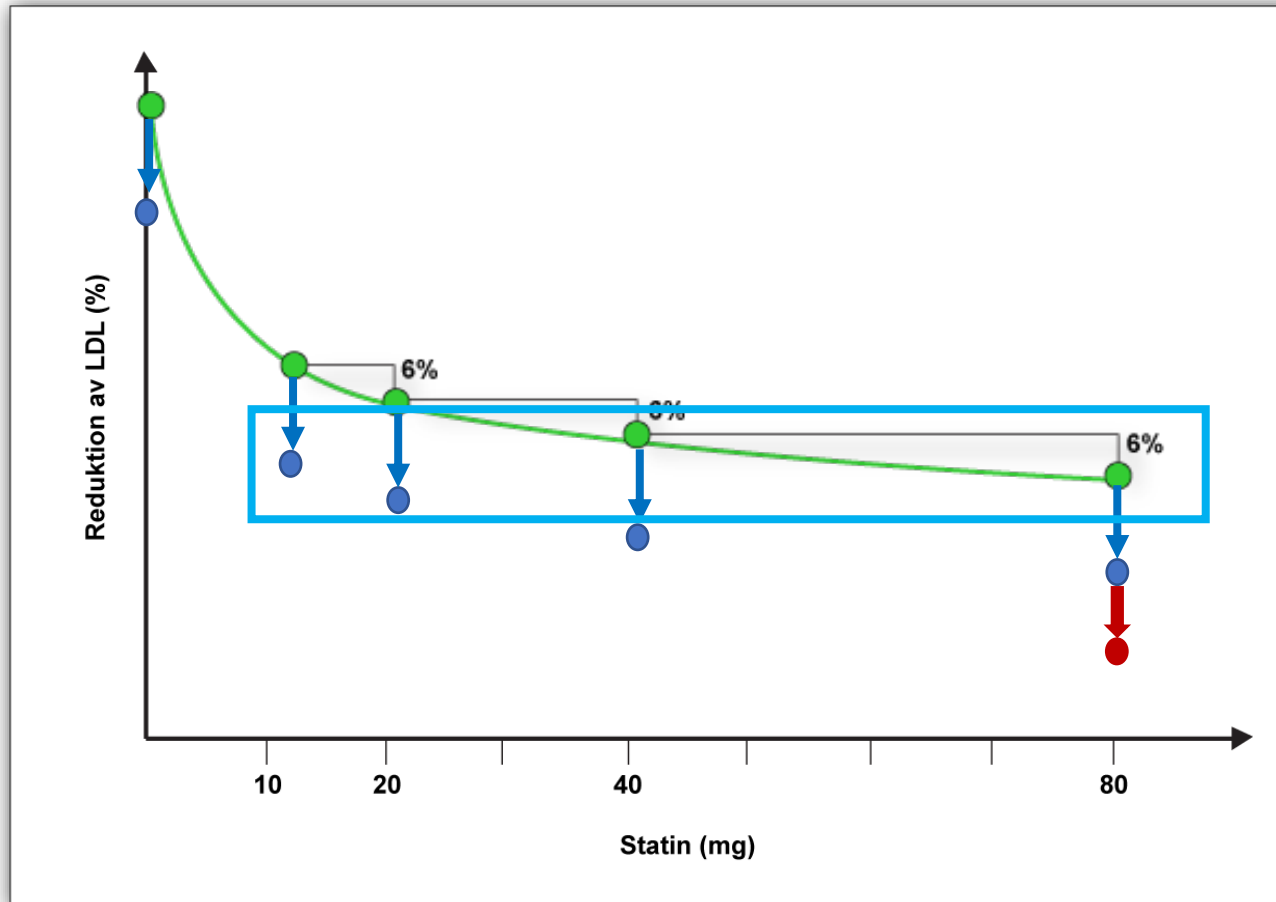


Statinernas LDL-sänkande effekt (populationsnivå)



Weng et al. J Clin Pharm Ther 2010;35:139-151

6%-regeln -20% -55%



Tillägg av ezetimib ger 20% ytterligare LDL-sänkning

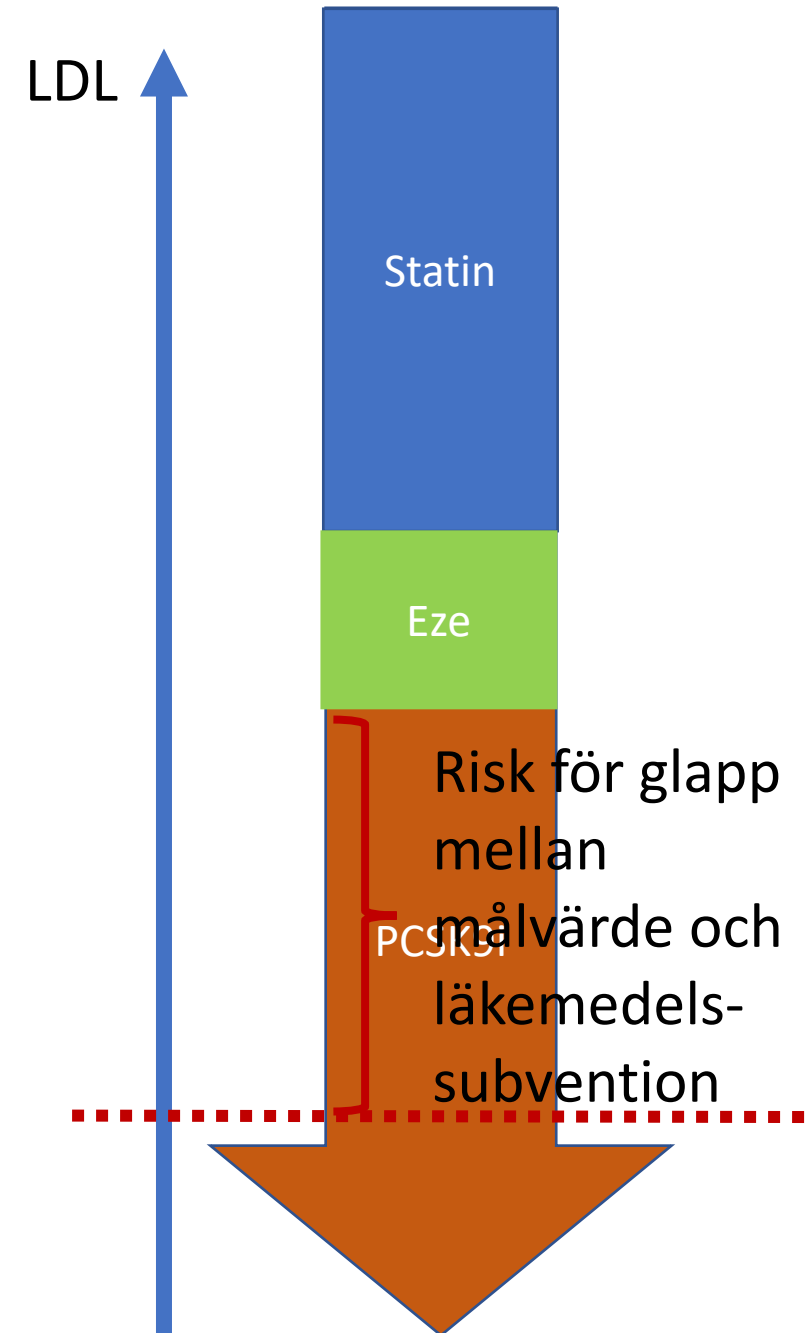
Låg dos statin + ezetimib kan ge samma LDL-sänkning som maxdos statin

PCSK9i sänker ytterligare 55%

"The rule of six" - en dubbling av statindosen ger endast en genomsnittlig LDL reduktion på 6%

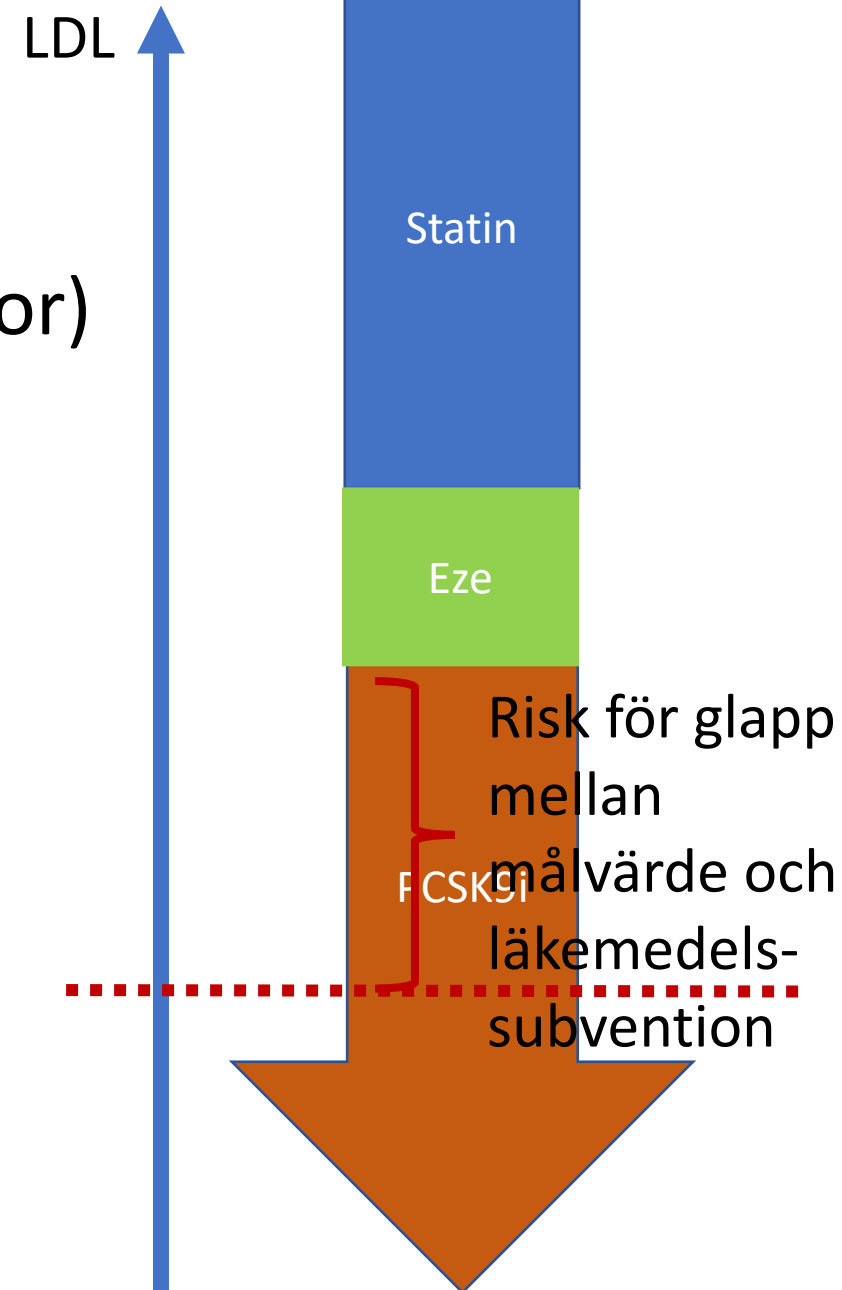
Behandling vid ASCVD

1. Mål LDL $<1,4$ + $\geq 50\%$ (1,0...multipla händelser <2 år)
2. Livsstil/kost + atorva 80 mg/rosuva 40 mg
3. 4-6 v inte i mål: ezetimib 10 mg
4. 4-6 v
 1. LDL $\geq 2,5$: PCSK9i
 2. LDL 1,4-2,5: ~~PCSK9i~~ fortsatt optimera oral behandling/livsstil
5. Hjärtinfarkt/hög risk med höga LDL: atorva/rosuva + eze direkt vid infarkt



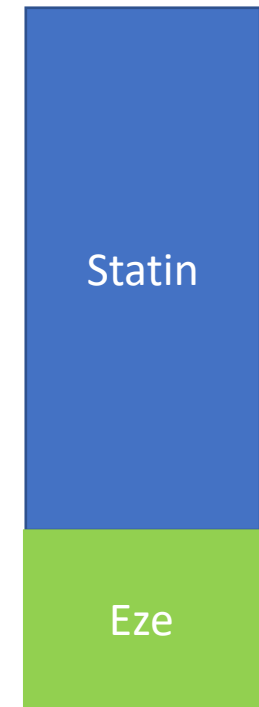
Behandling vid FH

1. Mål LDL < 1,8 + $\geq 50\%$ (< 1,4 ASCVD/ riskfaktor)
2. Livsstil/kost + atorva 20 mg /rosuva 10 mg
3. 4-8 v, längre, titrera upp
4. 4-8 v, längre, titrera upp
5. Vb ezetimib 10 mg (kan ges tidigare)
6. 4-8 v, längre
 - LDL $\geq 3,0$: PCSK9i (max statin/ezetimib)
 - LDL 1,8-3,0: ~~PCSK9i~~ fortsatt optimera oral behandling/livsstil/imaging...
 - Gallsyrabindare (Cholestagel)

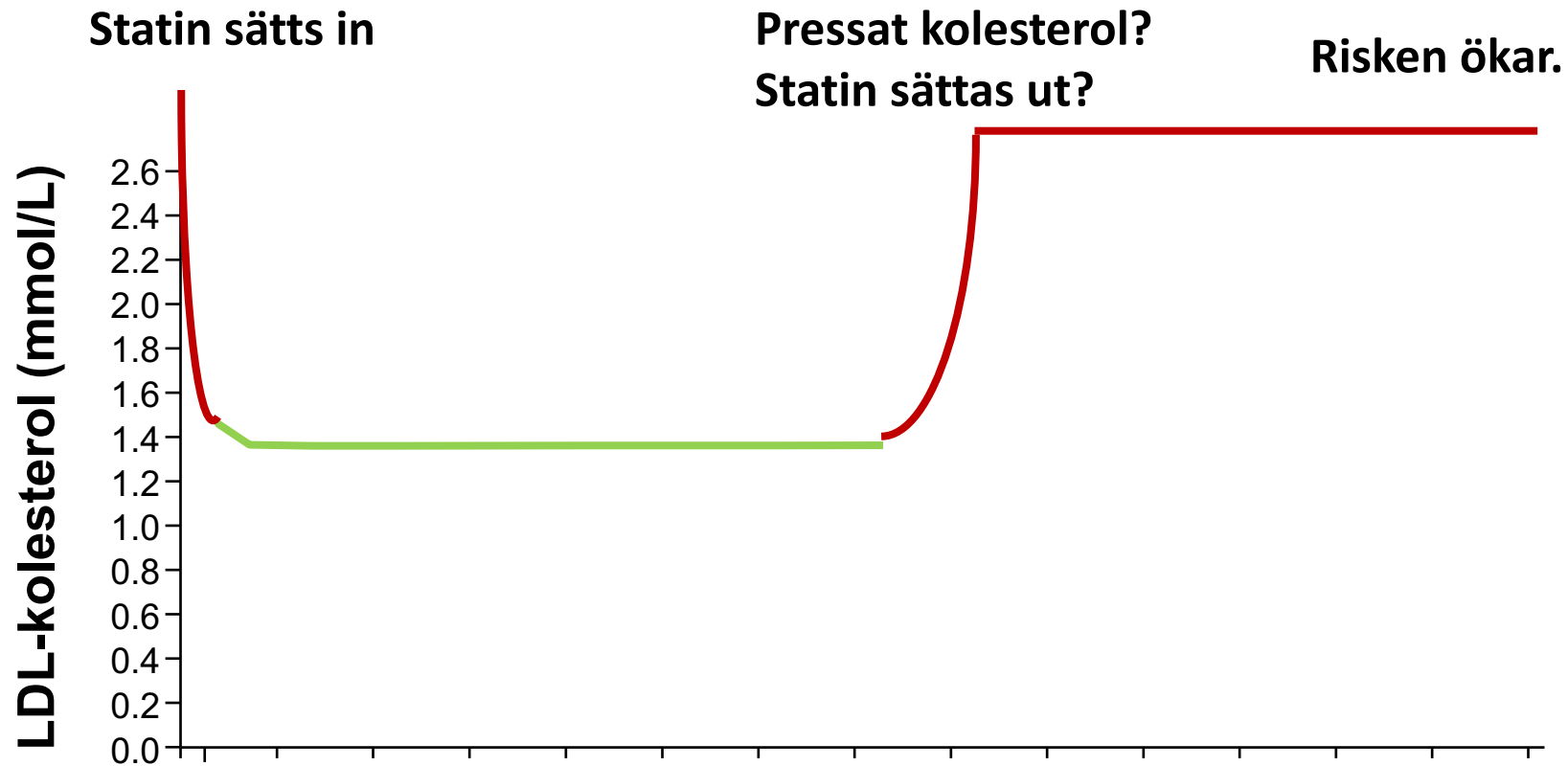


Behandling vid primärprevention

1. Mål LDL < 1,4-3,0 beroende på risk (ex CKD, DM) + $\geq 50\%$
2. Livsstil/kost + atorva 20 mg /rosuva 10 mg
3. 4-8 v, längre, titrera upp
4. 4-8 v, längre, titrera upp
5. Vb ezetimib 10 mg (kan ges tidigare)
6. 4-8 v, längre
 - ~~PCSK9i~~
 - Fortsätt optimera oral behandling/livsstil/imaging...



Avsluta eller minska inte behandling om inte biverkningar



Sammanfattning

- Riskskatta
- Primärprevention: börja försiktigt
 - NB! DM2 + u-alb=mycket hög risk
- Sekundärprevention: börja intensivt
 - Ex plack kranskärl, hjärtinfarkt, PAD, stroke
 - Alltid högrisk, även 10 år efter händelse/debut
- Sträva efter maxdos statin/målvärde
- Lägg till ezetimib om inte i mål, ibland vid första kontakt
- Lägg till PCSK9i om inte i mål till vissa



Tack för uppmärksamheten!

- Ju lägre desto bättre: aterogena lipoproteiner
- Ju längre duration desto bättre: intensiv behandling
- För lågt är inte för lågt: aterogena lipoproteiner