

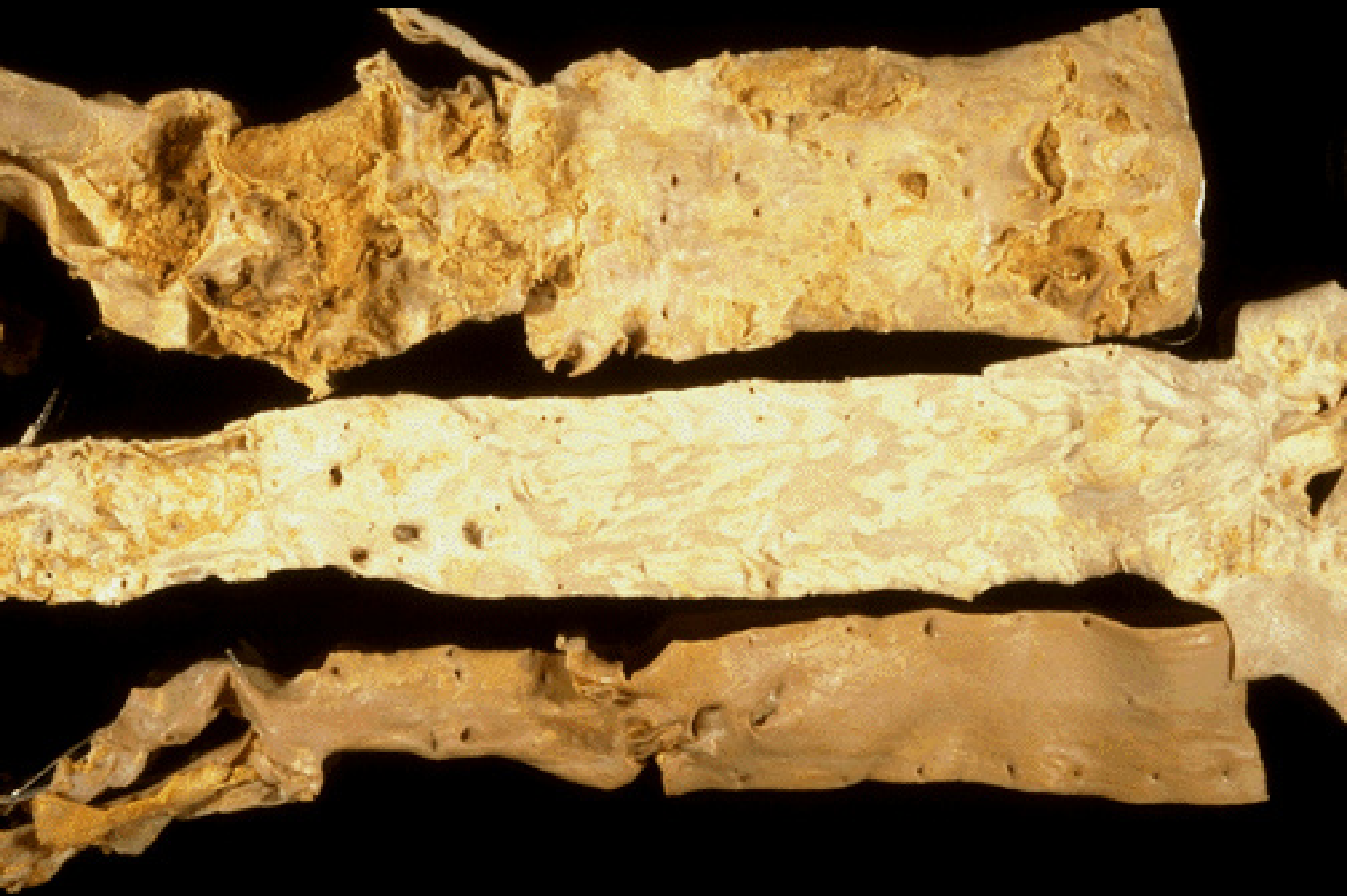
Lipid disease – does standardization affect clinical practice?

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Queen's University Belfast

Does lipid standardization affect clinical practice?

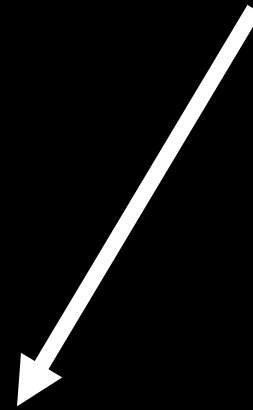
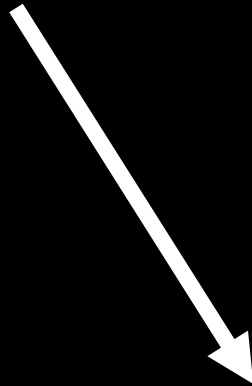
- Current understanding of significance of serum lipids
- Clinical utility of lipid measurements
- Impact of standardization
- Impact on clinical practice



Lipid oxidation

Lipid deposition

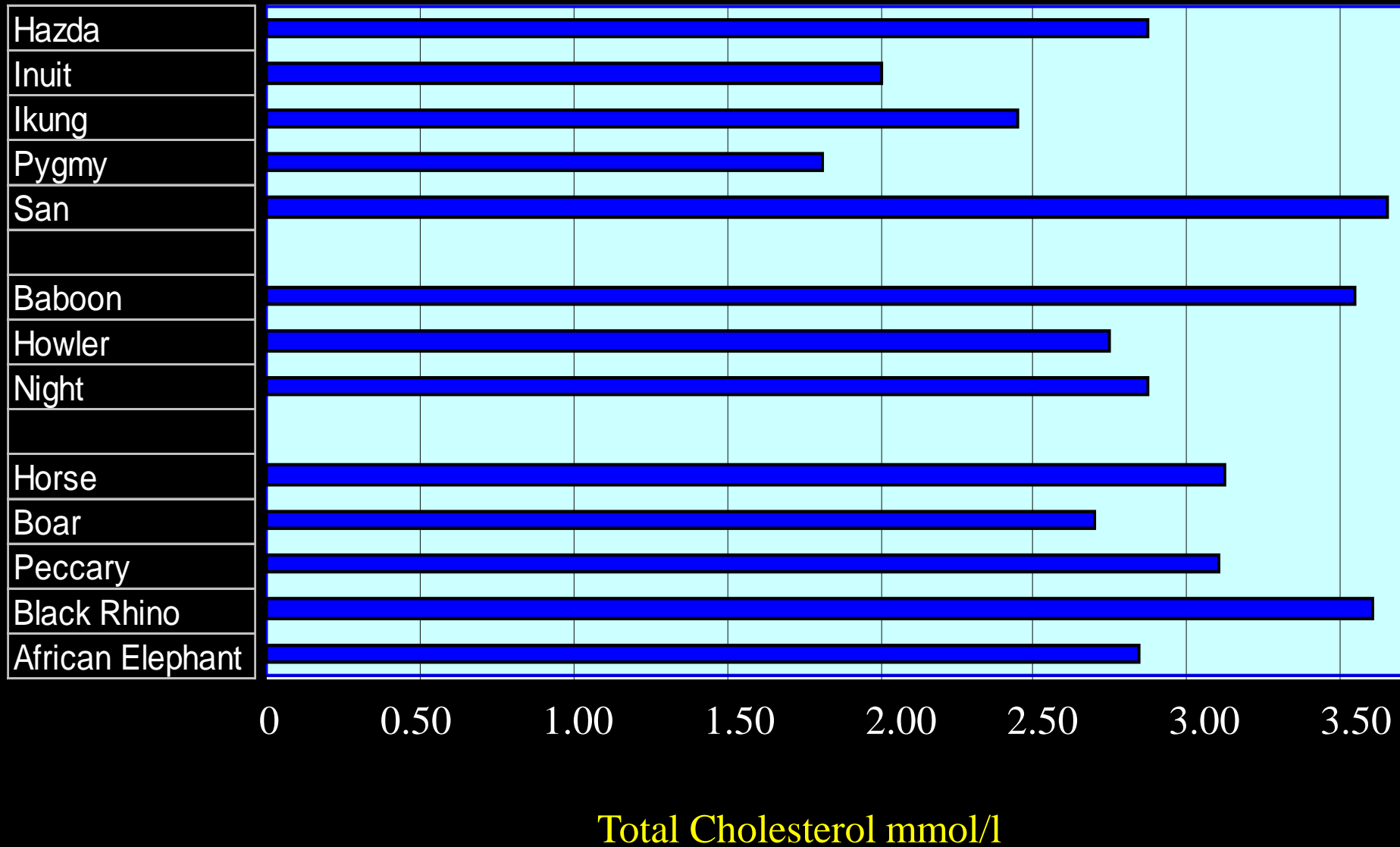
Inflammation



Atherosclerosis



Cholesterol in Hunter-Gatherers, Higher Primates and Other Mammals



PROVE IT - TIMI 22

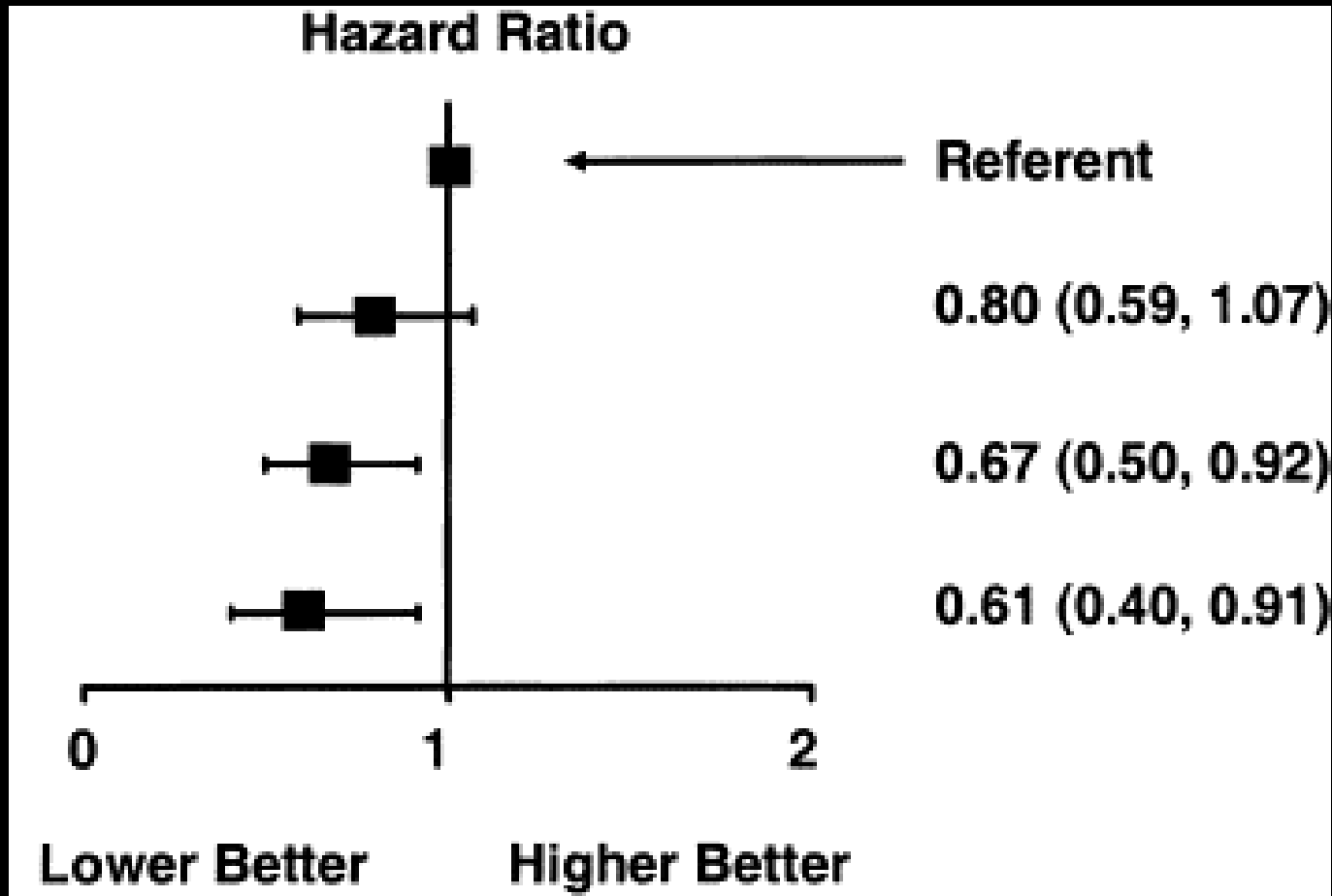
Achieved LDLc (mmol/L)

2.07-2.59

1.55-2.06

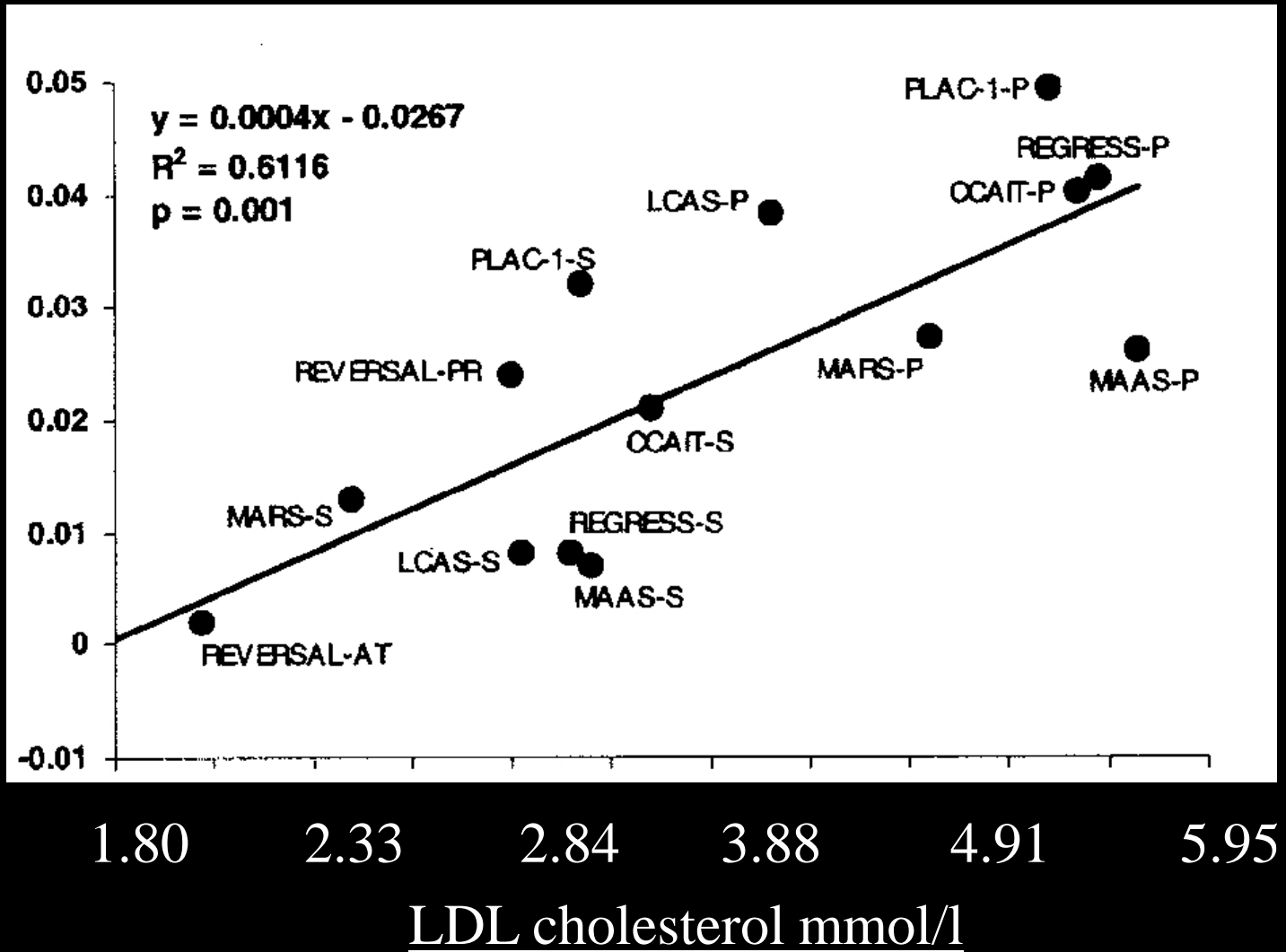
1.03-1.54

<1.03

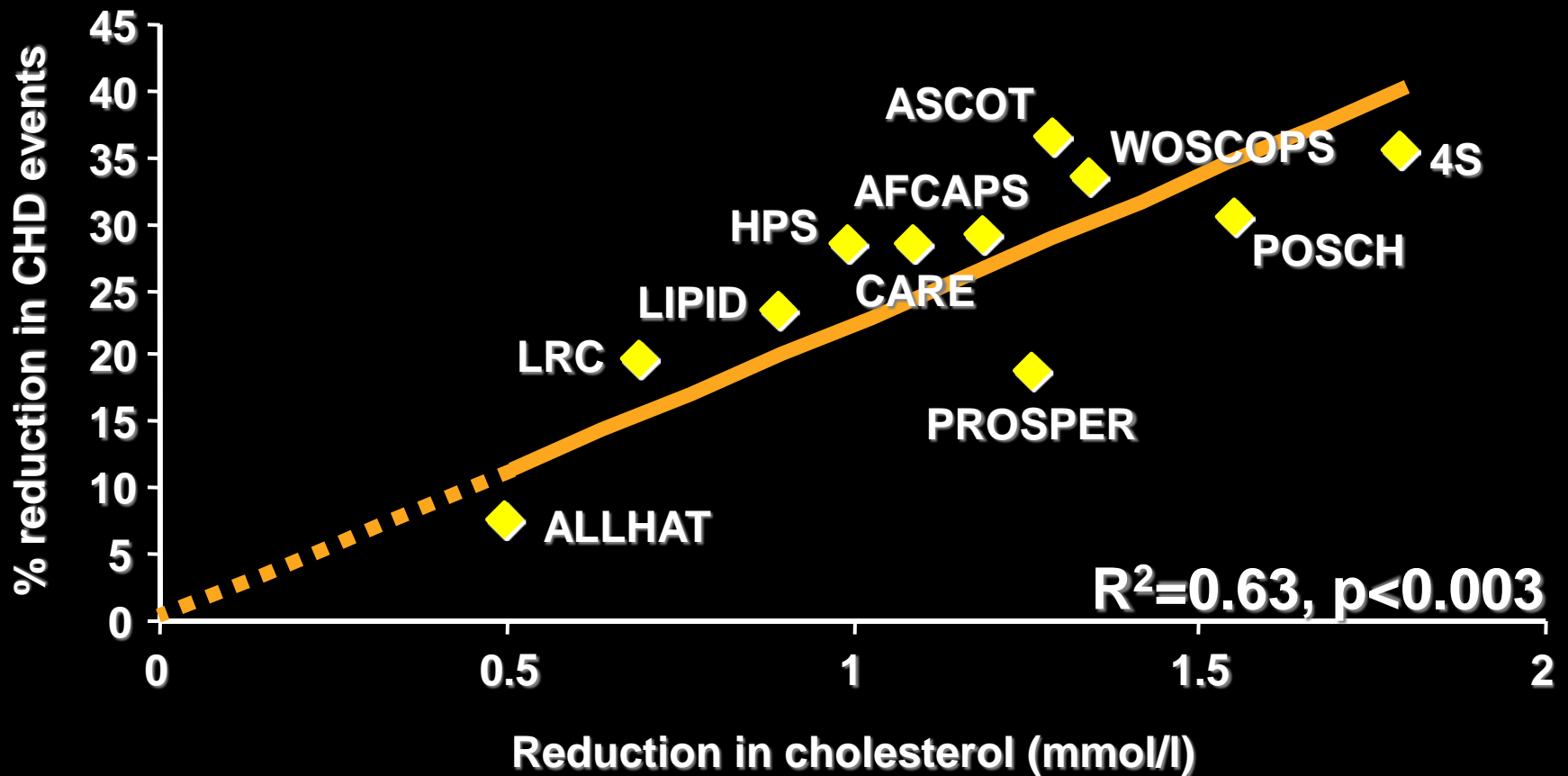


Atherosclerosis does not progress when LDL is < 1.73 mmol/l

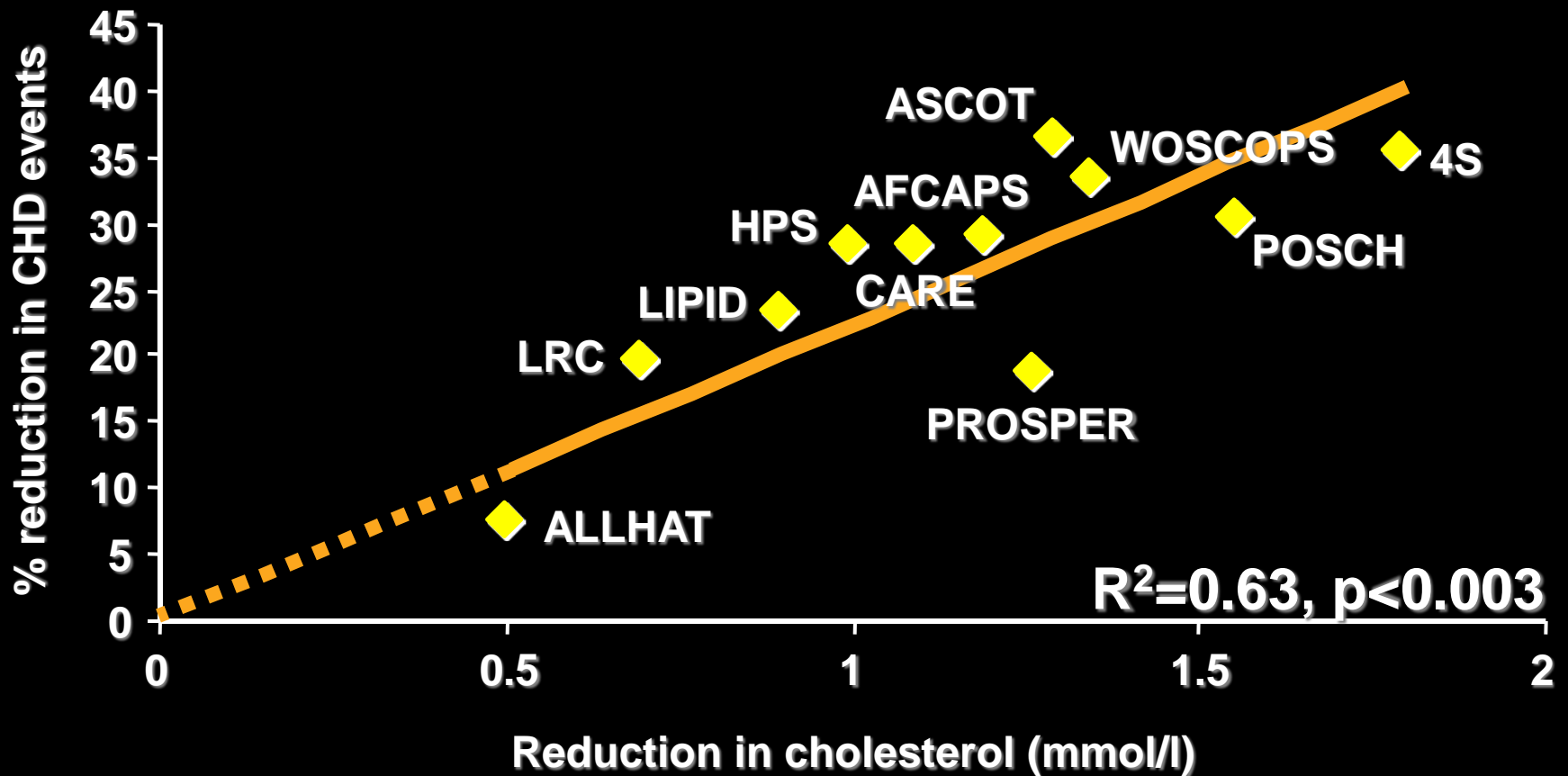
mean
luminal
diameter
decrease
mm/yr



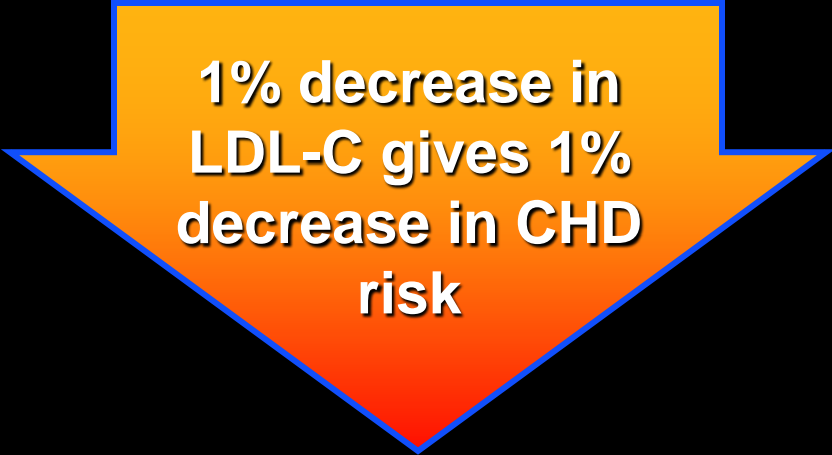
LDLc - The greater the reduction the greater the benefit



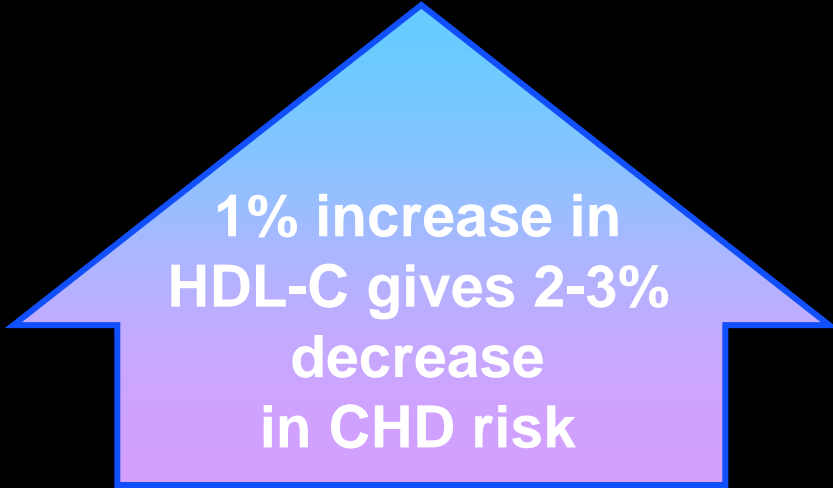
LDLc - The greater the reduction the greater the benefit



Reduce LDL-C and raise HDL-C

A large downward-pointing arrow with a blue outline and a yellow-to-orange gradient fill. The text is centered within the arrow.

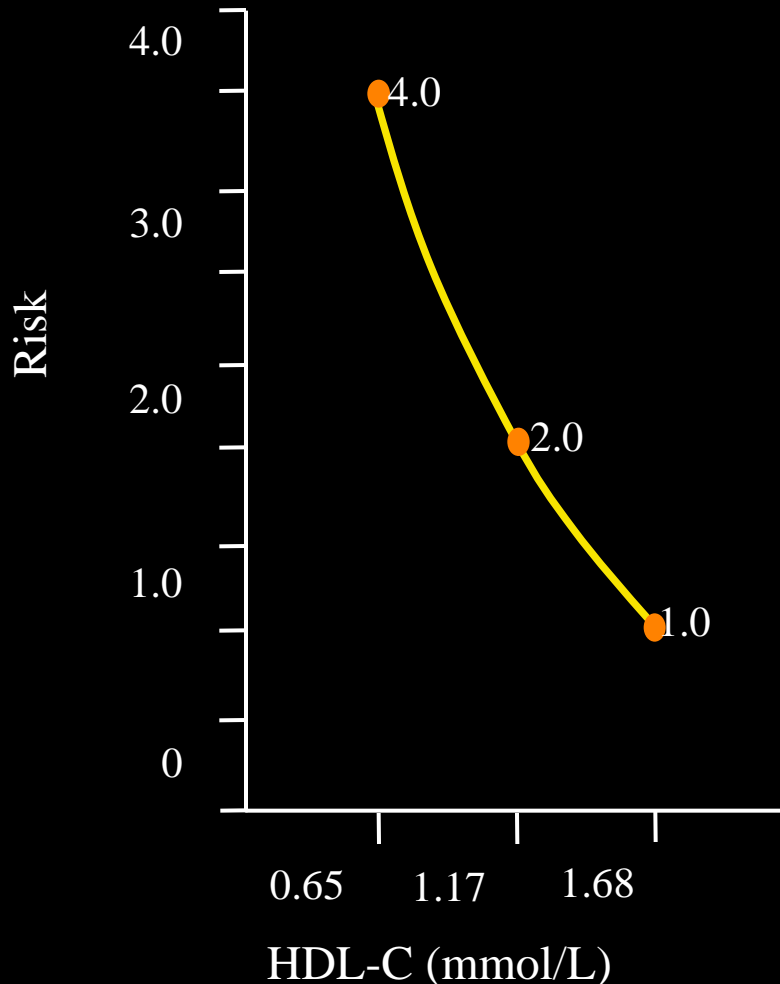
1% decrease in
LDL-C gives 1%
decrease in CHD
risk

A large upward-pointing arrow with a blue outline and a blue-to-purple gradient fill. The text is centered within the arrow.

1% increase in
HDL-C gives 2-3%
decrease
in CHD risk

Low HDL-C and Cardiovascular Risk

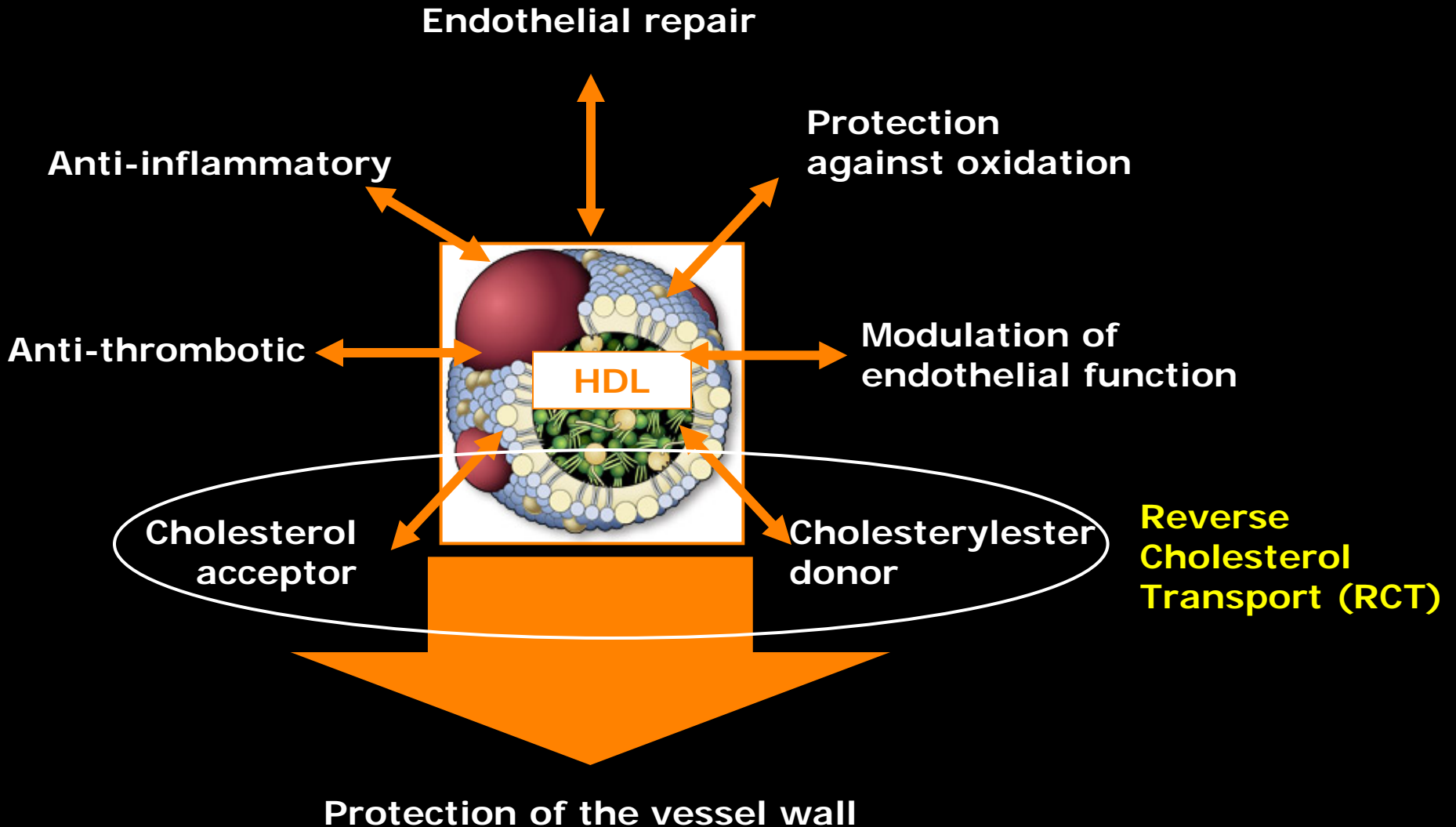
An Independent and Frequent Risk Factor



| Risk Factor | Controls (N=601) | Cases (N=321) |
|--------------------------------|---------------------|------------------|
| Cigarette smoking | 29% | 67%* |
| HDL-C <0.90 mmol/l | 19% | 63%* |
| Hypertension (BP >150/90 mmHg) | 21% | 41%* |
| LDL-C ≥160 mg/dL | 26% | 26%* |
| Diabetes mellitus | 1% | 12%* |

Kannel WB. AJC 1983; 52: Framingham Study;
Genest JJ et al. Am J Cardiol 1991; 67:1185-1189

Why Does HDL Protect?



Other serum lipids

- Non-HDLc
- Triglycerides
- Lp(a)

Does lipid standardization affect clinical practice?

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2011

Sex Ethnicity Age Postcode

- Has diabetes?
- Had a heart attack, angina, stroke or TIA?
- Angina or heart attack in a 1st degree relative < 60
- Smoking status
- Chronic kidney disease?
- Atrial fibrillation?
- On blood pressure treatment?
- Rheumatoid arthritis?

Clinical values -- enter if known

Cholesterol/HDL ratio Body mass index (kg/m²) Enter directly Use height and weightHeight (cm) Weight (kg) Systolic blood pressure (mmHg)

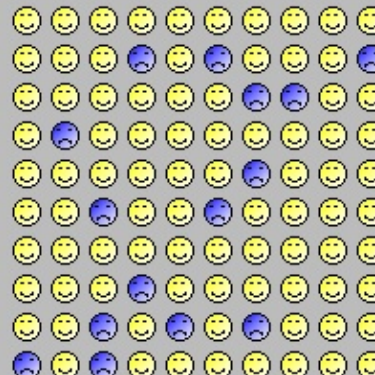
This person's QRISK score is 14.8.

Their QRiskAge is 62.

A person's QRiskAge is the age at which a typical person of their sex and ethnicity has their QRISK score.

This QRISK score is calculated using estimated or corrected data.
BMI was estimated to be 27.2.

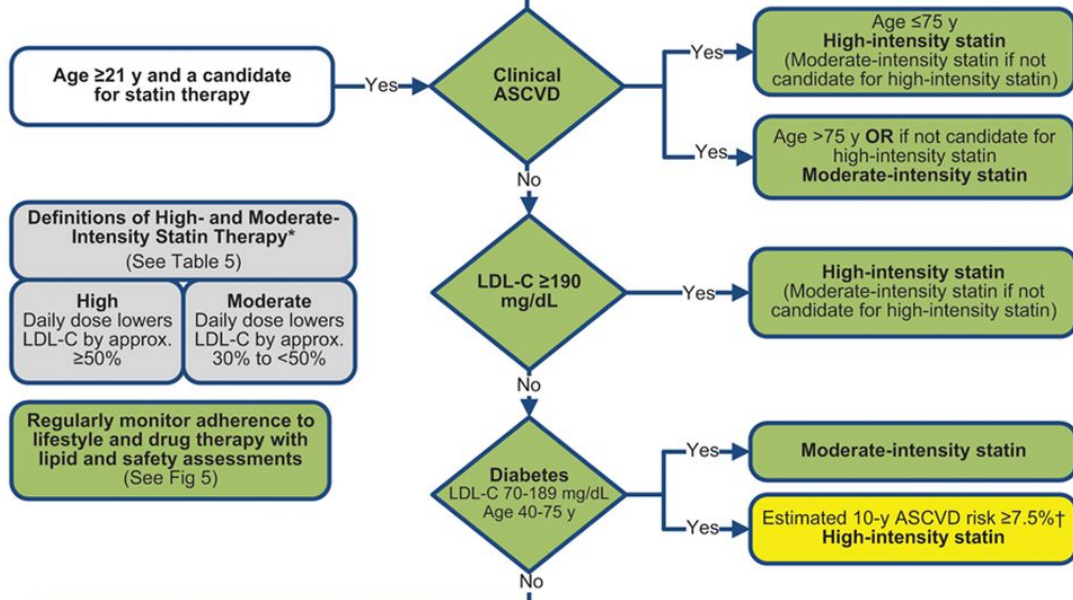
A typical person of the same age, sex and ethnicity has a score of 17.2.



In a crowd of 100 people like you,
15 will get heart disease in the next 10 years.

This Product is intended to aid and supplement, not substitute for, the expertise and judgement of physicians, pharmacists or other healthcare professionals. All information is provided on the basis that the healthcare practitioners responsible for patient care will retain full and sole responsibility for deciding any treatment to prescribe or dispense for all patients and, in particular whether the use of information provided by the Product is safe, appropriate, or effective for any particular patient or in any particular circumstances.

Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)



Definitions of High- and Moderate-Intensity Statin Therapy*
(See Table 5)

| High | Moderate |
|---|--|
| Daily dose lowers LDL-C by approx. ≥50% | Daily dose lowers LDL-C by approx. 30% to <50% |

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments (See Fig 5)

DM age <40 or >75 y or LDL-C <70 mg/dL

Primary prevention
(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)
Estimate 10-y ASCVD risk every 4-6 y using Pooled Cohort Equations†

<5% 10-y ASCVD risk‡

Age <40 or >75 y and LDL-C <190 mg/dL‡

≥7.5% 10-y ASCVD risk (Moderate- or high-intensity statin)

5% to <7.5% 10-y ASCVD risk (Moderate-intensity statin)

In selected individuals, additional factors may be considered to inform treatment decision making§

Clinician-Patient Discussion
Prior to initiating statin therapy, discuss:

1. Potential for ASCVD risk-reduction benefits ||
2. Potential for adverse effects and drug-drug interactions¶
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP ≥2 mg/L§

Emphasize adherence to lifestyle
Manage other risk factors
Monitor adherence

No to statin →
Yes to statin →

Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence* (See Fig 5)



Simon Broome Criteria

- **A diagnosis of definite familial hypercholesterolaemia requires:**
 - cholesterol >7.5 mmol/l in an adult (>6.7 mmol/l in children under 16) or LDL cholesterol >4.9 mmol/l in adults
 - plus tendon xanthomas in patient or first or second degree relative.

- **A diagnosis of possible FH requires:**
 - cholesterol >7.5 mmol/l in an adult (>6.7 mmol/l in children under 16) or LDL cholesterol >4.9 mmol/l in adults
 - plus family history of MI before 60 years in first degree relative or cholesterol >7.5 mmol/l in first or second degree relative.

Changes in use of serum lipids

- Continued use for risk estimation
- Decreasing use of absolute decision limits
- Increasing use of non-HDLc

Does lipid standardization affect clinical practice?

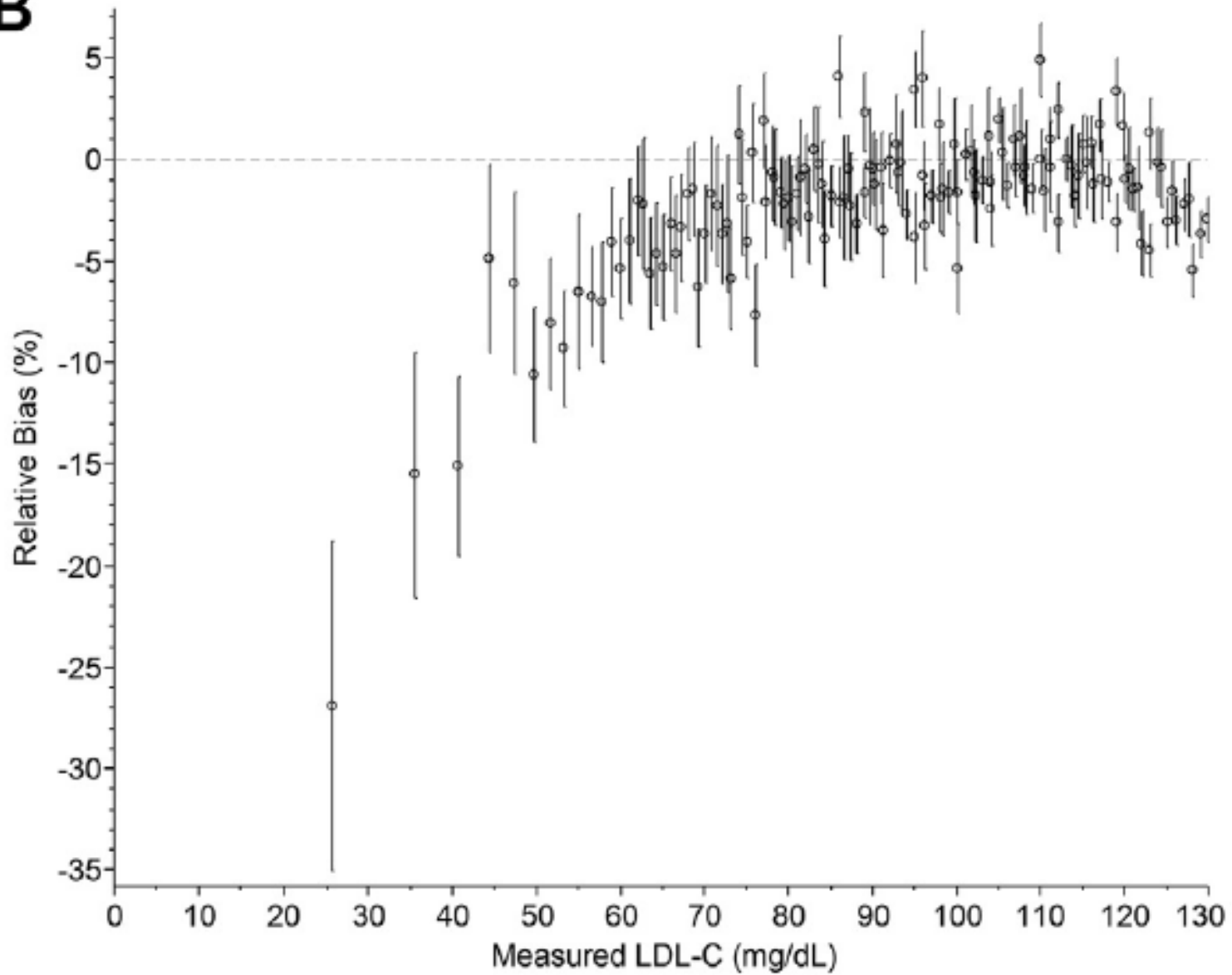
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Table 4. NCEP recommendations for acceptable analytic performance.

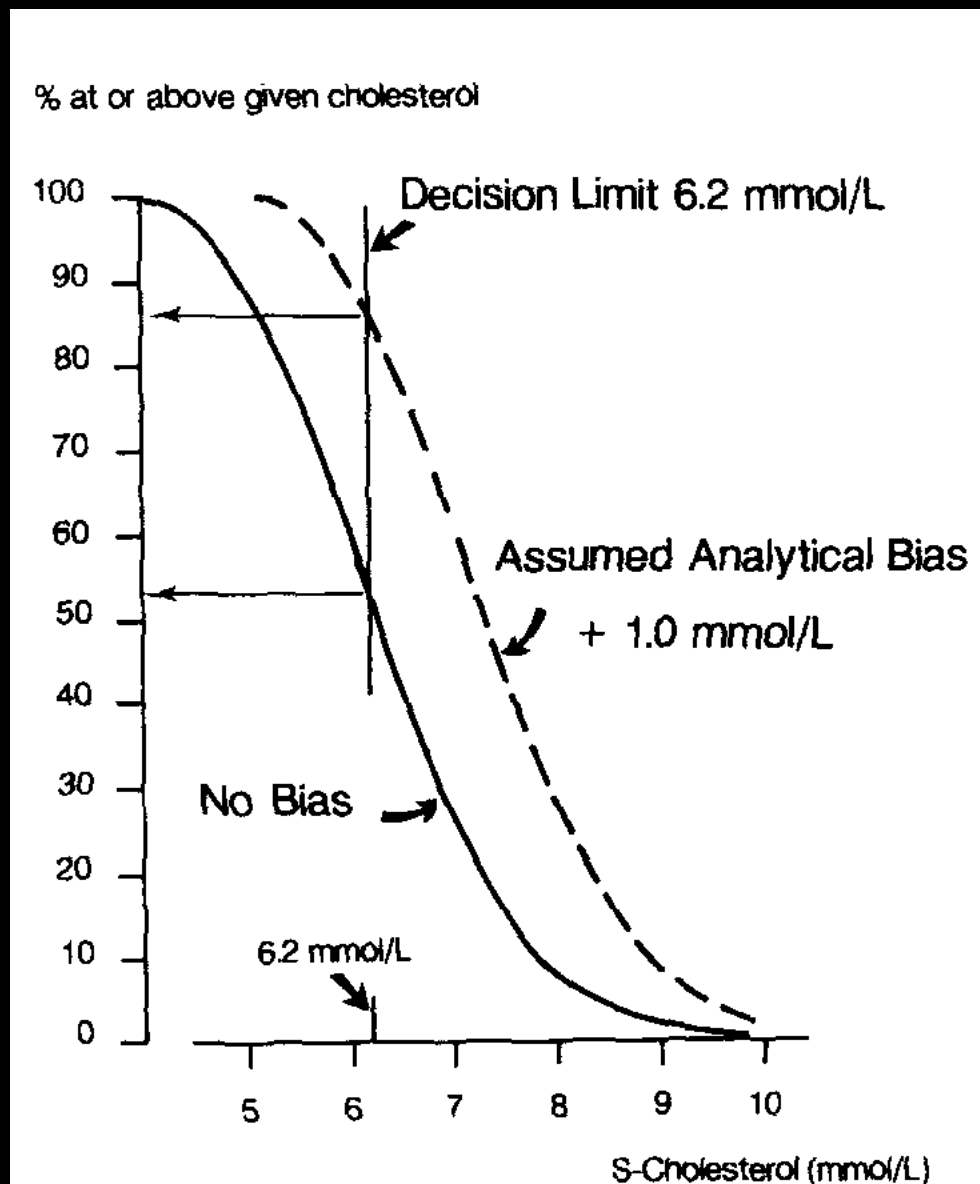
| | CV, % | Bias, % | Total error, % |
|-------|--|----------------|-----------------------|
| TC | 3 | 3 | 9 |
| LDL-C | 4 | 4 | 12 |
| HDL-C | SD ≤ 1.7 mg/L at < 420 mg/L CV $\leq 4\%$ at ≥ 420 mg/L | 5 | 13 |
| TGs | 5 | 5 | 15 |

Total cholesterol – 3% positive bias, 4% analytical CV

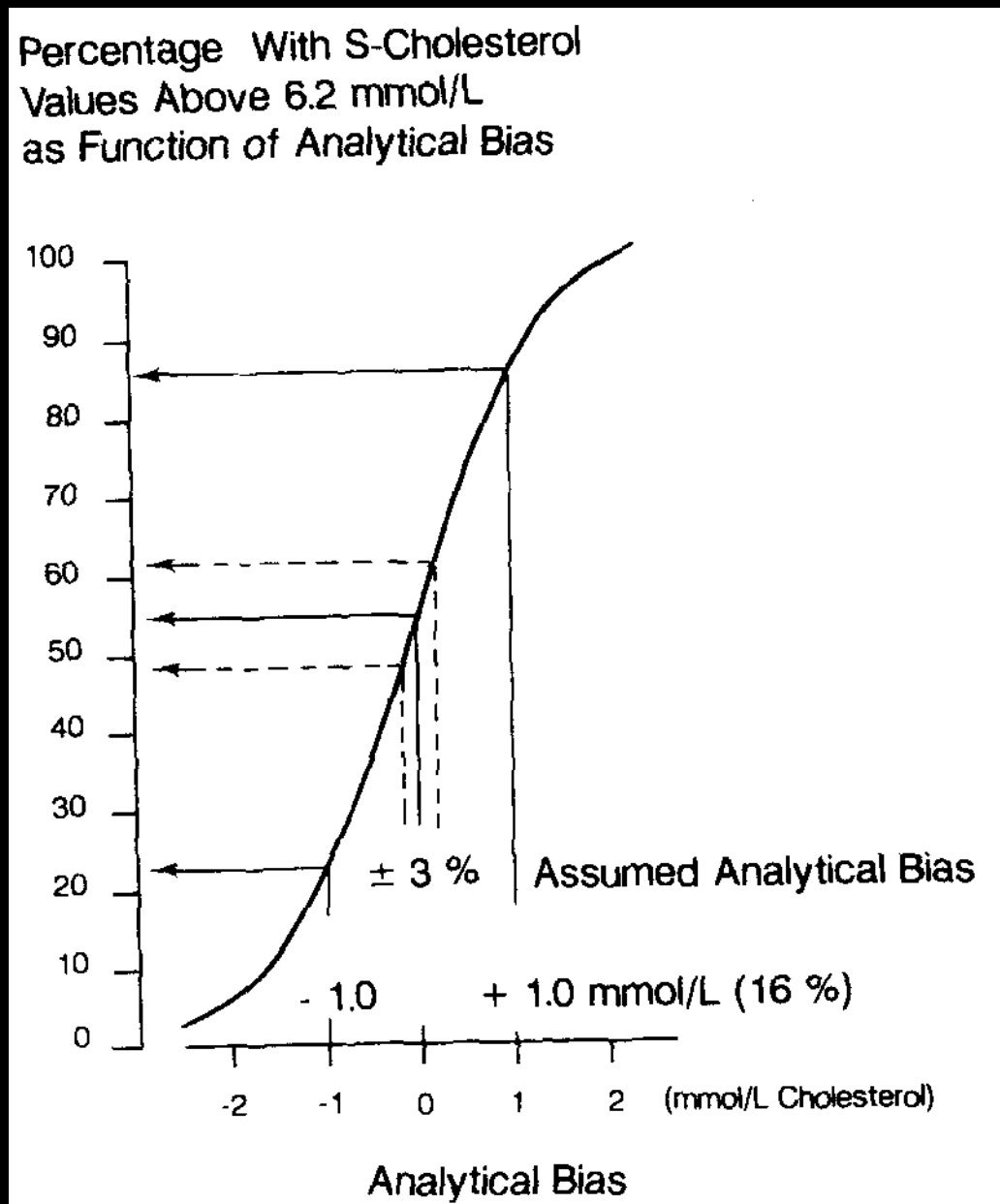
- 9% false positives using a treatment threshold of 6.2 mmol/l

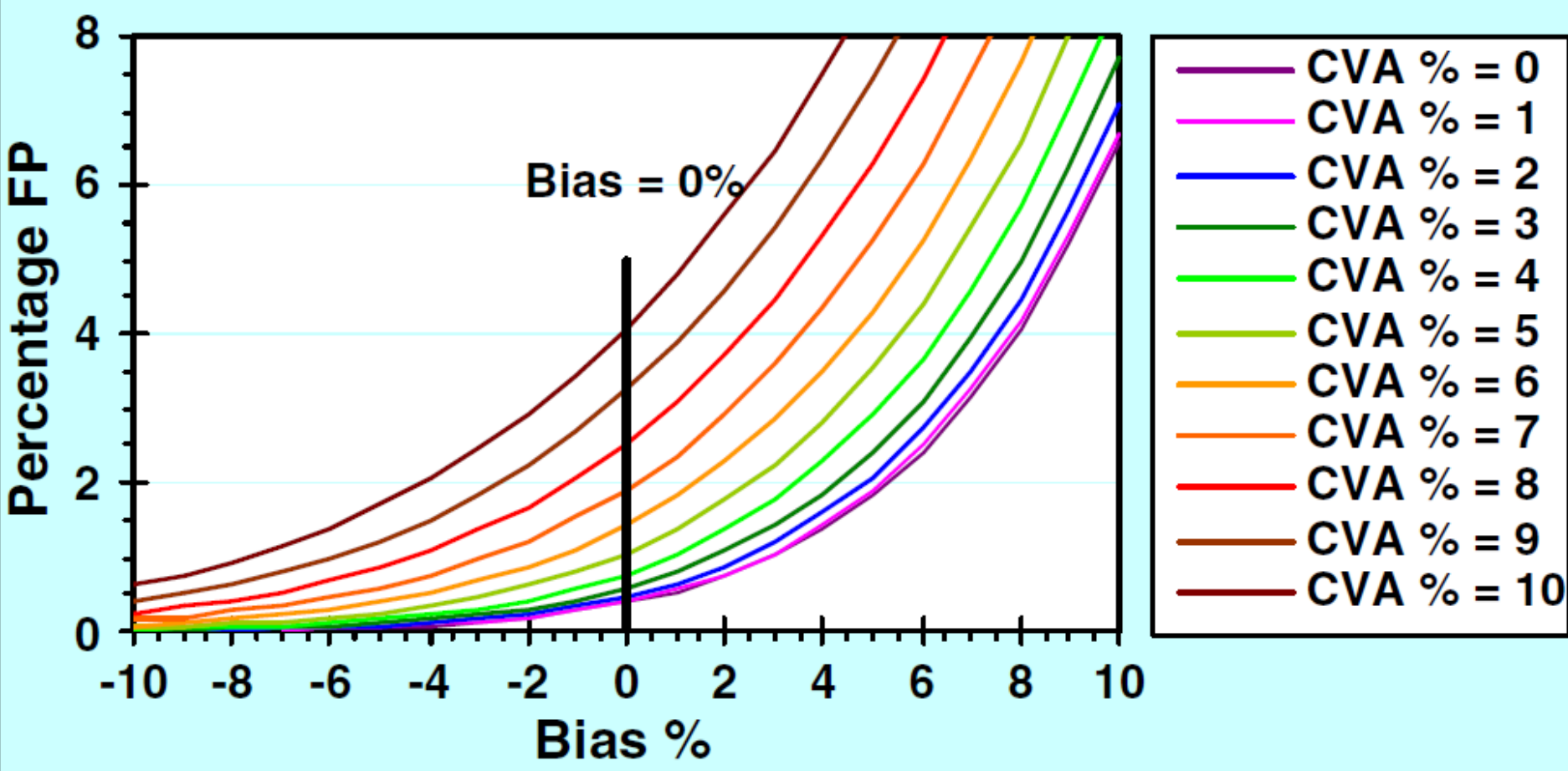
B

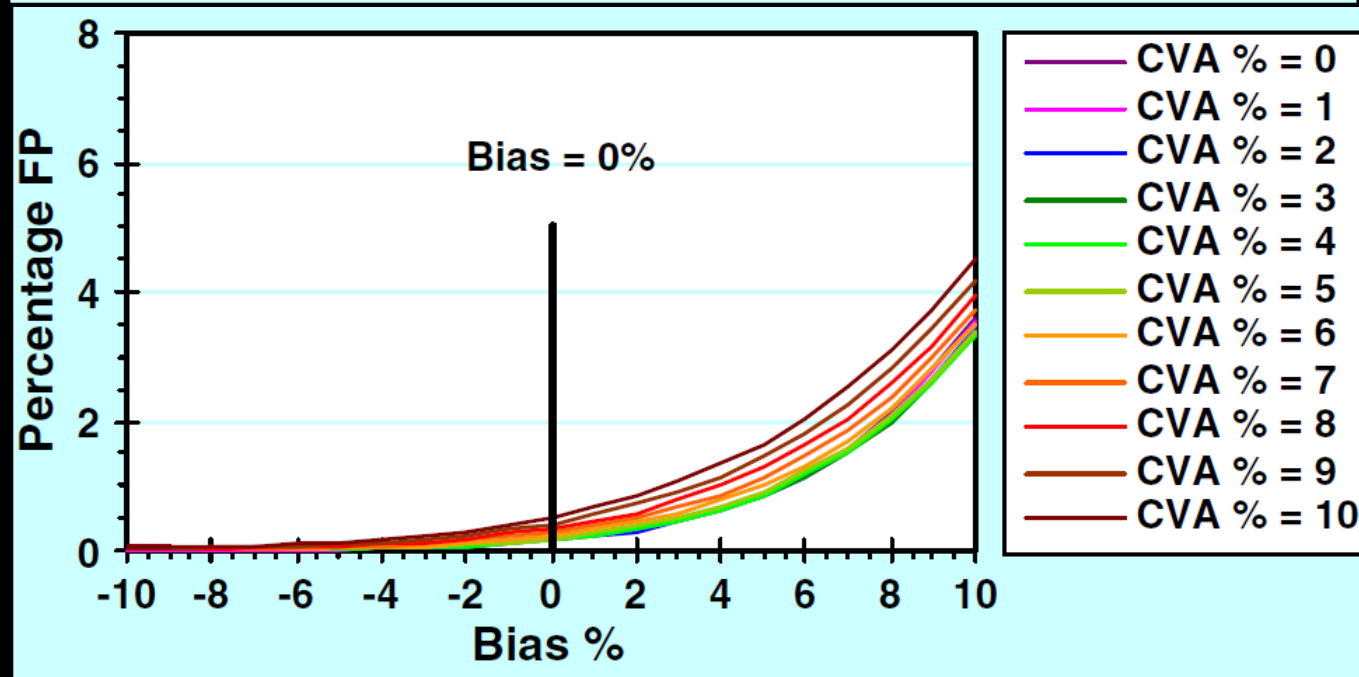
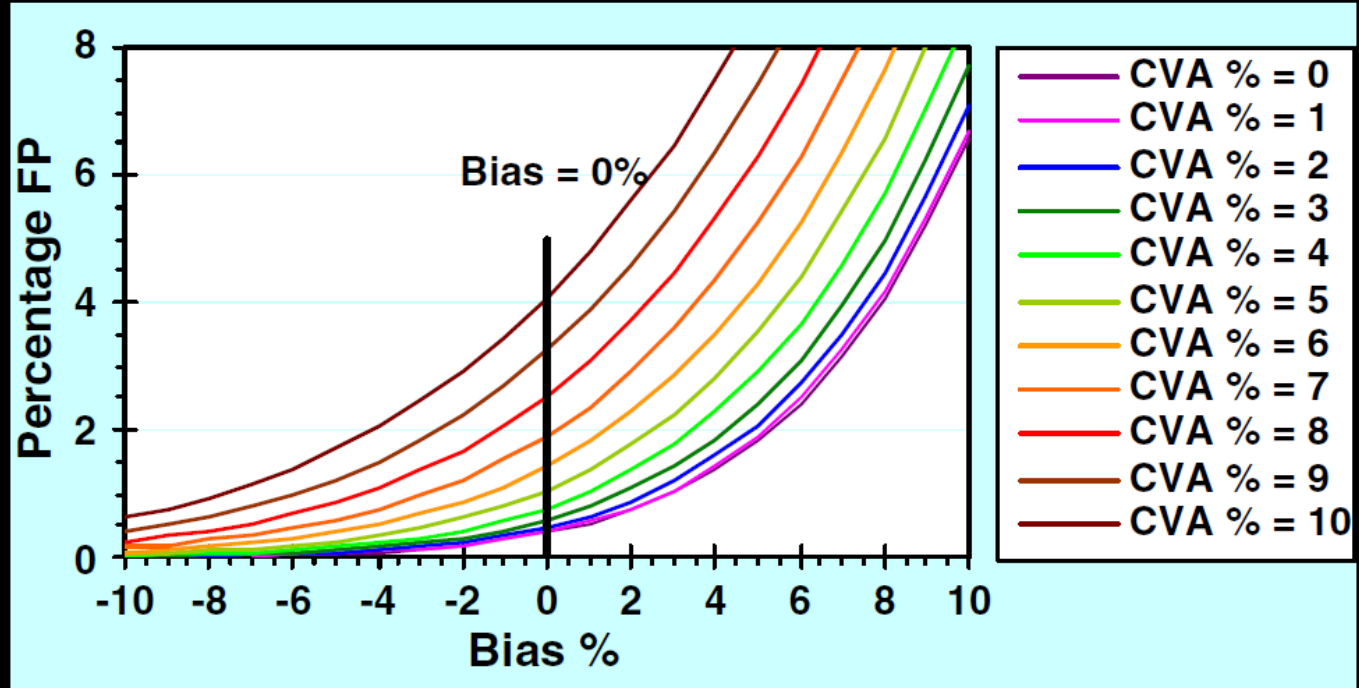
Impact of assay bias on distribution of cholesterol in middle aged men



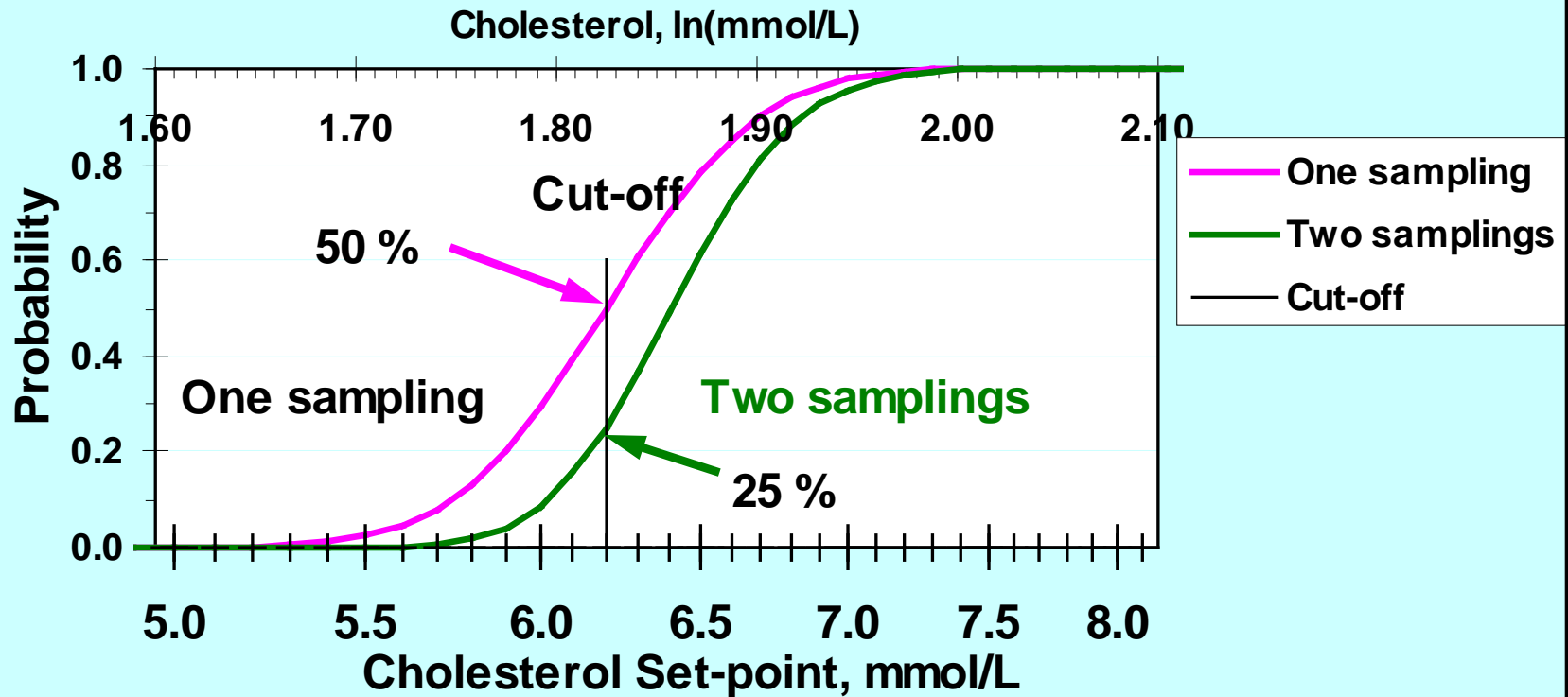
Impact of assay bias on distribution of cholesterol in middle aged men





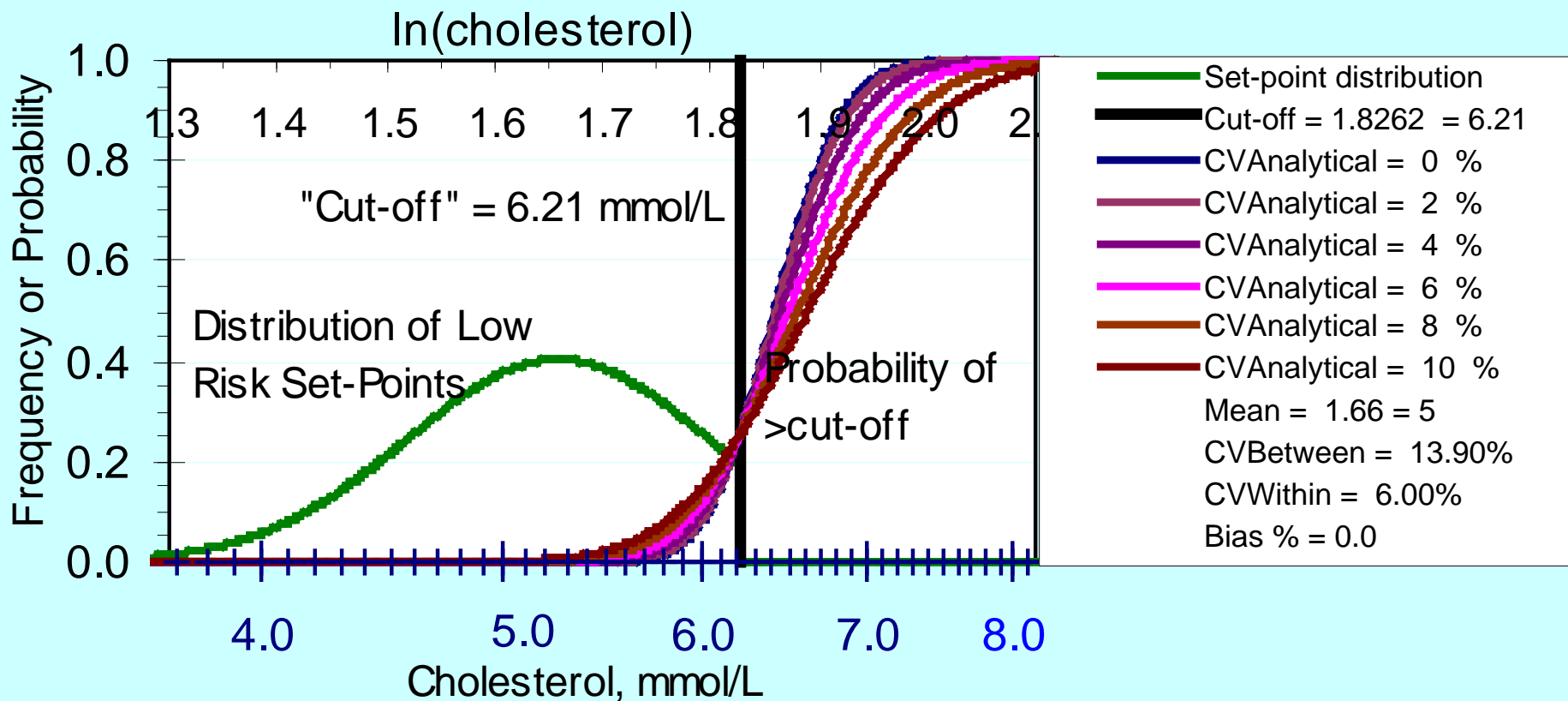


Cholesterol: Probability for Treatment with one and two Samplings as Function of Set-point



Supplementary Fig. 2. Effects of within-subject biological variation of serum-cholesterol, analytical bias and imprecision on cut-off, shown in the figure with two abscises, one lower for cholesterol in mmol/L and the other upper for the same in natural logarithms. The cumulated frequency distribution of values with a $CV_{within-subject} = 6.0\%$ around the cut-off point 6.21 mmol/L for one sampling (pink) and for two samplings (green).

Distribution of Set-Points of Low Risk Individuals and Probability of Results Above Cut-Off - No Bias



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Laboratory users and lipid standardization

- Specialists are aware of biological variability
- Other clinicians believe results
- Patients believe results

- We reinforce this by reporting exact values

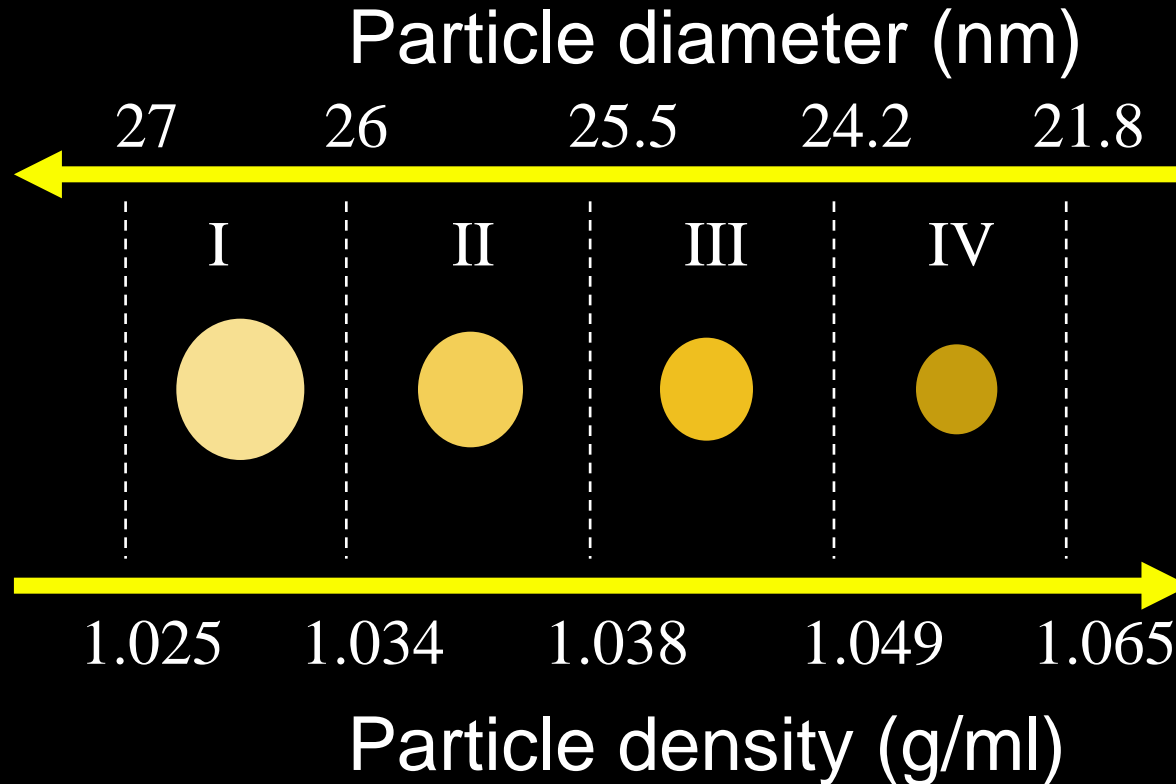
Impact on patient management

- Management decisions vary for patients close to decision thresholds
 - Family screening
 - Initiation of treatment
 - Intensification of treatment

Can we do better?

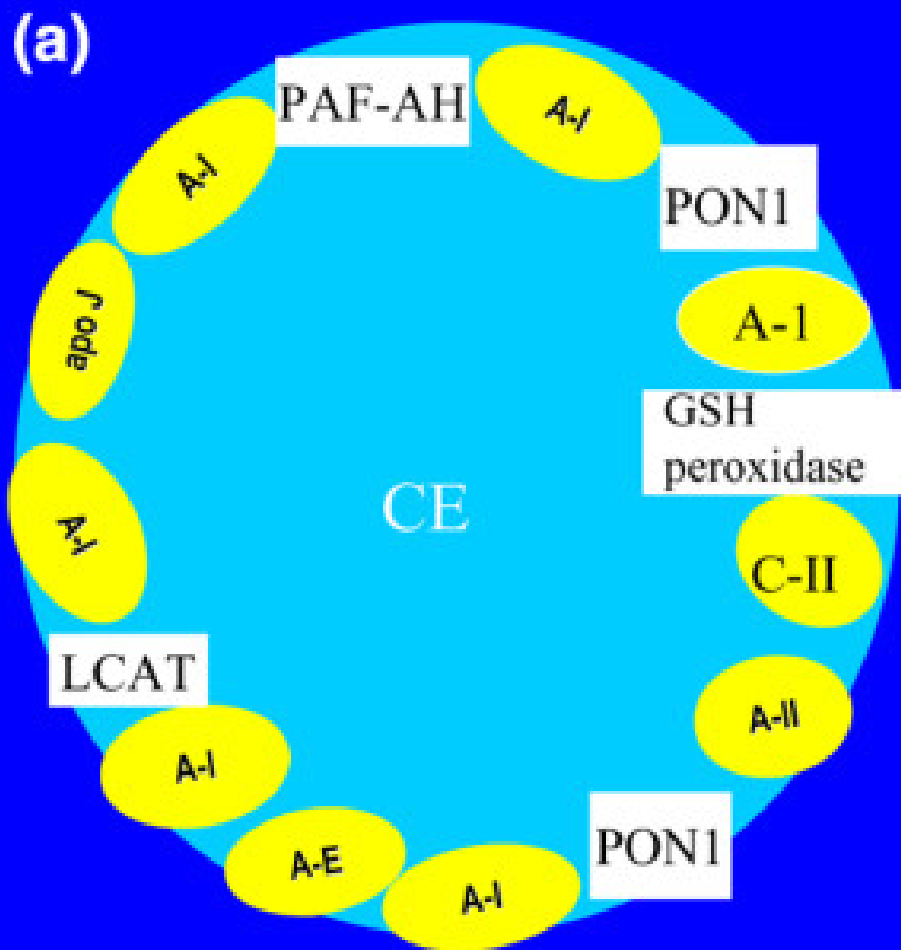
Heterogeneity of LDL

antioxidant content ↑
LDL receptor affinity

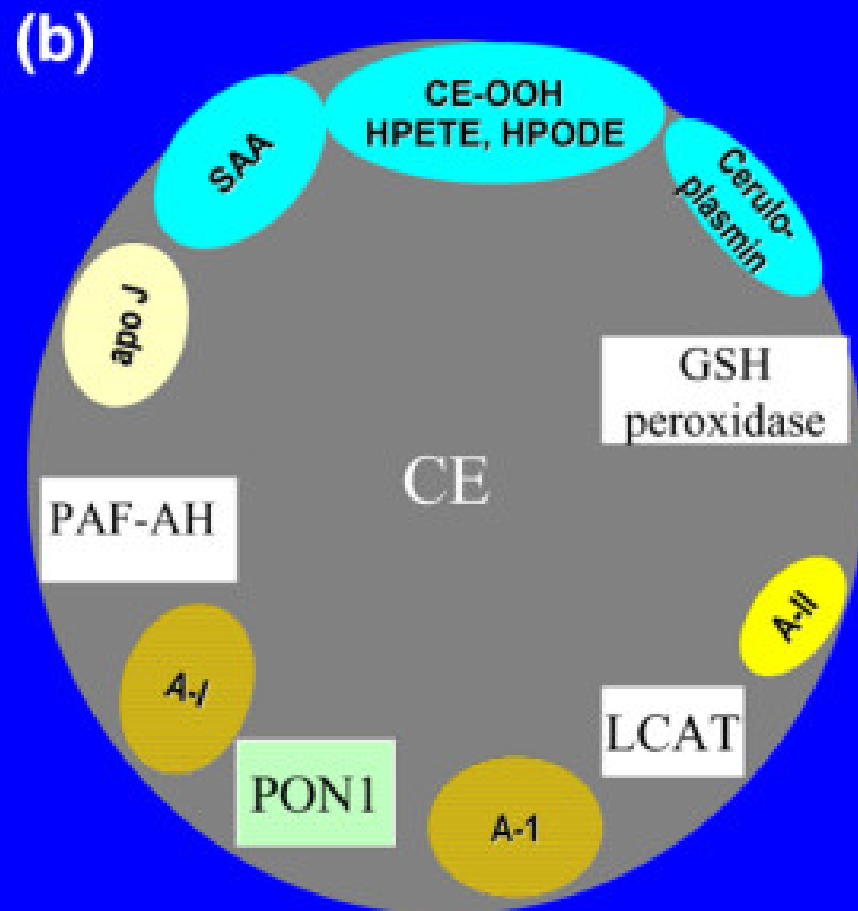


↑ triglyceride content
susceptibility to oxidation

HDL and inflammation



Anti-inflammatory HDL



Pro-inflammatory HDL

Apolipoprotein measurement

- ApoB and ApoA1
- Others
- May offer improved reproducibility and better clinical utility
- But measurement not widely available and guidelines are lipid based