

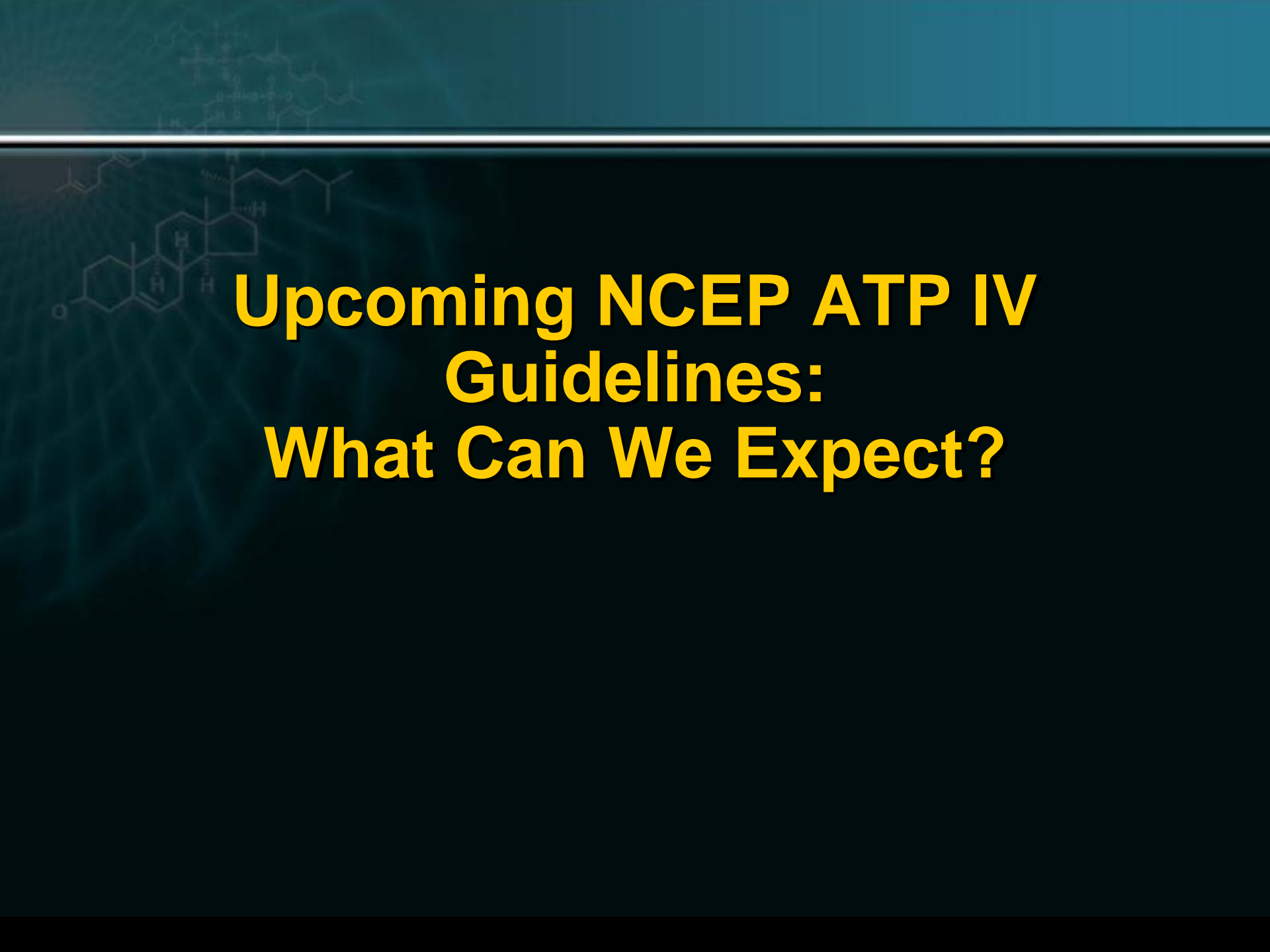
A faint, light blue chemical structure is visible in the upper left corner of the slide, set against a dark teal background. The structure appears to be a complex organic molecule, possibly a steroid or a similar lipid-related compound, with various rings and functional groups.

ATP IV, CVD Risk Assessment, and Dyslipidemia: Update 2012

**Pamela B. Morris, MD, FACC, FACP, FACPM, FAHA
Diplomate, American Board of Clinical Lipidology
Director, Seinsheimer Cardiovascular Health Program
Co-Director, Women's Heart Care
Medical University of South Carolina**

Points of Discussion

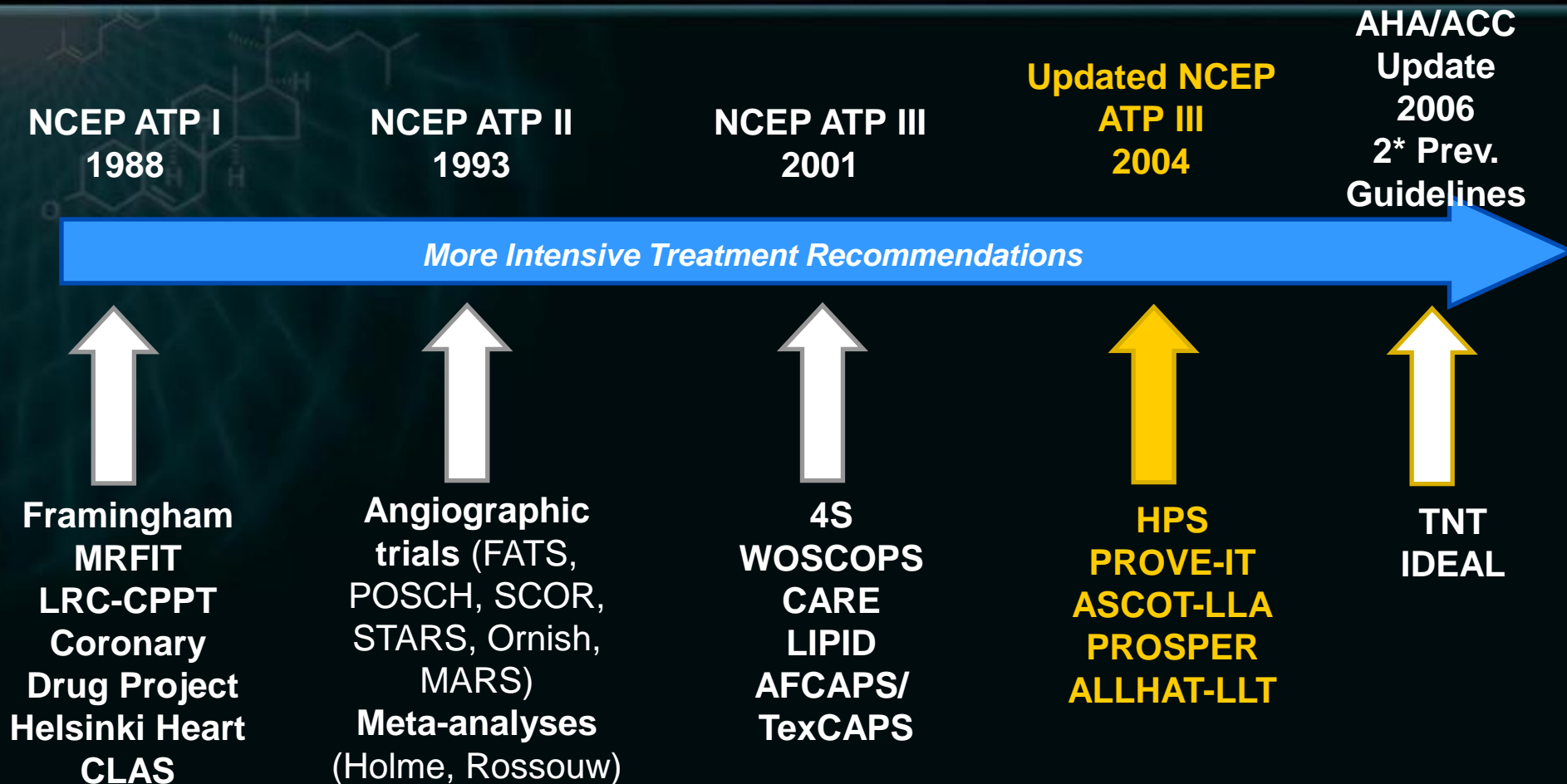
- **New guidelines on obesity, hypertension, and hyperlipidemia**
 - **ATP IV**
- **CVD Risk Assessment**
- **NLA position paper on role of biomarkers in CVD risk assessment**
- **Low levels of LDL-C**

The background of the slide features faint, light blue chemical structures. On the left side, there are several complex polycyclic molecules, including what appears to be a steroid-like structure with multiple fused rings and functional groups. To the right of these, there are more linear and branched chemical fragments, possibly representing various organic compounds or intermediates. The overall aesthetic is scientific and professional, with a dark teal-to-black gradient background.

Upcoming NCEP ATP IV Guidelines: What Can We Expect?



Evolution of NHLBI Supported Guidelines



NHLBI = National Heart, Lung, and Blood Institute.

NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel.

AHA = American Heart Association.

ACC = American College of Cardiology.

Intensive LDL-C Goals for High-Risk Patients

Recommended LDL-C treatment goals

**ATP III
Update 2004¹**

<100 mg/dL:
Patients with
CHD or CHD risk
equivalents
(10-year risk >20%)¹

<70 mg/dL:
Therapeutic
option for very
high-risk patients¹

<100 mg/dL

<70 mg/dL

**AHA/ACC guidelines
for patients with CHD^{*,2}**

<100 mg/dL:
Goal for all
patients with CHD^{†,2}

<70 mg/dL:
A reasonable
goal for all patients
with CHD^{†,2}

**2006
Update**

- If it is not possible to attain LDL-C <70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with more intensive LDL-C-lowering therapy, including drug combinations.

* And other forms of atherosclerotic disease.²

† Factors that place a patient at very high risk: established cardiovascular disease (CVD) plus: multiple major risk factors (especially diabetes); severe and poorly controlled risk factors (eg, cigarette smoking); metabolic syndrome (triglycerides [TG] ≥200 mg/dL + non-HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); and acute coronary syndromes.¹

1. Grundy SM et al. *Circulation*. 2004;110:227–239.

2. Smith SC Jr et al. *Circulation*, 2006; 113:2363–2372.

NHLBI Integrated Cardiovascular Risk Reduction Guidelines

■ Cardiovascular Risk Reduction Guidelines in Adults:

- Cholesterol Guideline Update (ATP IV)
 - Hypertension Guideline Update (JNC 8)
 - Obesity Guideline Update (Obesity 2)
-
- The National Heart, Lung, and Blood Institute is leading the development of an integrated set of cardiovascular risk reduction guidelines for adults using state-of-the-art methodology.
 - Cholesterol, hypertension, and obesity guidelines are being updated, and an integrated cardiovascular risk reduction guideline is being developed.

Methodology

- **NHLBI expert panels are putting final touches on new guidelines for**
 - **Adult obesity**
 - **Hypertension**
 - **Hyperlipidemia**
- **New methodology discussed at AHA Scientific Sessions 2011**
 - **Most comprehensive review of the literature ever with a systematic review process to evaluate evidence and establish recommendations**
 - **“...Goes well beyond anything NHLBI has ever attempted”**
 - **Recommendations of effective methods of implementation**
 - ▶ **Guidelines that will improve lives and sit on the shelf unused**
 - **High priority on conflicts of interest**
 - **Integrated guidelines—multiple guidelines in a common format**

Methodology: What's New

- Each committee created a list of critical questions its guidelines would answer
- Exhaustive literature review
- Relevant articles graded for the quality of evidence
 - Only good to fair articles included
- Distilled each qualified paper into an evidence statement to be used in creation of recommendations
- Less than 50-60% of papers identified as relevant were considered of usable quality
- Stronger emphasis on randomized clinical trials
- Limited use of expert opinion
- Concerned effort to SIMPLIFY guidelines

Methodology: What's Similar

- Focus on LDL-Cholesterol (LDL-C)
- Greatest intensity of treatment for patients at highest risk

Methodology

■ Obesity Panel Critical Questions

- What are the risks of being overweight?
- What are the benefits of weight loss?
- What amount of weight loss is necessary to achieve specific benefits?
- What is the most effective diet for weight loss?
- What is the evidence for short- and long-term efficacy of a comprehensive lifestyle approach?
- What are the benefits of obesity surgery?

■ Guidelines will NOT address pharmaceutical interventions due to lack of sufficient evidence

Methodology

■ JNC 8 Critical Questions

1. Does initiating antihypertensive pharmacological therapy at specific BP thresholds improve health outcomes? When should you initiate treatment?
2. Does treatment with an antihypertensive pharmacological therapy to a specified BP goal lead to improvements in health outcomes? How low should you go?
3. Do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes? How do you get there?

The antihypertensive guidelines are only using randomized controlled trial evidence

ATP IV Report

■ Aim:

- Assist clinicians in prevention to make decisions on cholesterol treatment by developing recommendations based on a detailed study of:
 - ▶ Randomized clinical trials (RCTs)
 - ▶ High quality meta-analyses of RCTs

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV)

Expert Panel Membership

Co-Chairs

Alice H. Lichtenstein, D.Sc.
Tufts University
Boston, Massachusetts

Neil Stone, M.D.
Northwestern University School of Medicine
Chicago, Illinois

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV)

C. Noel Bairey Merz, M.D.
University of California, Los Angeles

Conrad Blum, M.D.
Columbia University

Robert H. Eckel, M.D.
University of Colorado, Denver

Anne Carol Goldberg, M.D., FACP, FAHA
Washington University

Ronald M. Krauss, M.D.
Children's Hospital Oakland
Research Institute

Donald M. Lloyd-Jones, M.D., Sc.M.
Northwestern University

Patrick McBride, M.D., M.P.H.
University of Wisconsin

Daniel Rader, M.D.
University of Pennsylvania

Jennifer Robinson, M.D, M.P.H.
University of Iowa

Frank M. Sacks, M.D.
Harvard University
School of Public Health

J. Sanford Schwartz, M.D.
University of Pennsylvania

Sidney C. Smith, Jr. M.D.
University of North Carolina

Karol Watson, M.D., Ph.D.
University of California at Los Angeles

Peter W. F. Wilson, M.D.
Emory University School of Medicine

ATP IV Developing In-depth Answers to These Critical Questions

- Critical question 1: *What evidence supports LDL-C goals for secondary prevention?*
- Critical question 2: *What evidence supports LDL-C goals for primary prevention?*
- Critical question 3: *What is the impact of the major cholesterol drugs on efficacy and safety?*
- Diet and exercise are being addressed separately by the Lifestyle Working Group

Critical Question 1

- ***What evidence supports LDL-c goals for secondary prevention?***
 - **This question being evaluated in all adults and specific subpopulations of interest**
 - ▶ **Women**
 - ▶ **Diabetics**
 - ▶ **Metabolic syndrome**
 - ▶ **Chronic kidney disease**
 - ▶ **Current smoking**
 - ▶ **Baseline LDL-c <100 mg/dl, HDL-c < 40 mg/dl, triglycerides <200 mg/dl and non-HDL-c <130 mg/dl**

Critical Question 1: Background

- ***What evidence supports LDL-c goals for secondary prevention?***
 - ATP III recommended LDL-c goals of <100 mg/dl in secondary prevention
 - ATP III added the optional LDL-c therapeutic target of <70 mg/dl for patients with
 - ▶ Acute coronary syndrome
 - ▶ Diabetes or metabolic syndrome
 - ▶ Persistent strong risk factor such as cigarette smoking
 - BUT: clinical trials used fixed doses rather than titration to goal strategies
 - THUS: additional examination of the evidence is warranted

Critical Question 1: Publications screened



Studies excluded if they did not meet pre-specified inclusion/exclusion criteria

Critical Question 2

- ***What evidence supports LDL-c goals for primary prevention?***
 - This question being evaluated in all adults and specific subpopulations of interest
 - ▶ Diabetics
 - ▶ 10-year CHD risk categories: <5%, 5-10%, 10-20%, >20%
 - For all adults and each of the above groups
 - ▶ Men and women separately
 - ▶ Adults 18-64 years of age and \geq 65 years
 - ▶ Men 18-35 years and women 18-45 years
 - ▶ Race/ethnicity

Critical Question 2: Publications screened



Studies excluded if they did not meet pre-specified inclusion/exclusion criteria

Critical Question 3

- ***What is the impact of the major cholesterol drugs on efficacy/safety in the population?***
 - Baseline untreated LDL-c
 - ▶ <130 mg/dl or 130-159 mg/dl or >160 mg/dl (including patients with familial hypercholesterolemia)
 - Triglycerides \geq 150 mg/dl
 - HDL-c <40 mg/dl in men and <50 mg/dl in women
- **Populations with special safety concerns**
 - Heart, liver, or renal transplantation
 - HIV with or without protease inhibitor therapy

Critical Question 3: Publications screened



Studies excluded if they did not meet pre-specified inclusion/exclusion criteria

Meta-analyses used for statin efficacy and safety and they included data from additional studies.

Issues for ATP-IV: ???????

- CVD Risk Assessment
- More stringent targets versus a fixed dose strategy adjusting dose to risk
- hs-CRP
- Alternative treatment targets: Role of advanced lipoprotein testing
 - Apo B, LDL-P, non HDL-C
 - Direct targeting of HDL-C and triglycerides
- Role of fibrates, niacin, ezetimibe, BAS
- Role of imaging of subclinical atherosclerosis
- *"Let's put it this way. If what people are doing now is correct, and there's no change recommended, then we're fine. If we do come up with very substantial changes, we want to be very careful that they are strongly based in evidence." Dr. Sidney Smith, UNC Chapel Hill*

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Cardiovascular Risk Prediction



Continuum of Disease

- Asymptomatic
- Disease-free
- Risk factors may be present

Primary Prevention

- Risk factor identification
- Preventive strategies



- Asymptomatic
- Subclinical disease present

- Early disease detection
- Aggressive preventive strategies



- Onset of symptoms
- Heart attack, stroke, angina

Secondary Prevention

- Secondary preventive strategies



Cardiovascular Risk Prediction

- CVD is leading cause of death in US and entire western world
- At age 50 the lifetime risk of CVD is
 - 50% for men
 - 39% for women
 - Variations due to risk factor burden
- NCEP ATP III (and ATP IV ?)
 - Risk calculation based on assumption that the intensity of treatment and risk factor reduction should match the level of absolute predicted risk.

Current Guidelines

■ Office-based Assessment

(National Cholesterol Education Program, American Heart Association, American College of Cardiology)

■ Risk prediction algorithm derived from the Framingham Heart Study

- Age
- Total cholesterol
- HDL
- Blood pressure
- Smoking

ATP III Framingham Risk Scoring

Assessing CHD Risk in Women

Step 1: Age

Years	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Step 2: Total Cholesterol

TC (mg/dL)	Points at Age 20-39	Points at Age 40-49	Points at Age 50-59	Points at Age 60-69	Points at Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

Step 3: HDL-Cholesterol

HDL-C (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Step 4: Systolic Blood Pressure

Systolic BP (mm Hg)	Points if Untreated	Points if Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Step 6: Adding Up the Points

Age	—
Total cholesterol	—
HDL-cholesterol	—
Systolic blood pressure	—
Smoking status	—
Point total	—

Step 7: CHD Risk

Point Total	10-Year Risk	Point Total	10-Year Risk
<0	<1%	11	8%
0	1%	12	10%
1	1%	13	12%
2	1%	14	16%
3	1%	15	20%
4	1%	16	25%
5	2%	≥17	≥30%
6	2%		
7	3%		
8	4%		
9	5%		
10	6%		

Step 5: Smoking Status

	Points at Age 20-39	Points at Age 40-49	Points at Age 50-59	Points at Age 60-69	Points at Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Note: Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

ATP III Framingham Risk Scoring

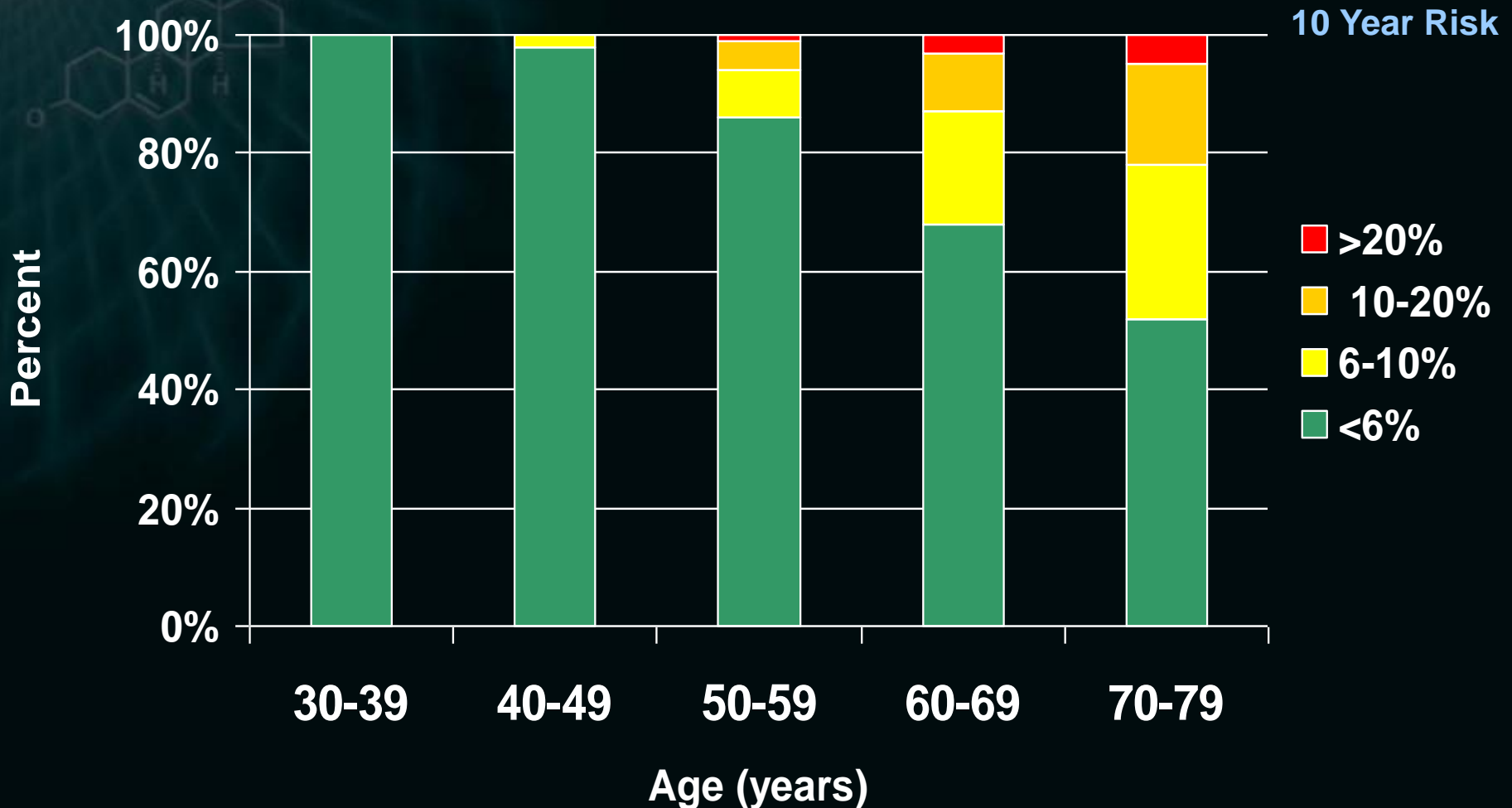
Step 7: CHD Risk for Women

**Framingham risk calculation
underestimates risk particularly
in women
and younger individuals.**

Note: Determine the 10-year absolute risk for hard CHD (MI and coronary death) from point total.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

Women Hardly Reach 10% FRS by Traditional Risk Factor Assessment!



How Good Is NCEP III At Predicting MI?

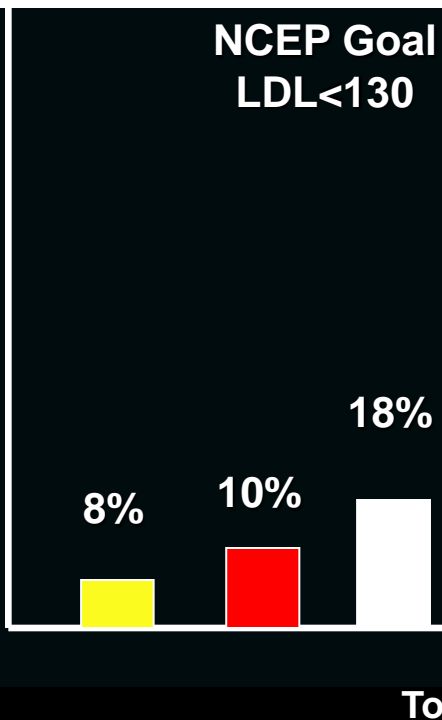
JACC 2003;41 1475-9

88% of these “young” patients who suffered a first Myocardial Infarction were in the Low to Intermediate “risk” category according To Framingham Risk Assessment and would have been missed as truly “High Risk” individuals who should have been treated “aggressively”.

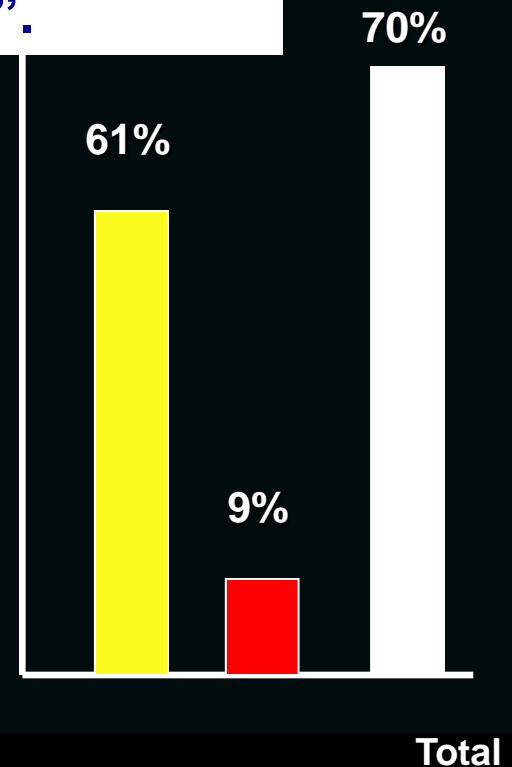
NCEP Goal
LDL<100



NCEP Goal
LDL<130



61%



Currently Available CVD Risk Prediction Scores

Table 1. Examples of Currently Available CVD Risk Prediction Scores

Risk Score	End Point	Comments
Framingham, 1998 ¹⁶	All CHD	Includes CHD death, MI, unstable angina, and angina pectoris
ATP-III risk estimator, 2001 ^{1,17} (Framingham)	Hard CHD	Includes CHD death and nonfatal MI
Framingham global CVD, 2008 ²³	Global CVD	Includes CVD death, all CHD, stroke, heart failure, and claudication
PROCAM ¹⁹	Hard CHD	Includes CHD death and nonfatal MI
QRISK ²⁰	CVD	Includes CHD, stroke, and transient ischemic attack
Reynolds risk score (women) ²¹	Global CVD	Includes CVD death, MI, stroke, and revascularization
Reynolds risk score (men) ²²	Global CVD	Includes CVD death, MI, stroke, and revascularization
SCORE ¹⁸	CVD death	Includes CVD death only; does not include nonfatal events; multiple region-specific (northern European, southern European) and country-specific versions available

MI indicates myocardial infarction.

Risk Classification Algorithm Used in the ATP-III 2004 Update

Table 2. Risk Classification Algorithm Used in the ATP-III 2004 Update

Risk Category	Definition
High risk	CHD or CHD risk equivalent* or ≥ 2 risk factors† and 10-y predicted risk of $>20\%$
Moderately high risk	≥ 2 Risk factors and 10-y predicted risk of 10% to 20%
Moderate risk	≥ 2 Risk factors and 10-y predicted risk of $<10\%$
Lower risk	0–1 Risk factor

Table data from Grundy et al.²⁴

*CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease, ie, transient ischemic attacks, stroke of carotid origin, or $>50\%$ obstruction of a carotid artery) or diabetes mellitus.

†Risk factors include cigarette smoking, hypertension (blood pressure $\geq 140/90$ mm Hg or on antihypertensive medication), low high-density lipoprotein cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥ 45 years; women ≥ 55 years).

Currently Available CVD Risk Prediction Scores

- 5- and 10-year risk estimates are most widely used
- Risk score is converted into an absolute probability of developing CVD within that time frame
- Consideration of 10-year risk identifies patients most likely to benefit from therapy in the near term
 - Improves cost-effectiveness and safety of therapy
- FRS performs poorly in women and younger men
 - Algorithm heavily weighted by age

Currently Available CVD Risk Prediction Scores

- Risk for CVD associated with traditional risk factors is continuous
- No obvious natural thresholds
- Thresholds used by ATP III for clinical decision making are based on population data and cost-effectiveness estimates in an era when statins were more expensive
- Majority of events occur in the intermediate risk population (simply because that is where the vast majority of the population at risk is found.)

Risk Classification Algorithm Used in the ATP-III 2004 Update

- Likely that future guidelines will choose lower thresholds for therapy in light of
 - Demonstrated benefit in populations at predicted risk $<20\%$
 - The availability of inexpensive statins
 - Longer-term safety data

Newer CVD Risk Prediction Algorithms

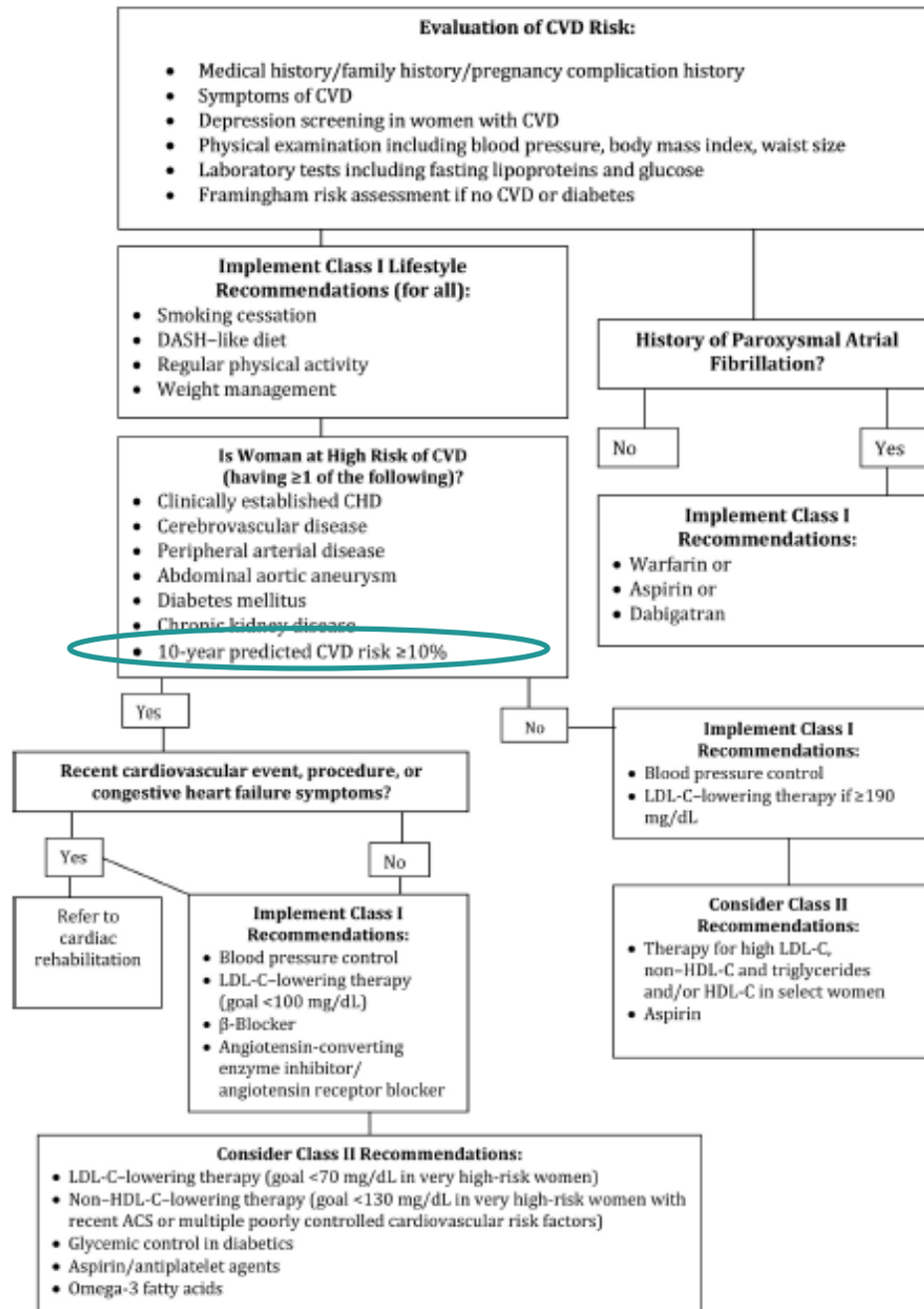
- Concept of vascular age from CAC or CIMT
- Lifetime risk
- 30 year risk
- Composite endpoints (all CVD, PAD, stroke, heart failure, include angina/revascularization, fatal and nonfatal...)
- Validation/calibration in other populations
- Inclusion of family history, hs-CRP, HgbA1C, social deprivation, BMI

*Effectiveness**-Based Guidelines for Cardiovascular Disease Prevention in Women—2011 Update

* *(therapies with sufficient evidence of clinical benefit for CVD outcomes)*

American Heart Association Guidelines

Endorsed by the American College of Cardiology, American College of Physicians, AMWA, WomenHeart, American Society for Preventive Cardiology, and others



Who is at risk among women?

■ Highest risk women

- Known heart disease, stroke, vascular disease (PAD or carotid disease), or aneurysm
- ESRD or CKD
- Diabetes
- 10 yr predicted CVD risk \geq 10%



Who is at risk among women?



■ “At-risk” women

- 1 or more of the following risk factors
 - ▶ Smoking
 - ▶ Poor diet
 - ▶ Sedentary
 - ▶ Obesity, especially if belly fat
 - ▶ Family history (female ≤ 65 , male ≤ 55)
 - ▶ High blood pressure ($>120/80$)
 - ▶ Abnormal lipids (high “bad” cholesterol, low “good” cholesterol, high triglycerides)
 - ▶ Metabolic syndrome
 - ▶ Poor exercise tolerance
 - ▶ Subclinical atherosclerosis
 - ▶ Systemic autoimmune collagen-vascular disorder (SLE, RA)
 - ▶ Hx of preeclampsia, gestational DM

Who is at risk among women?

- Optimal risk women
 - Ideal healthy lifestyle
 - No risk factors

***Only 1 out of
3 women!***



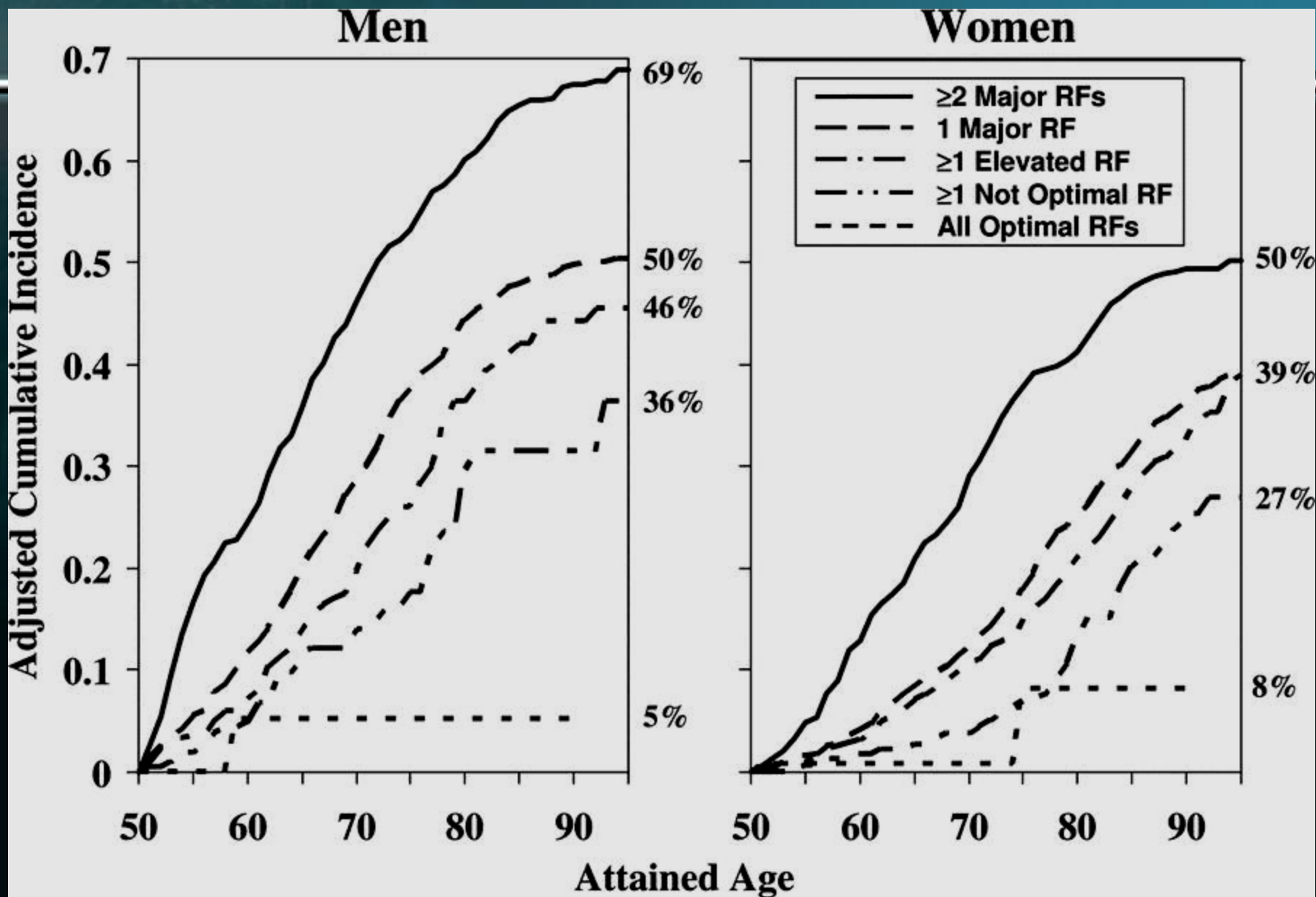
Who is at risk among women?

■ Optimal risk women

- Total cholesterol <200 mg/dl (untreated)
- BP <120/80 mmHg (untreated)
- Fasting glucose <100 mg/dl (untreated)
- BMI <25 kg/m²
- No smoking
- Physical activity ≥ 150 min/wk moderate intensity or ≥ 75 min/wk vigorous intensity
- Healthy DASH-like diet

Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age

Donald M. Lloyd-Jones et al
Circulation 2006;113:791-798



Generic Prevention Drugs

<u>Drug</u>		<u>Monthly Cost</u>
Statin		\$4.00
Beta blocker		\$4.00
Metformin		\$4.00
ACE-inhibitor	HCTZ	\$4.00
Amlodipine		\$4.00

- All national discount pharmacy chains
 - Lower price (\$10) for 3 months supply
 - Can potentially reduce cost further with a pill cutter

Beyond Cholesterol: Predicting Cardiovascular Risk In the 21st Century

Cardiovascular Risk

```
graph TD; A[Cardiovascular Risk] --- B[Lipids HTN Diabetes]; A --- C[Behavioral]; A --- D[Hemostatic Thrombotic]; A --- E[Inflammatory]; A --- F[Genetic]
```

Lipids
HTN
Diabetes

Behavioral

Hemostatic
Thrombotic

Inflammatory

Genetic

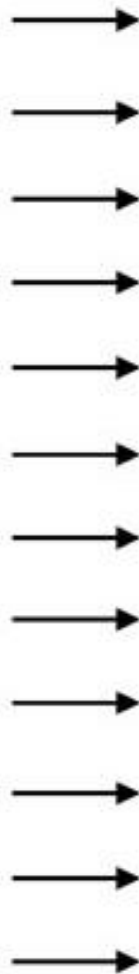
Screening for Atherosclerosis

Risk Factors vs Disease

Numerous Risk Factors

High LDL
Low HDL
High BP
Diabetes
Smoking
CRP
Metabolic Syn
Lp(a)
Homocysteine
Dense LDL
Lp-PLA2
ApoB/ApoA
Family History
Sedentary Life
Obesity
Stress
...
?

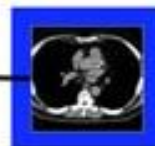
Over 200 risk factors have been reported.



Carotid IMT and Plaque Measured by Ultrasound



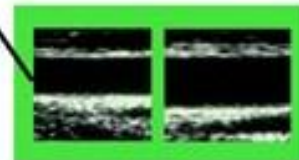
Aortic and Carotid Plaque Detected by MRI



Coronary Calcium Score Measured by CT



Ankle Brachial Index



Brachial Vasoreactivity Measured by Ultrasound



Vascular Compliance Measured by Radial Tonometry



Microvascular Reactivity Measured by Fingertip Tonometry

Examples of Arterial Structure Tests

Examples of Arterial Function Tests

PLUTO AND BEYOND • THE SKEPTICAL ENVIRONMENTALIST REPLIES

SCIENTIFIC AMERICAN

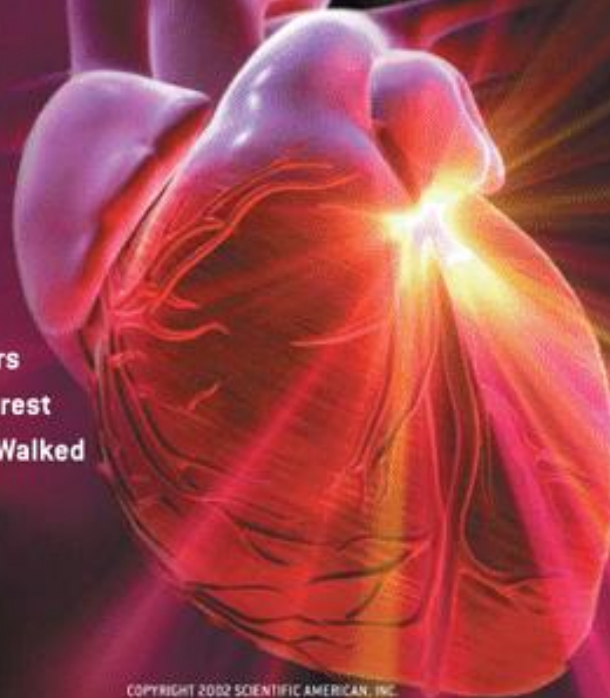
MAY 2002
WWW.SCIAM.COM

\$4.95

A FIRE WITHIN

Inflammation's Link to Heart Attacks

PLUS:
Extreme Lasers
Rent a Rain Forest
When Whales Walked



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Biomarkers

Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists

Michael H. Davidson, MD, FNLA, Chair*, Christie M. Ballantyne, MD, FNLA, Co-Chair, Inflammatory Biomarkers Sub-group, Terry A. Jacobson, MD, FNLA, Co-Chair, Lipoprotein Biomarkers Sub-group, Vera A. Bittner, MD, MSPH, FNLA, Lynne T. Braun, PhD, CNP, FNLA, Alan S. Brown, MD, FNLA, W. Virgil Brown, MD, FNLA, William C. Cromwell, MD, FNLA, Ronald B. Goldberg, MD, FNLA, James M. McKenney, PharmD, FNLA, Alan T. Remaley, MD, PhD, Allan D. Sniderman, MD, Peter P. Toth, MD, PhD, FNLA, Sotirios Tsimikas, MD, Paul E. Ziajka, MD, PhD, FNLA

Non-Panel Scientists: Kevin C. Maki, PhD, FNLA, Mary R. Dicklin, PhD

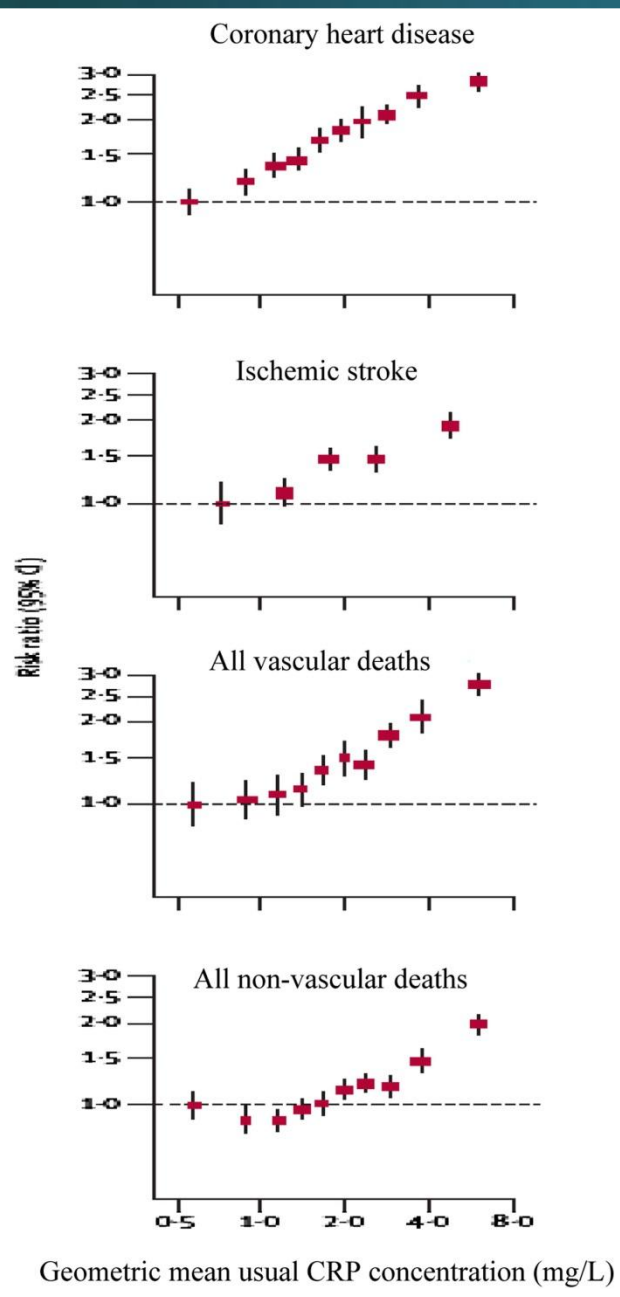
Table 2 Laboratory values of CRP, Lp-PLA₂, Apo B, LDL-P, and Lp(a) according to lower-, intermediate-, and greater-risk categories, approximated from population studies

Biomarker	Population-based approximations		
	Lower risk	Intermediate risk	Greater risk
CRP, mg/L ¹²	<1.0	1.0–3.0	>3.0
Lp-PLA ₂ , ng/mL ^{13,*}	<200	200–259	≥260
Apo B, mg/dL ^{14,†}	<80	80–119	≥120
LDL-P, nmol/L ^{15,16,‡}	<1000	1000–1559	≥1600
Lp(a), mg/dL ^{17,§}	<5	5–49	≥50

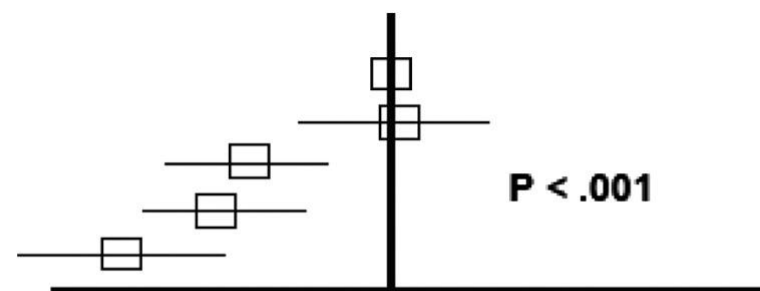
Laboratory values of CRP, Lp-PLA₂, Apo B, LDL-P, and Lp(a) according to lower-, intermediate-, and greater-risk categories, approximated from population studies

Population-based approximations

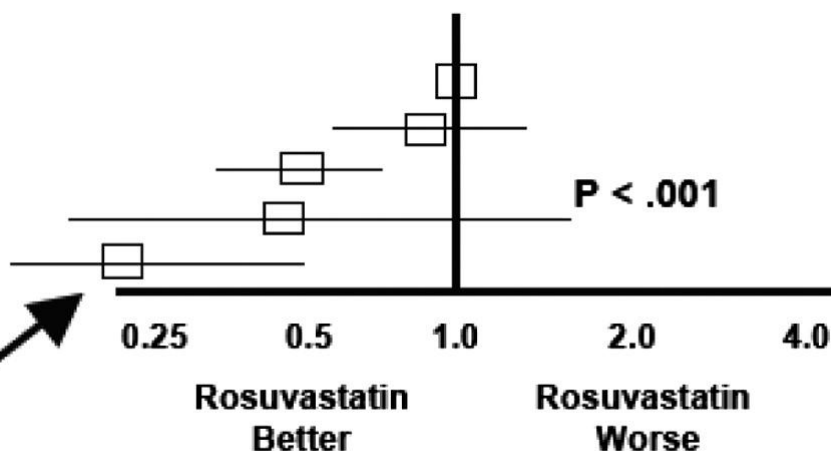
Biomarker	Lower risk	Intermediate risk	Greater risk
CRP, mg/L	<1.0	1.0–3.0	>3.0
Lp-PLA ₂ , ng/mL	<200	200–259	≥260
Apo B, mg/dL	<80	80–119	≥120
LDL-P, nmol/L	<1000	1000–1559	≥1600
Lp(a), mg/dL	<5	5–49	≥50



	N	Rate
Placebo	7832	1.11
LDL \geq 70mg/dL,hsCRP \geq 2 mg/L	1384	1.11
LDL<70mg/dL,hsCRP \geq 2 mg/L	2921	0.62
LDL \geq 70mg/dL,hsCRP<2 mg/L	726	0.54
LDL<70mg/dL,hsCRP<2 mg/L	2685	0.38



Placebo	7832	1.11
LDL \geq 70mg/dL,hsCRP \geq 1 mg/L	1874	0.95
LDL<70mg/dL,hsCRP \geq 1 mg/L	4662	0.56
LDL \geq 70mg/dL,hsCRP<1 mg/L	236	0.64
LDL<70mg/dL,hsCRP<1 mg/L	944	0.24



Full Adjusted Hazard Ratio
0.21, 95% CI 0.09-0.52, P < .0001

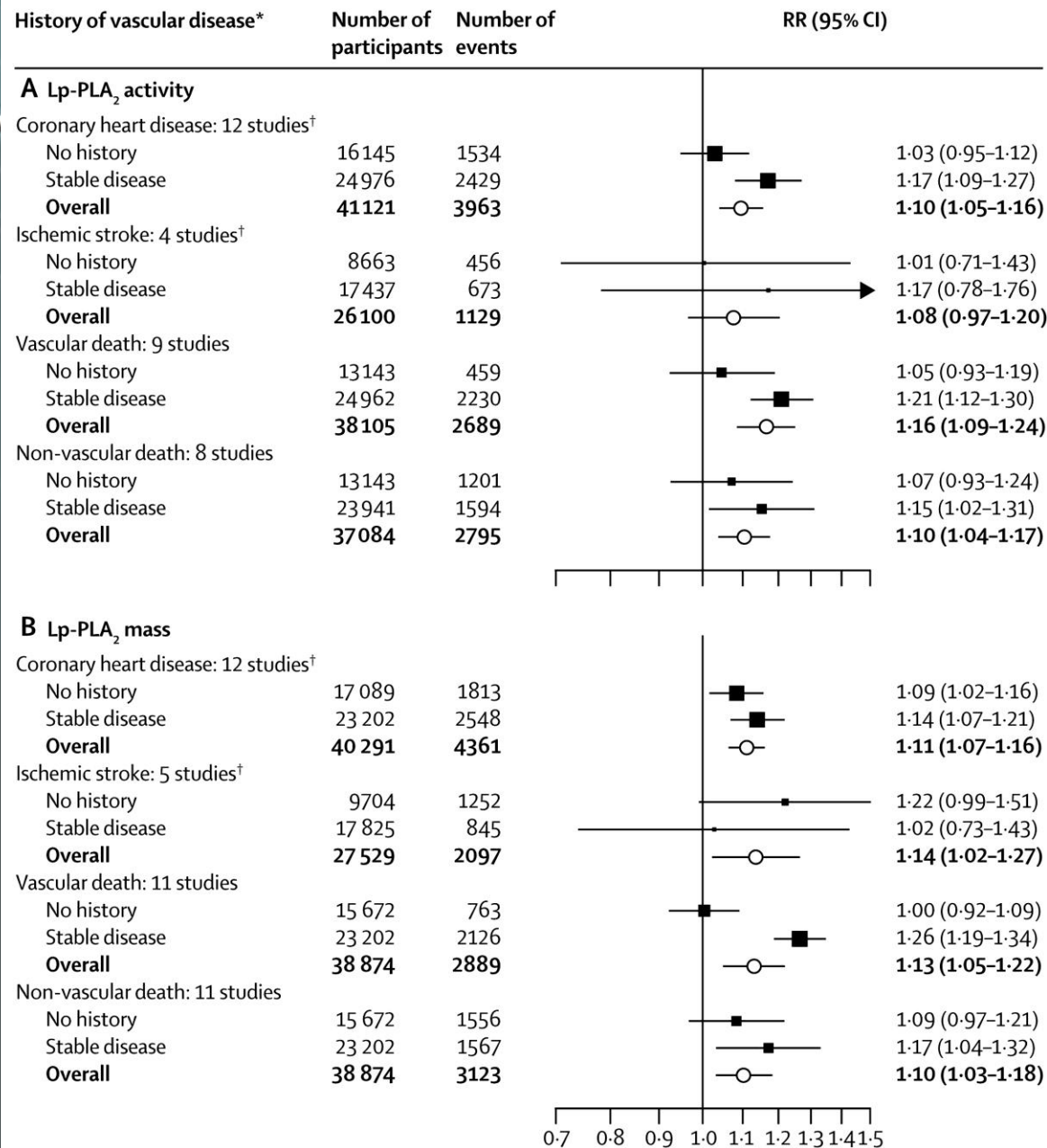
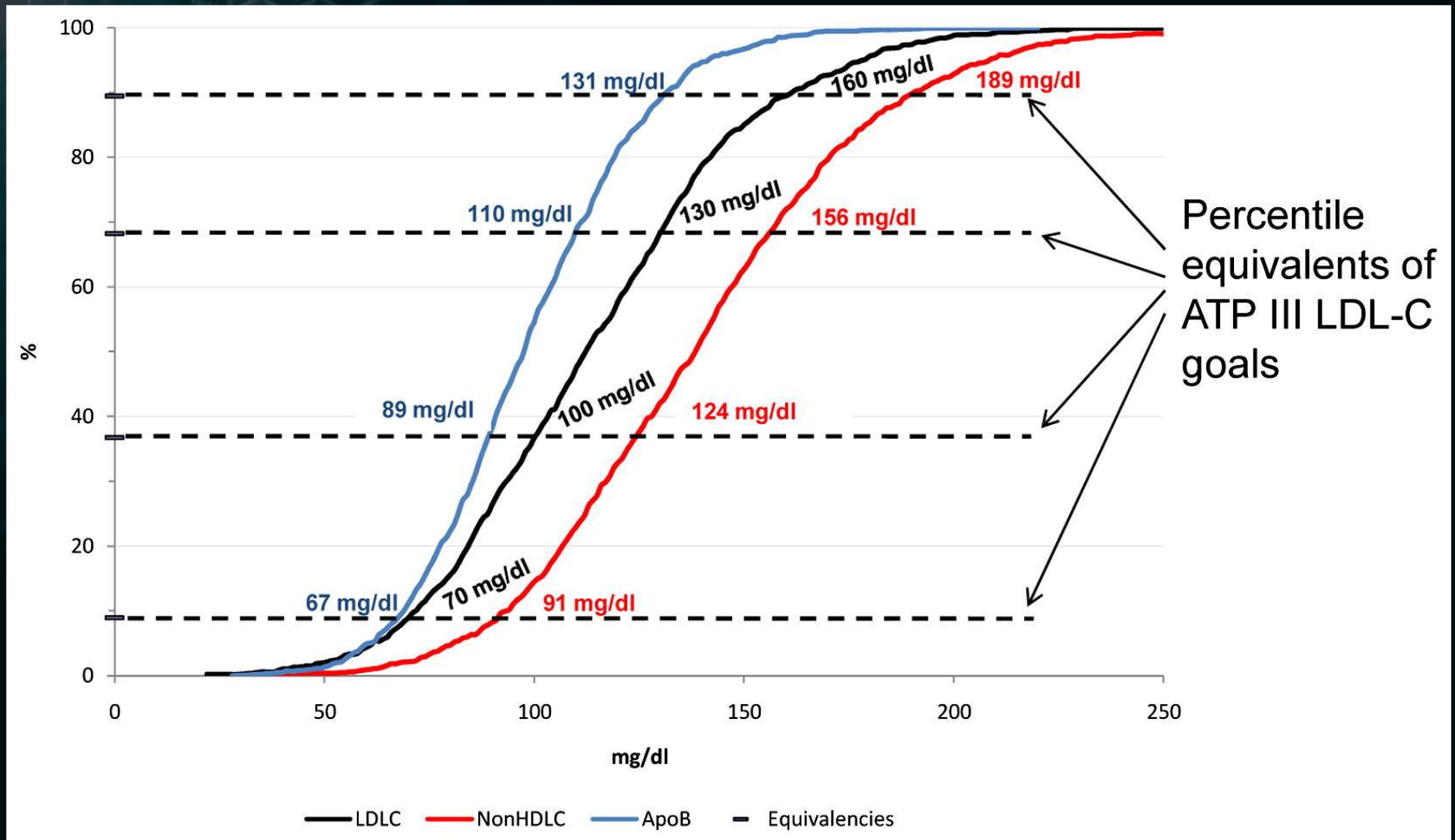
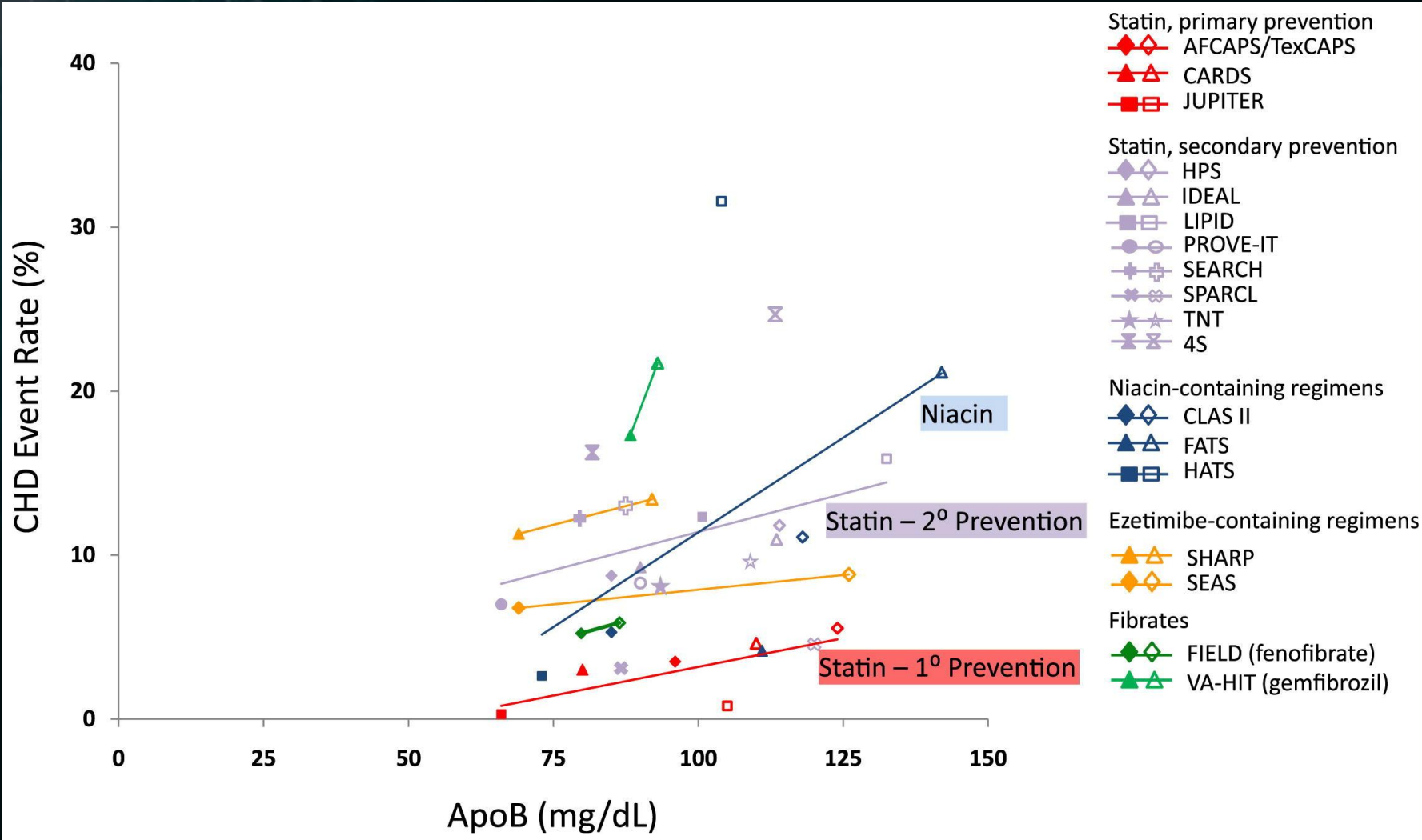
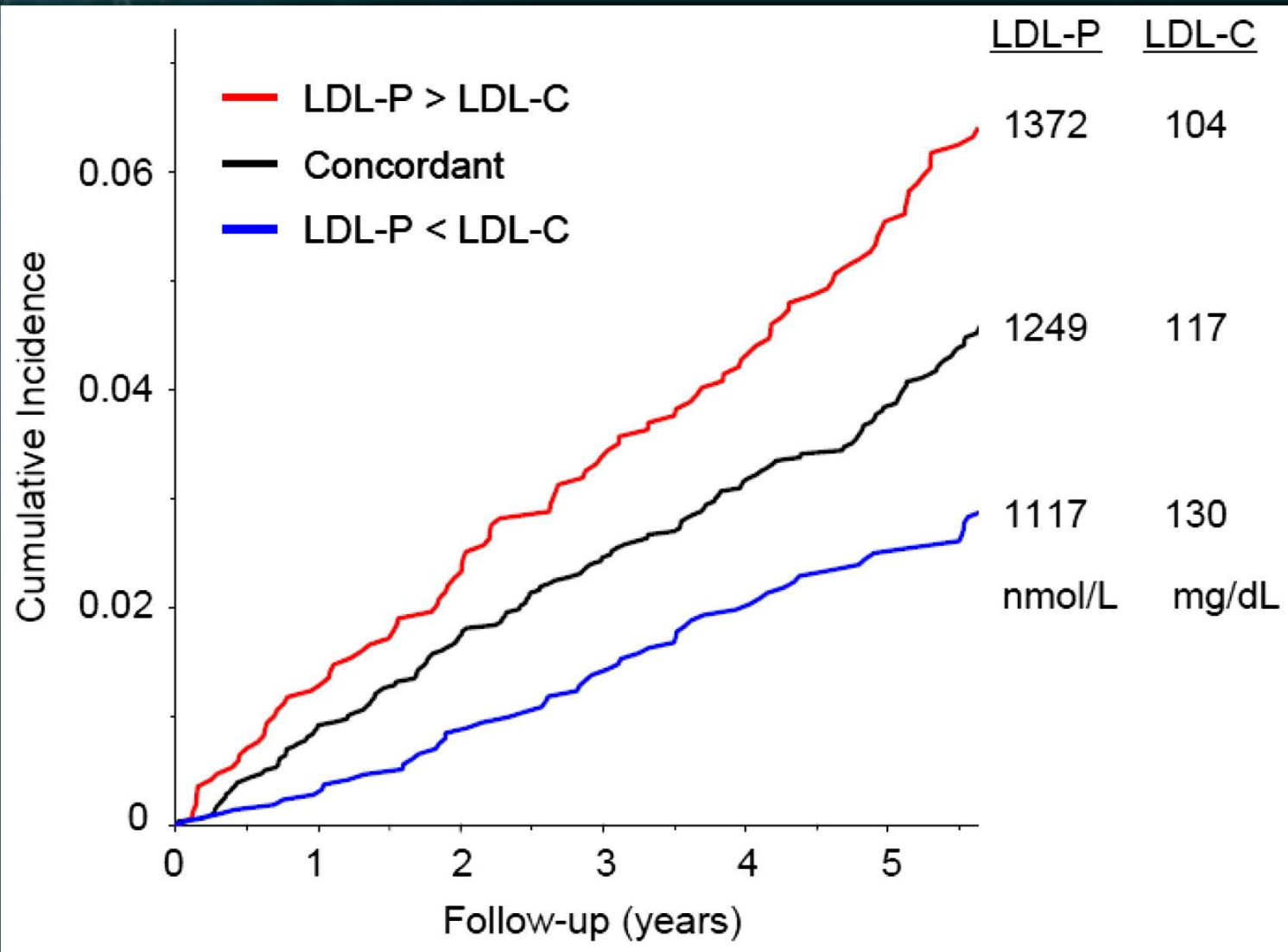


Figure 4







Lipoprotein(a)

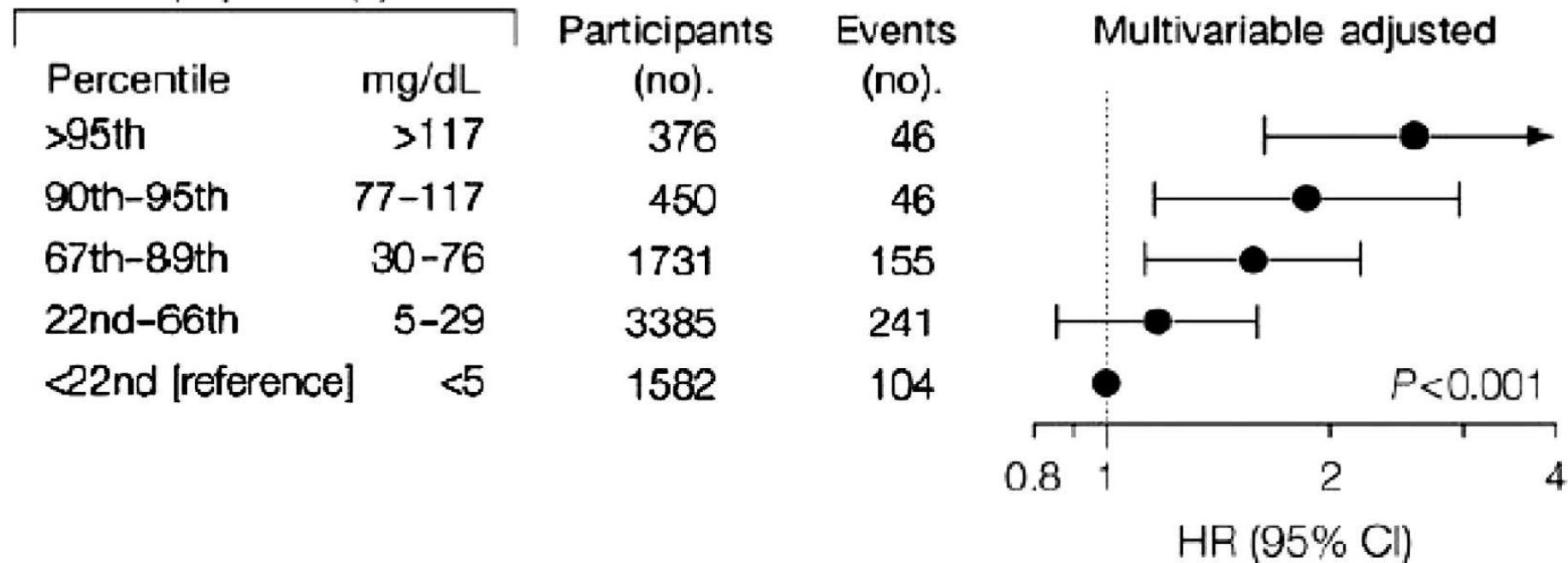
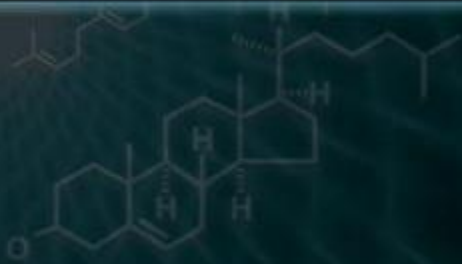


Table 1 Summary recommendations for measurement of inflammatory markers and advanced lipoprotein/subfraction testing in initial clinical assessment and on-treatment management decisions

	Initial Clinical Assessment					
	CRP	Lp-PLA ₂	Apo B	LDL-P	Lp(a)	HDL or LDL Subfractions
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate risk (5-20% 10-year CHD event risk)	Recommended for routine measurement	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
CHD or CHD Equivalent	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommended
Family History	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended
Recurrent Events	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended

	On-Treatment Management Decisions					
	CRP	Lp-PLA ₂	Apo B	LDL-P	Lp(a)	HDL or LDL Subfractions
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate risk (5-20% 10-year CHD event risk)	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Not recommended	Not recommended
CHD or CHD Equivalent	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
Family History	Consider for selected patients	Not recommended	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommended
Recurrent Events	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended

Is there risk or benefit associated with unusually low levels of LDL-C?

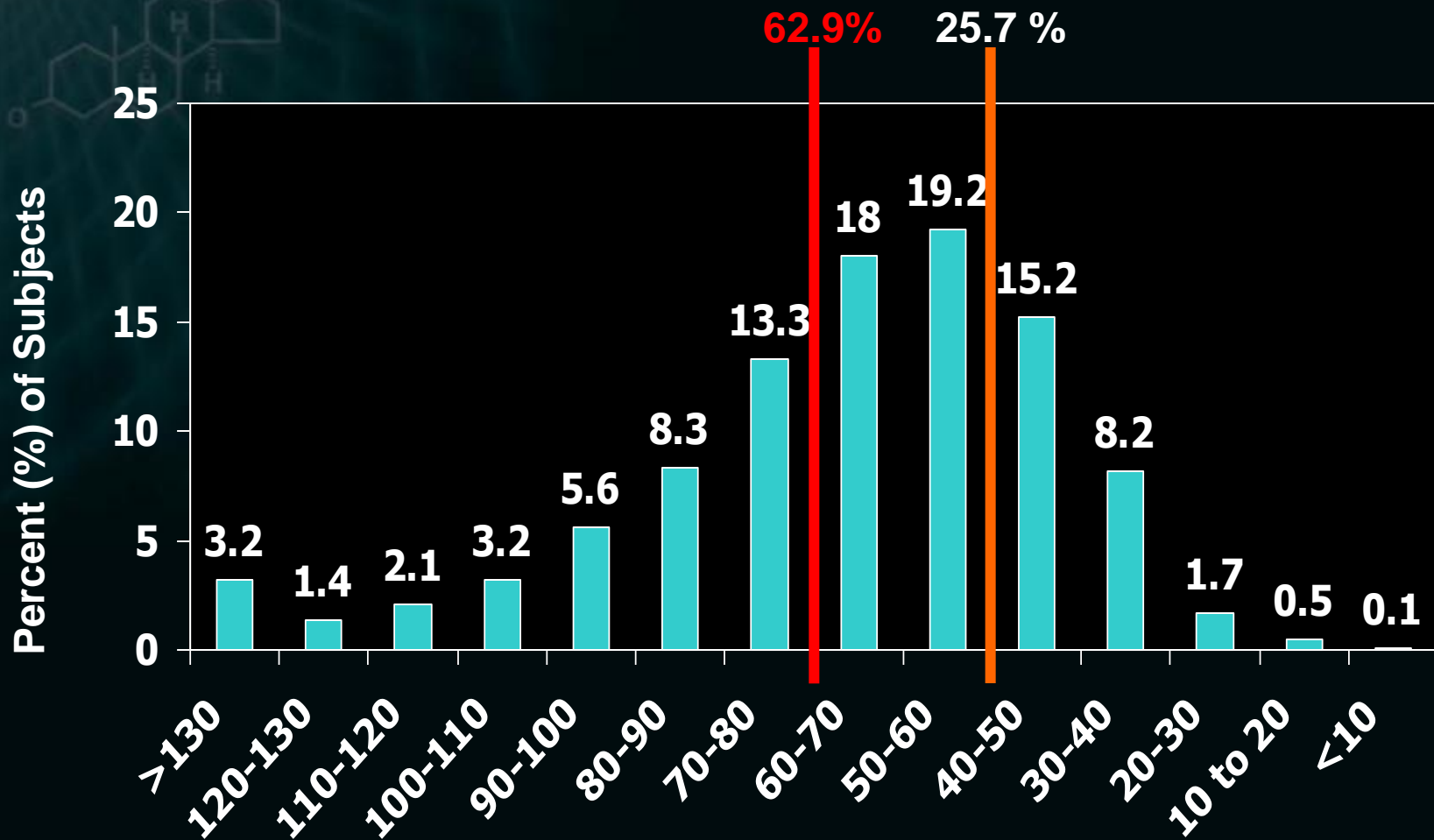


Can LDL Be Too Low?

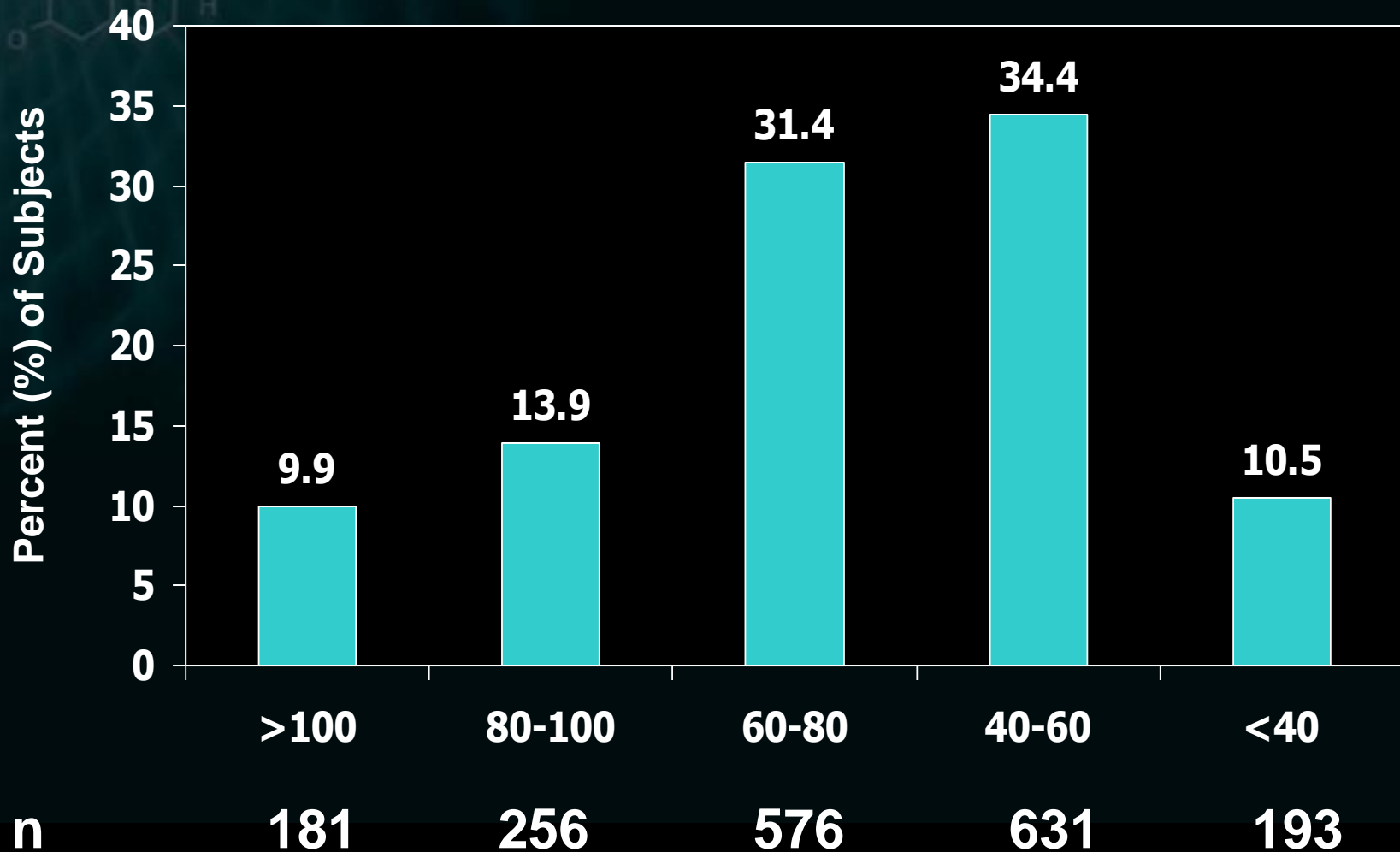
A safety analysis of the intensive treatment arm of PROVE IT - TIMI 22

Stephen D Wiviott, David A Morrow, Richard Cairns, Marc A Pfeffer, and Christopher P Cannon for the
PROVE IT - TIMI 22 Investigators

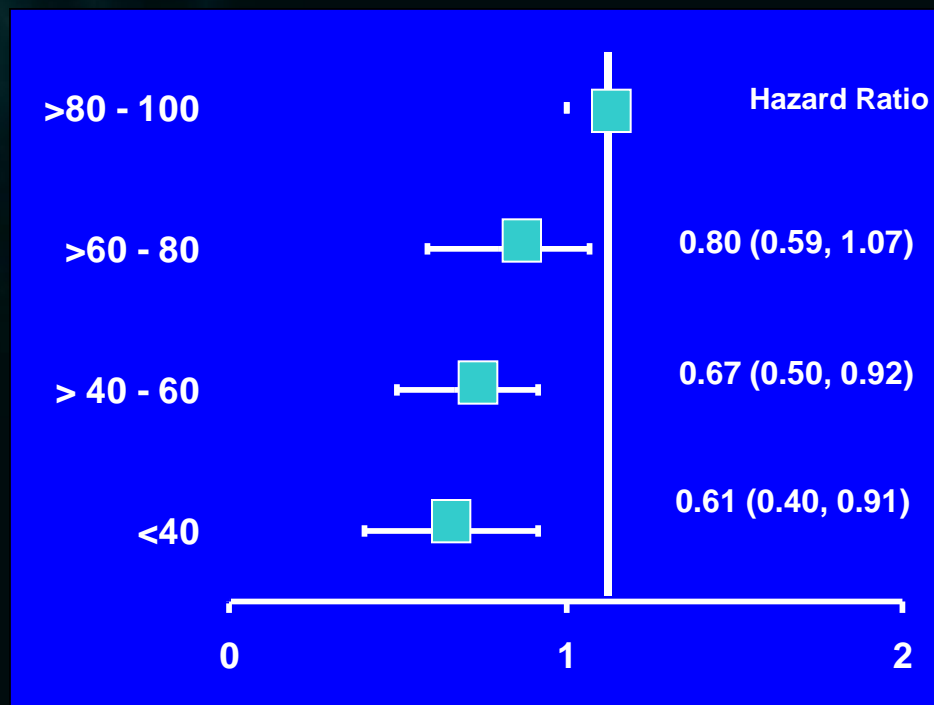
Results: Distribution of 4 Month LDL Cholesterol Levels



Results: Distribution of 4 Month LDL Cholesterol Levels



Results: Primary Endpoint by 4 month LDL level (multivariable adjustment)*



*Age, gender, DM, prior MI, baseline LDL

■ Abetalipoproteinemia (ABL) and familial hypobetalipoproteinemia (FHBL)

- Rare inborn errors of lipoprotein metabolism.
- ABL occurs in less than 1 in 1 million persons.
- FHBL occurs in approximately 1 in 500 heterozygotes and in about 1 in 1 million homozygotes.
- Approximately one third of ABL and FHBL cases result from consanguineous marriages.

Hepatocytes

Lipoproteins
in Media

LDLr
mediated
uptake

Cytosol

HMG CoA
Reductase

ACAT1

ACAT2

DGAT2

DGAT1

ER Membrane

(+)

Proteasome

Lumen

(-)

(-)

MTP

ApoB

Protease

VLDL

(-)

FC

CE

FC

CE

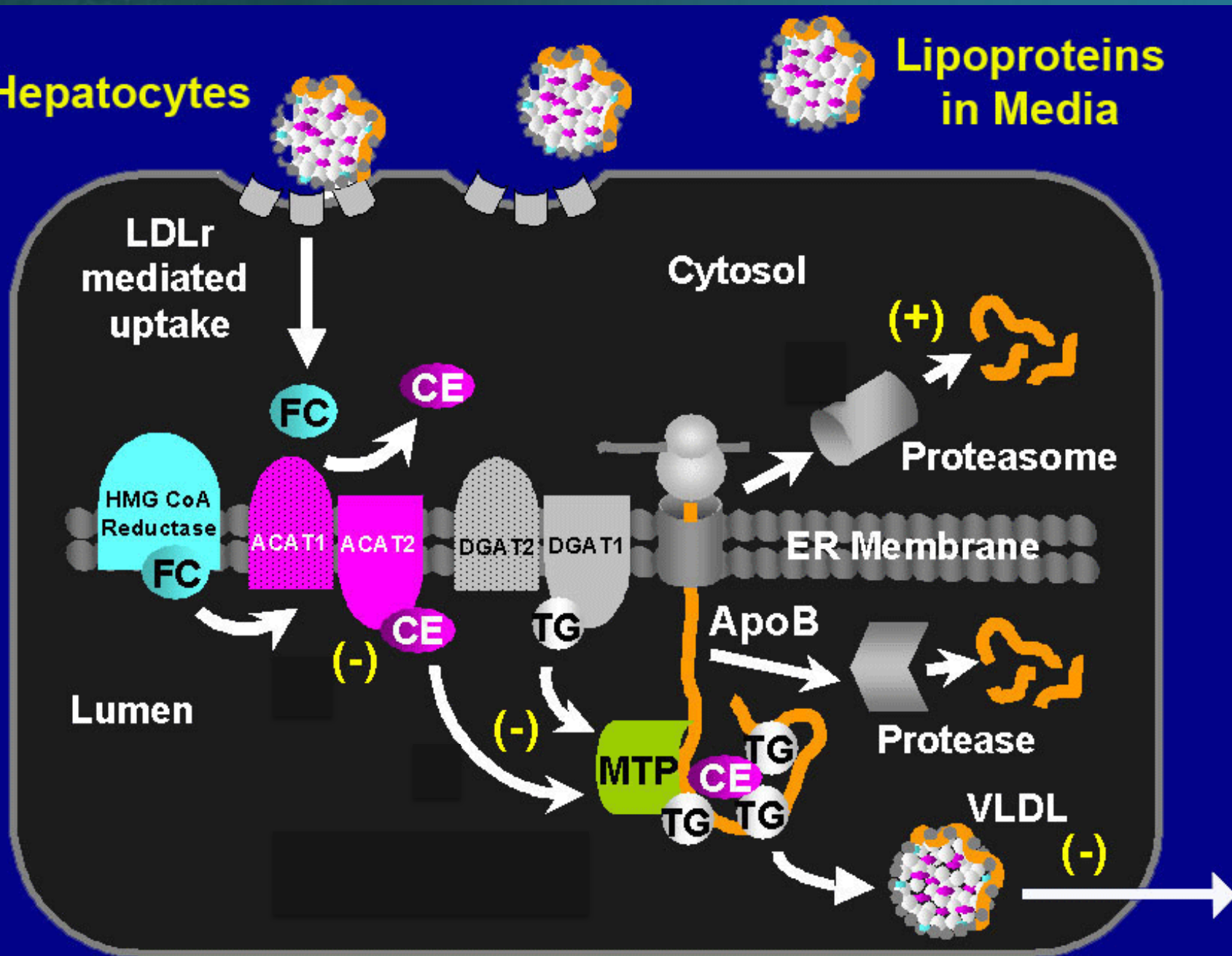
TG

TG

CE

TG

TG



Abetalipoproteinemia

- Rare disease
- LDL and very low-density lipoprotein (VLDL) are essentially *absent*.
- Characterized by fat malabsorption, spinocerebellar degeneration, acanthocytic red blood cells, and pigmented retinopathy.
- Homozygous autosomal recessive mutation in the gene for microsomal triglyceride transfer protein (MTP).
- MTP mediates intracellular lipid transport in the intestine and liver
- Ensures the normal function of chylomicrons (CMs) in enterocytes and of VLDL in hepatocytes.^[2]

Abetalipoproteinemia

- Affected infants may appear normal at birth, but by the first month of life, they develop steatorrhea, abdominal distention, and growth failure.
- Children develop retinitis pigmentosa and progressive ataxia,
 - Death usually occurring by the third decade.
- Early diagnosis, high-dose vitamin E (tocopherol) therapy, and medium-chain fatty acid dietary supplementation may slow the progression of the neurologic abnormalities.
- Obligate heterozygotes (ie, parents of patients with ABL) have no symptoms and no evidence of reduced plasma lipid levels.

Abetalipoproteinemia

- Clinical symptoms are the result of defects in the absorption and transport of vitamin E.
- Vitamin E transported from the intestine to the liver, where it is repackaged and incorporated into the assembling VLDL particle by the tocopherol-binding protein.
- In the circulation, VLDL is converted to LDL, and vitamin E is transported by LDL to peripheral tissues and delivered to cells via the LDL receptor.
- Patients with ABL are markedly deficient in vitamin E
- Most of the major clinical symptoms, especially those of the nervous system and retina, are primarily due to vitamin E deficiency.

Familial Hypobetalipoproteinemia

- Rare autosomal dominant disorder of apoB metabolism.
- Most cases of known origin result from mutations in the *APOB* gene, involving 1 or both alleles.
 - More than 30 mutations have been described.
- Mutations result in impaired synthesis of apoB-containing lipoproteins, or increased catabolism of these proteins.
- Heterozygotes may have LDL cholesterol levels less than or equal to 50 mg/dL, but they often remain asymptomatic and have normal life spans.
- In the homozygous state, the absence of apoB leads to significant impairment of intestinal CM formation and impaired absorption of fats, cholesterol, and fat-soluble vitamins.
- Leads to the development of degenerative neurologic disease.

Acquired Low LDL-C

■ Secondary causes

- Occult malignancy
- Malnutrition
- Liver disease
- Chronic alcoholism.
- These conditions must be excluded before the diagnosis of FHBL can be made.