# Marked LDL-C Reduction with Pharmacologic Agents: Potential Benefits and Safety Concerns

**Peter W. F. Wilson, MD**

**Atlanta VA Medical Center**

**Emory Clinical Cardiovascular Research Institute**

**Atlanta, GA**

# Outline

- Safety
  - Older LDL Lowering Medications
  - Safety Realms
  - FDA Lipid Medication Advisory
  - Newer LDL Lowering Medications
- Efficacy
  - LDL-C vs CVD Risk
  - Subclinical Outcomes
  - Clinical Trial Outcomes

# Cardiometabolic Safety Background

- Statins
  - Lovastatin
  - Cerivastatin
  - Simvastatin
- Fibrates
- Bile Acid Resins
- Niacin
- Cholesterol Absorption Inhibitors

# Low LDL-C
# Safety and Experience

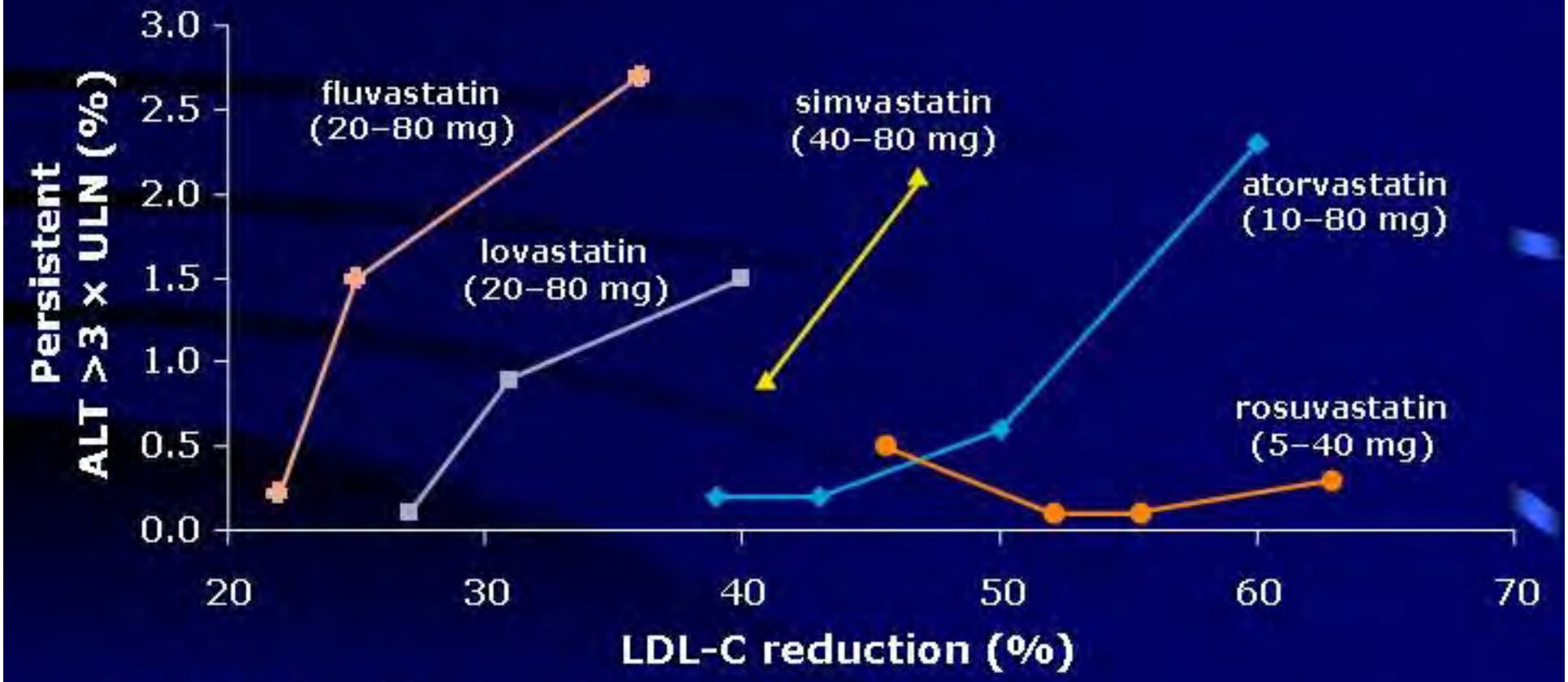
- Liver
- Muscle
- Kidney
- Glycemia
- Skin (injected meds)
- Immunologic
- Vitamin Deficiency
- Cognition
- Lab Accuracy
- Genetic low beta lipoprotein
- Others

# Muscle Adverse Events with Statin Therapy

| Muscle Adverse Events | Incidence |
|---|---|
| Myalgias | 0 to 10% |
| Myopathy (Symptoms + CK elevation) | ~ 1 % |
| Rhabdomyolysis | Less than 1/500 |

# Statin Benefit: Risk - Liver Effects

## Persistent ALT* >3× ULN: Frequency by LDL-C Reduction

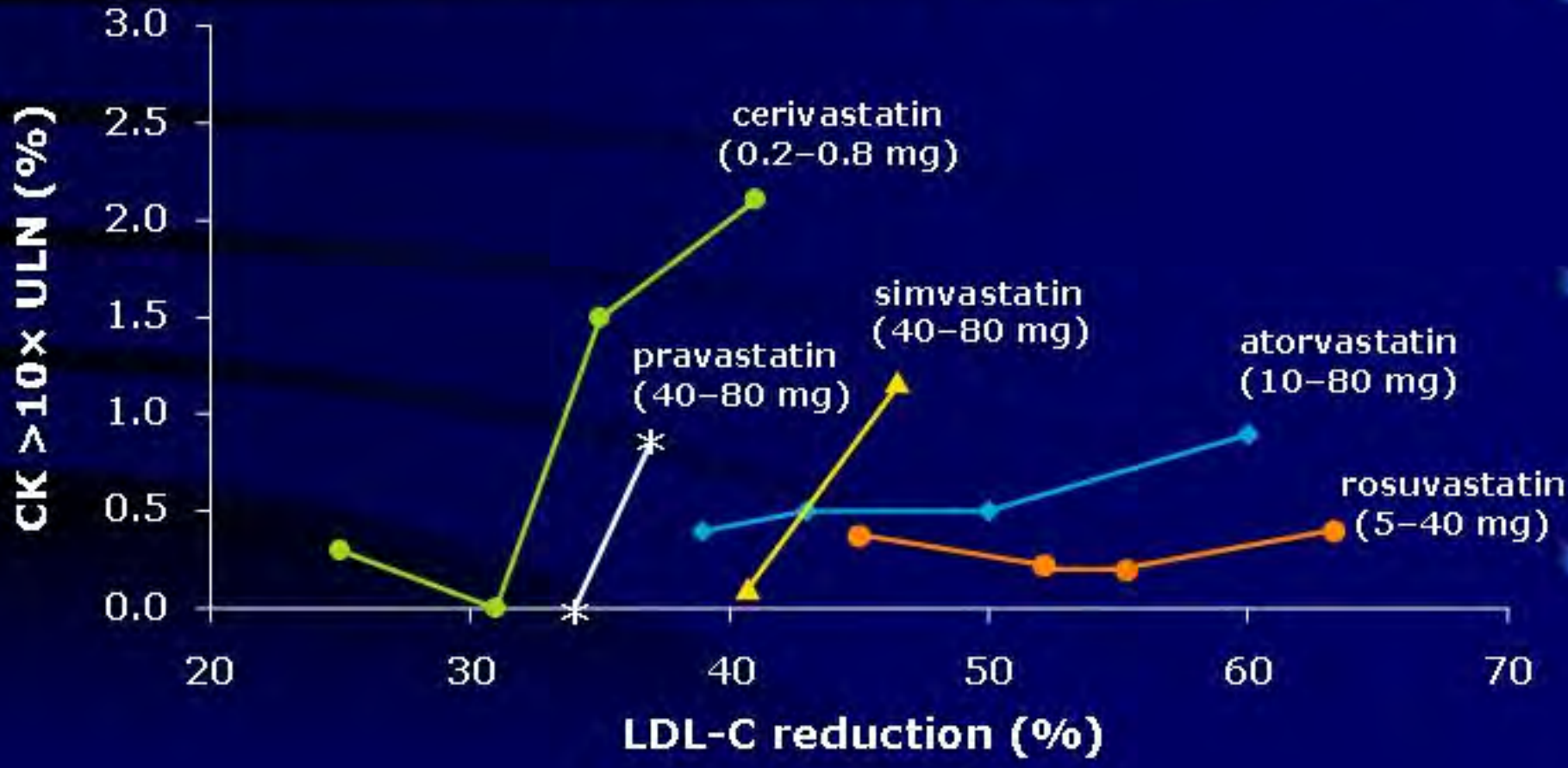



*Elevation to >3 x ULN on 2 successive occasions

Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K;
Davidson M, Exp Opin Drug Saf 2004;3(6:547–557)

# Rosuvastatin Tolerability and Safety – Muscle Effects

## CK >10x ULN: Frequency by LDL-C Reduction




Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K;
Davidson M, Exp Opin Drug Saf 2004;3(6:547–557)

# Simvastatin Warnings

- Do not use Simvastatin 80 mg/day
  - Unless > 12 months without side effects
- Do not exceed 10 mg simvastatin daily

  Verapamil

  Diltiazem
- Do not exceed 20 mg simvastatin daily

  Amlodipine

  Ranolazine

  Amlodipine
- Caution Simva + Niacin (> 1gm/d) in Chinese

# Statins and Incident Diabetes Meta-Analysis

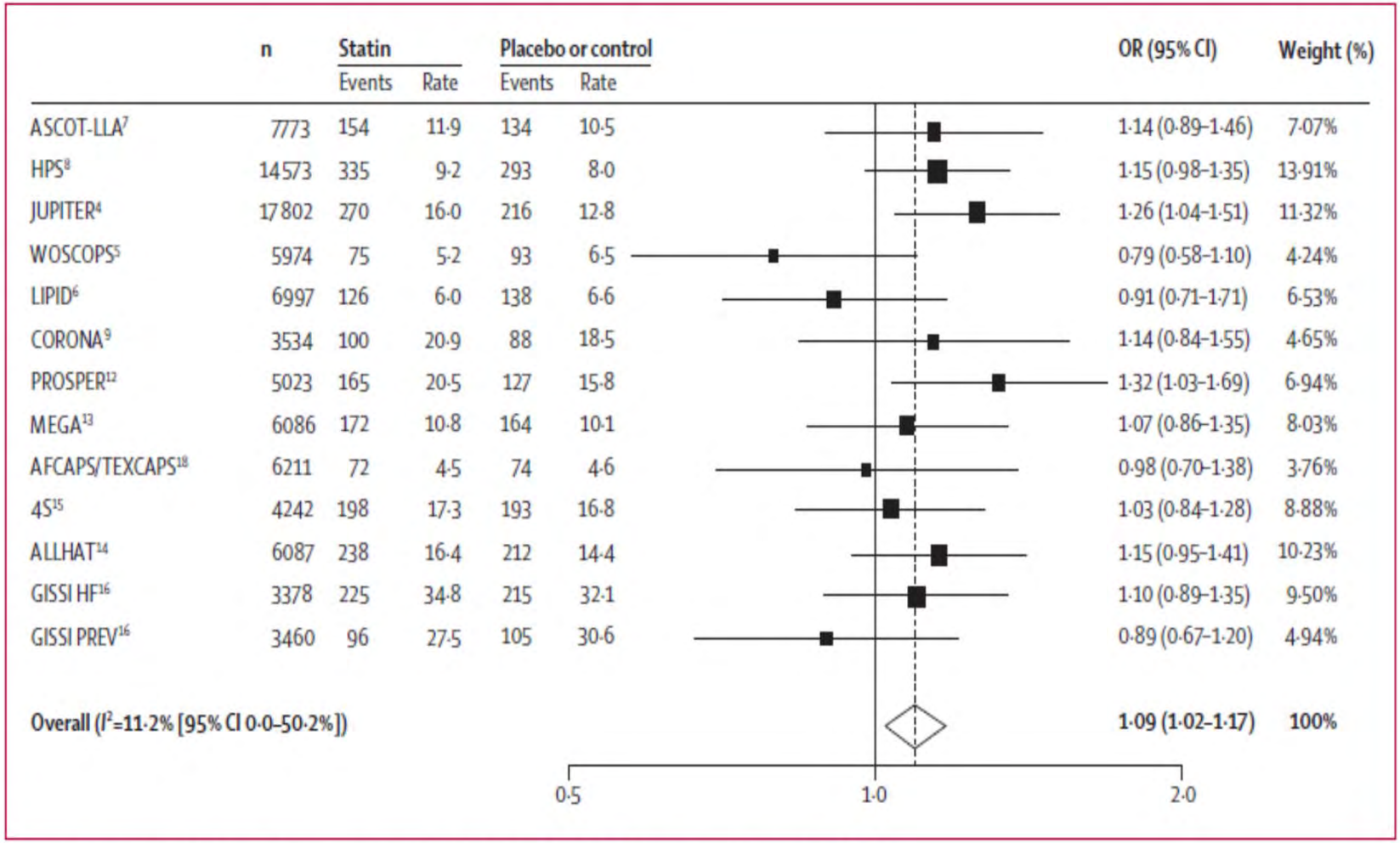
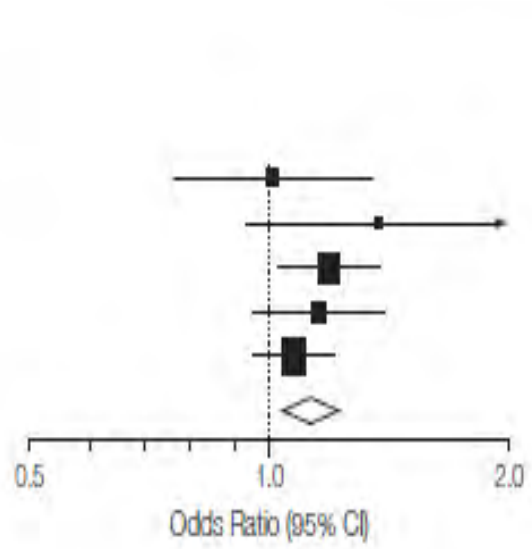


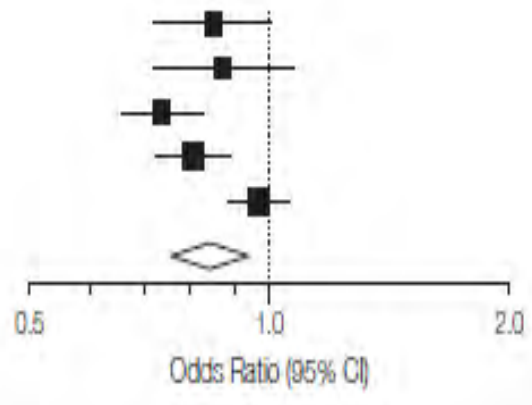

*Figure 2:* Association between statin therapy and incident diabetes in 13 major cardiovascular trials†

Sattar Lancet 2011; 375: 735

# Incident Diabetes and CVD Relative Risk According to Statin Potency

| | Cases/Total, No. (%) | | |
|---|---|---|---|
| | Intensive Dose | Moderate Dose | OR (95% CI) |
| **Incident Diabetes** | | | |
| PROVE IT–TIMI 22,[18] 2004 | 101/1707 (5.9) | 99/1688 (5.9) | 1.01 (0.76-1.34) |
| A to Z,[17] 2004 | 65/1768 (3.7) | 47/1736 (2.7) | 1.37 (0.94-2.01) |
| TNT,[15] 2005 | 418/3798 (11.0) | 358/3797 (9.4) | 1.19 (1.02-1.38) |
| IDEAL,[16] 2005 | 240/3737 (6.4) | 209/3724 (5.6) | 1.15 (0.95-1.40) |
| SEARCH,[5] 2010 | 625/5398 (11.6) | 587/5399 (10.9) | 1.07 (0.95-1.21) |
| Pooled odds ratio | 1449/16408 (8.8) | 1300/16344 (8.0) | 1.12 (1.04-1.22) |
| Heterogeneity: $I^2$=0%; $P$=.60 | | | |
| **Incident CVD** | | | |
| PROVE IT–TIMI 22,[18] 2004 | 315/1707 (18.4) | 355/1688 (21.0) | 0.85 (0.72-1.01) |
| A to Z,[17] 2004 | 212/1768 (12.0) | 234/1736 (13.5) | 0.87 (0.72-1.07) |
| TNT,[15] 2005 | 647/3798 (17.0) | 830/3797 (21.9) | 0.73 (0.65-0.82) |
| IDEAL,[16] 2005 | 776/3737 (20.8) | 917/3724 (24.6) | 0.80 (0.72-0.89) |
| SEARCH,[5] 2010 | 1184/5398 (21.9) | 1214/5399 (22.5) | 0.97 (0.88-1.06) |
| Pooled odds ratio | 3134/16408 (19.1) | 3550/16344 (21.7) | 0.84 (0.75-0.94) |
| Heterogeneity: $I^2$=74%; $P$=.004 | | | |




**Preiss JAMA 2011; 305: 2556**

# Statin Safety Summary

- **Liver Function abnormal**
  - 0.5 % > 3x ULN—assess patient
- **Muscle**
  - Myalgia (5% -15%)—consider non statin causes
  - Myositis (<1%, myalgias, CK >5X to 10 X ULN)
  - Rhabdomyolysis (0.2%, CK>10 X ULN)
    - Serum creatinine, urine for myoglobin, IV fluids
- **Blood glucose increase**
  - Diabetes risk outweighed by CVD benefit
  - Metabolic syndrome factors very important
- **Memory loss**
  - Not well substantiated for statin users

# FDA Guidance to Industry Developing Drugs for Diabetes Treatment and Prevention

"The objective of lipid-altering therapy is not merely to alter serum lipids  but to dminish the morbidity and mortality from cardiovascular disease and/or pancreatitis that is associated with abnormal serum lipid levels"

" Lipid altering agents should be shown to have a relatively low incidence of adverse effects priorto approval for marketing."

Psaty JAMA 2008; 299: 1474

http://www.fda.gov//cder/guidance/lipid.pdf

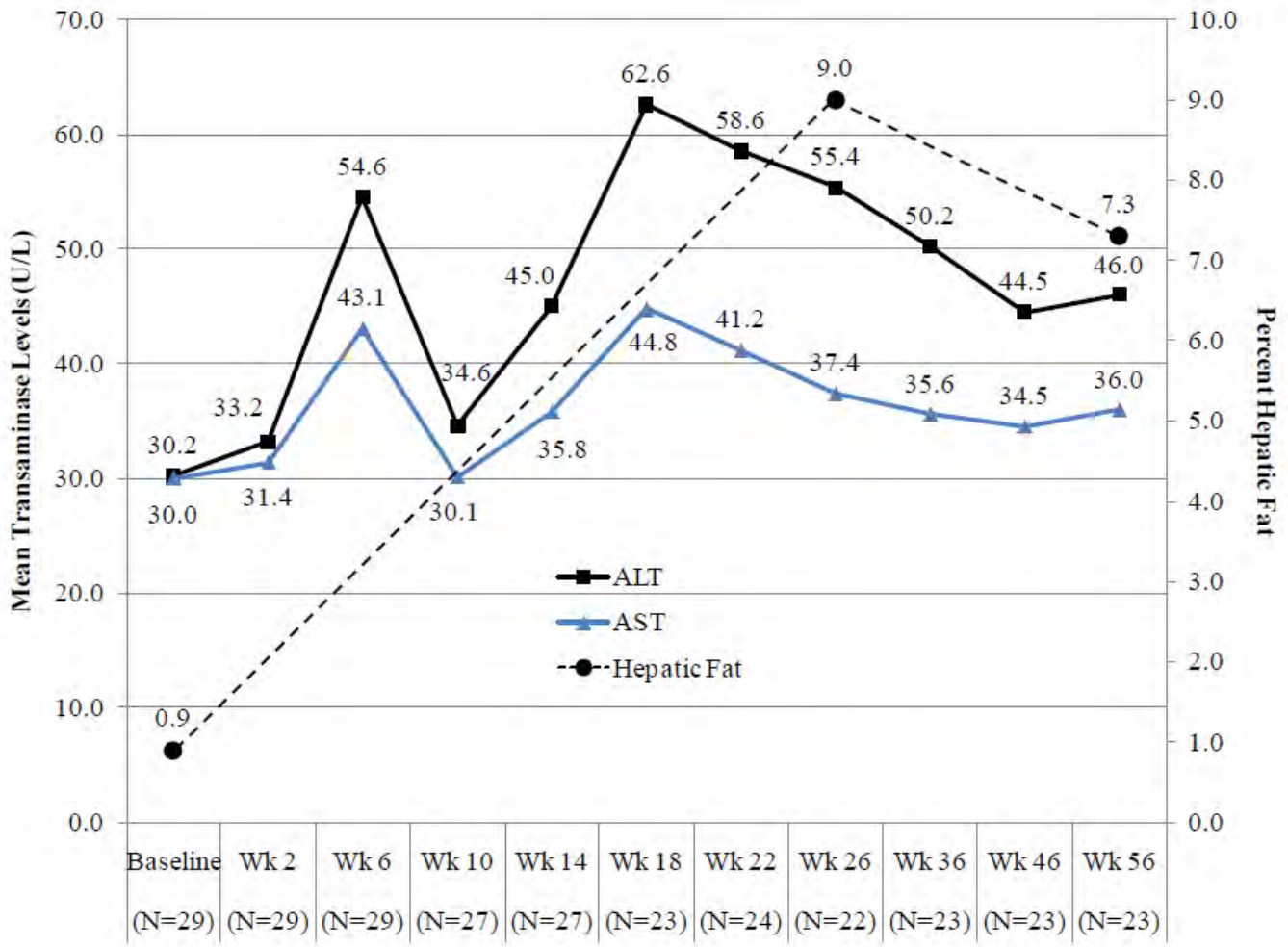
# CETP Safety

- Torcetrapib
  - BP increase 4 mm Hg
  - Hyperaldosteronism in some patients
  - Harm in clinical trial (ILLUMINATE)
- Dalcetrapib
  - Clinical outcomes trial no benefit (DALOUTCOMES)
- Anacetrapib

# Lomitapide Safety

- Liver Function Test Abnormalities
- Hepatic Steatosis

# ALT, AST and Hepatic Fat
# Lomitapide Therapy in Homozygous FH

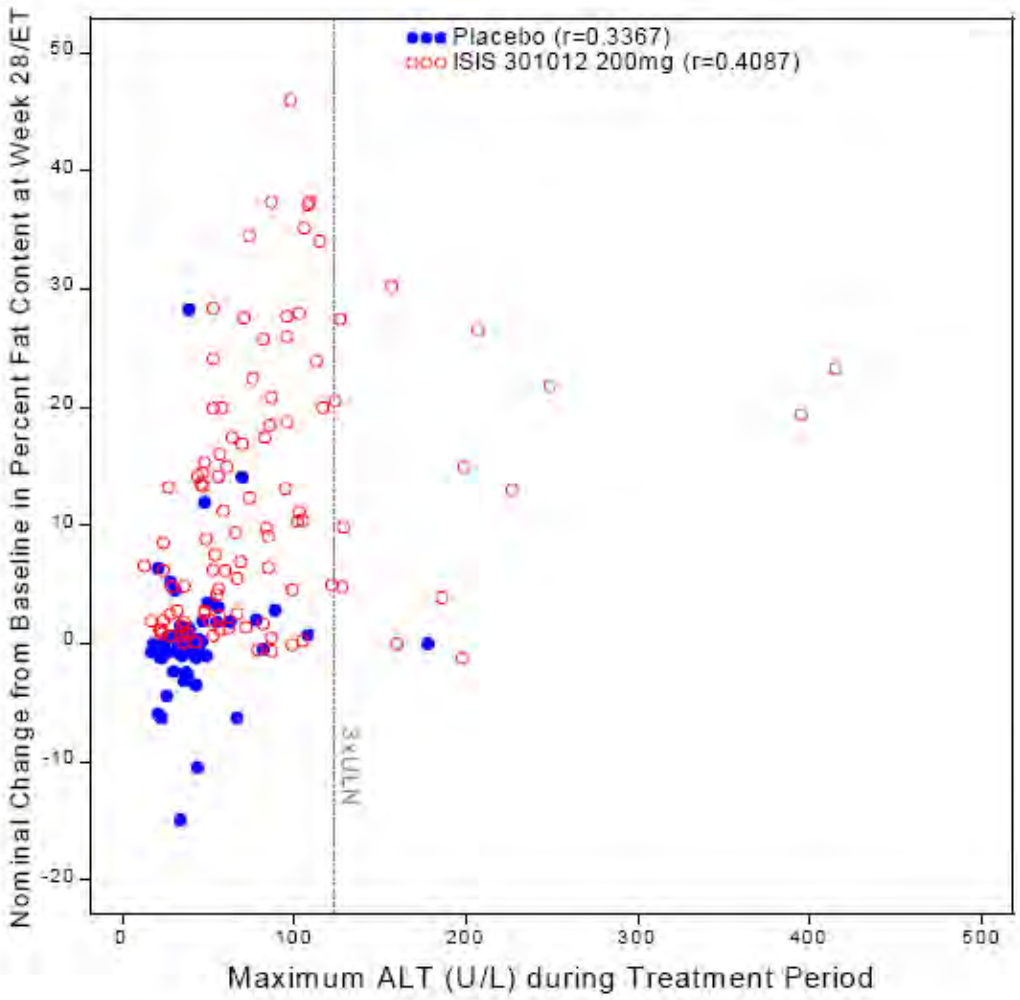



http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EMDAC/UCM323841.pdf

# Mipomersen Safety

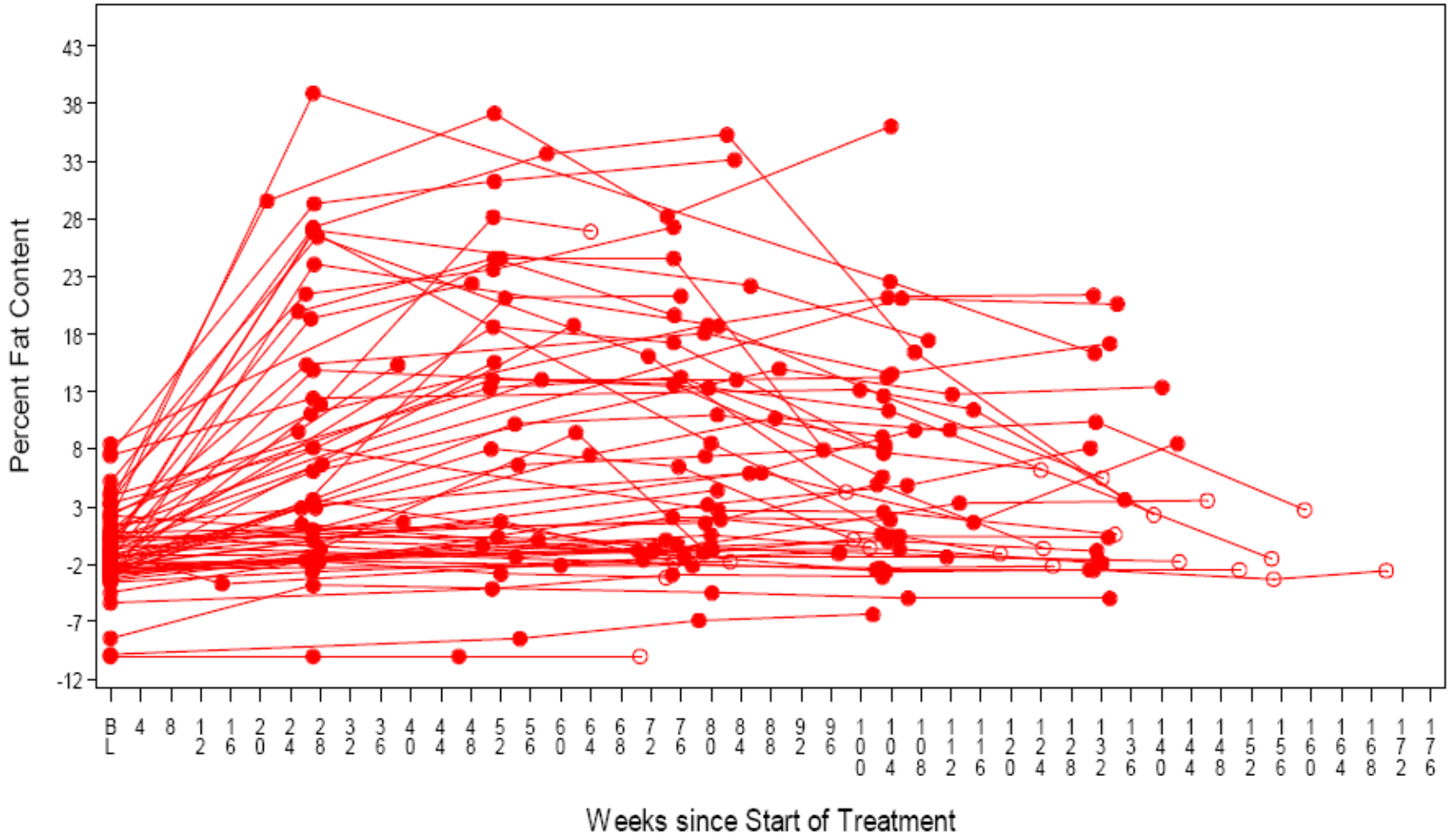
- Liver Function Test Abnormalities
- Hepatic Steatosis
- Injection site reactions
- Immunity

# ALT Change and Mipomersen Therapy 12 Months or Longer




http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EMDAC/UCM323927.pdf

# Liver Fat Content and Mipomersen Therapy 12 Months or Longer

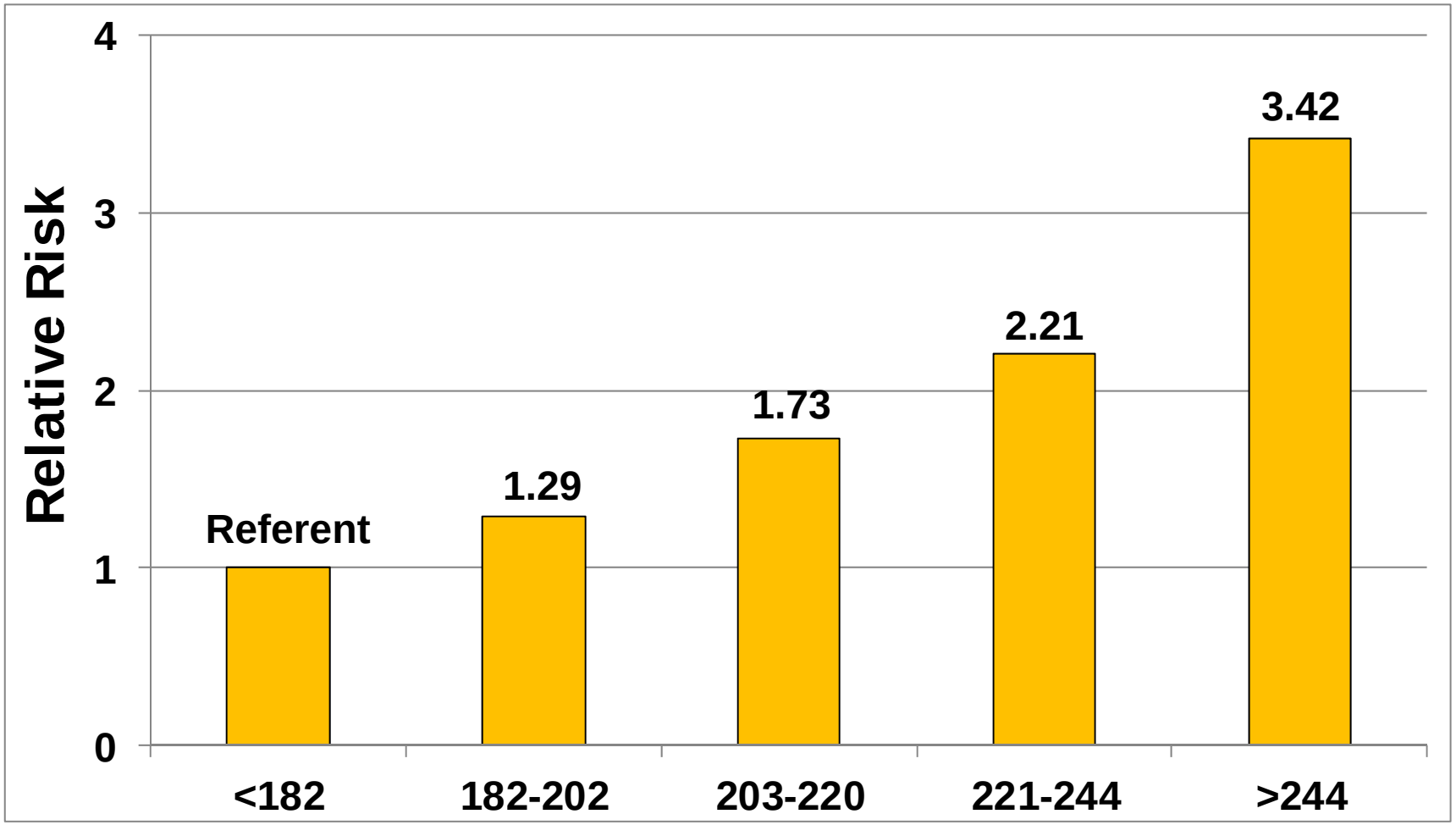



http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EMDAC/UCM323927.pdf

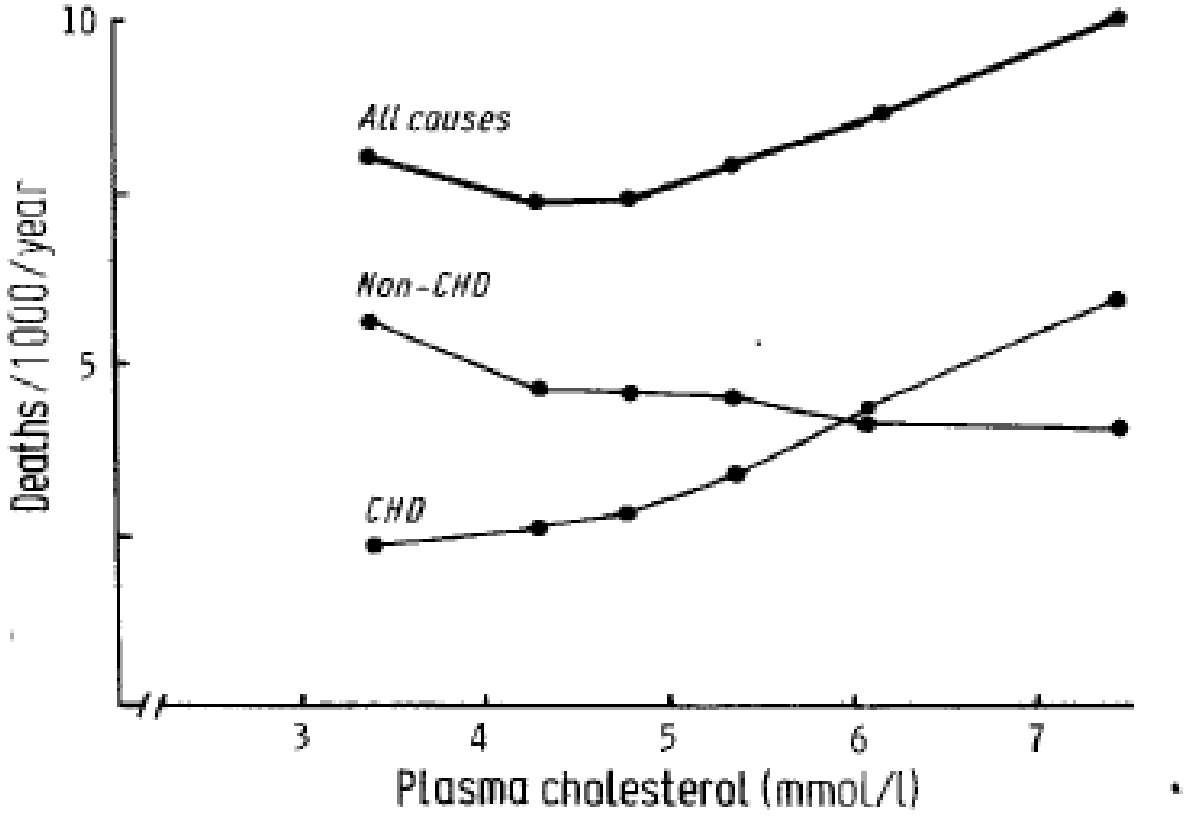
# LDL-C Level and CVD Risk

- LDL-C to CVD risk relationship
- Relative Risk Reduction
- Number needed to treat (NNT)
- Cost per event prevented

# Serum Cholesterol and CHD Death
# MRFIT Screenees

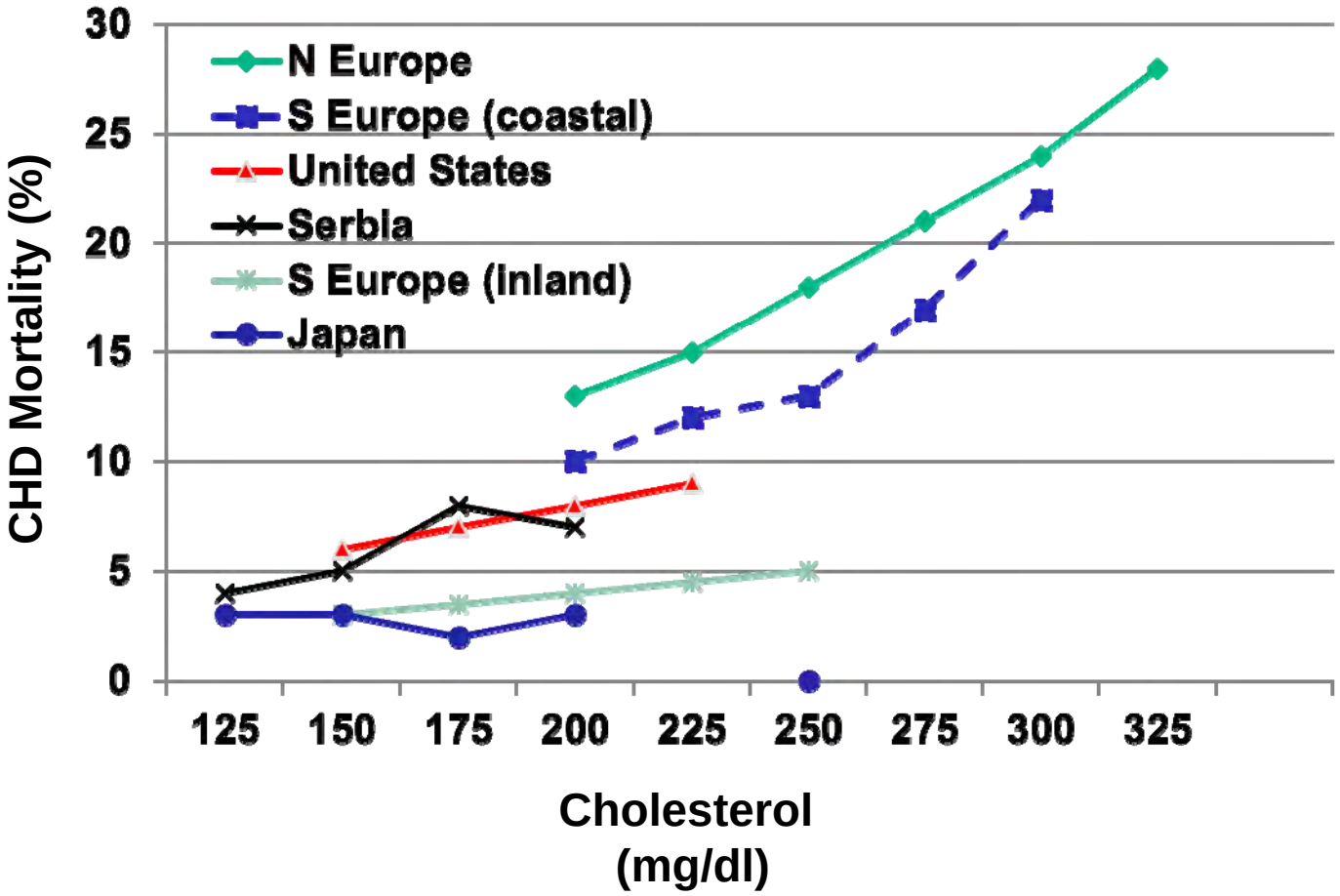


# Cholesterol Level and Mortality
# 17,718 Whitehall Study Men 40-64 Years



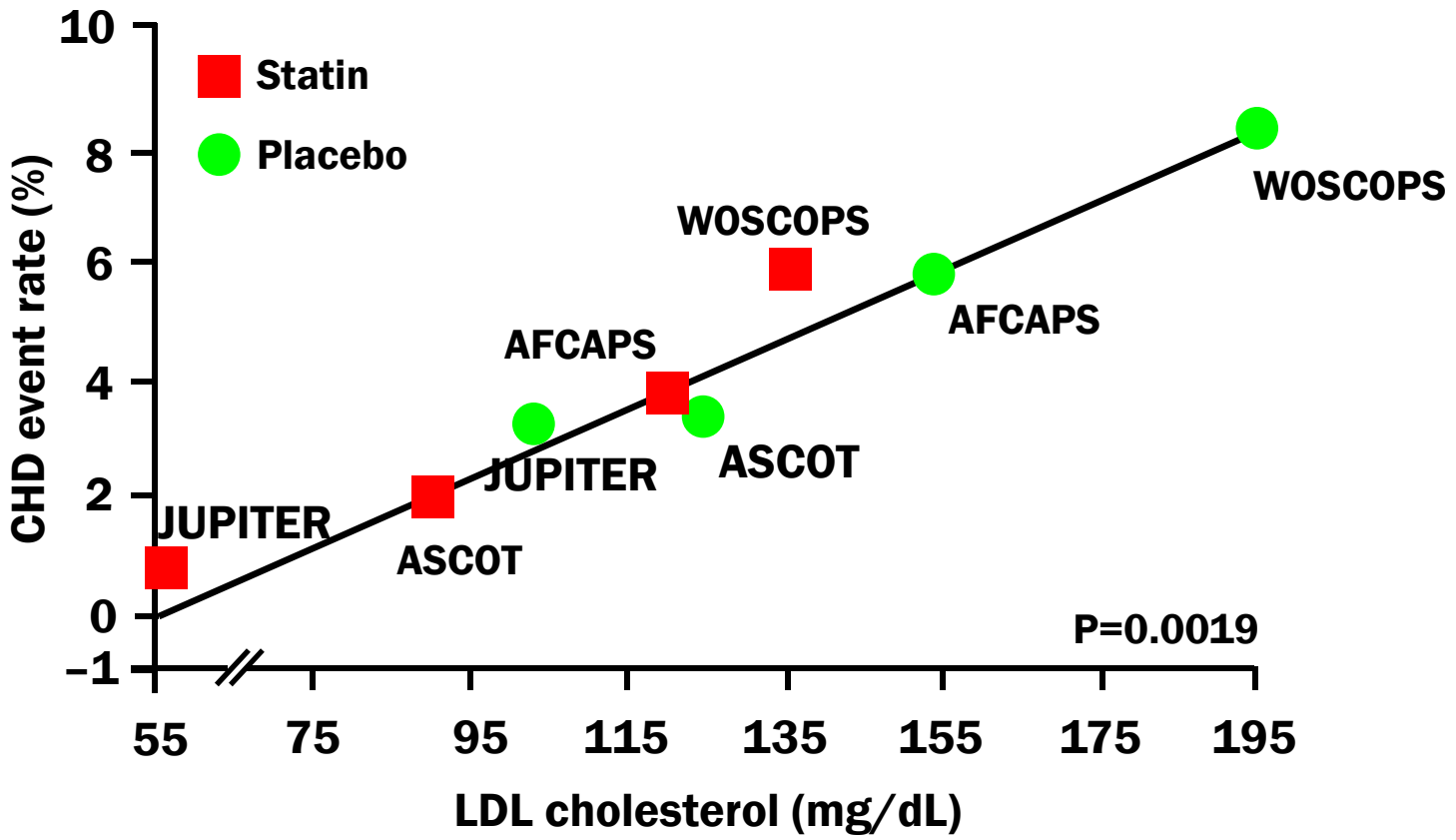

**Rose Lancet 1980; p523**

# 25 Year CHD Mortality in 12,467 Men age 40-59 yr
# 7 Countries Study




Verschuren JAMA 1995; 275: 131

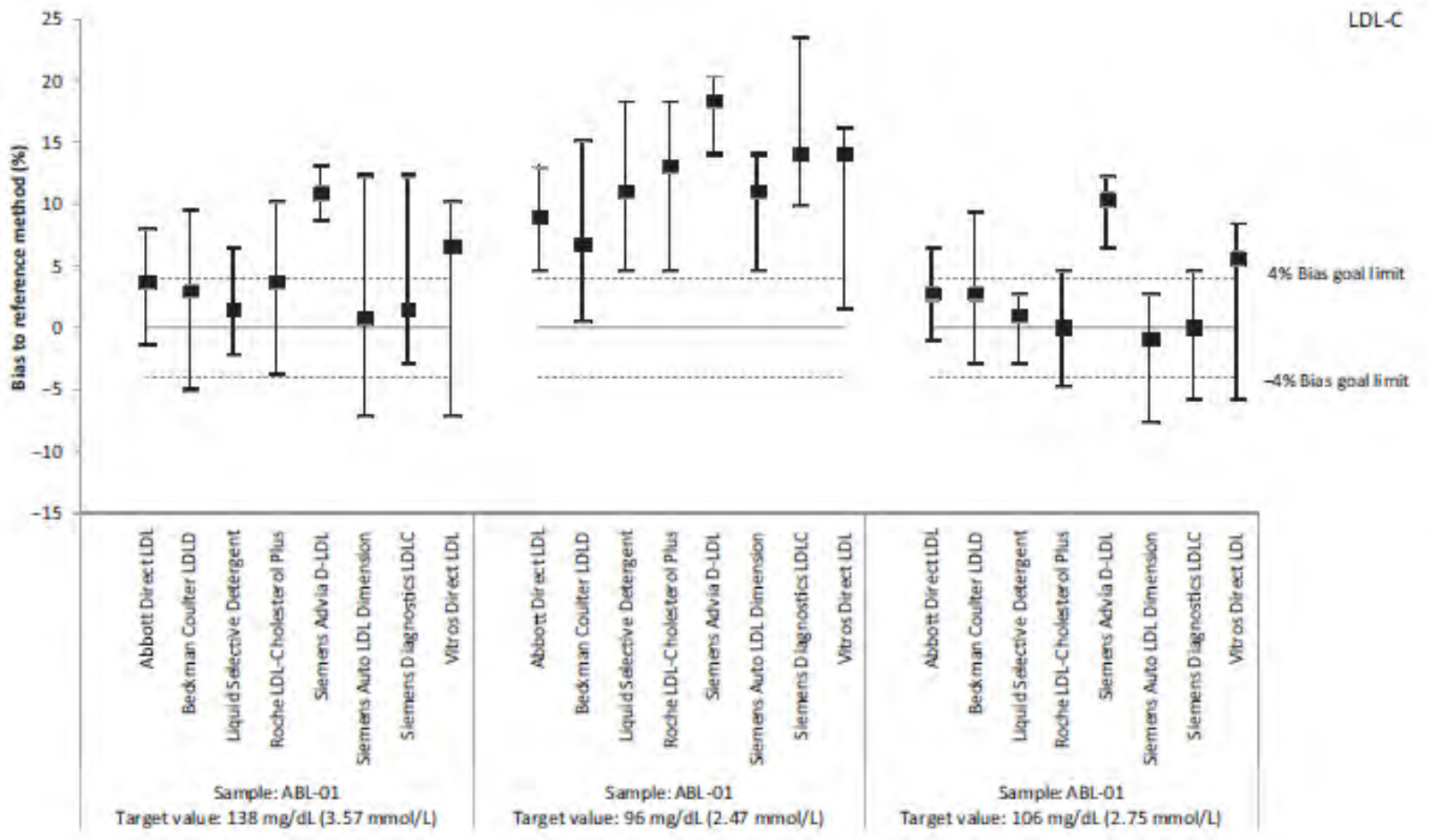
# HMG-CoA Reductase Inhibitor Evidence: Primary Prevention and LDL-C on Therapy




AFCAPS= Air Force/Texas Coronary Atherosclerosis Prevention Study, ASCOT= Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm, LDL-C=Low density lipoprotein cholesterol, WOSCOPS= West of Scotland Coronary Prevention Study

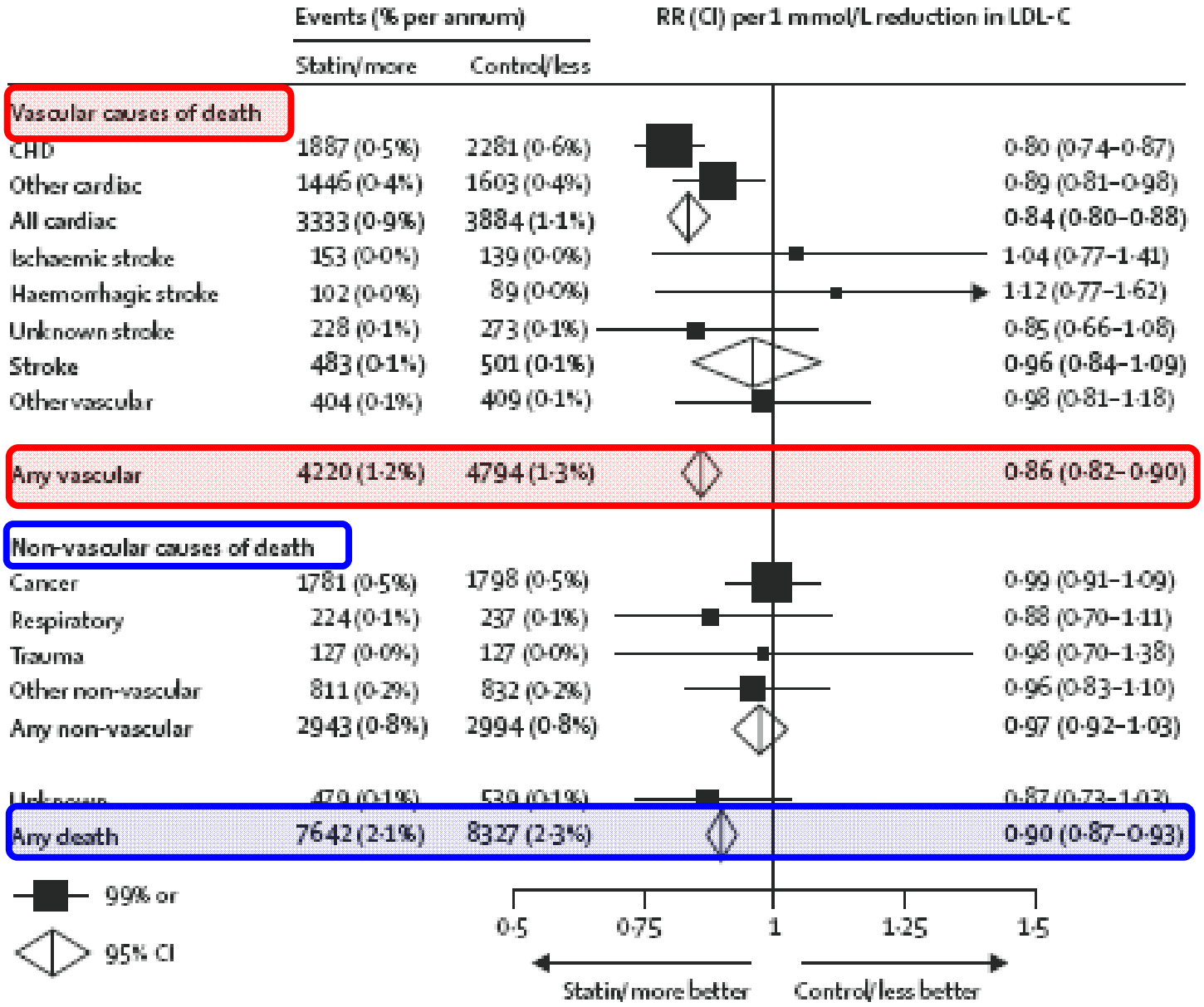
O'Keefe JH Jr et al. *JACC* 2004;43:2142-2146 and Ridker N Engl Med 2008

# LDL-C Bias and Error
# College of American Pathology Survey



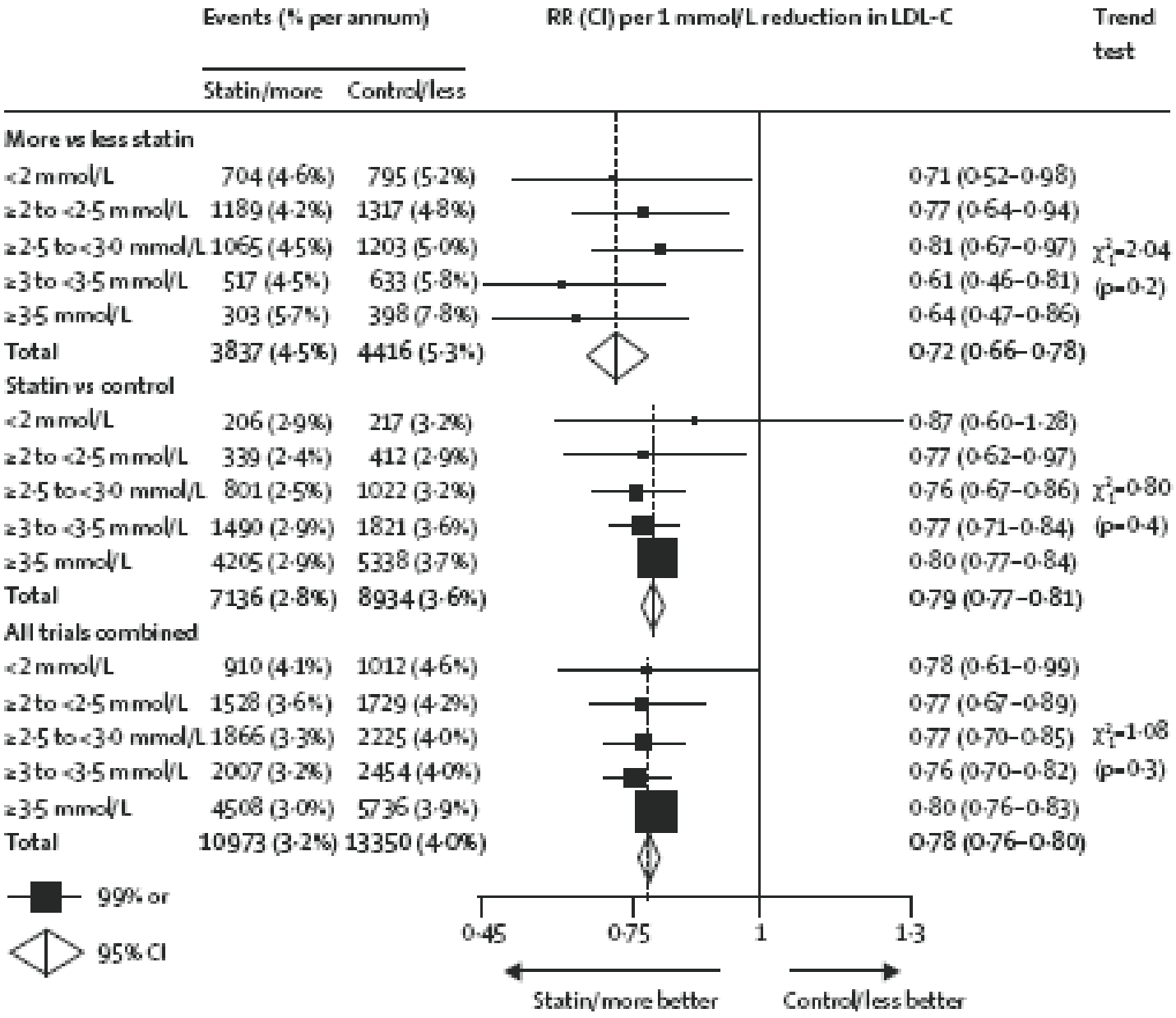

**Vesper Clin Chem 2012; 58: 523**

# CTT Meta-Analysis 2010: ↓1 mmol/L LDLc and Mortality




CTT : Lancet 2010; 376: 1670

# CTT Meta-Analysis 2010: ↓1 mmol/L CVD Effect by Baseline LDL-C

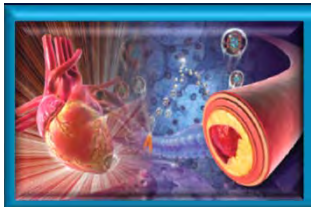



CTT : Lancet 2010; 376: 1670

# LDL-C Lowering, NNT and CVD Prevention Costs

| Study | Therapy | Time (yrs) | Relative Risk | Absolute Risk Difference | NNT | 2016 Rx Cost ($) | Annual Cost Per Event Prevented ($) |
|---|---|---|---|---|---|---|---|
| WOSCOPS (1º Prevent) | Pravastatin vs Placebo | 4.8 | 0.69 | 2.4% | 42 | 50 | 2,083 |
| TNT (2º Prevent) | Hi Atorva vs Lo Atorva | 5.0 | 0.78 | 2.2% | 45 | 50 | 2,273 |
| IMPROVE-IT (High risk) | Statin + Ezetimibe vs Statin | 7.0 | 0.94 | 2.0% | 50 | 1000 | 50,000 |
| ODYSSEY (HeFH) | Statin + Amab vs Statin | 1.5 | 0.52 | 1.6% | 63 | 12,000 | 756,000 |
| OSLER (HeFH) | Statin + Emab vs Statin | 1.0 | 0.47 | 0.012 | 81 | 12,000 | 972,000 |

***Ezetimibe cost $1000/yr, PCSK9 cost $12,000/yr**

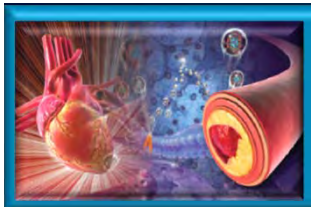


National Lipid Association's
Clinical Lipid Update

# Update on PCSK9 Inhibition: *How will approval change clinical lipidology?*

Pittsburg, PA
Sept 18, 2015

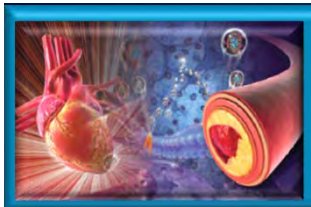
**James M. McKenney, PharmD**
President and CEO, National Clinical Research, Inc.
Professor Emeritus, Virginia Commonwealth University
Richmond, VA



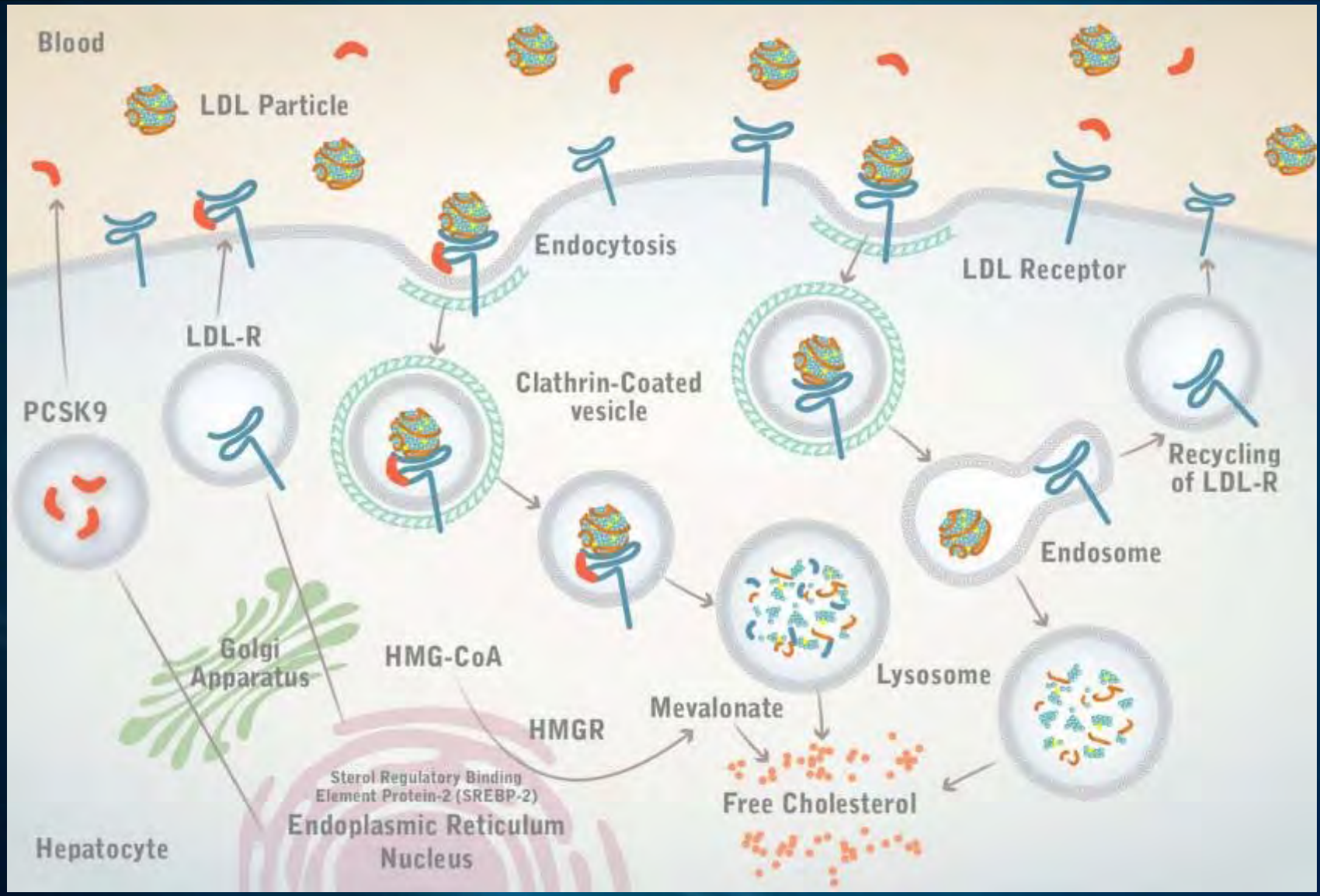
# PCSK9 Inhibitors in Development

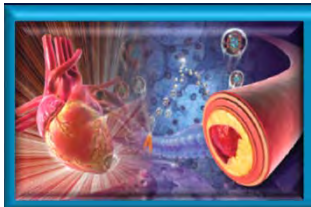
| Investigational Products | Company | Stage of Development |
|---|---|---|
| **Monoclonal Antibodies** | | |
| Alirocumab (Praluent) | Sanofi Regeneron | Approved |
| Evolocumab (Repatha) | Amgen | Approved |
| Bococizumab (PF0490615, RN316) | Pfizer Rinat | Phase III |
| LY3015014 | Lilly | Phase II – on hold |
| **Other PCSK9 biologics** | | |
| ALN-PCS (siRNA) | Alnylam, The Medicines Co | Phase I |
| Peptide-based vaccines | Affiris AG | Preclinical |

Clinicaltrials.gov

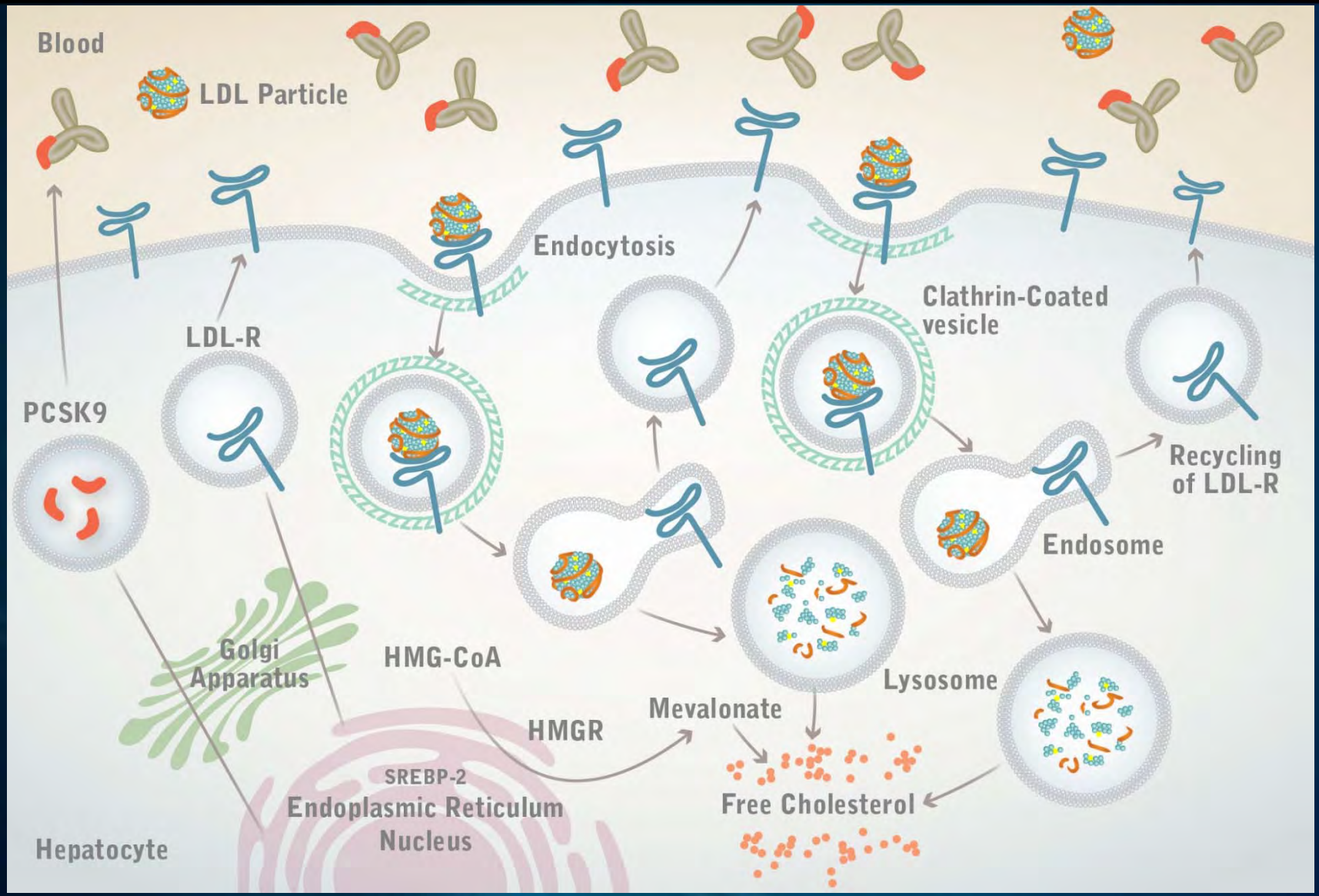


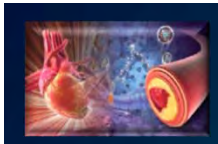
# The Interplay Between LDL-C, Hepatocyte Cholesterol Synthesis, LDL-R, and PCSK9





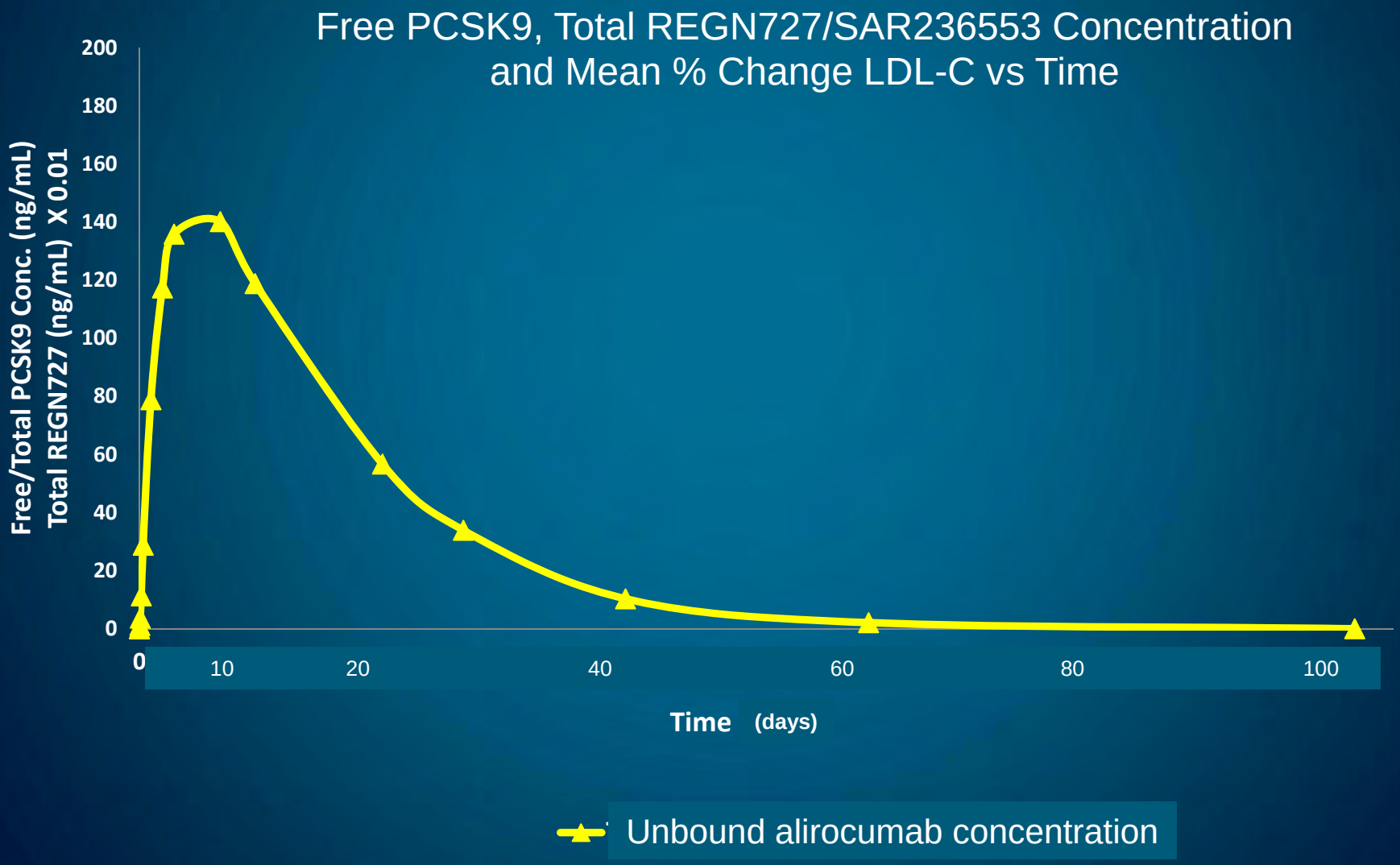
# The Impact of PSK9 mAb on LDL-C

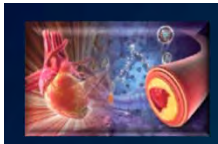




# ALIROCUMAB 150 mg SC

## Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C





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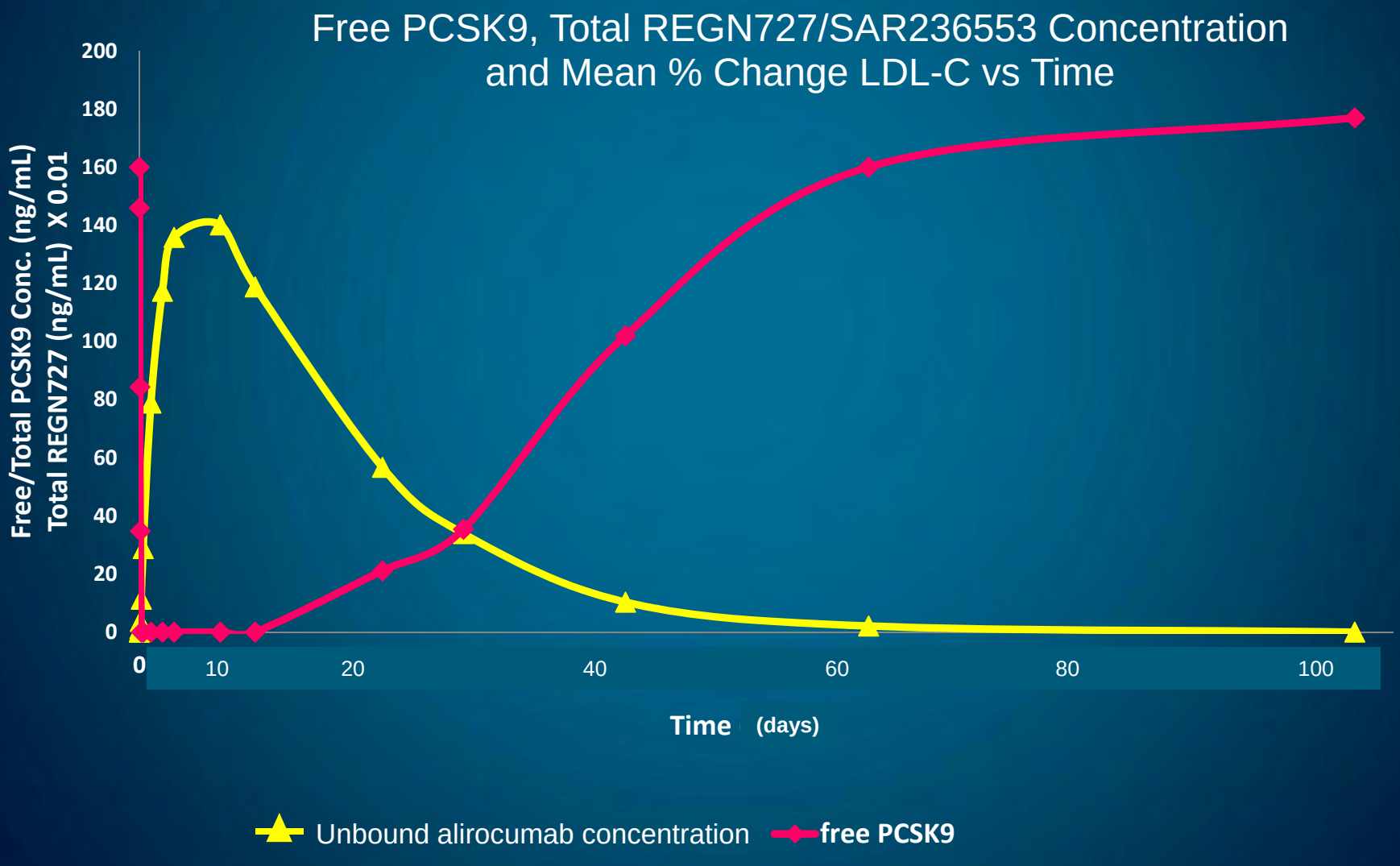

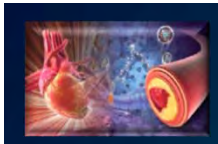

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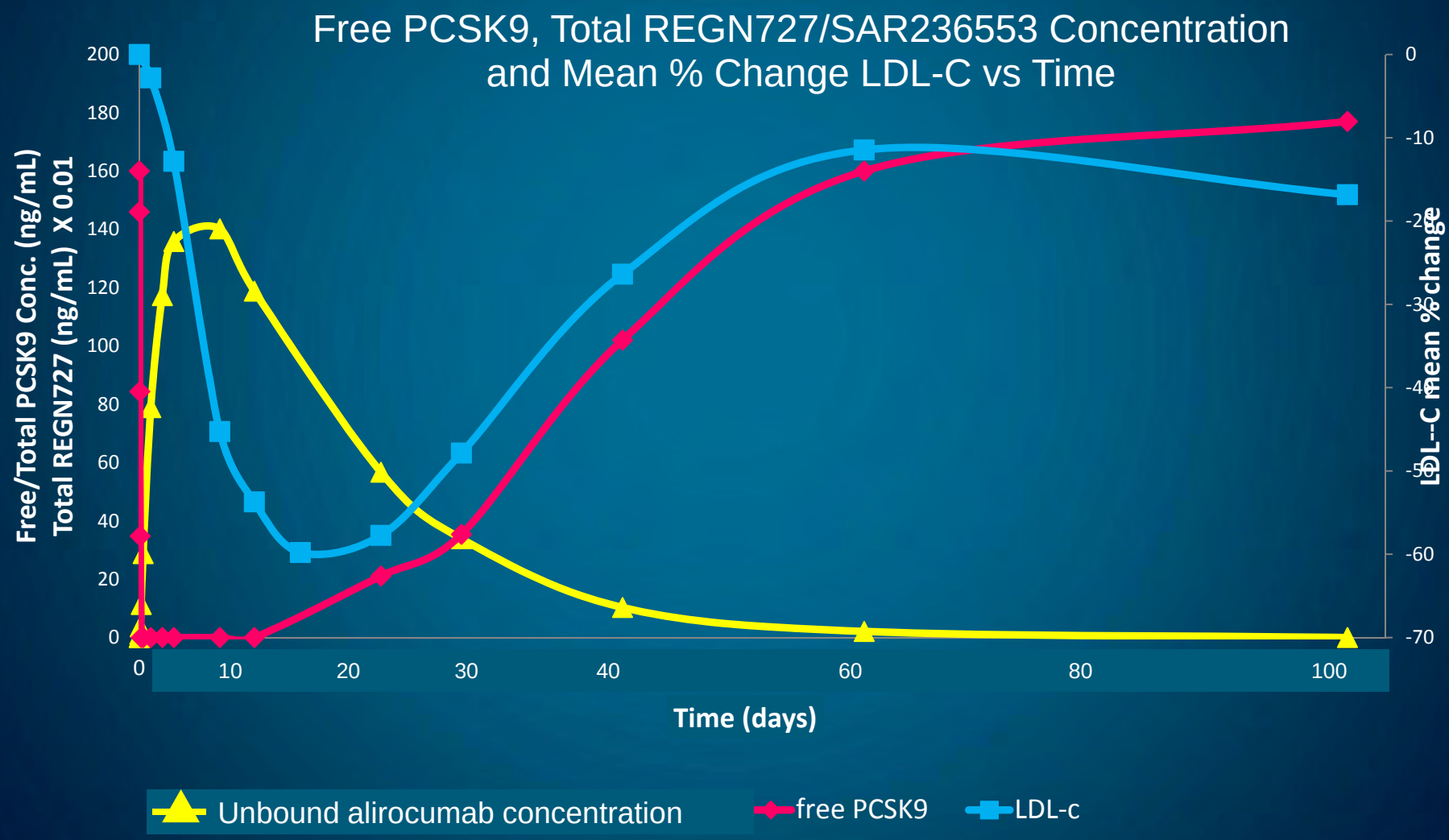
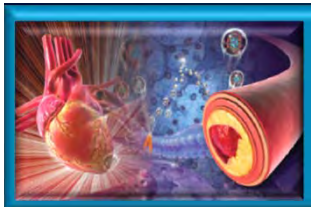




# Mean % Δ in LDL-C (Placebo Adjusted) from Baseline to Week 12 With PCSK9 mAb on a Stable Statin Dose

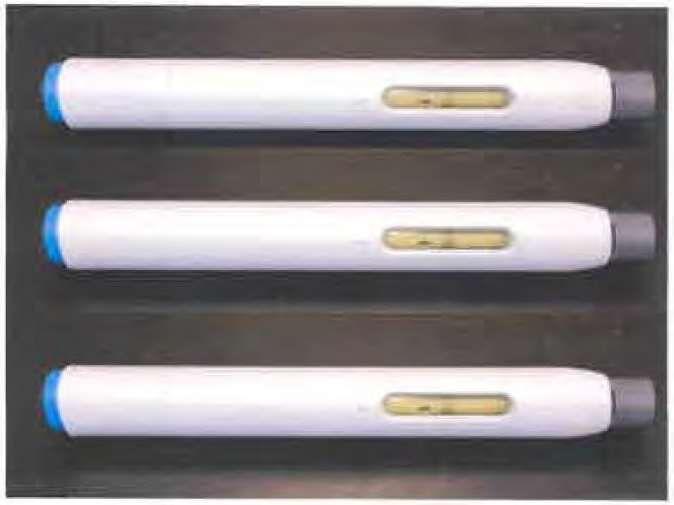
| Intervention<br>mAb added to stable atorva dose of 10-40 mg QD with LDL-C ≥ 100 mg/dL<br>n=183, Duration = 12 wks | % Change LDL-C | Intervention<br>mAb added to stable statin and LDL-C > ~85 mg/dL<br>n=631, Duration = 12 wks | % Change LDL-C |
|---|---|---|---|
| Alirocumab 50 mg Q2W | -35% | Evolocumab 70 mg Q2W | -42% |
| Alirocumab 75 mg Q2W | ≈50% | | |
| Alirocumab 100 mg Q2W | -59% | Evolocumab 105 mg Q2W | -60% |
| Alirocumab 150 mg Q2W | -67% | Evolocumab 140 mg Q2W | -66% |
| Alirocumab 200 mg Q4W | -38% | | |
| Alirocumab 300 mg Q4W | -43% | Evolocumab 280 mg Q4W | -42% |
| | | Evolocumab 350 mg Q4W | -50% |
| | | Evolocumab 420 mg Q4W | -50% |

McKenney et al. JACC 2012;59 2344-2353

Giugliano et al. Lancet 2012; 380: 2007-17

# Administration of Q2W and Q4W mAb

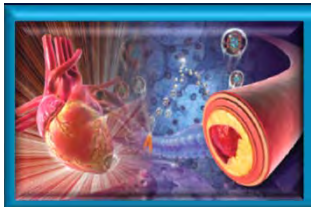
Evolocumab 420 mg SC
3 x 1ml 140 mg SC autoinjections



Alirocumab 75 mg and 150 mg SC
Evolocumab 140 mg SC

**OR**
1 x 3.5 ml (120 mg/ml) autoinjection

27 g needle



# Mean % Δ in LDL-C From Baseline to End of Study With PCSK9 mAbs on a Stable Statin Dose

Alirocumab and atorva 80 uptitration was given to randomized patients who were receiving a stable atorva 10 mg QD regimen and had a LDL-C ≥ 100 mg/dL

| **Intervention**<br>**8 wks, n=92**<br>**Baseline LDL-C = 122 mg/dL** | **% Change LDL-C** |
|---|---|
| Atorvastatin 80 mg QD | -17% |
| Atorvastatin 10 mg QD + Alirocumab 150 mg Q2W | -66% |
| Atorvastatin 80 mg QD + Alirocumab 150 mg Q2W | -73% |

7%

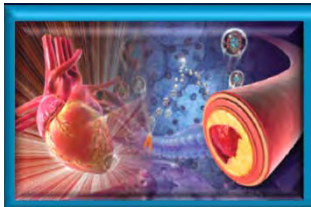
Evolocumab was added to a stable diet or atorvastatin regimen (4 to 12 wks) in patients with LDL-C ≥ 75 mg/dL.

| **Intervention**<br>**52 wks, n=901**<br>**Baseline LDL-C = 104 mg/dL** | **% Change LDL-C** |
|---|---|
| Lifestyle only<br>Evolocumab 420 mg Q4W | -56% |
| Atorvastatin 10 mg QD +<br>Evolocumab 420 mg Q4W | -62% |
| Atorvastatin 80 mg QD +<br>Evolocumab 420 mg Q4W | -57% |
| Atorvastatin 80 mg QD +<br>Ezetimibe 10 mg QD +<br>Evolocumab 420 mg Q4W | -49% |

5%

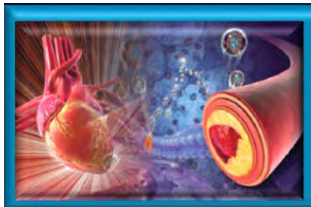
Roth et al. NEJM 2012;367: 1891-1900

Blom et al. NEJM 2014; 370: 1809-19



# Summary

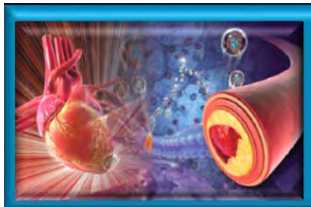
- Max dose PCSK9 mAb can suppress PCSK9 activity completely for 10-14 days.
- Max dose PCSK9 mAb reduces LDL-C 50-60% when added to a statin.
- Tripling the Q2W dose reduces LDL-C 50-60% with QM dosing.
- PCSK9 mAb has an additive LDL-C lowering with a statin. Tripling the statin dose with PCSK9 mAb lowers LDL-C only 5-7% additionally.
- Alirocumab and evolocumab have similar efficacies. What is different is their administration regimens:
  - max dose Q2W or QM (evolocumab)
  - starting dose and an up-titration dose (alirocumab)



# Patient Populations Evaluated for PCSK9 mAb Therapy in Phase III Development

- Patients with familial hypercholesterolemia
- Patients with high CVD risk and not at desirable LDL-C with max dose statin
- Patients intolerant to statin therapy
- Patients receiving monotherapy

Clintrials.gov (4/1/15)



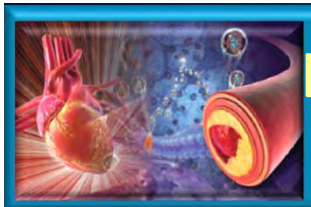
# Homozygous FH Patients

## Mean % in LDL-C from Baseline to Week 12 With Evolocumab

Randomized, double-blind, placebo-controlled trial involving 50 pts with homozygous FH on stable lipid-regulating therapy were randomly allocated to evolocumab or placebo for 12 weeks.

| **Patients**<br>**Mean age 31**<br>**CHD = 38%**<br>**Rx: high intensity statin + ezetimibe (no aphresis)**<br>**Mean baseline LDL-C = 349 mg/dL** | **Evolocumab 420 mg Q4W** | **Difference** |
|---|---|---|
| **All subjects (50)** | **-30.9%** | **<0.0001** |
| **Receptor defective/defective (n=5)** | **-46.9** | **0.0006** |
| **Receptor defective/negative (N=3)** | **-24.5%** | **0.0128** |
| **Receptor negative/negative (n=1)** | **10.3%** | **NA** |

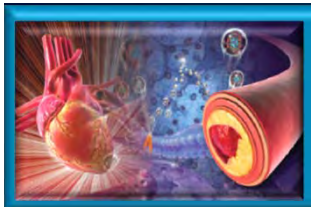
**Raal et al** Lancet **2014; 385: 341-350**



# LS Mean LDL-C % Reductions in the Phase III Programs of Evolocumab (12 wks) and Alirocumab (24 wks)

| Intervention | Baseline LDL-C | LDL-C Change | LDL-C Goal Attainment |
|---|---|---|---|
| **HeFH Patients** | | | |
| Evolocumab 420 mg SC Q4W[1] | 155 mg/dL | -61% | 63% |
| Alirocumab 75 mg SC Q2W (⬆prn)[2] | 148 mg/dL | -58% | 70% |
| **Statin Intolerant Patients** | | | |
| Evolocumab 420 mg SC Q4W[3] | 192 mg/dL | -55% | 82% |
| Alirocumab 75 mg SC Q2W (⬆prn)[4] | 191 mg/dL | -45% | 41% |
| **High Risk, Not at Desirable LDL-C Patients** | | | |
| Evolocumab 420 mg SC Q4W[5] | 110 mg/dL | -65% | 93% |
| Alirocumab 75 mg SC Q2W (⬆prn)[6] | 109 mg/dL | -51% | 77% |
| Monotherapy Patients | | | |
| Evolocumab 420 mg SC Q4W[7] | 144 mg/dL | -56% | 69% |
| Alirocumab 150 mg SC Q2W[8] | 123 mg/dL | -66% | 93% |


1. Raal et al. Lancet 2015; 385: 331-40
2. Kastelein et al Presented to ESC, 2014
3. Stroes et al. 2014; 63: 2541-8
4. Moriarty et al. Presented to AHA, 2014.
5. Robinson et al. JAMA 2014; 311: 187.
6. Cannon et al Eur Heart J online 2/25/15
7. Koren et al Am J Cardiol 2014; 63: 2531-40.
8. Roth et al Int J Cardiol 2014; 176: 55-61



# Efficacy in Long-term Studies

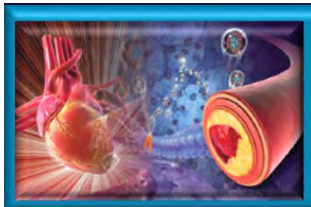
Osler[1]: Open label study of 4465 pts randomized to evolocumab 140 mg SC Q2W or 420 mg SC QM + standard of care (SOC) vs SOC for 48 weeks

Odyssey Long Term[2]: Blinded study of 2341 high risk pts on max-tolerated statin with LDL-C > 70 randomized to alirocumab 150 mg or placebo SC Q2W for 78 wks

| Patients | % LDL-C Δ At 12/24 wks | % LDL-C Δ At 48/72 wks |
|---|---|---|
| **Evolocumab 140 mg SC Q2W or 420 mg SC QM[1] (baseline LDL-C = 120 mg/dL)** | **-61% (P<0.001)*** | **-61% (P<0.001)** |
| **Alirocumab 150 mg SC Q2W[2] (baseline LDL-C = 123 mg/dL)** | **-62% (P<0.001)ǂ** | **-56% (P<0.001)** |

*Proportion of patients with LDL-C < 70 mg/dL = 74%
ǂProportion of patients with LDL-C < 70 mg/dL = 79%


1. Sabatine et al NEJM 2015; 372:1500-9
2. Robinson et al NEJM 2015;372:1489-99.



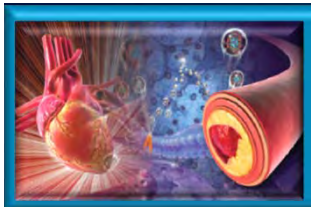
# Efficacy in Long-term Studies

Osler[1]: Open label study of 4465 pts randomized to evolocumab 140 mg SC W2W or 420 mg SC QM + standard of care (SOC) vs SOC for 12 wks

Odyssey Long Term[2]: Blinded study of 2341 high risk pts on max-tolerated statin with LDL-C > 70 randomized to alirocumab 150 mg or placebo SC Q2W for 24 wks

| Treatments | LDL-C | nonHDL-C | Apo B | Lp(a) | TG | HDL-C | Apo A1 |
|---|---|---|---|---|---|---|---|
| Evolocumab[1] | -61% | -52% | -47% | -26% | -13% | 7.0% | 4.2% |
| Alirocumab[2] | -62% | -52% | -54% | -26% | -17% | 4.6% | 2.9% |


1. Sabatine et al NEJM 2015; 372:1500-9
2. Robinson et al NEJM 2015;372:1489-99.



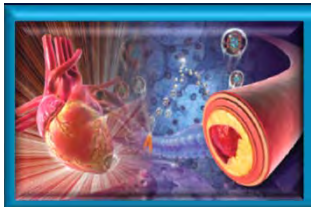
# Approved Indications

## FDA (Praluent, alirocumab and Rapatha, evolocumab)

- In combination with maximum tolerated statin in adults with heterozygous familial hypercholesterolemia
- In combination with maximum tolerated statin therapy in patients with ASCVD, who require additional lowering of LDL-C
- In patients with homozygous familial hypercholesterolemia (evolocumab only)

## European Commission (Repatha, evolocumab)

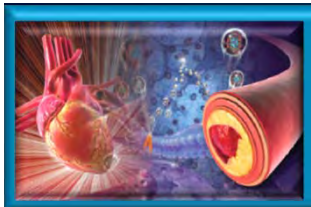
- In combination with maximum tolerated statin therapy in patients unable to reach LDL-C goal
- Alone or in combination with other LLT in patients who are statin-intolerant or for whom a statin in contraindicated
- In patients with homozygous familial hypercholesterolemia



# Safety

| Adverse Event | Osler[1] (n=4465 pts, 48 weeks) | | Odyssey Long Term[2] (n=2341 pts, 72 weeks) | |
|---|---|---|---|---|
| | Evolocumab | SOC | Alirocumab | Placebo |
| Any adverse events | 69.2% | 64.8% | 81.0% | 82.5% |
| Serious AEs | 7.5% | 7.5% | 18.7% | 19.5% |
| AE leading to DC of Rx | 2.4% | NA | 7.3% | 5.8% |
| Injection site reaction | 4.3% | NA | 5.9% | 4.2% |
| Transaminase > 3x ULN | 1.0% | 1.2% | 1.6% | 2.2% |
| Muscle-related/myalgia | 6.4% | 6.0% | 5.4% | 2.9% |
| CK > 5x/> 3x ULN | 0.6% | 1.7% | 3.7% | 4.9% |
| Neurocognitive events/disorders | 0.9% | 0.3% | 1.2% | 0.5% |

1. Sabatine et al NEJM 2015; 372:1500-9 2. Robinson et al NEJM 2015;372:1489-99.

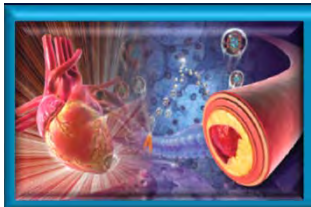


# "Low LDL-C"

## Alirocumab-treated patients in the Global Safety Pool

| | Alirocumab n=3340 | ≥ 2 LDL-C < 25 mg/dL n=796 | ≥ 2 LDL-C < 15 mg/dL n=288 | LDL-C ≥ 25 mg/dL n=2544 |
|---|---|---|---|---|
| **Musculoskeletal and connective tissue** | **24.2%** | **21.1%** | **20.1%** | **23.8%** |
| Myalgia | 4.9% | 3.1% | 3.8% | 4.9% |
| Musculoskeletal pain | 1.9% | 1.0% | 1.0% | 2.0% |
| **Gastrointestinal** | **17.0%** | **12.7%** | **10.1%** | **16.7%** |
| Diarrhea | 4.3% | 3.0% | 1.4% | 4.0% |
| **Nervous System** | **14.9%** | **10.3%** | **9.0%** | **15.1%** |
| Headache | 4.6% | 1.8% | 1.4% | 4.8% |
| **Metabolism and nutrition** | **6.9%** | **7.0%** | **7.3%** | **6.4%** |
| Diabetes mellitus | 1.2% | 1.5% | 2.4% | 1.1% |
| **Eye disorders** | **4.6%** | **5.3%** | **6.9%** | **4.0%** |
| Cataract | 0.8% | 1.5% | 2.4% | 0.5% |
| **Neoplasms** | **2.5%** | **2.8%** | **2.4%** | **2.3%** |

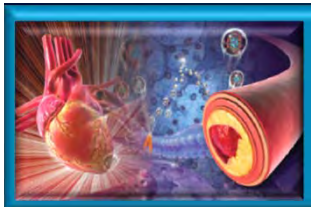
Sanofi & Regeneron. Briefing Document Praluent (alirocumab) BLA 125559. Presented to the FDA's Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Gaithesburg, MD USA June 9, 2015



# New Onset DM or IFG in Patients Receiving Alirocumab in the Global Safety Pool

| Global Safety Pool | Placebo-Controlled Studies | | Ezetimibe-Controlled Studies | |
|---|---|---|---|---|
| | Alirocumab | Placebo | Alirocumab | Ezetimibe |
| **New Onset Diabetes** | | | | |
| **Baseline normoglycemia (FBG < 100 mg/dL)** | **0.1%** n=718 | **0.3%** n=365 | **0.4%** n=223 | **0%** n=174 |
| **Baseline impaired fasting glucose (FBG 100-126 mg/dL)** | **5.7%** n=865 | **3.8%** n=420 | **3.9%** n=333 | **3.3%** n=243 |
| **New Onset Impaired Fasting Glucose** | | | | |
| **Baseline normoglycemia (FBG < 100 mg/dL)** | **31.2%** n=718 | **26.6%** n=365 | **26.5%** n=223 | **24.1%** n=174 |
| **Reverted to Normoglycemia** | | | | |
| **Baseline impaired fasting glucose (FBG 100-126 mg/dL)** | **20.6%** n=865 | **18.1%** n=420 | **28.2%** n=333 | **31.7%** n=243 |

Smith JP (CDER, FDA). Alirocumab: FDA Introductory Remarks. Presented to the FDA's Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Gaithesburg, MD USA June 9, 2015 (http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm452345.pdf)

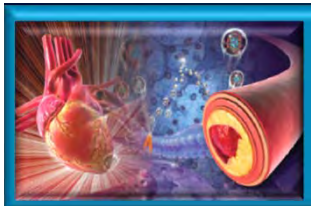


# Neurologic Events

Logic: Cholesterol is major component of cellular membranes and myelin. Indicators of Neurologic AE include central (unlikely b/c mAb unlikely to cross BBB) and peripheral neuropathies

| Global Safety Pool | Placebo-Controlled Studies | | Ezetimibe-Controlled Studies | |
|---|---|---|---|---|
| | Alirocumab n=2476 | Placebo n=1276 | Alirocumab n=864 | Ezetimibe n=618 |
| **Patients with TEAE** | **3.5%** | **3.5%** | **2.4%** | **3.4%** |
| **Hazard Ratio (95% CI)** | **0.98 (0.68-1.41)** | | **1.43 (0.76-2.69)** | |
| **Demyelination** | 0.2% | 0% | 0.1% | 0% |
| **Guillain-Barre** | 3.2% | 3.1% | 2.8% | 2.3% |
| **Peripheral neuropathy** | 2.8% | 3.3% | 2.3% | 2.1% |
| **DC due to neurologic event** | **0.2%** | **<0.1%** | **0.2%** | **0.2%** |

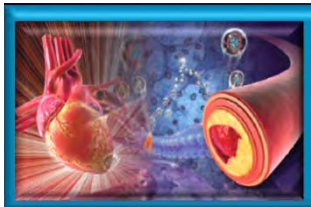
Roberts MD. Alirocumab. BLA 125559. Clinical Safety Review. Presented to the FDA's Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Gaithesburg, MD USA June 9, 2015 (http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm452345.pdf)



# Neurocognition

| Global Safety Pool | Phase II/III Studies | | Open-label year 1 | |
|---|---|---|---|---|
| | Any control n=2080 | Evolocumab n=3946 | SOC n=1489 | Evolocumab n=2976 |
| **Median exposure (mo)** | **3.2** | **3.1** | **10.2** | **10.3** |
| **Neurocognition TEAE** | **0.3%** | **0.1%** | **0.2%** | **0.8%** |
| **DC due to TEAE** | **<0.1%** | **<0.1%** | **-** | **<0.15** |
| Memory impairment | <0.1% | <0.1% | 0.2% | 0.8% |
| Amnesia | - | 0.1% | 0.1% | 0.2% |
| Dementia | - | - | - | 0.1% |
| Mental impairment | - | - | - | 0.1% |
| Disorientation | 0.1% | <0.1% | - | <0.1% |

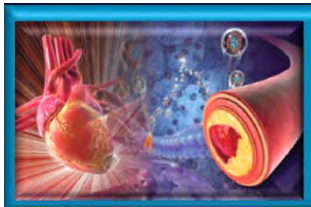
Wasserman SM Amgen). Evolocumab: Program Overview, Efficacy & Safety. Presented to the FDA's Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Gaithesburg, MD USA June 10, 2015 (http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm452345.pdf)



# Immunogenicity

- Antidrug antibodies (binding antibodies) were detected in 146 or 3033 (4.8%) alirocumab-treated subjects and 13 of 4915 (0.3%) in evolocumab-treated subjects.
  - Most are transient
  - Low concentration
  - Have no effect on efficacy or PK
- Neutralizing antibodies were detected in 36 of 3033 (1.2%) alirocumab-treated patients and none with evolocumab
  - Most are transient
  - Low concentration
  - Most had no effect on efficacy or PK but some did

Golden J (CDER, FDA). Alirocumab and Craig E. (CDER, FDA) Evolocumab. Clinical Efficacy and Safety Review. Presented to the FDA's Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Gaithesburg, MD USA June 9-10, 2015 (http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm452345.pdf)



# ODYSSEY LONG TERM Study

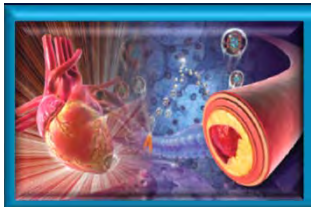
## *Post-hoc* Adjudicated Cardiovascular Events

| **% (n) of patients**<br>All patients on background of max tolerated statin ± other lipid-lowering therapy | **Alirocumab (n=1550)** | **Placebo (n=788)** |
|---|---|---|
| **CV events confirmed by adjudication** | **1.7%** (27) | **3.3%** (26) |
| **CHD death** | **0.3%** (4) | **0.9%** (7) |
| **Non-fatal MI** | **0.9%** (14) | **2.3%** (18) |
| **Fatal + non-fatal ischaemic stroke** | **0.6%** (9) | **0.3%** (2) |
| **Unstable angina requiring hospitalisation** | 0 | **0.1%** (1) |

Patients are censored at the end of TEAE period (last injection of study treatment + 70 days).

[†]Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. "Unstable angina requiring hospitalisation" is limited to the UA events with definite evidence of progression of the ischemic condition (strict criteria).

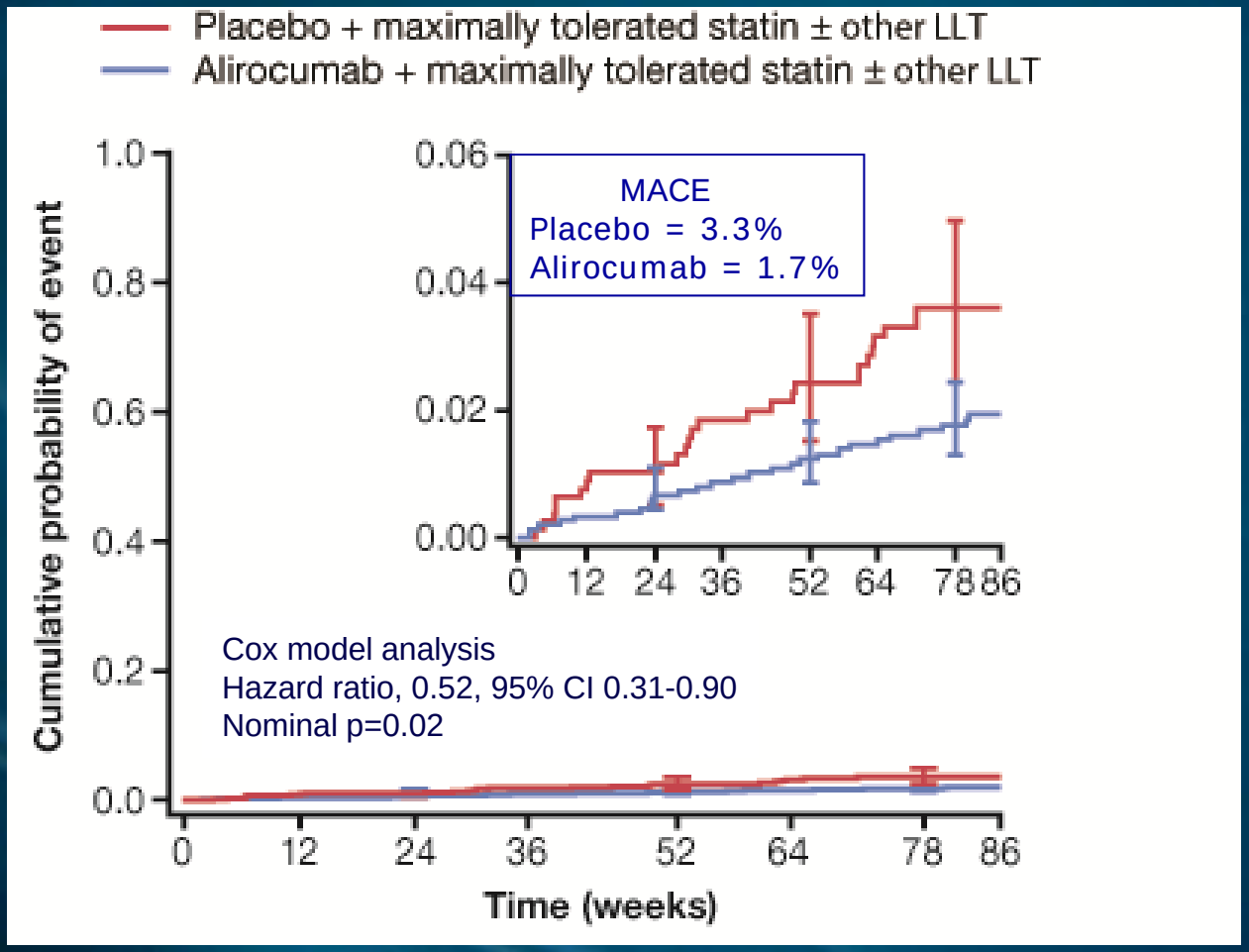
Robinson et al NEJM 2015; 16;372:1489-99.
ClinicalTrials.gov. - NCT01507831



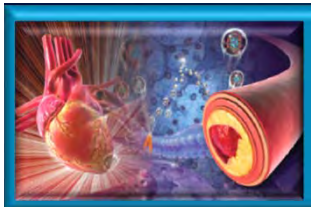
# Impact Of Alirocumab vs Placebo on MACE in 2341 Patients in the Odyssey Long Term Study

Odyssey Long Term: Blinded study of 2341 high risk pts on max-tolerated statin with LDL-C > 70 randomized receiving alirocumab 150 mg or placebo SC Q2W for 78 wks

MACE
- CHD death
- Nonfatal MI
- Fatal/nonfatal ischemic CVA
- UA requiring hospitalization




Robinson et al NEJM 2015; 16;372:1489-99.

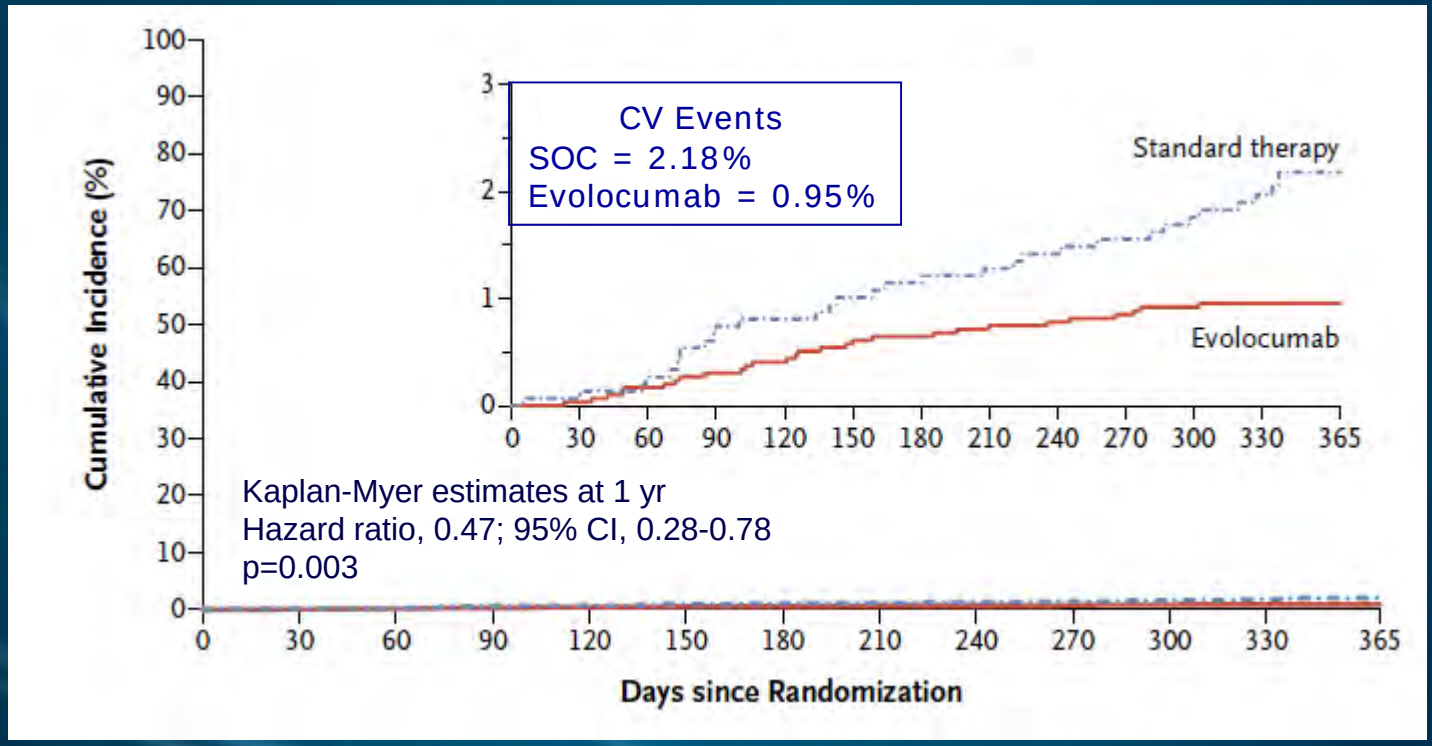


# Impact Of Evolocumab vs Placebo on MACE in 4465 Patients in the Osler Study

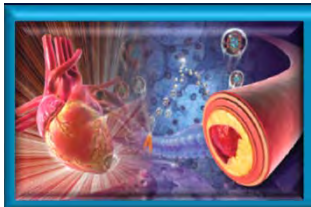
Osler: Open label study of 4465 pts randomized to evolocumab 140 mg SC Q2W or 420 mg SC QM + standard of care (SOC) or SOC for 48 wks

## CV Events

- Death
- MI
- UA requiring hospitalization
- CVA
- TIA
- Hosp w CHF



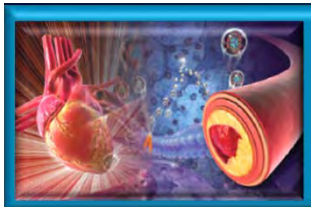

Sabatine et al NEJM 2015; 372:1500-9



# Outcome Studies

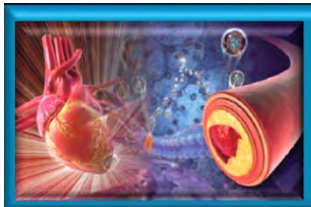
| | |
|---|---|
| **Alirocumab** | |
| **ODYSSEY OUTCOMES (NCT01663402)** | Enrolling post-acute MI or hospitalized UA w/in 12 mon; Rx w/ atorvastatin 40/80 mg/d, rosuva 20/40 mg/d or max tolerated; LDL > 70, nonHDL > 100, or apo B > 80; Endpoint – time to ASCVD event; n=18,000; **est completion January 2018** |
| **Evolocumab** | |
| **Fourier (NCT01764633)** | Enrolling MI, CVA, or PAD + RF; Rx with atorvastatin ≥ 20 mg or equivalent; LDL > 70 or nonHDL > 100; Endpoint – time to 1st ASCVD event; Rx w/ evo 140 Q2W or 420 mg QM vs placebo; n=22,500; **est completion October 2017** |
| **Glagov (NTC01813422)** | IVUS study enrolling pts with evidence for coronary stenosis; LDL > 80 or 60-80 w/ RF; Rx w/ statin, niacin or eze; Rx evo 420 mg SC QM for 72 mon; n=950 |
| Bococizumab | |
| **Sprire-1** (NCT01975376) | Enrolling high risk CVD event; LDL 70-100 or nonHDL 100-130; on LLRx; Randomized to Boco 150 mg SC Q2W vs placebo; n=12,000; **est completion April 2018** |
| **Spire-2** (NCT01975389) | Same as above except LDL > 100 or nonHDL > 130; n=6300; est **completion January 2018** |

www.clinicaltrials.gov

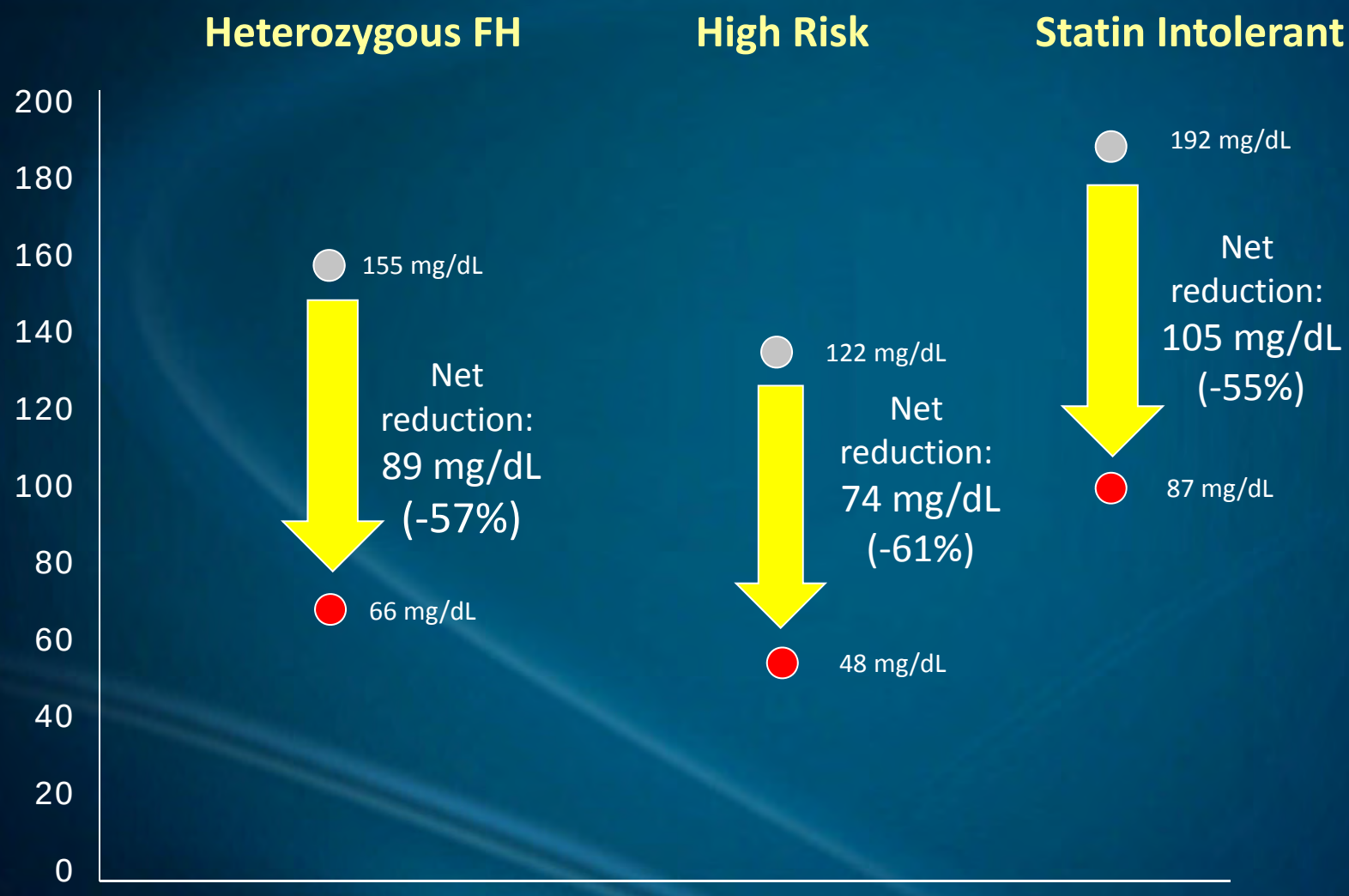


# Conclusions
## Monoclonal Antibodies for PCSK9

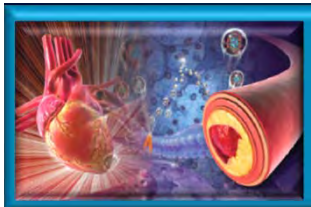
- Both evolocumab and alirocumab consistently lower LDL-C ≥ 50% with and without background statin therapy in patients with:
  - HeFH
  - High risk on max dose statin and not at a desirable LDL-C level
  - Statin intolerant
- PCSK9 mAb *may* increase incident diabetes and IFG
- 5 yr outcome studies are underway for 3 PCSK9 mAbs and should begin reporting results in 2-3 years
- The mAbs for PCSK9 are well tolerated with no signal of significant adverse events at this point, including in patients with on-treatment LDL-C < 25 mg/dL
- **Early evaluation of adjudicated CV events with PCSK9 inhibitors provides a hopeful signal**



# How will approval change clinical lipidology?




Raal et al Lancet 2015; 385: 331-40 | Robinson et al NEJM 2015; 16;372:1489-99 | Stroes et al. JACC 2014; 63: 2541-8

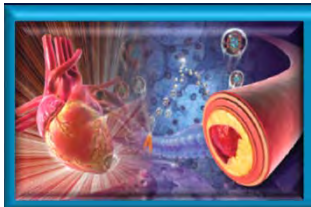


# How will approval change clinical lipidology?

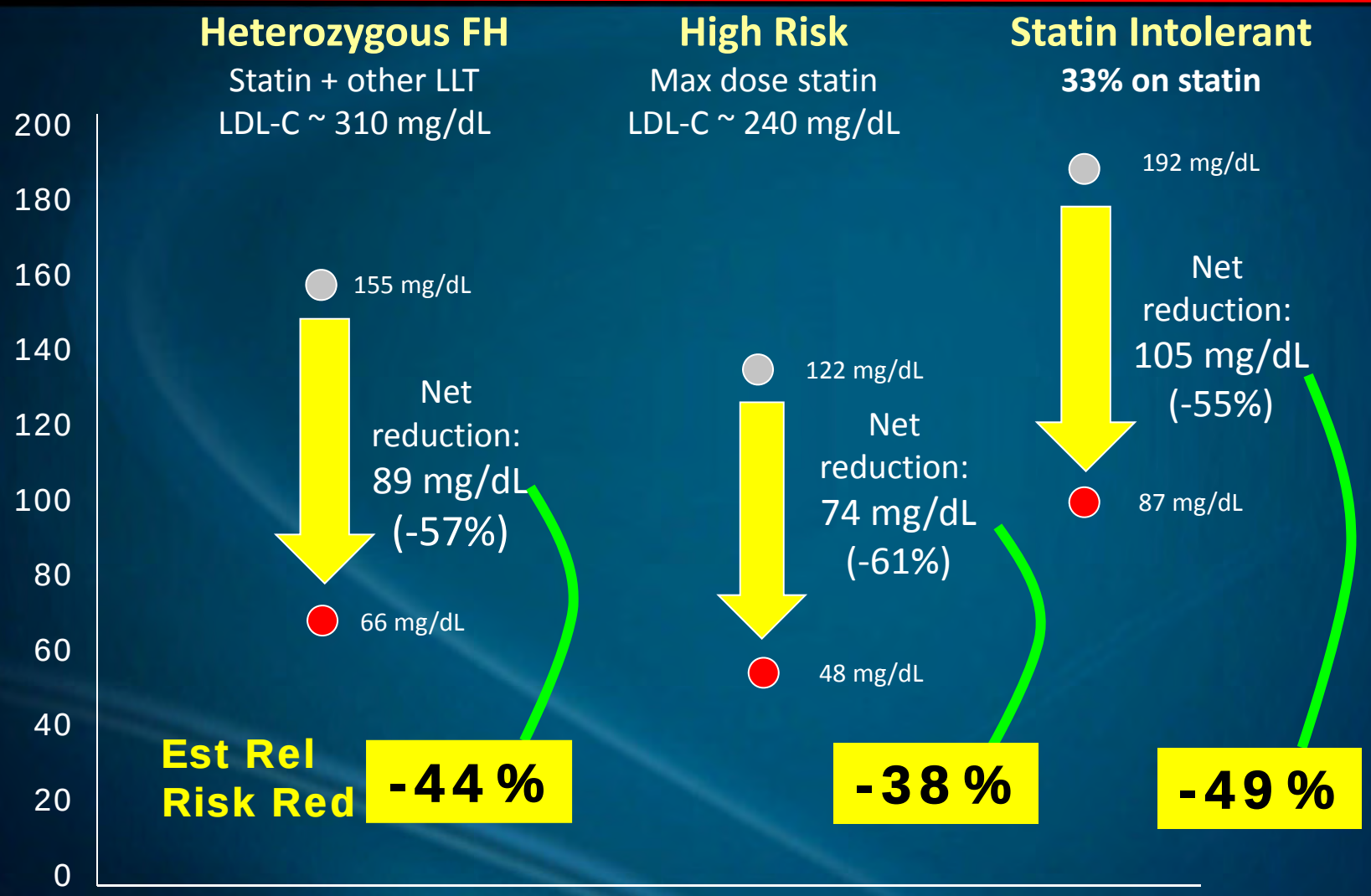
| An analysis of 170,000 Patients in 26 statin RCT<br>Reduction in Major Vascular Events<br>(nonfatal MI, CHD death, stroke, revascularization) | |
|---|---|
| **Baseline** | **RR per 39 mg/dL⬇ in LDL-C** |
| **≤ 78 mg/dL** | **-22%** |
| **79-97 mg/dL** | **-23%** |
| **98 to 117 mg/dL** | **-23%** |
| **118 to 136 mg/dL** | **-24%** |
| **≥ 137 mg/dL** | **-20%** |
| **OVERALL** | **-22%** |

- 39 mg/dL⬇in LDL-C = HR 0.78 = 22%⬇in MVE
- 78 mg/dL⬇in LDL-C = HR 0.78 x 0.78 = 40%⬇in MVE
- 117 mg/dL⬇in LDL-C = HR 0.78 x 0.78 x 0.78 = 53%⬇in MVE

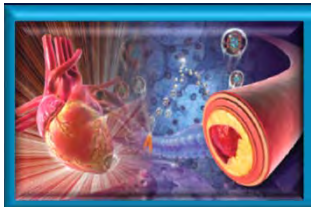
Cholesterol Ttreatment Trialists. Lancet 2010; 376: 1670-1681



# How will approval change clinical lipidology?




Raal et al Lancet 2015; 385: 331-40 | Robinson et al NEJM 2015; 16;372:1489-99 | Stroes et al. JACC 2014; 63: 2541-8

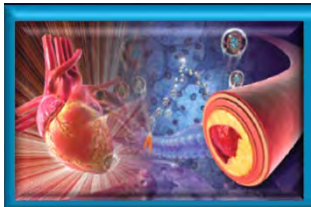


# How will approval change clinical lipidology?

## LDL-C Lowering Efficacy of PCSK9 mAbs

| Intervention | Baseline Mean LDL-C (mg/dL) | % Change LDL-C | Attained Mean LDL-C (mg/dL) |
|---|---|---|---|
| Alirocumab 150 mg Q2W[1] | 124 | -67% | 34 (min, max = 10, 63) |
| Evolocumab 420 mg Q4W[2] | 120 | -66% | 45 |


1. McKenney et al. JACC 2012;59: 2344-2353
2. Giugliano et al. Lancet 2012; 380: 2007-17



# Case Reports of Patients Double Loss-of-Function PCSK9 Mutations

- 32 year-old woman had no measurable PCSK9 and a LDL-C of 14.

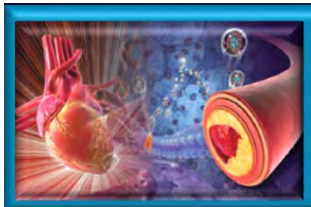
  (*Am J Hum Genet*. 2006;79: 514-523).

- 21 year-old AA woman had no measurable PCSK9 and a LDL-C of 15.

  (*Atherosclerosis*. 2007;193: 445-448)

- 49 year-old French male had no detectable PCSK9 levels and a LDL-C of 16.

  (*Arterioscler Thromb Vasc Biol.* 2009;29:2192-2197)



# *How will approval change clinical lipidology?*

PCSK9 mAb:

- Will give us the power to effectively manage patients with:
  - HeFH
  - High risk on max dose statin and not at LDL-C goal
  - Statin intolerant
- May give us great power to substantially lower ASCVD risk
- May challenge us to find a new lower LDL-C target

# ATP Citrate Lyase Inhibition–A New Mechanism for LDL-C Reduction

Christie M. Ballantyne, MD

Center for Cardiovascular Disease Prevention
Houston Methodist DeBakey Heart & Vascular Center

Baylor College of Medicine
Houston, Texas

Baylor College of Medicine

Methodist DeBakey Heart & Vascular Center

# ETC-1002

- Mechanism of action
- Efficacy on lipids
  - Monotherapy
  - Statin-intolerant patients ± ezetimibe
  - Added to background statin therapy

# ETC-1002
# Pharmacologic Properties

- Oral, once-daily small molecule
- Half-life: 15-24 hours
- Target organ: Liver
  - Minimal metabolism in preclinical and clinical studies
  - Primary biliary and minimal kidney excretion
- No competitive liver uptake with statins (e.g. OATP1B1)
- MOA: Inhibits ATP-citrate lyase (ACL) and activates AMP-activated protein kinase (AMPK)

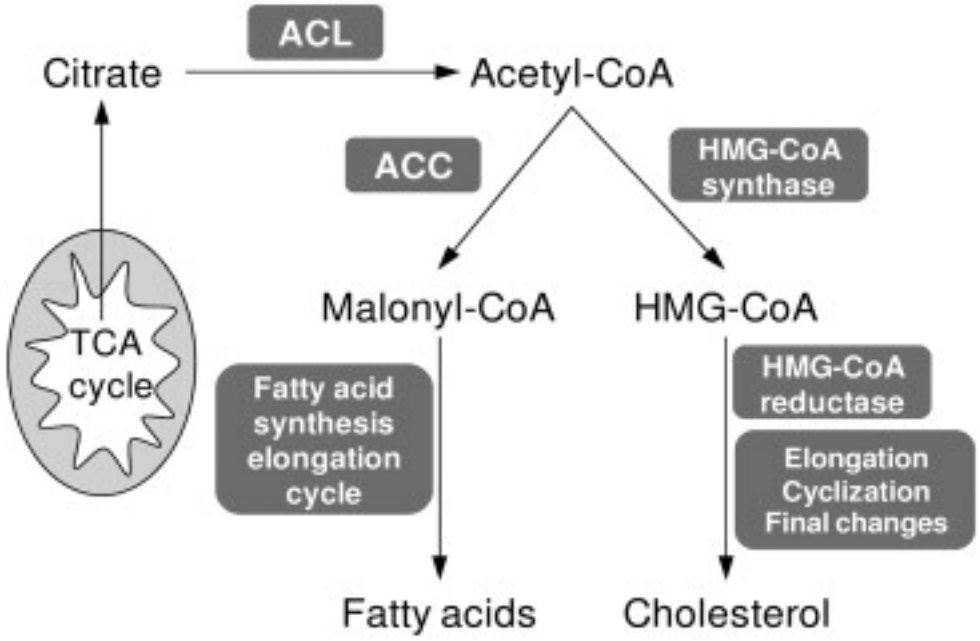
# ATP-Citrate Lyase

*HISTORICAL PERSPECTIVE*

- **1960s:** (-)-hydroxycitrate identified as an ACL inhibitor by Watson and Lowenstein
- **1970s:** Roche characterized (-)-hydroxycitrate and analogues for inhibition of cholesterol and fatty acid synthesis
- **1980s-1990s:** Multiple large pharmaceutical companies initiated ACL inhibitor discovery programs
- **1990- 2000s:** Programs halted due to the inability to synthesize inhibitors that were bioavailable and cell permeable

*Groot et. al. Curr. Med. Chem. – Imun., Endoc. & Metab. Agents, 2003, 3, 211-217*

# Crucial role of ACL as a precursor supplier for both fatty acid and cholesterol synthesis



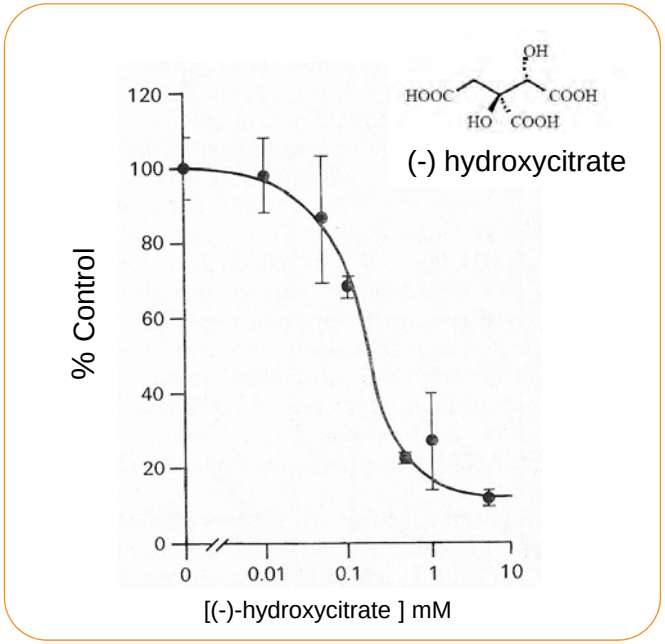

ACC, acetyl-CoA carboxylase; ACL, ATP citrate lyase; ATP, adenosine triphosphate; CoA, coenzyme A; HMG, hydroxymethylglutaryl; TCA, tricarboxylic acid

Mendivil CO et al. *J Clin Lipidol* 2015;9:384–389.

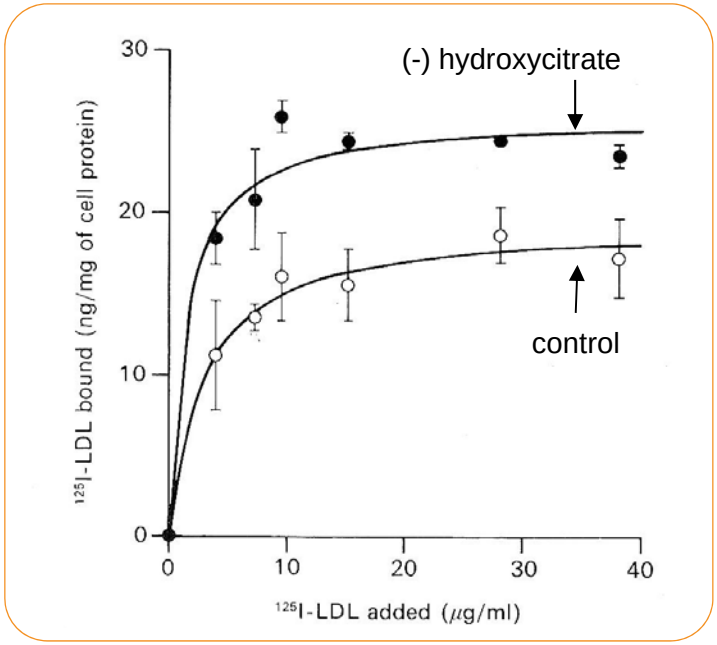
# ATP-CITRATE LYASE AND THE LDL RECEPTOR

*AN ESTABLISHED MECHANISM*

## Cholesterol Synthesis




## LDL Receptor Binding



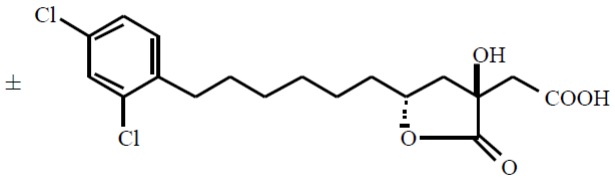

Inhibition of ATP-Citrate Lyase by(-)- hydroxycitric acid increases LDL receptor binding in HepG2 Cell

*Adapted from Berkhout et. al. BiochemJ:272 181-186 (1990)*

# STRATEGIES FOR ATP-CITRATE LYASE INHIBITION

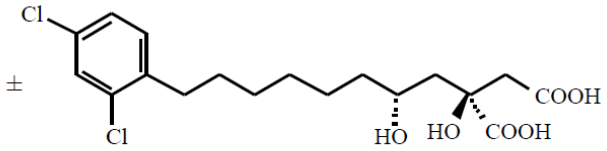
*CITRYL-COA MIMETICS AND IMPROVED CELL PERMEABILITY*

Cell-Penetrant γ-Lactone Prodrug

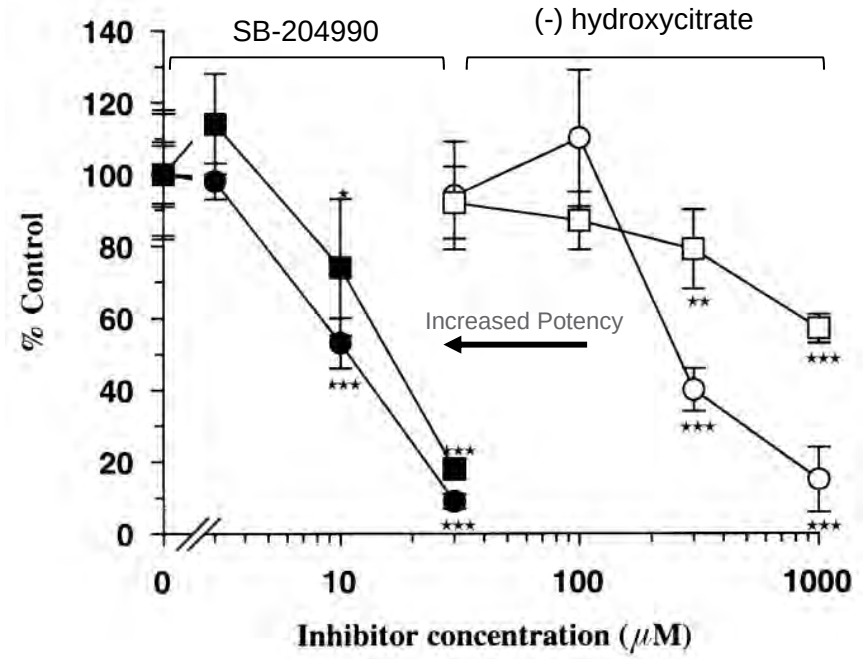



**Intracellular Conversion**

Active ACL Inhibitor



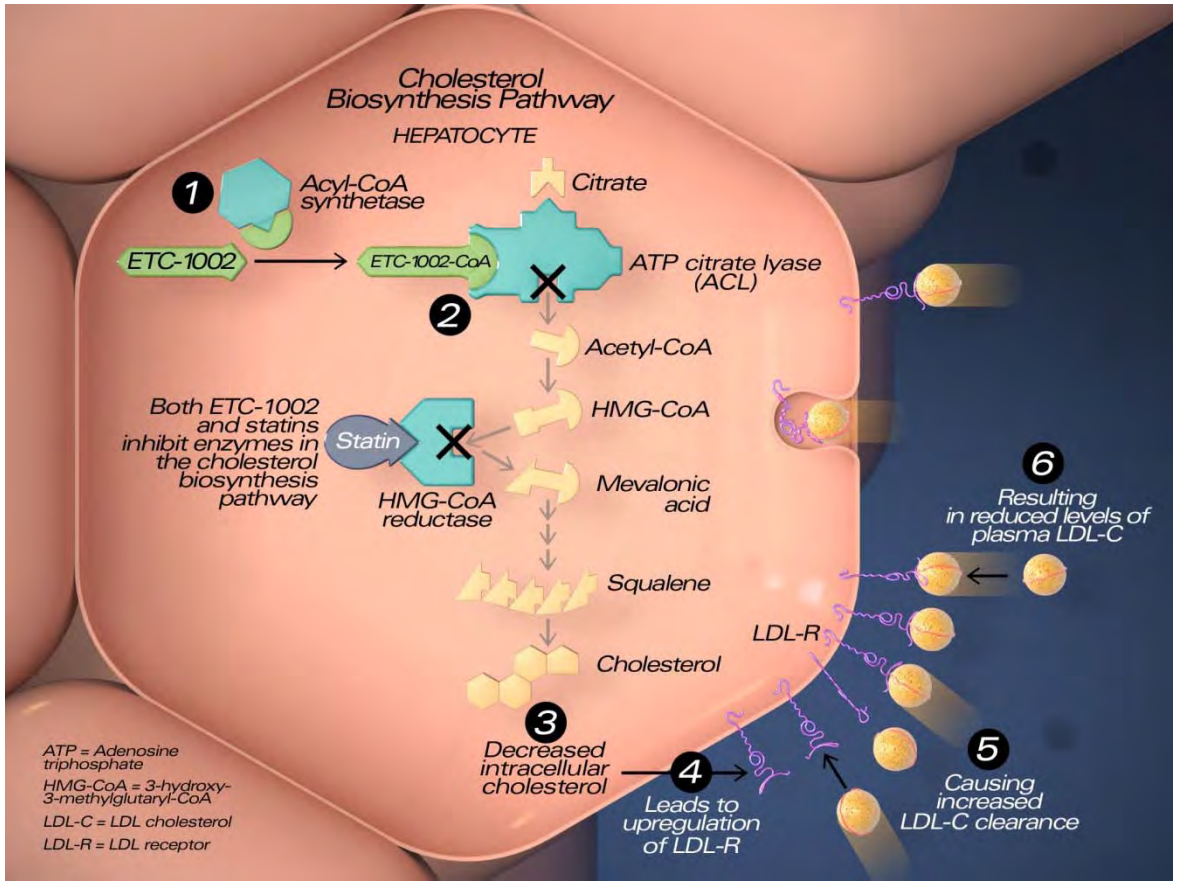

## Lipid Synthesis




*Adapted from Biochem. J. (1998) 334, 113±119*

# MECHANISM OF ACTION

*ETC-1002 Reduces LDL-C via Inhibition of ATP-Citrate Lyase (ACL)*



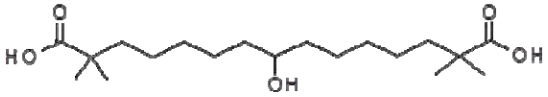

ETC-1002 is converted to ETC-1002-CoA in the liver which directly inhibits ACL, reduces cholesterol synthesis, and up-regulates LDL receptor activity

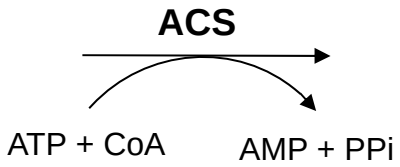
# ATP-CITRATE LYASE INHIBITION BY ETC-1002

*BUILDING ON THE PRODRUG CONCEPT*

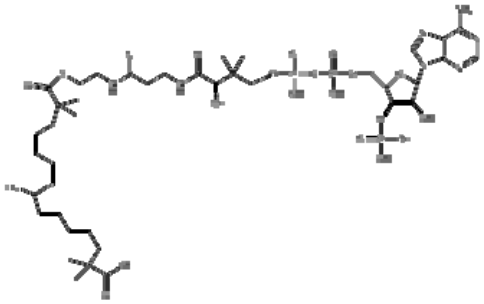
## Coenzyme Activation by Acyl-CoA Synthetase (ACS)

**Inactive Prodrug**
**ETC-1002**




**Active ACL Inhibitor**
**ETC-1002-CoA**

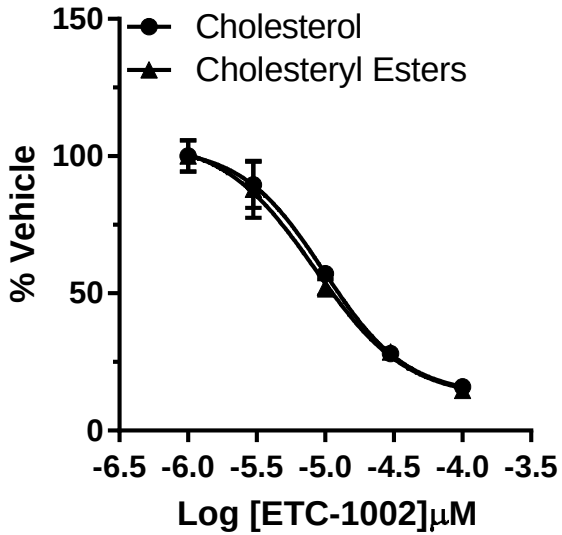


ETC-1002 is converted to an active ACL inhibitor (ETC-1002-CoA) by endogenous liver ACS activity

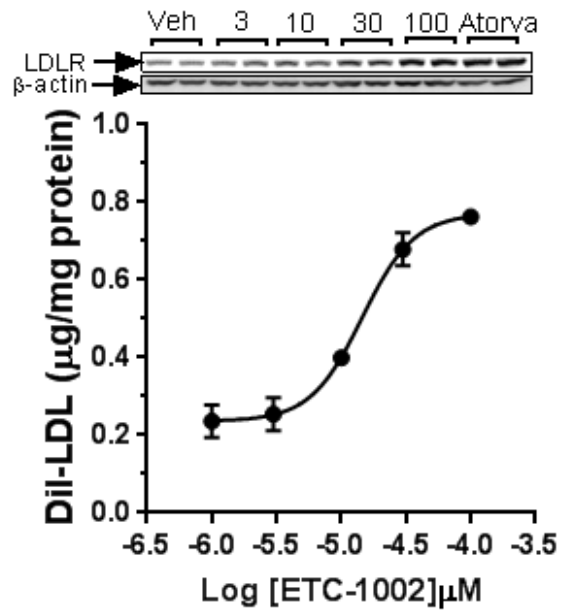
# ETC-1002 INHIBITS LIPID SYNTHESIS AND UP-REGULATES LDL RECEPTOR ACTIVITY

*McArdle Cells*

## Cholesterol Synthesis




## LDL Receptor Activity

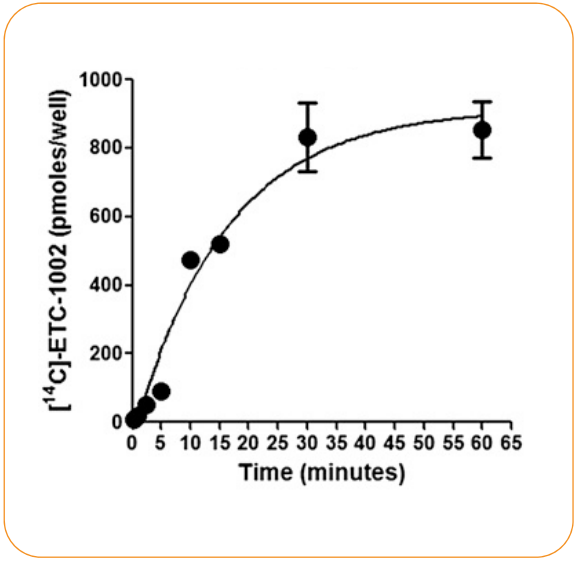



ETC-1002 inhibits cholesterol and cholesteryl ester synthesis, and increases LDL receptor protein expression and activity in McArdle cells

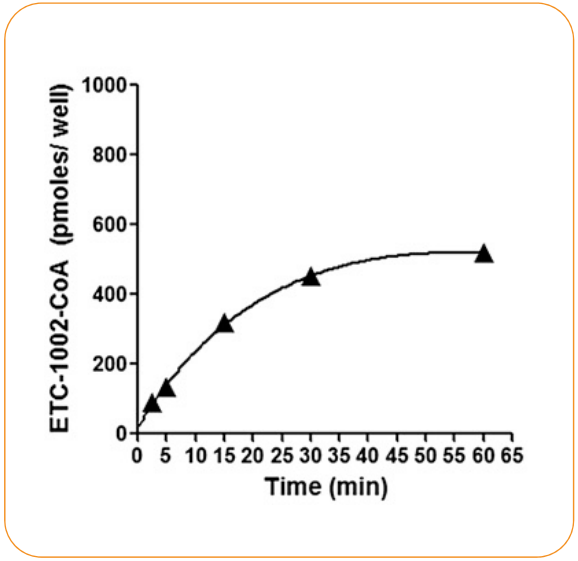
# ETC-1002 IS RAPIDLY CONVERTED TO ETC-1002-COA

*PRIMARY RAT HEPATOCYTES*

**ETC-1002 (prodrug)**




**ETC-1002-CoA (active ACL inhibitor)**



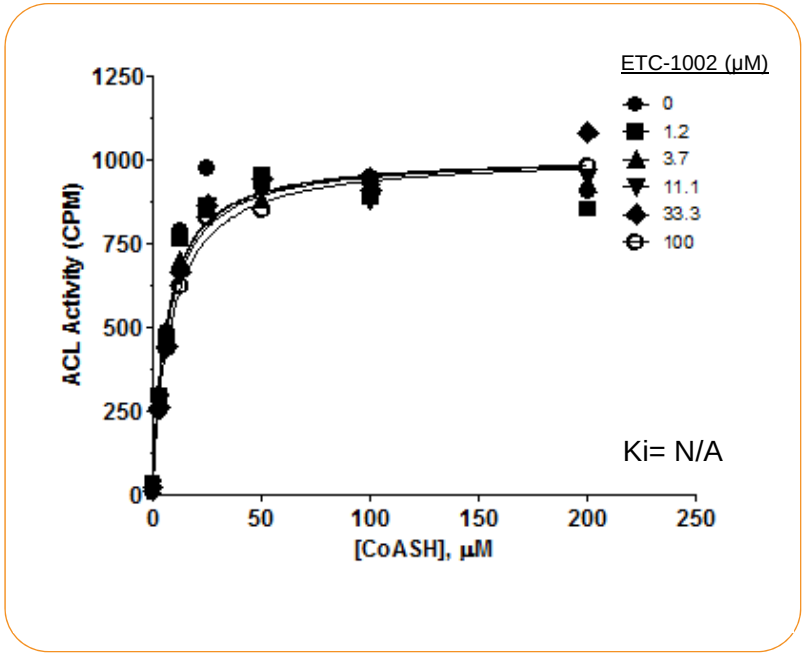

ETC-1002 is rapidly converted to ETC-1002-CoA in rat liver cells

Source: Pinkosky (2013)

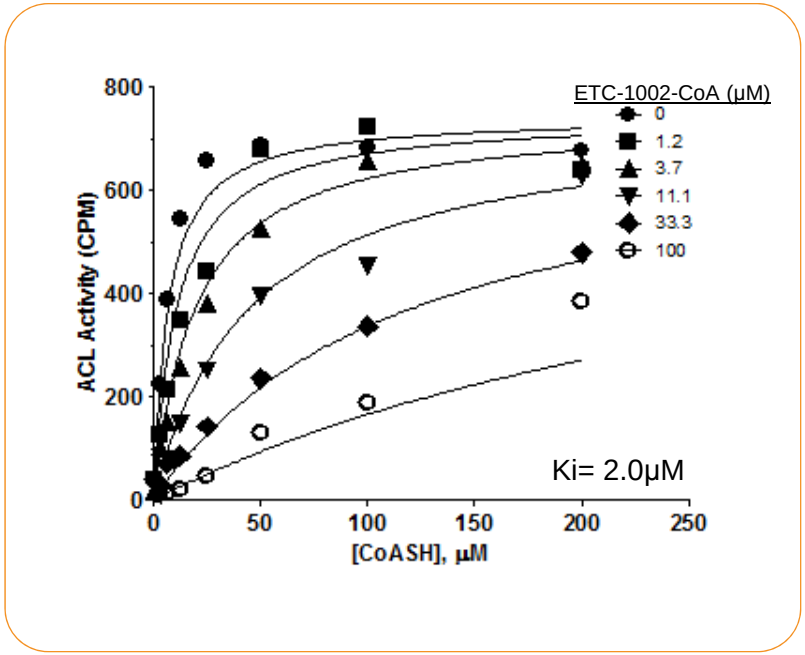
# ETC-1002-COA INHIBITS RECOMBINANT HUMAN ATP-CITRATE LYASE

*ENZYME KINETICS*

**ETC-1002 (prodrug)**




**ETC-1002-CoA (Active ACL Inhibitor)**

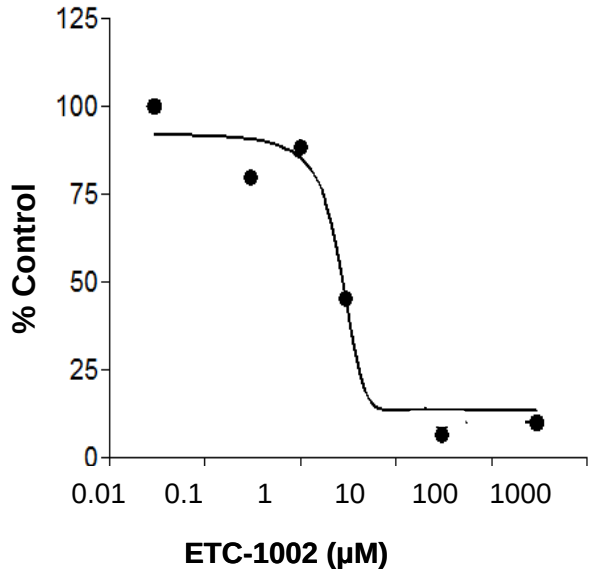



ETC-1002-CoA inhibits rhuATP citrate lyase and is competitive for coenzyme A

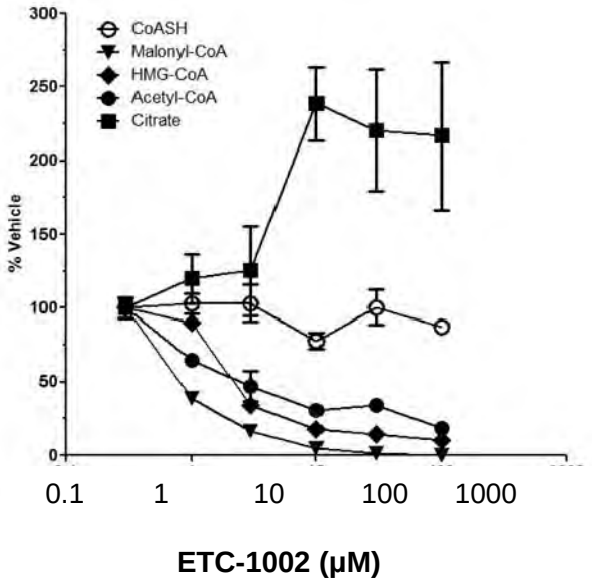
# ETC-1002 REDUCES LIPID SYNTHESIS IN VITRO

*PRIMARY RAT HEPATOCYTES*

## Cholesterol Synthesis




## Metabolites of Lipid Synthesis



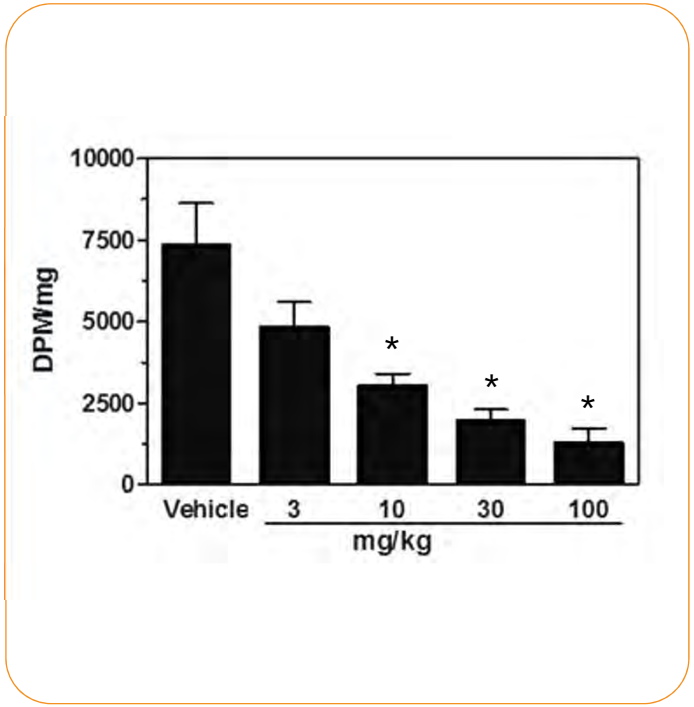

ETC-1002 inhibits cholesterol synthesis and reduces metabolic intermediates of lipid synthesis consistent with ACL inhibition in rat liver cells

Source: Pinkosky (2013)

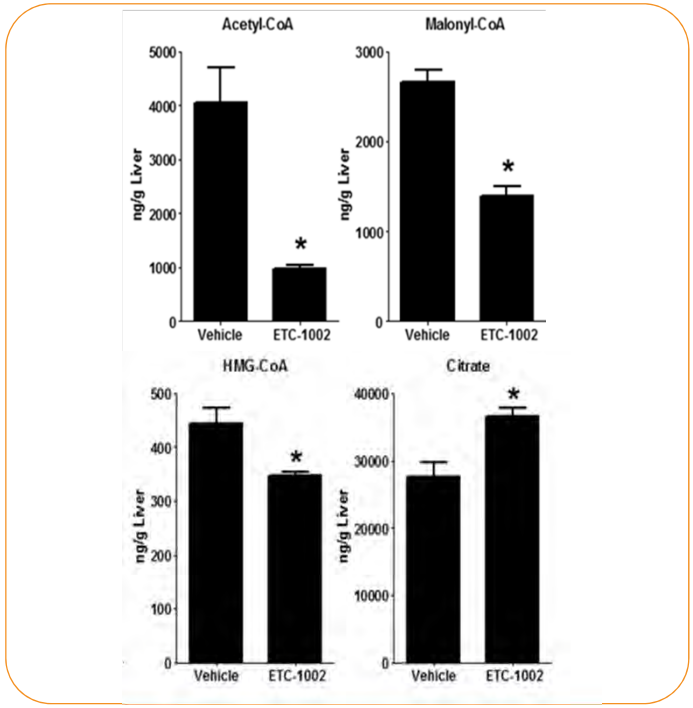
# ETC-1002 REDUCES LIPID SYNTHESIS IN VIVO

*RAT LIVER*

## Cholesterol Synthesis
### ETC-1002 Dose Response




## Intermediates of Lipid Synthesis
### ETC-1002 30 mg/kg




A single dose of ETC-1002 inhibits sterol synthesis and reduces metabolic intermediates of cholesterol synthesis in rats. n = 5, * $p < 0.05$

Source: Pinkosky *(*2013)

# ACYL-COA SYNTHETASES

- Endogenous enzymes that catalyze the CoA thioesterification (metabolic activation) of endogenous fatty acids
- 26 Acyl-CoA Synthetase (ACS) genes or isoforms identified
- Differences in biological roles among genes is largely unknown
- ACS isoforms differentiated by:
  - Fatty acid preference
    - Chain length (2 to ~30 carbons)
    - Level of saturation (saturated, monounstaurated, or polyunsaturated)
    - Methyl branches
  - Intracellular localization
  - Tissue expression profile (liver, adipose, skeletal muscle, etc.)

# ETC-1002 MECHANISM SUMMARY

*LDL-C LOWERING VIA TISSUE-SPECIFIC ACL INHIBITION*

- ETC-1002 inhibits cholesterol synthesis by inhibiting ACL – an enzyme upstream of HMG-CoA reductase
- ETC-1002 upregulates LDL receptors and lowers LDL-C similar to statin drugs
- ETC-1002 is CoA activated by endogenous ACS activity
- ETC-1002 is an inactive prodrug while its CoA activated form (ETC-1002-CoA) is a direct inhibitor of recombinant human ACL
- Studies aimed to identify the specific ACS isoform that activates ETC-1002 to ETC-1002-CoA are ongoing

# ETC-1002: PHASE 2 CLINICAL STUDIES

| Study Number | Short Title (N=total/ETC-1002 treated) | LDL-C Lowering* (pbo corrected) | Dose Range (mg) | Treatment Duration |
|---|---|---|---|---|
| 003 | Phase 2a in Patients with Hypercholesterolemia (N=177/133) | Up to 27% (25%) | 40, 80, 120 | 12 Wks |
| 005 | Phase 2a in Patients with Hypercholesterolemia and Type 2 Diabetes (N=60/30) | 43% (39%) | 80, 120 | 4 Wks |
| 006 | Phase 2a in Patients with Hypercholesterolemia and a History of Statin Intolerance (N=56/37) | 32% (29%) | 60, 120, 180, 240 | 8 Wks |
| 007 | Phase 2a in Patients with Hypercholesterolemia Added-on to Atorvastatin 10 mg (N=58/42) | 22% (22%) | 60, 120, 180, 240 | 8 Wks |
| 008 | Phase 2b in Patients with Hypercholesterolemia with or without Statin Intolerance vs. Ezetimibe (N=349/249) | Up to 30% (1002)<br>Up to 48% (1002 + ezetimibe) | 120, 180,<br>120 + ezetimibe, 180 + ezetimibe | 12 Wks |
| 009 | Phase 2b in Patients with Hypercholesterolemia while on Stable Statin Therapy (N=134/88) | | 120, 180 | 12 Wks |
| 014 | Phase 2a in Patients with Hypercholesterolemia and Hypertension (N=143/72) | | 180 | 6 Wks |

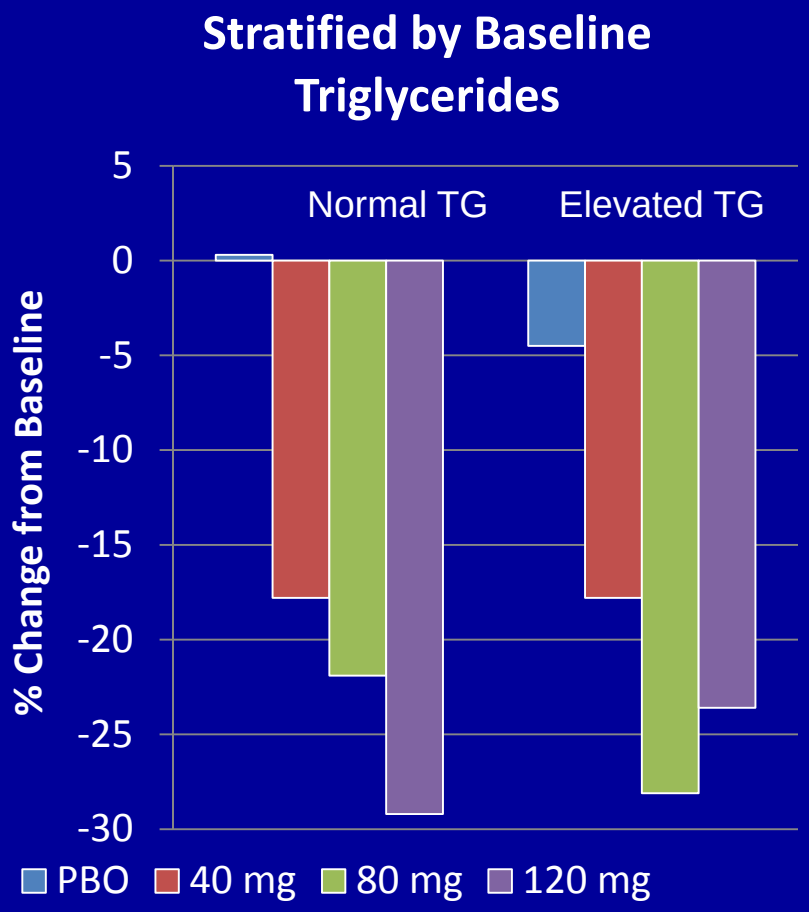
*Average LDL-C % Change from Baseline

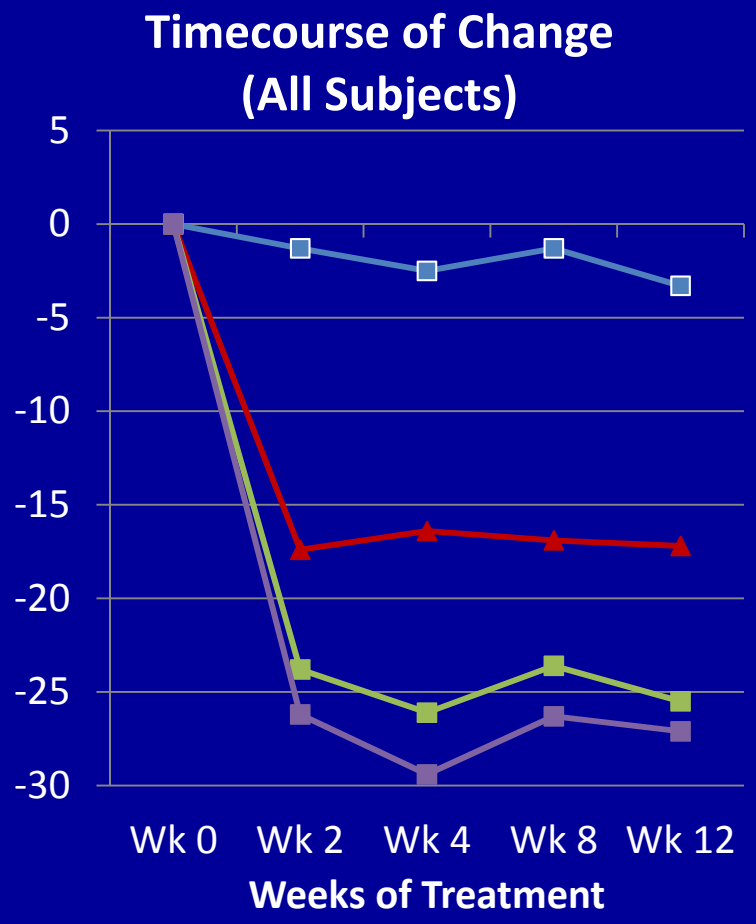
# Efficacy and safety of ETC-1002-003in patients with hypercholesterolemia

- Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial
- 177 patients with LDL-C 130–220 mg/dL, stratified by baseline TG (<150 mg/dL or 150–<400 mg/dL)
- Randomized to 40, 80, or 120 mg of ETC-1002 or placebo once daily for 12 weeks
- Endpoints: changes in LDL-C (primary endpoint), other lipids, and cardiometabolic risk factors; safety

Ballantyne CM et al. *J Am Coll Cardiol* 2013;62:1154-62.

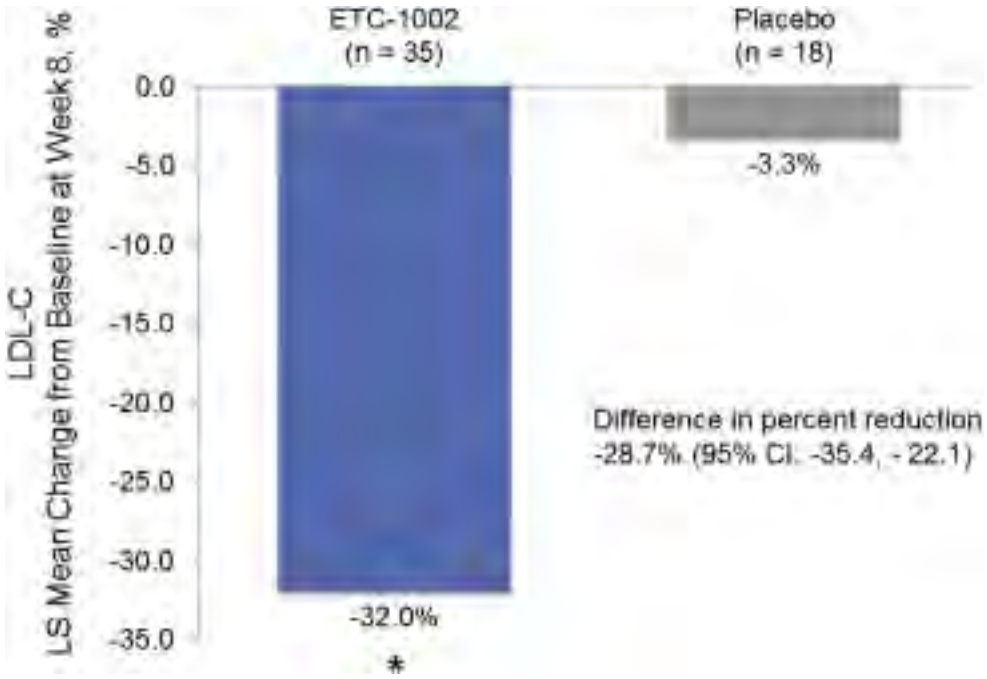
# ETC-1002-003: Percent Change from Baseline in LDL-C




Ballantyne CM et al. *J Am Coll Cardiol* 2013;62:1154-62.

# Use of ETC-1002-006 to treat hypercholesterolemia in patients with statin intolerance

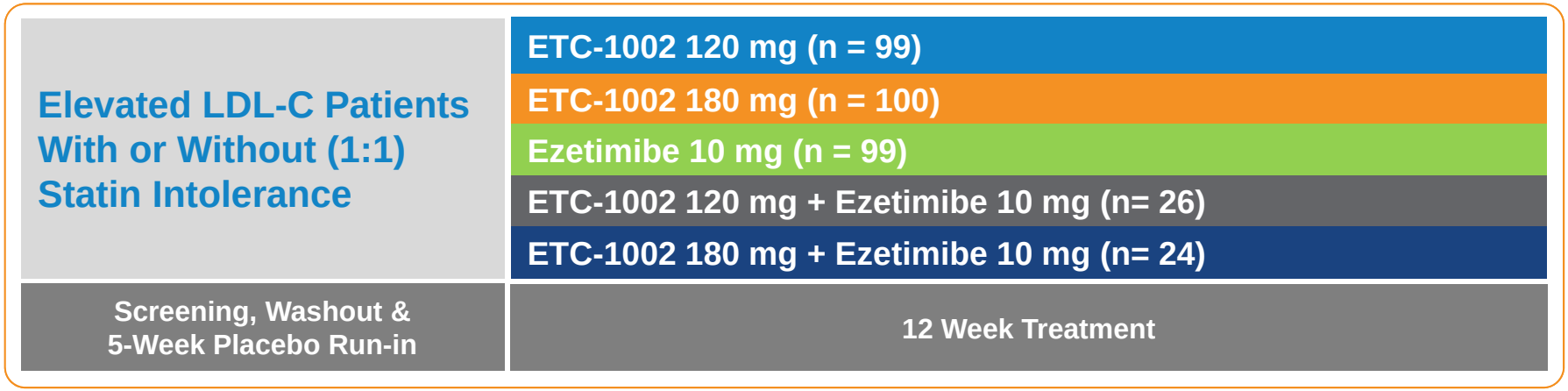



Least squares mean percent change from baseline to week 8 in calculated LDL-C (primary endpoint). *$P$ < .0001 based on analysis of covariance model with effect of treatment and baseline value as a covariate..

Thompson PD et al. *J Clin Lipidol* 2015;9:295-304.

# ETC-1002-008 PHASE 2B STUDY

*OVERVIEW AND OBJECTIVES – "STATIN INTOLERANT STUDY"*




- Characterize the effects of ETC-1002 vs. ezetimibe in patients with (n = 177) or without (n = 171) statin intolerance (total n = 348)
  - Assess the LDL-C lowering of ETC-1002 monotherapy vs. ezetimibe (primary endpoint)
  - Assess ETC-1002 dose response
  - Assess additional lipid and cardiometabolic biomarkers (non-HDL-C, HDL-C, ApoB, ApoA-I, TC, TG, hsCRP and LDL-, HDL- and VLDL- particle number)
  - Assess the LDL-C lowering of ETC-1002 + ezetimibe combination vs. ezetimibe
  - Characterize the safety, tolerability, and rates of muscle-related adverse events of ETC-1002, ezetimibe and the combination

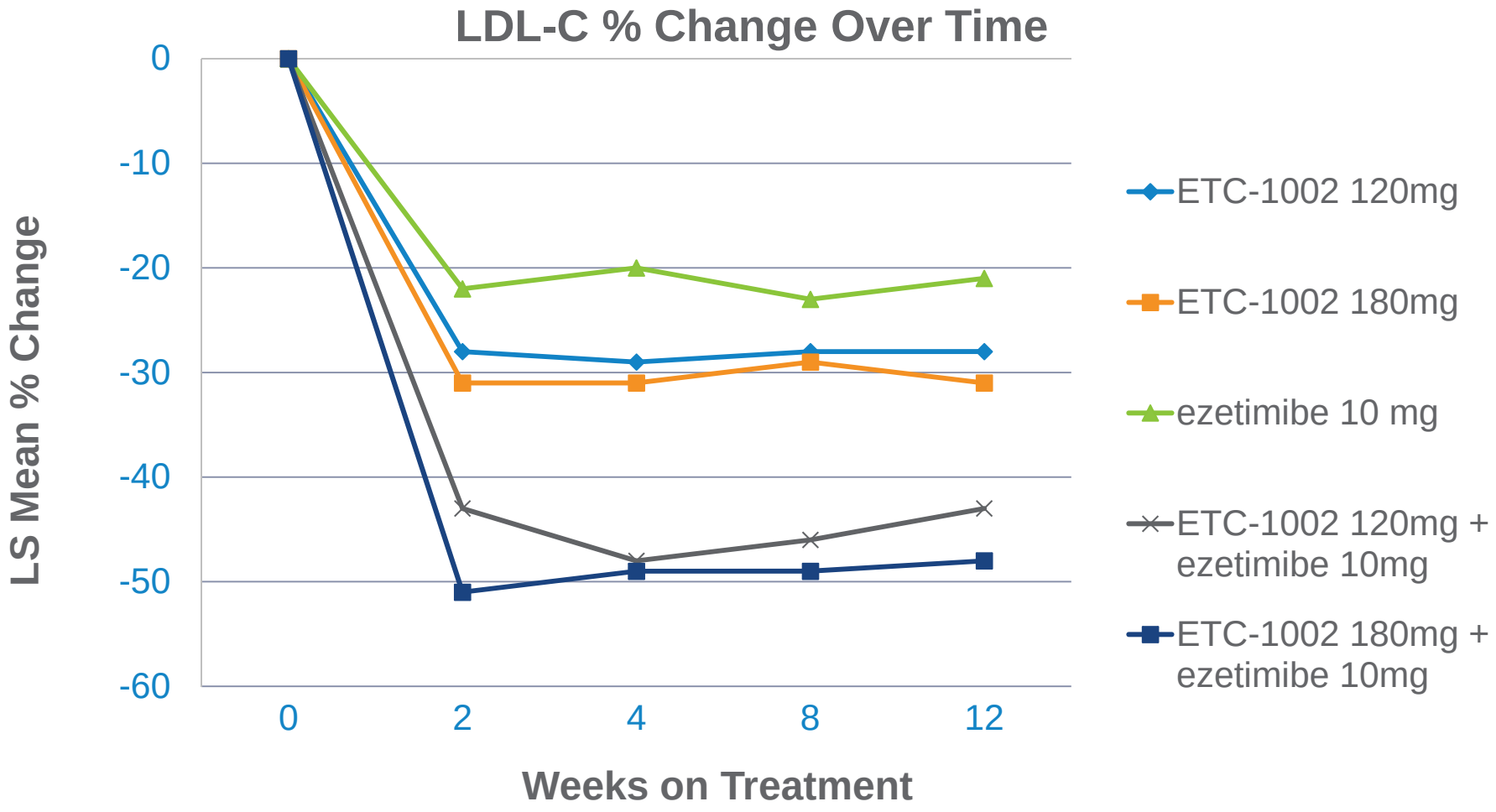
Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# DEFINITION OF STATIN INTOLERANCE (SI)

- Statin intolerance (for relevant patients only) defined as patient-reported inability to tolerate at least 2 statins due to skeletal muscle-related symptoms (other than those due to strain or trauma), such as pain, aches, weakness, or cramping, that began or increased during statin therapy and resolved when statin therapy was discontinued
- Inability to tolerate at least 2 statins must meet the following criteria:
  - Inability to tolerate one statin at the lowest daily approved dose, defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg (current treatment with less than the lowest daily approved dose of a statin [i.e., skipping days/intermittent therapy provided that the average daily dose is less than the lowest daily approved dose] will be considered equivalent to not tolerating one statin at the lowest daily approved dose) **AND**
  - Inability to tolerate another statin at any dose
- Patients NOT meeting this definition will be considered statin tolerant (ST)

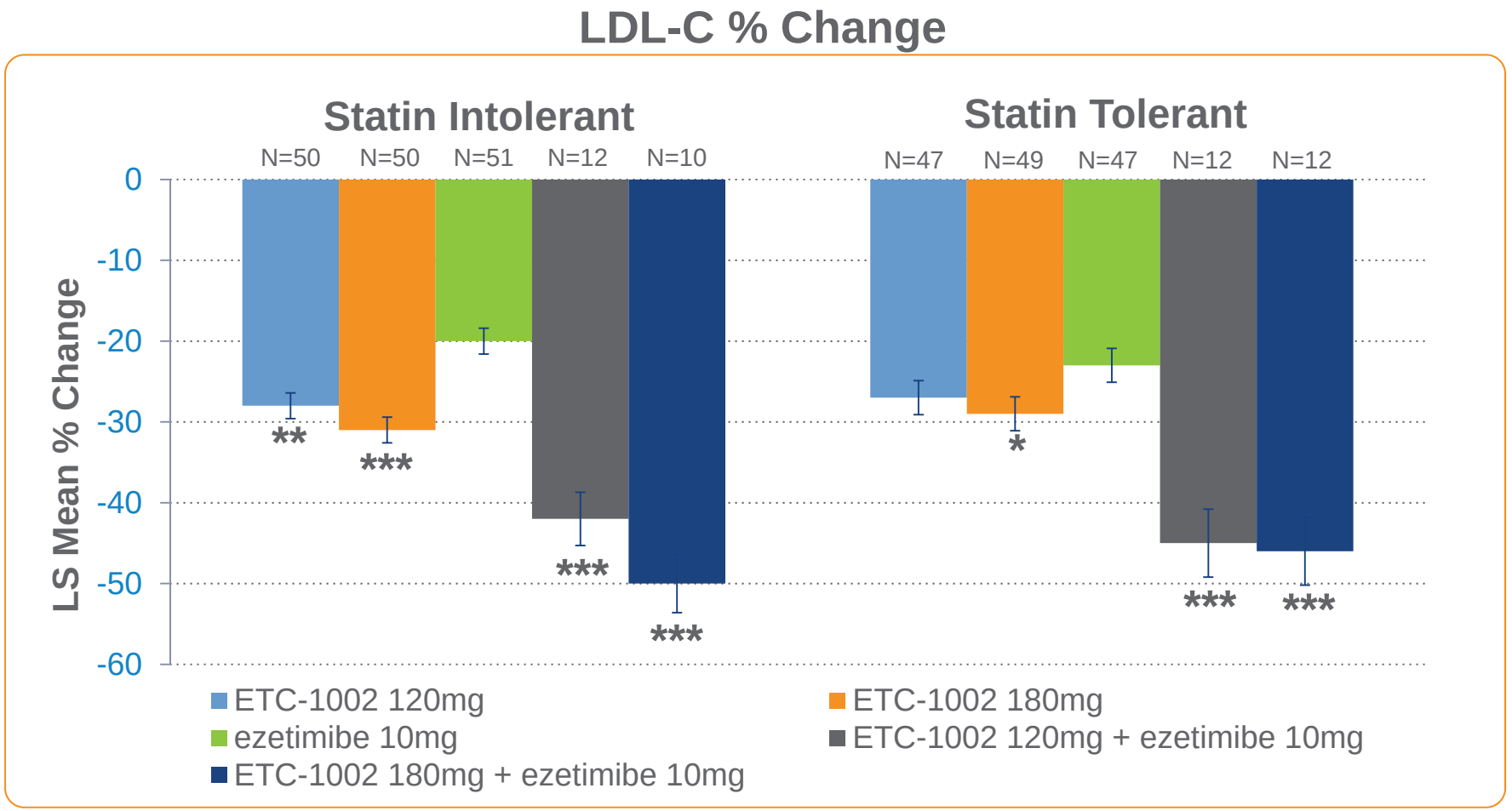
Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# LDL-C REDUCTION OCCURRED WITHIN FIRST 2 WEEKS OF DOSING AND WAS SUSTAINED OVER THE TREATMENT PERIOD




Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

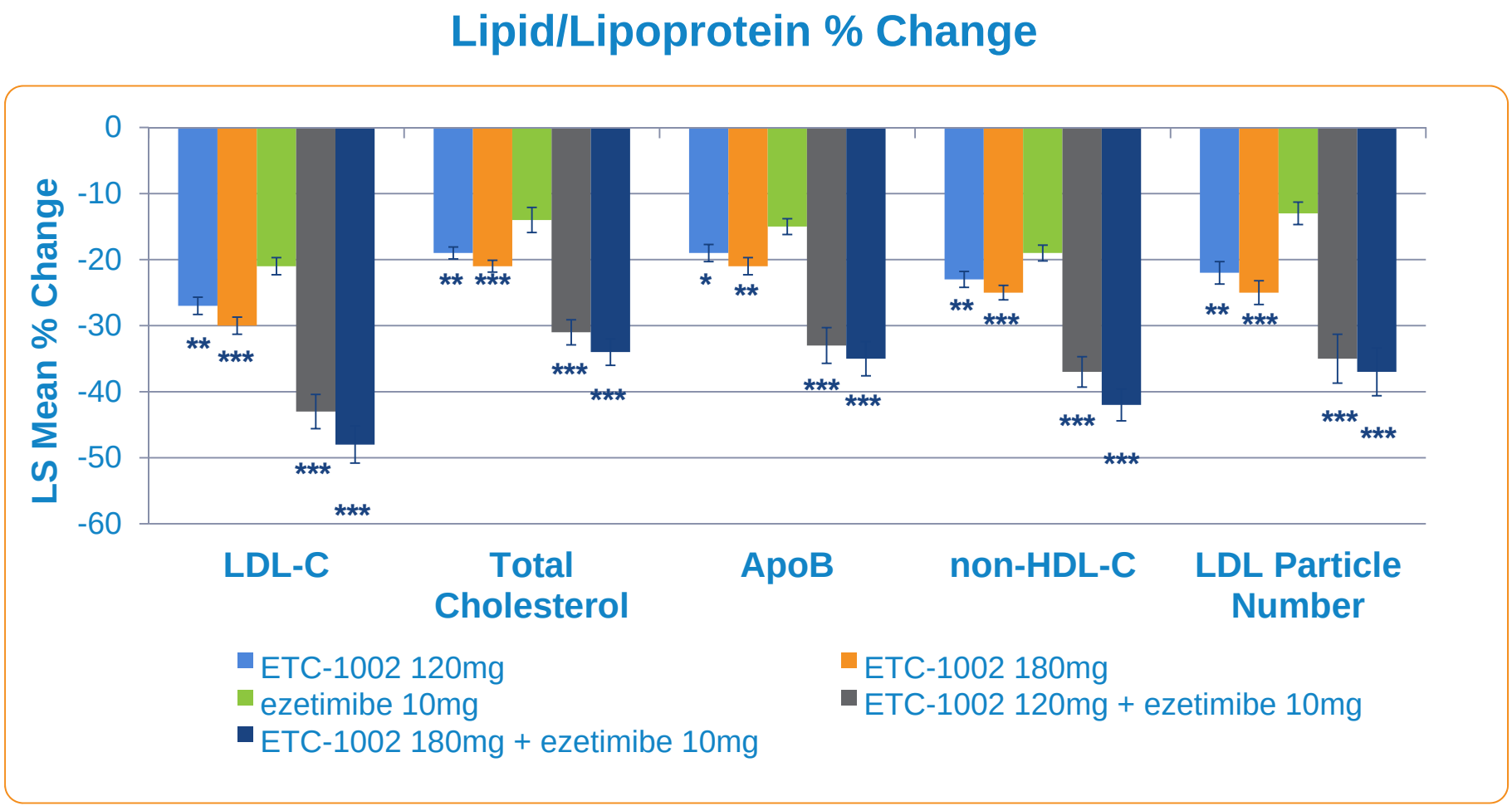
# ETC-1002 LOWERED LDL-C SIMILARLY IN BOTH STATIN INTOLERANT AND TOLERANT PATIENTS




*p≤0.05 vs. ezetimibe **p≤0.01 vs. ezetimibe ***p<0.0001 vs. ezetimibe

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

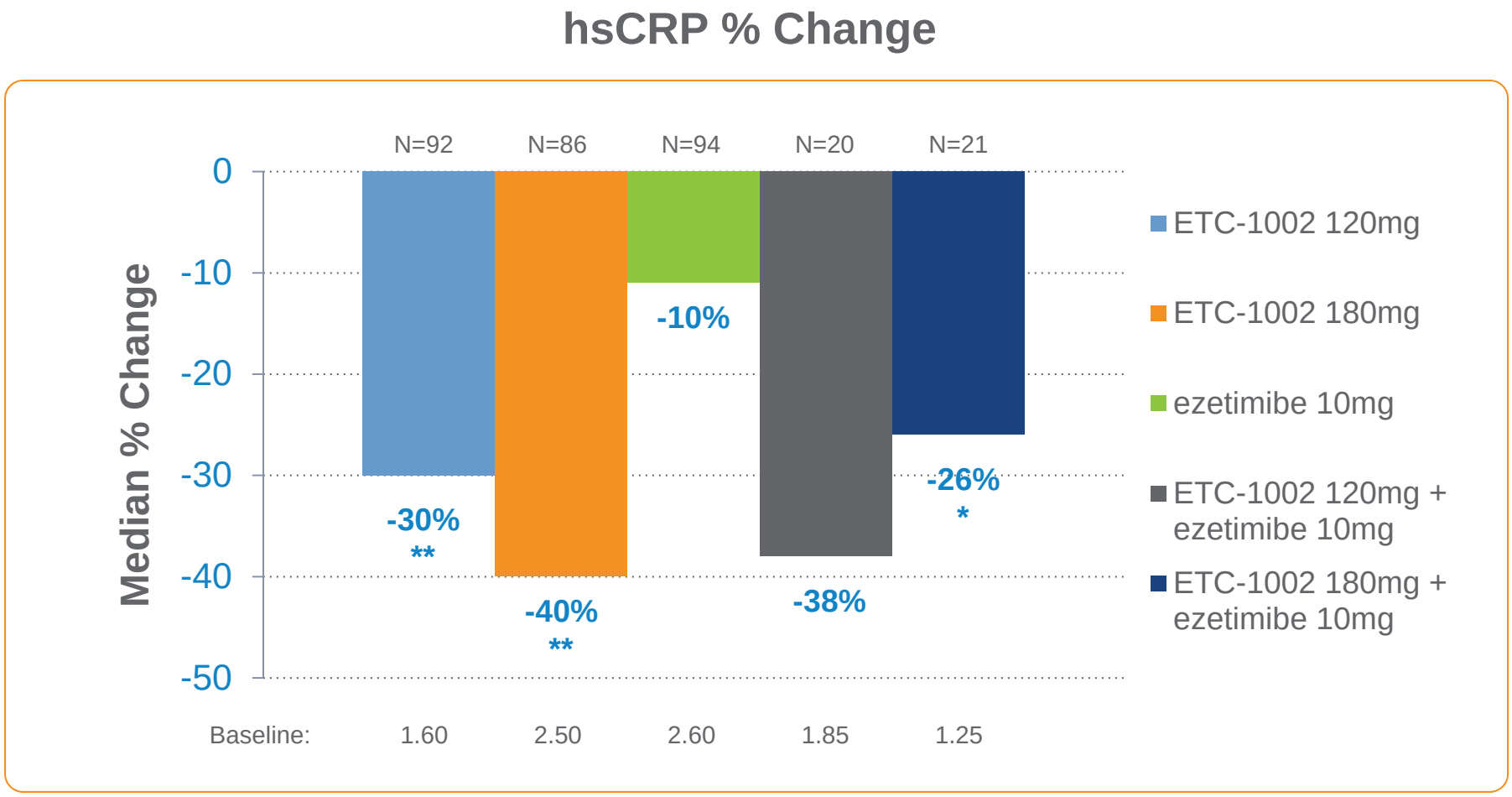
# LOWERING OF ATHEROGENIC LIPIDS AND LIPOPROTEINS WAS CONSISTENT WITH LDL-C LOWERING (1002-008)




***p≤0.05 vs. ezetimibe** ****p≤0.01 vs. ezetimibe** *****p<0.0001 vs. ezetimibe**

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# ETC-1002 ALSO LOWERED HSCRP MORE THAN EZETIMIBE




*p≤0.05 vs. ezetimibe **p≤0.01 vs. ezetimibe

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# INCONSISTENT CHANGES WERE NOTED IN HDL PARAMETERS

## HDL Parameter % Change

| Treatment Group | n | Baseline Mean (SD) | Week 12 Mean (SD) | % Change from Baseline | |
|---|---|---|---|---|---|
| | | | | LS Mean (SE) | p-value vs. ezetimibe |
| **HDL-C (mg/dL)** | | | | | |
| ETC-1002 120mg | 97 | 54 (16) | 50 (15) | -5.84% (1.4) | <0.0001 |
| ETC-1002 180mg | 99 | 52 (13) | 50 (16) | -4.80% (1.4) | <0.0001 |
| Ezetimibe 10mg | 98 | 49 (12) | 51 (13) | 5.00% (1.4) | - |
| ETC-1002 120mg + eze 10mg | 24 | 52 (15) | 50 (15) | -3.08% (2.8) | 0.0111 |
| ETC-1002 180mg + eze 10mg | 22 | 50 (16) | 49 (20) | -3.72% (3.0) | 0.0082 |

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# INCONSISTENT CHANGES WERE NOTED IN HDL PARAMETERS

## HDL Parameter % Change

| Treatment Group | n | Baseline Mean (SD) | Week 12 Mean (SD) | % Change from Baseline | |
|---|---|---|---|---|---|
| | | | | LS Mean (SE) | p-value vs. ezetimibe |
| **ApoA-I (mg/dL)** | | | | | |
| ETC-1002 120mg | 92 | 161 (28) | 159 (25) | -0.19% (1.1) | 0.1811 |
| ETC-1002 180mg | 86 | 160 (28) | 159 (30) | 0.13% (1.2) | 0.2610 |
| Ezetimibe 10mg | 94 | 152 (25) | 154 (23) | 1.97% (1.1) | - |
| ETC-1002 120mg + eze 10mg | 20 | 164 (30) | 156 (27) | -2.77% (2.4) | 0.0804 |
| ETC-1002 180mg + eze 10mg | 21 | 154 (20) | 149 (25) | -4.09% (2.4) | 0.0221 |
| **HDL Particle Number (µmol/L)** | | | | | |
| ETC-1002 120mg | 92 | 34 (7) | 35 (6) | 5.00% (1.3) | 0.3769 |
| ETC-1002 180mg | 83 | 33 (6) | 35 (7) | 6.19% (1.4) | 0.8061 |
| Ezetimibe 10mg | 93 | 32 (5) | 34 (6) | 6.66% (1.3) | - |
| ETC-1002 120mg + eze 10mg | 19 | 35 (7) | 37 (7) | 7.34% (2.9) | 0.8333 |
| ETC-1002 180mg + eze 10mg | 20 | 33 (5) | 35 (5) | 5.10% (2.8) | 0.6169 |

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# ETC-1002'S EFFECT ON TRIGLYCERIDES APPEARS TO BE NEUTRAL

## Triglyceride % Change

| Treatment Group | n | Baseline Median | Week 12 Median | % Change from Baseline | |
|---|---|---|---|---|---|
| | | | | Median (IQR) | p-value vs. ezetimibe |
| **Triglycerides (mg/dL)** | | | | | |
| ETC-1002 120mg | 97 | 136 | 143 | 0% (42) | 0.1110 |
| ETC-1002 180mg | 99 | 161 | 160 | -3% (46) | 0.5428 |
| Ezetimibe 10mg | 98 | 163 | 146 | -7% (35) | - |
| ETC-1002 120mg + eze 10mg | 24 | 154 | 131 | -19% (25) | 0.2235 |
| ETC-1002 180mg + eze 10mg | 22 | 158 | 130 | -12% (37) | 0.3546 |

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# MUSCLE-RELATED AES WERE SIMILAR BETWEEN THE GROUPS IN STATIN INTOLERANT PATIENTS

| Muscle-Related Treatment Emergent Adverse Events (AEs) | Number (%) of Patients | | | | |
|---|---|---|---|---|---|
| | ETC-1002 120mg N=51 | ETC-1002 180mg N=51 | ezetimibe 10mg N=51 | ETC-1002 120mg + eze 10mg N=12 | ETC-1002 180mg + eze 10 mg N=12 |
| **Overview of Muscle-Related AEs in Statin Intolerant Patients** | | | | | |
| Any Muscle-related AE | 7 (14%) | 6 (12%) | 9 (18%) | 2 (17%) | 2 (17%) |
| Leading to Discontinuation | 1 (2%) | 2 (4%) | 4 (8%) | 0 | 0 |
| **Muscle-Related AE(s) in Statin Intolerant Patients by MedDRA Preferred Term** | | | | | |
| Muscle spasms | 3 (6%) | 2 (4%) | 1 (2%) | 0 | 0 |
| Muscular weakness | 2 (4%) | 1 (2%) | 1 (2%) | 0 | 0 |
| Musculoskeletal chest pain | 0 | 1 (2%) | 0 | 0 | 0 |
| Musculoskeletal stiffness | 0 | 0 | 1 (2%) | 0 | 0 |
| Myalgia | 2 (4%) | 1 (2%) | 6 (12%) | 2 (17%) | 1 (8%) |
| Pain in extremity | 1 (2%) | 1 (2%) | 3 (6%) | 0 | 1 (8%) |
| Sensation of heaviness | 0 | 0 | 1 (2%) | 0 | 0 |

Pre-specified analysis of all *Musculoskeletal and Connective Tissue Disorders AE terms* except arthralgia, back pain, bone pain, bunion, bursitis, groin pain, intervertebral degeneration, intervertebral disc protrusion, joint stiffness, joint swelling, neck pain, osteoarthritis, plantar fasciitis, rotator cuff syndrome, and synovial cyst.

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# LABORATORY

| Lab Abnormality (Repeated and Verified) | Number (%) of Patients | | | | |
|---|---|---|---|---|---|
| | ETC-1002 120mg N=99 | ETC-1002 180mg N=100 | ezetimibe 10mg N=99 | ETC-1002 120mg + eze 10mg N=26 | ETC-1002 180mg + eze 10 mg N=24 |
| ALT or AST > 3 x ULN | 1 (1%) | 2 (2%) | 1 (1%) | 1 (4%) | 0 |
| CK > 5 x ULN | 0 | 0 | 0 | 1 (4%) | 0 |

| Lab Parameter | | Mean (SD) at Baseline and Week 12 | | | | |
|---|---|---|---|---|---|---|
| Uric Acid | Baseline<br>Week 12 | 5.8 (1.3)<br>6.8 (1.5) | 6.0 (1.3)<br>7.0 (1.6) | 5.8 (1.4)<br>5.7 (1.6) | 6.3 (1.3)<br>6.9 (1.5) | 5.9 (1.4)<br>7.0 (1.5) |
| Homocysteine | Baseline<br>Week 12* | 11.5 (3.3)<br>13.5 (3.9) | 11.3 (2.9)<br>13.6 (3.7) | 12.0 (4.1)<br>11.5 (3.5) | 11.4 (2.7)<br>12.9 (3.3) | 11.1 (3.1)<br>13.5 (4.6) |
| Hemoglobin | Baseline<br>Week 12 | 14.4 (1.2)<br>13.9 (1.3) | 14.3 (1.2)<br>13.9 (1.1) | 14.2 (1.2)<br>14.1 (1.1) | 14.3 (1.6)<br>13.9 (1.3) | 14.4 (1.5)<br>13.9 (1.4) |
| Alkaline Phosphatase | Baseline<br>Week 12 | 77 (20)<br>62 (14) | 82 (22)<br>65 (16) | 79 (22)<br>80 (21) | 83 (20)<br>70 (19) | 74 (19)<br>60 (16) |

Normal range for uric acid (3-7$^{F}$/4-8.5$^{M}$ mg/dL); homocysteine (6-15 µmol/L); hemoglobin (12-16$^{F}$/13.6-18$^{M}$ g/dL); and alkaline phosphatase (37-116 U/L)

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

# ETC-1002-008 STUDY

*SUMMARY*

- This was the largest ETC-1002 clinical study completed to date (n=348)
- In patients receiving ETC-1002 monotherapy:
  - LDL-C lowering of up to 30% with ETC-1002 – significantly more LDL-C lowering than ezetimibe
  - hsCRP lowering of up 40% with ETC-1002 – significantly more hsCRP lowering than ezetimibe
  - ETC-1002 appeared to be safe and well tolerated
- In patients receiving ETC-1002 and ezetimibe:
  - LDL-C lowering of up to 48%
  - The combination appeared to be safe and well tolerated
- In patients treated with ETC-1002, including those with statin intolerance, there was no increases in muscle-related adverse events as compared to ezetimibe

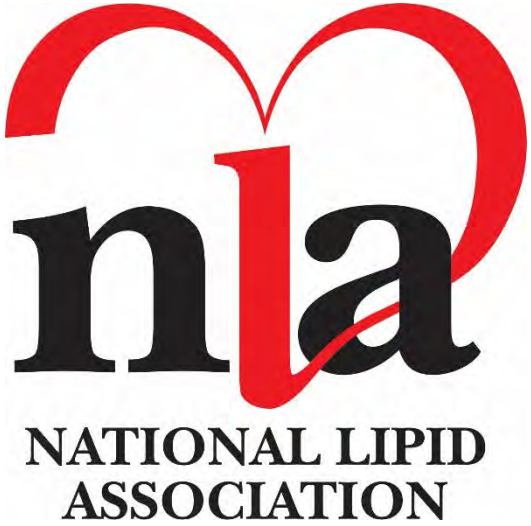
Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).

"ETC-1002 Incrementally Lowers Low Density Lipoprotein-Cholesterol in Patients with Hypercholesterolemia Receiving Stable Statin Therapy"

to be presented at AHA Scientific Sessions, 9 November 2015.

# Summary

- In phase 2 studies, ETC-1002 has been shown to reduce LDL-C as monotherapy, combined with ezetimibe, and added to statin therapy
- Although rodent studies had suggested potential effects of inhibition of ATP citrate lyase on both fatty acid synthesis and cholesterol synthesis, the clinical profile in humans shows major effect is on cholesterol synthesis
- Phase 3 program will be needed to gain more information on both efficacy and safety in a larger patient population with longer exposure




# Clinical Lipidology: A Subspecialty Whose Time Has Come

**Carl E. Orringer, MD, FACC, FNLA**

# Goals of Today's Presentation

- To define the subspecialty of Clinical Lipidology
- To identify major ongoing clinical controversies in our field
- To define the scope of knowledge required for excellence in clinical lipidology consultation as defined by the NLA Core Curriculum
- To discuss the educational initiatives designed by the NLA to enhance the knowledge base of clinical lipidology consultants
- To explore the steps that have been taken by the ABCL and ACCL to document academic proficiency in Clinical Lipidology
- To review current obstacles to the recognition of clinical lipidologists as subspecialists and suggest solutions
- To define the steps that are being taken by the NLA to achieve external recognition of Clinical Lipidology as a subspeciality

# Definition of Clinical Lipidology

- An academic discipline focused primarily on knowledge of the pathophysiology, diagnosis and management of lipid and lipoprotein disorders to reduce or prevent detrimental clinical consequences
- Primary focus on ASCVD prevention, but also on prevention and treatment of triglyceride-related complications (pancreatitis, hepatosplenomegaly, xanthomas); and of disorders due to severely compromised lipid transport (fat soluble vitamin deficiencies, central and peripheral neuropathy and growth retardation).

# Which Health Professionals are Involved?

- Basic and clinical researchers
- Academic and practicing primary and subspecialty care physicians
- Pharmacists
- Registered dietitian-nutritionists
- Exercise physiologists
- Nurses
- Nurse educators
- Health behavior professionals

# Current Patient Care Controversies in the Domain of the Clinical Lipidiologist

- Which guidelines should be used and when?
- Should the main focus be on statin adherence or on reduction of atherogenic cholesterol?
- Is statin dosage titration proven and useful?
- Should we set lipid/lipoprotein goals?
- How often and with what objective(s) should lipid/lipoprotein monitoring be performed?
- Can we support the viewpoint that “lower is better”?
- When should non-statins be used?
- How do we best define success or failure of therapy?
- When should population-based versus individualized lipid management be used?

# More Lipidology Controversies

- How is ASCVD risk best estimated?
- Is risk factor counting of value?
- Are risk calculators of value, and if so, when and which one?
- Is long-term risk defined enough to be of value?
- When should blood biomarkers and/or subclinical atherosclerosis testing be done?
- When, at what level, and how should TG be addressed?
- What is the best strategy for lipid management in special populations?

# Special Populations

- Children and adolescents
- Older patients
- Women throughout the lifespan
- Ethnic groups: African-Americans, Hispanics, south Asian Indians, American Indians/Alaska natives, others
- Patients with chronic inflammatory states
- HIV patients
- Patients with progressive ASCVD despite evidence-based therapy

# Key Drivers of Clinical Lipidology Education in the U.S.

- The National Cholesterol Education Program Adult Treatment Panels I, II and III
- The American College of Cardiology/ American Heart Association
- **The National Lipid Association**

# The Role of the NLA in Clinical Lipidology Education

# History of the NLA

**1997:** Southeast Lipid Association **(**SELA) was established by a group of pioneering lipid researchers and clinicians

**2000:** SELA BOD voted to formulate a national association to promote the specialization of Clinical Lipidology

**2002:** NLA officially incorporated in Florida as a 501(c)6 non-profit professional membership organization

Southeast Lipid Association

**Today…**

- **5 Regional Chapters:** Southeast, Northeast, Midwest, Southwest, Pacific
- **3,000+ members**
- **Regularly issues recommendations, position statements, consensus statements, clinical practice tools, patient education materials…**

# NLA Core Curriculum (Updated July 2015)

- A collated outline developed by a committee of NLA academicians that enumerates and classifies a series of topics, the working knowledge of which serves as a basis for expertise in the management of lipid disorders and facilitates
  - High quality patient care
  - Educational activities to enhance provider knowledge
  - The identification of core competencies of individuals involved in lipid management

# NLA Clinical Lipidology Core Curriculum

- Classification, measurement and metabolism of lipids and lipoproteins
- Pathophysiology and vascular biology of atherosclerosis
- Pathophysiology and diagnosis of genetic dyslipidemias
- Evidence-based medicine and clinically applicable statistical methods
- Identification and clinical significance of dyslipidemia-related risk factors, risk assessment tools, novel risk markers and subclinical atherosclerosis testing
- The appropriate use of national and international lipid management recommendations

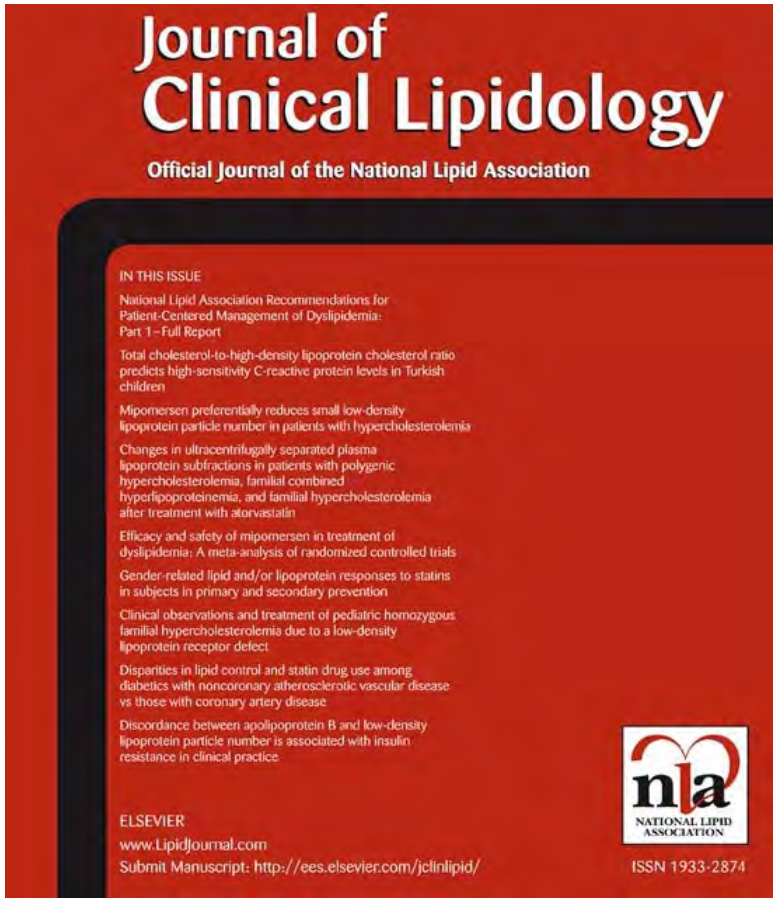
# NLA Clinical Lipidology Core Curriculum

- Dietary, exercise and behavioral interventions for dyslipidemia prevention and treatment
- Pharmacologic lipid therapy, including knowledge of drug metabolism, interactions and management of drug-related side effects, and the use of drugs for rare lipid disorders
- An understanding of indications for, expected benefits of, and patient safety issues related to LDL apheresis
- Dyslipidemia management in patients with other ASCVD risk factors and other complicating medical conditions
- Management of lipid disorders in special populations

# NLA Educational Activities to Promote Clinical Lipidology

- NLA Annual Meeting and regional Clinical Lipid Updates
- NLA enduring materials (JCL, Lipid Spin)
- NLA self-assessment programs
- Web-based education (Lipid Insights; LipidEducation.com; NLA slide sets)
- Masters in Lipidology
- Lipid Academy
- Lipid Insights
- JCL Annual Summary of Clinical Lipidology

# The Journal of Clinical Lipidology




- First edition 2007
- Bimonthly Elsevier journal
- Focuses on science and practice of Clinical Lipidology
- Available in print, web or as iOS/Android app

Editor in Chief: W. Virgil Brown, MD, FNLA

# The Journal of Clinical Lipidology


- Included in Medline and PubMed
- 2014 impact factor 3.904 (83rd %-ile of 254 journals in pharmacy and pharmacology)
- Average monthly article downloads: 6, 615

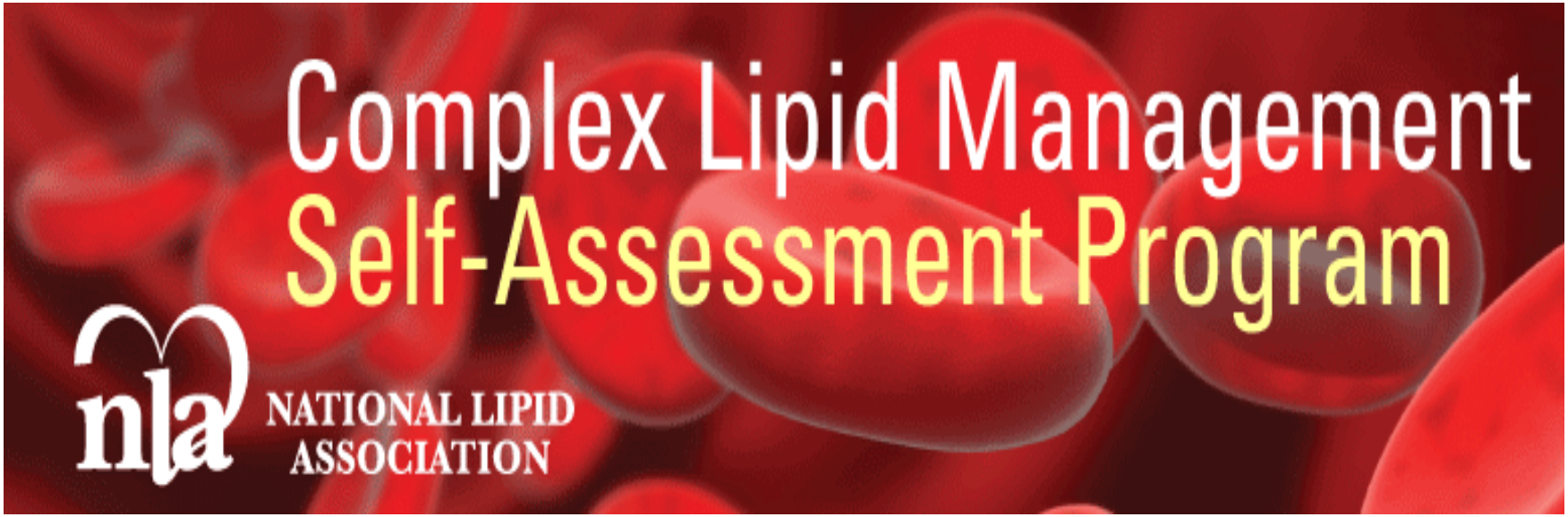
# Lipid*Spin*


- Quarterly magazine
- Each issue sponsored by a regional chapter
- 9 - 12 articles per issue
  - Clinical reviews
  - Practical articles
  - Editorials

# NLA Self Assessment Program-Volume 3


- Volume 1: The science of Clinical Lipidology
- Volume 2: Cardiometabolic risk assessment and management
- Volume 3: Therapeutic lifestyle change
- Volume 4: Pharmacologic management of dyslipidemia
- Volume 5: Consultative issues in Clinical Lipidology

525 multiple choice questions
150 CME hours
170 ABIM MOC credit hours
Available in print or on-line




# CLM-SAP 17: Guidelines in Clinical Lipidology – Concepts and Controversies

**Available on web at: www.lipid.org/education/clmsap**

**CLM-SAP App available on:**

All of the following except for which one are basic tenets of the National Lipid Association Recommendations for the Patient-Centered Management of Dyslipidemia?

- A) An elevated level of cholesterol carried by circulating apolipoprotein B-containing lipoproteins (non-HDL-C and LDL-C, termed atherogenic cholesterol) is a root cause of atherosclerosis, the key underlying process contributing to most clinical ASCVD events.
- B) Reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies.
- C) For patients in whom lipid-lowering drug therapy is indicated, the identification of statin benefit groups and treatment based upon such identification is the optimal method for reducing ASCVD risk.
- D) The intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event.
- E) Atherosclerosis is a process that often begins early in life and progresses for decades before resulting in a clinical ASCVD event. Therefore, both intermediate-term and long-term/lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies.

**Correct! The answer is C) For patients in whom lipid-lowering drug therapy is indicated, the identification of statin benefit groups and treatment based upon such identification is the optimal method for reducing ASCVD risk.**

Options A, B, D and E described in this question are basic tenets of the 2014 NLA Recommendations for the Patient-Centered Management of Dyslipidemia. Option C, the correct answer, is the only incorrect statement. While the NLA Expert Panel recognized the importance of identifying those patients who would most likely benefit from lipid- lowering therapy and initiating and maintaining such therapy, their approach to ASCVD prevention is based on the initiation and maintenance of patient-specific lipid and lipoprotein goal-directed reduction in atherogenic cholesterol (non-HDL-C and LDL-C). Such reduction is accomplished by lifestyle therapy, often with supplemental moderate- or high-statin, and if necessary, non-statin therapy, the intensity of which depends upon the patient's estimated absolute ASCVD risk.


- Offers an in-depth review of the core curriculum in Clinical Lipidology for healthcare professionals who desire to practice at an advanced level within the field and/or are pursuing ABCL certification
- Available formats: Live or web-based
- Live activity supplemented with Q and A sessions using an audience response system to facilitate interactive learning
- Access to resource page containing downloadable resources and additional self-study materials


**Curriculum:**

- Lipoprotein Metabolism, Genetics and Familial Lipid Disorders
- Vascular Biology and Atherosclerosis Pathogenesis
- Evidence-Based Medicine, Cardiovascular Risk Assessment and Guidelines
- Cardiovascular Biomarkers, Atherosclerosis Imaging and Evidence-based Practice
- Obesity, Metabolic Syndrome and Diabetes Mellitus
- Nutrition and Non-Pharmacologic Therapy
- Pharmacology Part I: Lipid Lowering Drugs, Drug Interactions and Drug Safety
- Pharmacology Part II: Randomized Controlled Trials, Evidence-Based Treatment and Combination Therapy
- Complex Cases and Consultative Lipidology


- Offers an introduction to applied lipid science
- Open to all healthcare professionals interested in developing a core competency in the diagnosis and treatment of dyslipidemia.
- Serves as a preparatory course for other advanced lipid training.
- Available formats: Live or web-based
- Live activity includes interactive group discussions on literature evaluation and patient cases

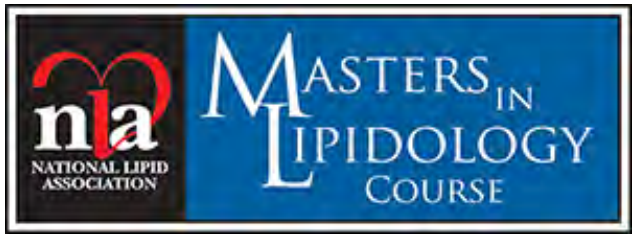

## Curriculum:

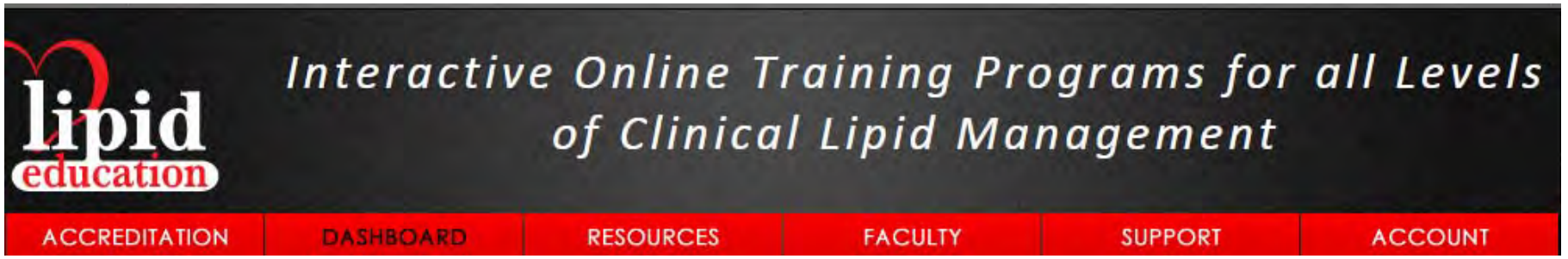
- Lipids, Lipoproteins and Atherosclerosis
- Clinical Trials
- Primary Literature Evaluation and Discussion
- Dyslipidemia Diagnosis and Risk Assessment
- Pharmacologic Therapies
- Therapeutic Lifestyle Changes
- Overview of Clinical Guidelines in Lipid Management
- Challenging Patient Cases

# LipidEducation.com

- Provides online adaptation of the NLA's live training courses
- Slide-audio presentations recorded by expert faculty
- Evidence-based lecture notes and references
- Embedded assessment questions








- Multimedia slide lecture modules (with downloadable PDFs of slide-audio presentation modules with evidence-based notes and references)
- Learning reinforcement test questions and answers
- A complete pre- and post-test to determine your achievement of the educational objectives for the program
- A personalized learning dashboard containing your assignments, transcript and assessment scores
- Glossaries of common terms, common abbreviations and key clinical studies
- A complete list of references per module
- Links to additional educational resources

## Nicole's Master's in Lipidology Course Curriculum

*Estimated Total Time for Completion: 12.5 hours*

Course Progress 37% Complete

**PRE-TEST** Masters in Lipidology Pre-Test

*You have already completed the Pre-Test.*

**PRE-COURSE** Pre-Course Reading Materials

*Prior to completing the course modules, it is recommended that you review the materials presented here. The 'NLA Recommendations for Patient-Centered Management of Dyslipidemia provides a detailed overview of available clinical practice guidelines and recommendations related to lipid management to reduce atherosclerotic cardiovascular risk.This resource may be used to provide an updated knowledge base before beginning the activity or may serve as a reference to which clinicians may refer when taking the program. The NLA Annual Summary of Clinical Lipidology 2015 provides updates based on emerging science, clinical considerations, and new NLA position and consensus statements.*

*After reviewing these materials, you should proceed to the modules of the course.*

**MODULE 1** Lipoprotein Metabolism, Genetics, and Familial Lipid Disorders

*You have already completed this module.*

**MODULE 2** Vascular Biology and Atherosclerosis Pathogenesis

*You have already completed this module.*

**MODULE 3** Evidence Based Medicine, Cardiovascular Risk Assessment, and Practice Guidelines

*You have already completed this module.*


**Seamlessly move backwards and forward**

**View notes related to specific slides**

**Search for specific terms**

National Lipid Association

# Lipid Insights

a virtual journal club

- 60-minute interactive CME Webcast with Q&A
- Intended to encourage critical appraisal skills, impact clinical practice and encourage regular literature review
- Available both to NLA members and non-members
- Offered quarterly
- CME/CE accredited

National Lipid Association

# Lipid Insights

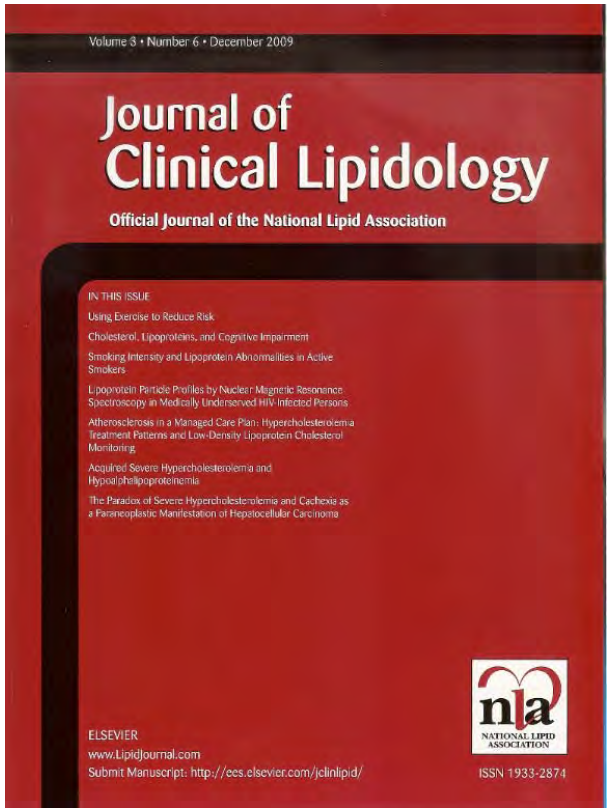
a virtual journal club

## Previous Webcast Topics:

- A Case Study in Dyslipidemia Management- Incorporating the NLA Recommendations into Practice
- Lysosomal Acid Lipase (LAL) Deficiency
- New Therapies for HoFH
- The Role of Omega-3's in Cardiovascular Disease
- CETP Inhibition - An Important Potential Strategy in Reducing Cardiovascular Events
- The Effects of Statin Therapy on Diabetes Incidence and Glycemic Control

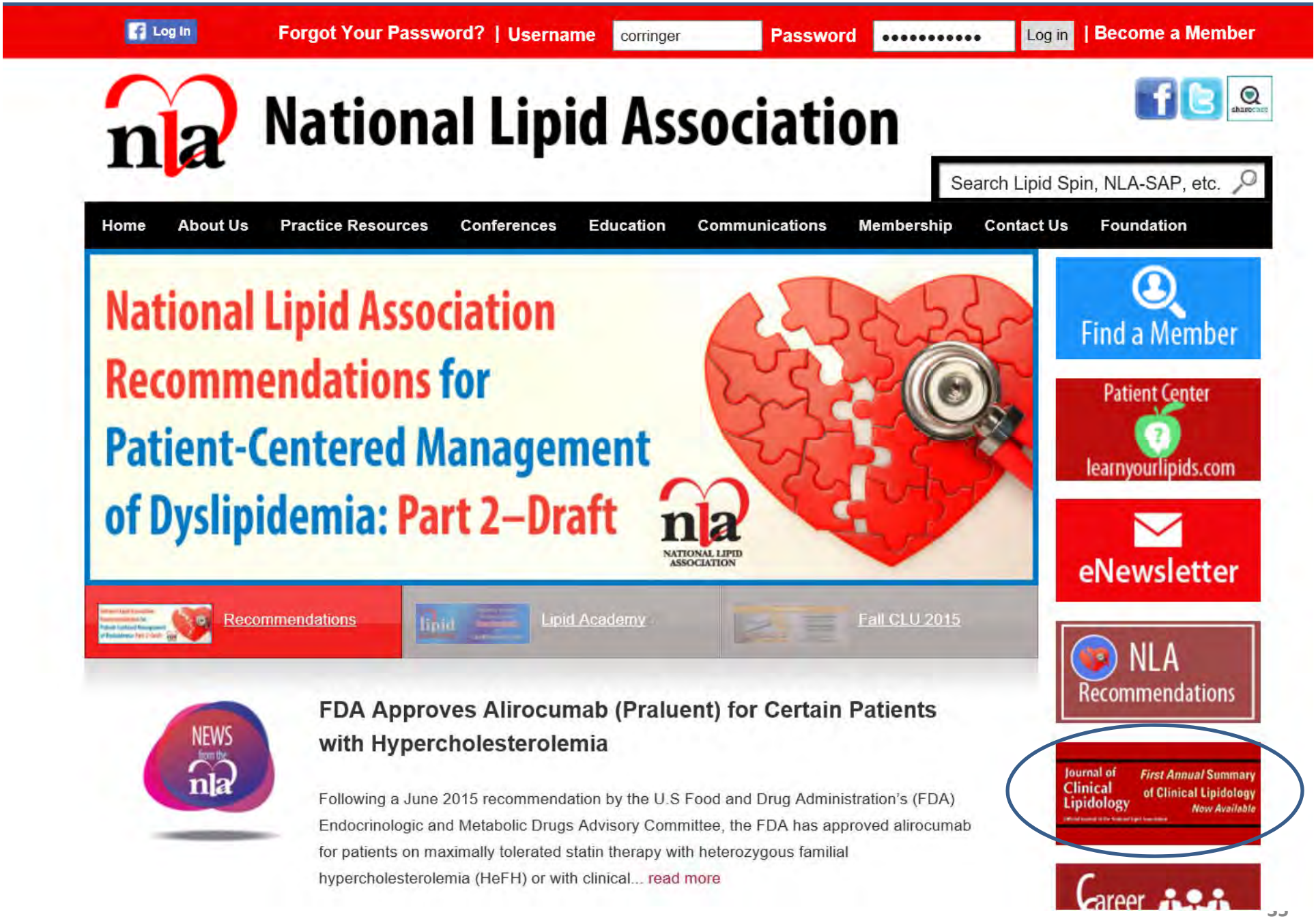
# Annual Summary of Clinical Lipidology

- First Annual Summary of Clinical Lipidology published as supplement to 2014 Nov/Dec issue of JCL
- "Living document" founded on principles of evidence-based medicine and based on emerging science, clinical considerations, and new NLA position and consensus statements
- Open access (available to NLA members and non-members)



# How to Utilize Annual Summary

- Online version hyperlinks to information (tables, figures, journal articles, appendix etc.) so users can easily navigate and retrieve data
- Provides a central directory of tables and figures useful for both medical science as well as the day-to-day management of patients with dyslipidemia
- Available on www.lipid.org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National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2–Draft
NATIONAL LIPID ASSOCIATION
Recommendations
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NLA Recommendations
Journal of Clinical Lipidology
First Annual Summary of Clinical Lipidology Now Available
Career
NEWS from the nla
FDA Approves Alirocumab (Praluent) for Certain Patients with Hypercholesterolemia
Following a June 2015 recommendation by the U.S Food and Drug Administration's (FDA) Endocrinologic and Metabolic Drugs Advisory Committee, the FDA has approved alirocumab for patients on maximally tolerated statin therapy with heterozygous familial hypercholesterolemia (HeFH) or with clinical... read more

# NLA and AHA/ACC Slide Review Panel


**Carl E. Orringer, MD (Chair)**

**Reviewers**

**Harold E. Bays, MD**

**Mary R. Dicklin, PhD**

**Matthew K. Ito, PharmD**

**Terry A. Jacobson, MD**

**Peter H. Jones, MD**

**Kevin C. Maki, PhD**

**James M. McKenney, PharmD**


www.lipid.org
Click Recommendations
Click "View" or "Download this slide deck"

# Central Focus of Guideline

## ACC/AHA

- Identification of statin benefit groups
- Initiation and maintenance of high- or moderate-intensity statin therapy
- No recommendation for or against lipid goals
- Recommendation against non-statin therapy because of less favorable net benefit

## NLA

- Identification of an individual patient's ASCVD risk based on clinical parameters and risk factors
- Initiation of ASCVD risk-based lipid-lowering therapy
- Maintenance of lipid goals to assess effective reduction of atherogenic lipoproteins and enhance adherence
- Use of high- or moderate-intensity statins, ± non-statins, if necessary, to achieve goals

# Recognition of Clinical Lipidology as a Legitimate Subspecialty

# Who is the ABIM?

- The AMA and the ACP formed the ABIM in 1936 to ensure uniform high standards for new physicians.
- A non-profit, independent evaluation organization that is physician-run, but is independent of any physician societies or membership organizations.
- Certifies 1 out of every 4 practicing physicians in the United States.
- Accountable to both the profession of medicine and to the public.

# History of ABIM Recognition of New Subspecialties

- With the evolution of subspecialties, The American Board of Internal Medicine (ABIM) has introduced Certification exams in:
  - CVD, Clinical Cardiac Electrophysiology, Interventional Cardiology, Advanced Heart Failure and Transplant Cardiology and Adult Congenital Heart Disease
- Physician certification in CVD has evolved outside the more traditional ABIM pathways, and derivative boards have been established and recognized

**"We must promote actual accountability based on standards set unimpeachably high. That is how we will show the public that we take their trust in us seriously." – Douglas Zipes, MD (2001 ACC President)**

# ABIM Criteria for Recognition of a New Subspecialty

- Must have a unique body of knowledge that cannot be fully incorporated into the “parent” discipline.
- Must have clinical applicability to be practiced in a form that is distinct from the “parent” discipline.
- Must contribute to the scholarly generation of new information and must advance research in the field.
- Must be an important social need for the discipline and evidence that practice of the discipline improves patient care.
- The positive value of certification in the new discipline must outweigh any negative impact on the practice of general internal medicine or an existing subspecialty or on the basic education in the core competencies of internal medicine.

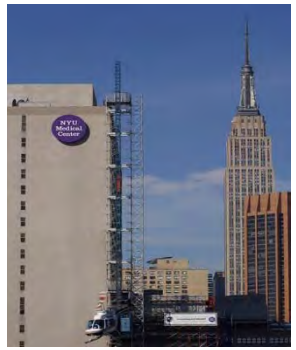
# Steps in the Right Direction

- **Clinical Lipidology fellowships**
  - Next steps:
    - Standardization of application of NLA Core Curriculum among current fellowship programs
    - Formation of more fellowships
    - Accreditation Council for Graduate Medical Education (ACGME) accreditation
- **Establishment and maintenance of certification boards in Clinical Lipidology**
  - American Board of Clinical Lipidology (ABCL)
  - Accreditation Council for Clinical Lipidology (ACCL)

# Clinical Lipidology Fellowships

**NYU Langone Medical Center Lipids/Obesity Fellowship med.nyu.edu**

In-patient and outpatient consultation, academic conferences, apheresis, research



**Baylor College of Medicine Lipid and Atherosclerosis Fellowship bcm.edu**

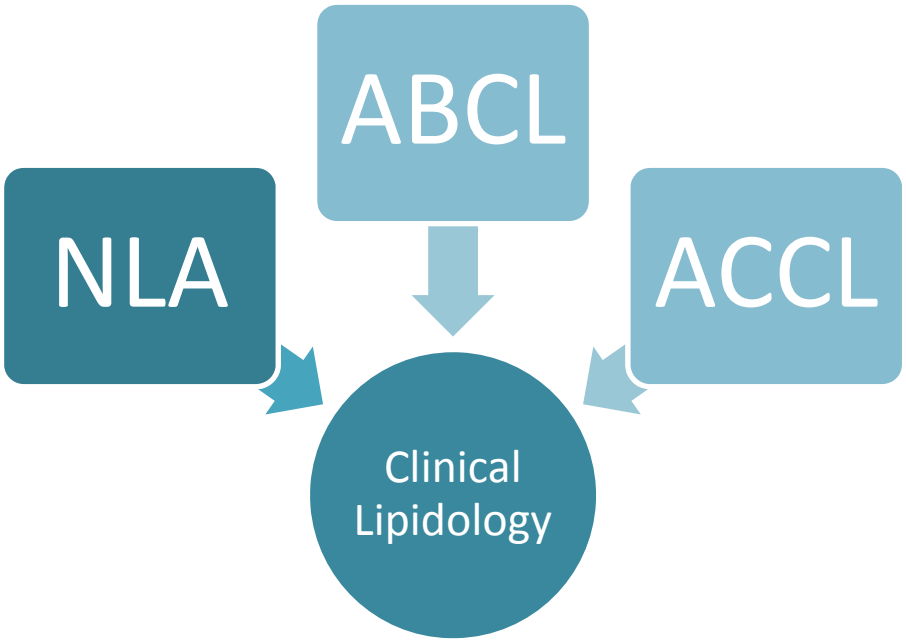
In-patient and outpatient consultation, clinical/translational research; basic research may be elected

**Medical University of South Carolina musc.edu**

Outpatient consultation, education in obesity, core curriculum 20 topic lecture series, research

# Certification

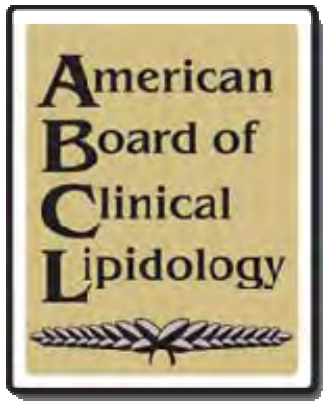
Although independent from each other, the NLA, ABCL and ACCL work closely together to ensure adequate educational opportunities for lipid professionals.




**COMMON GOAL: Recognition of Clinical Lipidology as a legitimate subspecialty of medicine.**

# American Board of Clinical Lipidology

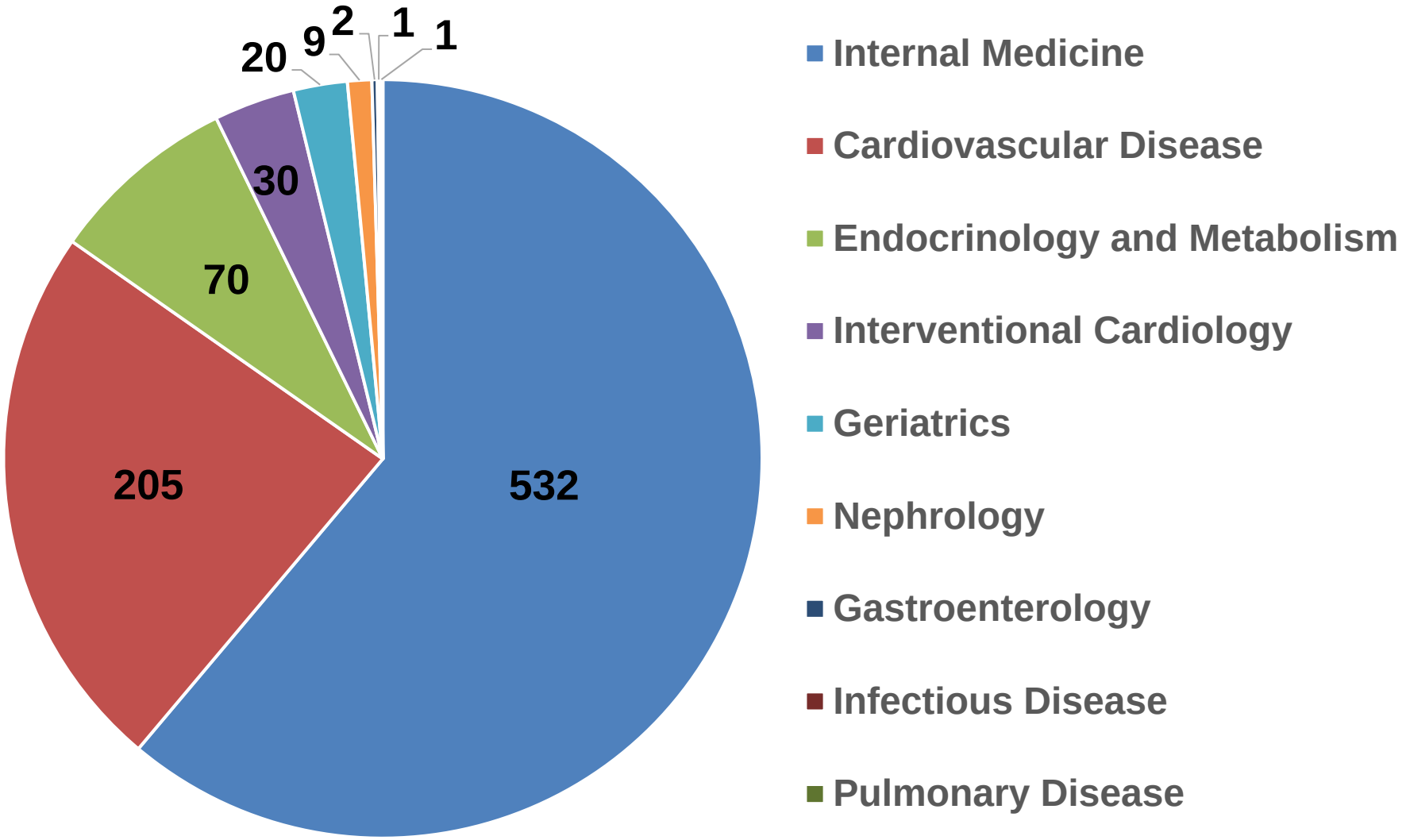
- The only certification program for physicians specializing in Clinical Lipidology
- Documents and validates the specialized knowledge and advanced training required to practice in the field
- Enacts standards that mirror ABIM and other ABMS member boards
  - Undergoes yearly review and psychometric process –Current ABCL exam to be updated in 2015
  - Maintenance of Certification created in 2015
  - The ABCL anticipates that ABIM recognition of the specialty will improve reimbursement of clinical lipidologists



# Pathway Toward ABIM Recognition

- Phone conference between NLA leadership and Furman MacDonald, MD,VP for Graduate Medical Education, ABIM 6/3/15
- The ABIM will not be considering applications for new subspecialty recognition until, the earliest, late 2016 or early 2017
- The NLA's current educational programming is favorably viewed by the ABIM, including ABCL examination process and ABCL's MOC process
- Maintaining these programs is an important step in a positive review by the ABIM
- The pathway for application for ABIM recognition is outlined in a document, "Final Report of the Committee on Recognizing New and Emerging Disciplines in Internal Medicine (NEDIM)-2
- The Presidents of the NLA and ABCL met on 8/1/15 and developed plans to convene a joint committee to facilitate the process

# ABIM Diplomates Who Are ABCL Certified



# Accreditation Council for Clinical Lipidology

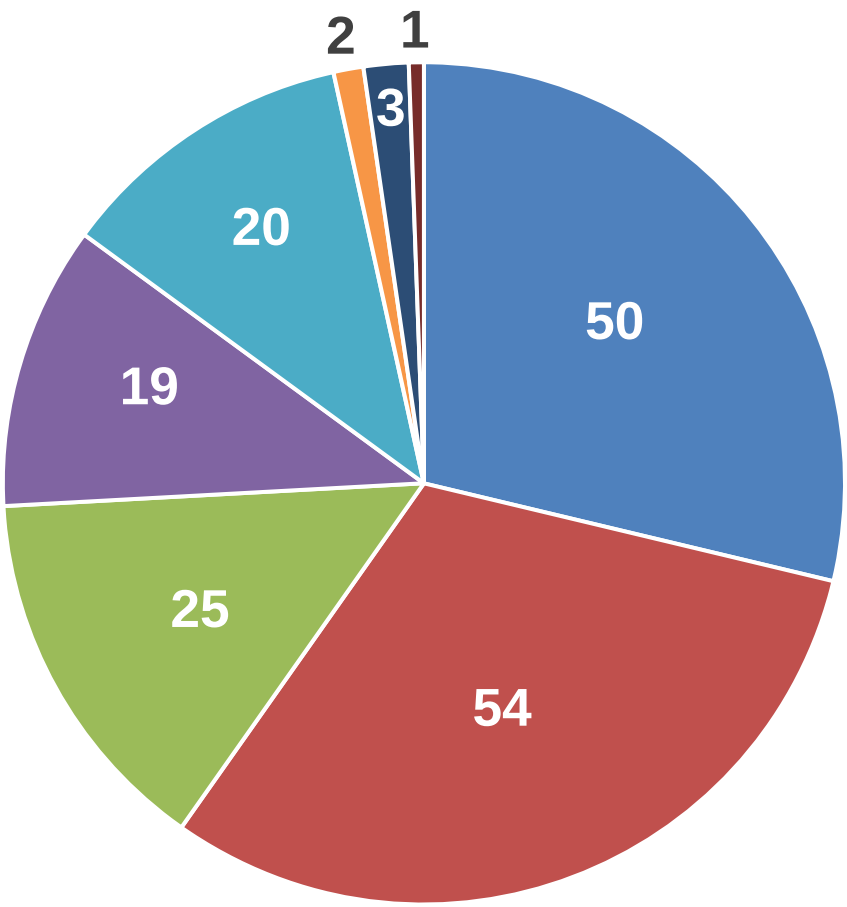
- Provides recognition and distinction in the field for the following healthcare professionals:

**♦ Pharmacists ♦ Nurses ♦ Physician Assistants ♦ Dietitians ♦ ♦ Exercise Specialists ♦ Physicians* ♦ PhDs**

- Provides benefits to both the practitioner and the profession by:
  - Improving the quality of patient care
  - Setting benchmarks of clinical competency for lipid specialists
  - Enhancing the credibility of the health care professionals and the specialty of Clinical Lipidology in the medical community
- 2 levels of certification offered:
  - **Advanced: Clinical Lipid Specialist (CLS)**
  - **Core: Basic Competency in Clinical Lipidology (BCCL)**

***Those not wishing to or not ready to pursue ABCL certification**

# Breakdown of CLS Diplomates




- Pharmcists
- Nurse Practitioner
- Nurse
- Dietitian
- Physicican Assistant
- Exercise Specialist
- PhD
- MD

# Pathway Towards ACCL Recognition

- National Commission for Certifying Agencies (NCCA)
- NCCA accreditation demonstrates compliance with its *Standards for the Accreditation of Certification Programs*
  - Enables credentialing organizations to demonstrate to the profession it represents, and to the general public, that the program has met the stringent standards set by the credentialing community
  - Enhances a program's credibility and legitimacy by providing impartial, third party oversight of a conformity assessment system
-

# Current Obstacles Toward Recognition of Clinical Lipidologists as Subspecialists

- Non-lipidologists can prescribe high-intensity statins, the most evidence-based ASCVD risk reduction therapy
- Non-lipidologists can prescribe adjunctive non-statin therapies
- Cardiologists and endocrinologists may believe that clinical lipidology is their domain
- Subspecialists may be hesitant to refer to primary care providers with clinical lipidology expertise
- Primary care providers may hesitate to refer to other primary care providers with clinical lipidology expertise

# The NLA's Role in Addressing the Obstacles

- Produce scientific statements and educational activities that enhance the role of the NLA as a significant source for evidence-based lipid-related education
- Sanction and promote the work of the ABCL and ACCL, which work to demonstrate mastery of the knowledge base defined by our core curriculum
- Promote the importance of demonstrated MOC, both to enhance patient care and to externally demonstrate our commitment to educational achievement
- Actively pursue ABIM, ACGME and NCCA accreditation

# Summary

- Clinical Lipidology is a legitimate subspecialty with a well-defined knowledge base, the mastery of which qualifies clinicians to render high-quality patient care. Such knowledge provides the basis for engagement in lipidology-related educational and clinical research activities.
- The NLA serves the Clinical Lipidology community by providing a variety of educational activities and supporting the ABCL and ACCL, whose purpose is to certify educational achievement in the field.
- The NLA, ABCL and ACCL continue to collaborate to seek external recognition of the unique skills and services provided by certified clinical lipidologists and lipid specialists.

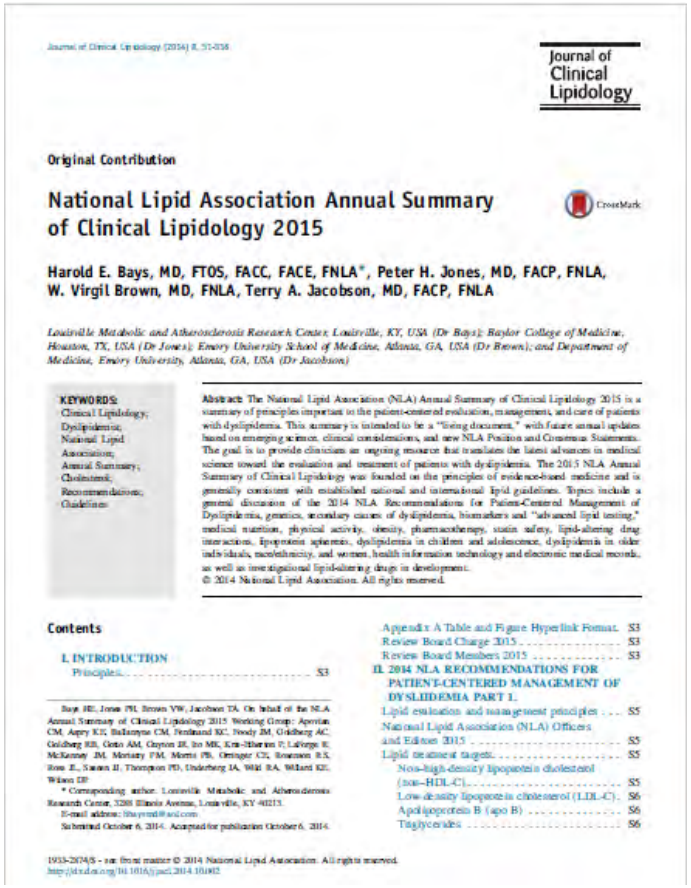

# Keeping NLA Members Up-to-Date: Key Articles for the 2016 NLA Annual Summary

# Learning Objectives Are To Describe The Processes By Which:

- New science is currently summarized for NLA members
- New science is updated for NLA members
- Future content is provided to NLA members

# History National Lipid Association Annual Summary 2015

- 2012: NLA Annual Summary of Clinical Lipidology proposed to the NLA Board of Directors
  - Most current science in lipidology
  - Hyperlinks relevant to lipidologists
- 2015: First publication of the 2015 NLA Annual Summary
- 2016: Next version currently undergoing review and revisions
  - 2015 included Part 1 NLA Recommendations
  - 2016 is to include Part 2 NLA Recommendations



Journal of Clinical Lipidology

Original Contribution

# National Lipid Association Annual Summary of Clinical Lipidology 2015

Harold E. Bays, MD, FTOS, FACC, FACE, FNLA*, Peter H. Jones, MD, FACP, FNLA, W. Virgil Brown, MD, FNLA, Terry A. Jacobson, MD, FACP, FNLA

*Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY, USA (Dr Bays); Baylor College of Medicine, Houston, TX, USA (Dr Jones); Emory University School of Medicine, Atlanta, GA, USA (Dr Brown); and Department of Medicine, Emory University, Atlanta, GA, USA (Dr Jacobson)*

**KEYWORDS:**
Clinical Lipidology;
Dyslipidemia;
National Lipid Association;
Annual Summary;
Cholesterol;
Recommendations;
Guidelines

**Abstract** The National Lipid Association (NLA) Annual Summary of Clinical Lipidology 2015 is a summary of principles important to the patient-centered evaluation, management, and care of patients with dyslipidemia. This summary is intended to be a "living document," with future annual updates based on emerging science, clinical considerations, and new NLA Position and Consensus Statements. The goal is to provide clinicians an ongoing resource that translates the latest advances in medical science toward the evaluation and treatment of patients with dyslipidemia. The 2015 NLA Annual Summary of Clinical Lipidology was founded on the principles of evidence-based medicine and is generally consistent with established national and international lipid guidelines. Topics include a general discussion of the 2014 NLA Recommendations for Patient-Centered Management of Dyslipidemia, genetics, secondary causes of dyslipidemia, biomarkers and "advanced lipid testing," medical nutrition, physical activity, obesity, pharmacotherapy, statin safety, lipid-altering drug interactions, lipoprotein apheresis, dyslipidemia in children and adolescence, dyslipidemia in older individuals, race/ethnicity, and women, health information technology and electronic medical records, as well as investigational lipid-altering drugs in development.


Contents



Bays HE, Jones PH, Brown WV, Jacobson TA, On behalf of the NLA Annual Summary of Clinical Lipidology 2015 Working Group: Ayerian CM, Aspry KE, Ballantyne CM, Ferdinand KC, Moody JM, Goldberg AC, Goldberg RB, Goto AM, Grayson JR, Ito MK, Kris-Etherton P, LaForge R, McKenney JM, Moriarty PM, Morris PB, Orringer CE, Rosenson RS, Ross JL, Sasson JI, Thompson PD, Underberg JA, Wild RA, Willard KE, Wilson DP.
* Corresponding author. Louisville Metabolic and Atherosclerosis Research Center, 3288 Illinois Avenue, Louisville, KY 40213.
E-mail address: hbaymd@aol.com
Submitted October 6, 2014. Accepted for publication October 6, 2014.

1933-2874/$ - see front matter © 2014 National Lipid Association. All rights reserved.
http://dx.doi.org/10.1016/j.jacl.2014.10.002

Bays HE, Jones PH, Brown WV, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2015. J Clin Lipidol. 2014 Nov-Dec;8(6 Suppl):S1-36.

# National Lipid Association Annual Summary 2015

## Contents

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* Corresponding author. Louisville Metabolic and Atherosclerosis Research Center, 3288 Illinois Avenue, Louisville, KY 40213.

E-mail address: hbaysmd@aol.com



Submitted October 6, 2014. Accepted for publication October 6, 2014.

Journal of Clinical Lipidology (2014) 8, 473–488

Journal of Clinical Lipidology

Original Articles

# National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary☆

Terry A. Jacobson, MD*, Matthew K. Ito, PharmD, Kevin C. Maki, PhD, Carl E. Orringer, MD, Harold E. Bays, MD, Peter H. Jones, MD, James M. McKenney, PharmD, Scott M. Grundy, MD, PhD, Edward A. Gill, MD, Robert A. Wild, MD, PhD, Don P. Wilson, MD, W. Virgil Brown, MD

# National Lipid Association Annual Summary 2015

# National Lipid Association Annual Summary 2015

# National Lipid Association Annual Summary 2015

**Lipids and Bariatric Procedures Part 1 of 2: Scientific Statement from the National Lipid Association (NLA), American Society for Metabolic and Bariatric Surgery (ASMBS)**

**Lipids and Bariatric Procedures Part 2 of 2: Scientific Statement from the American Society for Metabolic and Bariatric Surgery (ASMBS) and the National Lipid Association (NLA),**

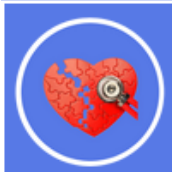
# National Lipid Association Annual Summary 2015

# National Lipid Association Annual Summary 2015

## X. LIPOPROTEIN APHERESIS

# National Lipid Association Annual Summary 2015

## XI. DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS



# NLA Recommendations for Patient-Centered Management of Dyslipidemia

## Part 1

The NLA Recommendations for Patient, published in the *Journal of Clinical Lipidology*, re-affirm the importance of cholesterol goals for the prevention of heart attack and stroke. The recommendations should serve as guidance to clinicians for treating patients with dyslipidemia.

## Part 2 - NEW

Part 2 of the NLA Recommendations provides a unique set of recommendations for patient-centered management of dyslipidemia for special populations and conditions. It includes recommendations for the following:

- Hispanics
- South Asians
- African Americans
- Older patients
- Children and adolescents
- Women and unique issues in women's health
- Lifestyle therapies, including nutrition and physical activity
- Improving patient outcome through adherence and team-based collaborative care
- Patients with Human Immunodeficiency Virus, Rheumatoid Arthritis and Residual Risk

*The full paper will be published later in 2015.*

# National Lipid Association Annual Summary 2015

## XII. DYSLIPIDEMIA IN SELECT POPULATIONS

# National Lipid Association Annual Summary 2015

## XIII. HEALTH INFORMATION TECHNOLOGY AND ELECTRONIC MEDICAL RECORDS: LIPID MANAGEMENT AND VALUE-BASED HEALTH CARE

# National Lipid Association Annual Summary 2015

## IV. INVESTIGATIONAL LIPID-ALTERING AGENTS IN DEVELOPMENT 2015

# National Lipid Association Annual Summary 2015

## XIV. INVESTIGATIONAL LIPID-ALTERING AGENTS IN DEVELOPMENT 2015 (Table 1)

**Table 1** Brief summary of lipid-altering pharmacotherapies in development

| Class of agent and mechanism of action | Name | Manufacturer | Sample references and/or Clinical Trials.gov Identifiers | Sentinel, reported safety/ tolerability findings | Sentinel lipid effects |
|---|---|---|---|---|---|
| Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors | Alirocumab | Regeneron/ Sanofi | [142,143] | Rare injection site reactions, with most cases being mild | >50% reduction in LDL-C and non–HDL-C levels |
| | Evolocumab | Amgen | [144–146] | | |
| | Bococizumab | Pfizer (RN316) | NCT01243151 | | |
| | LY3015014 | Lilly | NCT01426412 | | |
| | ALN-PCS | Alnylam and the Medicines Company | [147] | | |
| Dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated kinase | ETC-1002 | Esperion | [148] | Possible increase in myalgia, mild increase in homocysteine and mild decrease in hemoglobin | 15%–25% reduction in LDL-C levels<br>15%–21% reduction in non–HDL-C levels |
| Cholesteryl ester transfer protein (CETP) inhibitor | Anacetrapib | Merck | [149,150] | Generally well tolerated with no increase in blood pressure; drug concentration still detectable 2–4 years after last dosing | As much as 40% reduction in LDL-C<br>As much as 150% increase in HDL-C |
| | Evacetrapib | Lilly | [151] | Generally well tolerated with no increase in blood pressure | |
| Diacylglycerol acyltransferase-1 (DGAT-1) inhibitor | Pradigastat | Novartis (LCQ908) | NCT01514461* | Transient diarrhea and other gastrointestinal adverse experiences | Lowers triglyceride and other lipid levels, HbA1c, and body weight |
| Antisense Apo C3 inhibitor | Isis-APO CIII Rx | Isis | † | Injection site reactions | Up to 77% reduction in triglyceride levels |
| Botanic extract from red yeast Chinese rice with multiple components, some having statin-like activity | ZueZhiKang | Beijing Peking University WBL Biotech Co. (WPU) | [152,153] NCT01327014 | [154] | Lowers cholesterol |

**Table 1** *(continued)*

| Class of agent and mechanism of action | Name | Manufacturer | Sample references and/or Clinical Trials.gov Identifiers | Sentinel, reported safety/ tolerability findings | Sentinel lipid effects |
|---|---|---|---|---|---|
| Structurally enhanced omega-3 fatty acid | Icosabutate (PRC-4016) | Pronova Biopharm | NCT01972178 | Not reported | May reduce triglyceride and have other lipid effects |
| Niacin analogue | ARI-3037MO | Arisaph | NCT02250105 | Not reported | May reduce triglyceride and have other lipid effects |

* Abstract: https://www.lipid.org/util/posters/PDF/107.pdf. Lise Kjems, Charles Daniel Meyers, Tom Thuren. Diacylglycerol Acyltransferase 1 (DGAT1) Inhibition as a Metabolic Regulator: Clinical Benefits of Pradigastat in Obese Patients With Type 2 Diabetes. Poster 107 presented at 2014 NLA Annual Scientific Sessions, Orlando, Florida, May 1-4, 2014.

† Abstract: Vickie Alexander, Trish Novak, Nicholas Viney, John Su, Jennifer Burkey, Walter Singleton, Richard Geary, Isis Pharmaceuticals, Inc., Carlsbad, CA, USA. An Antisense Inhibitor of Apolipoprotein C-III Lowers Fasting Plasma Apolipoprotein C-III and Triglyceride Concentrations in Healthy Volunteers. ACC Moderated Poster Contributions. McCormick Place South, Hall A, Sunday, March 25, 2012, 9:30 a.m.-10:30. E1685JACC March 27, 2012 Volume 59, Issue 13. a.m. Session Title: Prevention: Clinical: Current Research in Lipidology Abstract Category: 9. Prevention: Clinical Presentation Number: 1190-529.

# National Lipid Association Annual Summary 2015

**APPENDIX A:** National Lipid Association (NLA) Annual Summary of Clinical Lipidology 2015: Tables, Figures, and Hyperlinks

| Section of this NLA Annual Summary | Table/figure number and title description as found in the original publication and hyperlink | Reference |
|---|---|---|
| **NLA Executive Summary** | Table 1. Classifications of cholesterol and triglyceride Levels in mg/dL | 1 |
| | Table 2. Treatment goals for non-HDL-C, LDL-C, and Apo B in mg/dL | 1 |
| | Table 3. Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy | 1 |
| | Table 7. Major risk factors for ASCVD | 1 |
| | Table 8. Criteria for classification of ASCVD | 1 |
| | Table 9. High- or very high-risk patient groups | 1 |
| | Table 10. Sequential steps in ASCVD risk assessment | 1 |
| | Table 11. Risk indicators (other than major ASCVD risk factors) that might be considered for risk refinement | 1 |
| **Genetics and Classification of Dyslipidemia** | Figure 5. Refrigerated plasma portion of test tubes of blood drawn from three dyslipidemic patients. | 3 |
| | Table 1. Genetic classification of dyslipidemia. | * |
| | Table 2. Genetic causes of hypolipidemias | * |
| **Evaluation and Management of Familial Hypercholesterolemia** | Table 3: Simon Broome diagnostic criteria for familial hypercholesterolemia | * |
| | Table 4. Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia | * |
| | Table 5. MEDPED diagnostic criteria for heterozygous familial hypercholesterolemia | * |
| | Table Summary Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia | 8 |
| **Secondary Causes of Dyslipidemia** | Table 6. Secondary causes of dyslipidemia due to disordered metabolism or disease | * |
| | Table 7. Secondary causes of dyslipidemia due to drugs | * |
| **Medical Nutrition Therapy** | Table 8. Nutritional content, characteristics and diseases/disorders/altered metabolic states that may elevate LDL-C and/or triglyceride concentrations | * |

**Table 1.** Genetic classification of dyslipidemia.

| Classification | Examples of Genetic Diseases* (Frequency) | Genetic Defect | Common Lipid Abnormalities** | Clinical Findings |
|---|---|---|---|---|
| Type I 'Chylomicronemia syndrome' (Increased triglyceride levels and chylomicron particles) | Lipoprotein lipase deficiency | Genetic defect of LPL gene – autosomal recessive | TG levels in the 1000's, with as high as over 10,000 mg/dl | Eruptive xanthomas<br>Pancreatitis |
| | ApoCII deficiency (1:1,000,000 for either of the above) | Genetic defect of ApoCII gene – autosomal recessive | Partial genetic defects may have TG levels > 500 mg/dL | |
| Type IIa (Increased LDL cholesterol levels and/or particles) | Polygenic hypercholesterolemia (1:20) | Multiple genetic defects – inheritance likely dependent upon underlying genetic abnormality | LDL-C levels > 130 mg/dL | Increased risk of ASCVD |
| | Heterozygous familial hypercholesterolemia (1:500) | Dysfunction or absence of LDL receptor – autosomal dominant | LDL-C levels > 190 mg/dL | Increased risk of premature ASCVD<br>Tendon xanthoma |
| | Homozygous familial hypercholesterolemia (1:1,000,000) | | LDL-C levels sometimes > 350 mg/dL, but most often 500 - 1000 mg/dL | Increased risk of premature ASCVD<br>Tendon xanthoma |
| Type IIb (Increased triglyceride levels, and increased LDL and VLDL cholesterol levels and/or particles) | Familial combined hyperlipidemia (1:50-1:200) | Multiple genetic defects of various apolipoproteins and/or LPL genes - ? autosomal dominant | LDL-C levels > 160 mg/dL<br>TG levels> 300 mg/dL | Increased risk of ASCVD |
| Type III (Increased triglyceride levels and increased intermediate-density lipoprotein cholesterol levels and/or particles) | Familial dysbetalipoproteinemia (1:1000-1:5000) | Genetic defect of apoE gene – autosomal recessive, or more rarely, autosomal dominant | LDL-C > 220 mg/dL<br>TG levels > 300 mg/dL | Palmar xanthomata (orange discoloration of skin creases, tuberoeruptive xantomata of elbows and knees<br>Increased risk of premature ASCVD |
| Type IV (Increased triglyceride levels and increased VLDL cholesterol levels and/or particles) | Familial hypertriglyceridemia (1:50-1:100) | Unknown genetic defect – autosomal dominant | TG levels > 150 mg/dL | Unclear if increased risk of ASCVD |
| Type V (Increased triglyceride levels and increased chylomicron and VLDL cholesterol levels and/or particles) | Hyperprebetalipoproteinemia (unknown frequency, very rare) | Unknown genetic defect – possibly due to an LPL inhibitor – unknown inheritance | TG levels > 500 mg/dL<br>LDL-C levels > 130 mg/dL | Eruptive xanthomas<br>Pancreatitis<br>Increased risk of ASCVD |

LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; Apo = apolipoprotein; LPL = lipoprotein lipase.

# National Lipid Association Annual Summary 2015

**APPENDIX A** *(continued)*

| Section of this NLA Annual Summary | Table/figure number and title description as found in the original publication and hyperlink | Reference |
|---|---|---|
| **Physical Activity** | Table 9. Physical exercise recommendations for improvement in lipid levels | * |
| | Table 10. Primary factors influencing exercise-generated weight loss and exercise training lipid/lipoprotein response | * |
| **Obesity, Adiposopathy, Metabolic Syndrome, and Diabetes Mellitus** | Table 1. Adiposopathy ("sick fat"): summary of causality and examples of anatomic, pathophysiologic, and clinical manifestations | 15 |
| | Figure 3. Adiposopathy in the fasting state and the contribution to the lipid pattern typically found with the metabolic syndrome | 15 |
| | Figure 4. Inter-relationship between adiposopathy, type 2 diabetes mellitus, dyslipidemia, and atherosclerosis | 15 |
| | Table 1. Metabolic syndrome definitions. | 48 |
| | Table 4. Examples of Endocrine and Immune Adipocyte and Adipose Tissue Factors as Potential Contributors to "Adiposopathic Dyslipidemia." | 15 |
| | Table 11. Non-weight management pharmaceuticals that that may affect body weight. | * |
| **Statin & Non-Statin Pharmacotherapy** | Table 12. Intensity of statin therapy | 1 |
| | Table 3. Focus on ASCVD risk reduction: 4 statin benefit groups | 58 |
| | Table 13. Drugs affecting lipoprotein metabolism | 1 |

# National Lipid Association Annual Summary 2015

| | | |
|---|---|---|
| **Lipid-Altering Drug Prescribing Information** | Atorvastatin: http://labeling.pfizer.com/ShowLabeling.aspx?id=587 | NA |
| | Simvastatin: http://www.merck.com/product/usa/pi_circulars/z/zocor/zocor_pi.pdf | NA |
| | Pravastatin: http://packageinserts.bms.com/pi/pi_pravachol.pdf | NA |
| | Fluvastatin: https://www.pharma.us.novartis.com/product/pi/pdf/Lescol.pdf | NA |
| | Mevacor: http://www.merck.com/product/usa/pi_circulars/m/mevacor/mevacor_pi.pdf | NA |
| | Pitavastatin: http://www.kowapharma.com/documents/LIVALO_PI_CURRENT.pdf | NA |
| | Ezetimibe: http://www.merck.com/product/usa/pi_circulars/z/zetia/zetia_pi.pdf | NA |
| | Omega-3-acid ethyl esters (EPA and DHA): https://www.gsksource.com/gskprm/htdocs/documents/LOVAZA-PI-PIL.PDF | NA |
| | Icosapent ethyl (EPA only): http://www.vascepa.com/full-prescribing-information.pdf | NA |
| | Omega-3-carboxylic acids (EPA and DHA free fatty acid formulation): http://www1.astrazeneca-us.com/pi/epanova.pdf | NA |
| | Colesevelam HCl: http://dsi.com/prescribing-information-portlet/getDocument?product=WC&inline=true | NA |
| | Cholestyramine: http://www.rxlist.com/questran-drug/side-effects-interactions.htm | NA |
| | Colestipol: http://www.rxlist.com/colestid-drug/side-effects-interactions.htm | NA |
| | Fenofibrate: http://www.rxlist.com/tricor-drug/side-effects-interactions.htm | NA |
| | Fenofibric acid: http://www.rxabbvie.com/pdf/trilipix_pi.pdf | NA |
| | Gemfibrozil: http://www.rxlist.com/lopid-drug/side-effects-interactions.htm | NA |
| | Extended-release niacin: http://www.rxabbvie.com/pdf/niaspan.pdf | NA |
| | Lomitapide: http://www.juxtapidremsprogram.com/_pdf/012187_JuxtapidPI_8.5x11_FIN.PDF | NA |
| | Mipomersen: http://www.kynamro.com/~/media/Kynamro/Files/ | NA |

# National Lipid Association Annual Summary 2015

**APPENDIX A** *(continued)*

| Section of this NLA Annual Summary | Table/figure number and title description as found in the original publication and hyperlink | Reference |
|---|---|---|
| **Statin safety: Muscle** | Table 1. Spectrum of statin-associated muscle adverse events (page S60) | 74 |
| | Table 12. Non-statin causes of elevated muscle enzymes | * |
| | Table 4. Diagnostic criteria for myopathy (page S65) | 74 |
| | Table 5. Indications for skeletal muscle biopsy (page S67) | 74 |
| | Figure 2. Algorithm for the evaluation of statin-associated muscle injury (page S68) | 74 |
| **Statin safety: Liver** | Table 1. Hy's law criteria (page S49) | 74 |
| | Table 2. Questions addressed by liver experts in the 2006 and 2014 National Lipid Association Statin Safety Task Force Reports (page S50) | 74 |
| | Table 3. Illustrative causes of elevated liver enzymes in adolescents and adults (page S52) | 74 |
| | Figure 1. Comprehensive approach to patients with elevated liver blood testing (transaminases <3 times the upper limits of normal) (page S54) | 74 |
| | Figure 2. Comprehensive approach to patients with elevated liver blood testing (transaminases >3 times the upper limits of normal) (page S55) | 74 |
| **Statin safety: Cognition** | Figure 1. Evaluation of the patient with cognitive symptom (page S12) | 74 |
| **Statin safety: Diabetes mellitus** | Table 1. Criteria for screening for prediabetes and diabetes before or concurrent with initiation of statin therapy (page S23) | 74 |
| | Table 2. Criteria for the diagnosis of prediabetes and diabetes (page S26) | 74 |
| | Table 3. Summary of clinical trial evidence for CVD event reduction in patients with diabetes (page S27) | 74 |

# National Lipid Association Annual Summary 2015

**Statin drug interactions**

# National Lipid Association Annual Summary 2015

| | | |
|---|---|---|
| Lipoprotein-apheresis | Table 14. LDL apheresis | 1 |
| Biomarkers and "Advanced Lipid Testing" | Table 1. Summary recommendations for measurement of inflammatory markers and advanced lipoprotein/subfraction testing in initial clinical assessment and on treatment management decisions. | 16 |
| Health Information Technology and Electronic Medical Records | About the National Quality Strategy: Three aims; six priorities | NA |
| | Table 1. National Quality Forum-endorsed lipid measures | 141 |
| | Table 4. Determinants of adherence/non-adherence and persistence/poor persistence | 141 |

# National Lipid Association Annual Summary 2015

***Journal of Clinical Lipidology*** **Electronic Resources (accessible at www.lipid.org) 2015**

**E1 National Lipid Association Position Statements and Hyperlinks**

2014 National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary.

2014 Statin Safey Update.

2013 Obesity, adiposity, and dyslipidemia: A consensus statement from the NLA.

2011 Clinical Utility of Inflammatory Markers and Advanced Lipoprotein Testing: Advice from an Expert Panel of Lipid Specialists.

2011 Familial Hypercholesterolemia: Screening, Diagnosis and Management of Pediatric and Adult Patients.

2008 National Lipid Association Statement Regarding Reporting of Non-HDL on Standard Laboratory Reports.

2007 Report of the National Lipid Association's Safety Task Force: The Non-statins.

2006 A Symposium: Report of the National Lipid Association's Statin Safety Task Force.

**E2 Other National Lipid Association documents**

**Lipid Clinic and CMR operations manual/course**
(https://www.lipid.org/practicetools/operations_manual)

**Coding and reimbursement**
(https://www.lipid.org/practicetools/reimbursement)

# NLA Recommendations Part 2

# NLA Annual Summary 2016: NLA Recommendations Part 2

| Section | Chair(s) | Expert Panel Member(s) |
|---|---|---|
| **Lifestyle therapies** | | |
| Exercise | Ralph La Forge, MSc, FNLA | Kevin Maki, PhD, FNLA |
| Nutrition | Penny Kris-Etherton, PhD, RD, FNLA<br>Geeta Sikand, RD, MA, FNLA<br>Kevin Maki, PhD, CLS, FNLA<br>Mary Dicklin, PhD | Julie Bolick, MS, RDN,CLS,FNLA<br>Carol Kirkpatrick, PhD, RDN, CLS FNLA<br>Kathy Rhodes, PhD, RDN<br>Nancy Smith, MS, RDN, CLS,FNLA |
| **Groups with special considerations** | | |
| Children and adolescents | Stephen Daniels, MD, PhD, FNLA<br>Don Wilson, MD, FNLA | |
| Gender | | |
| Gender differences | Pamela Morris, MD, FNLA | |
| Unique women's issues | Robert Wild, MD, MPH, PhD, FNLA, NCMP | Thomas Dayspring MD, FNLA, NCMP<br>James A. Underberg MS, MD, FNLA |
| Ethnic groups | | |
| African American | Keith Ferdinand, MD, FNLA | |
| Hispanic | Martha Daviglus, MD, PhD | |
| South Asian | Kris Vijay, MD, FNLA<br>Prakash Deedwania, MD | |

# NLA Annual Summary 2016: NLA Recommendations Part 2

| | | |
|---|---|---|
| **Older patients** | **Carl Orringer, MD, FNLA**<br>**Scott Grundy, MD, PhD, FNLA**<br>**Joyce Ross, MSN, CRNP, FNLA** | |
| **Patients with HIV** | Judith Aberg, MD | Carl Fichtenbaum, Joel E. Gallant, Michael Horberg, Chris T. Longenecker, Turner Overton and<br>Merle Myerson |
| **Patients with inflammation** | Katherine Liao, MD, MPH | Jonathan S. Coblyn, MD<br>Jeffrey Curtis, MD, MS, MPH<br>Jorge Plutzky, MD, FNLA<br>Daniel Solomon, MD, MPH |
| **Patients with residual risk** | Peter Jones, MD, FNLA<br>James McKenney, PharmD, FNLA | |
| **Strategies to assist with adherence** | Lynne Braun, PhD, CNP, FNLA<br>Joyce Ross, MSN, CRNP, FNLA | |
| **Team-based collaborative care** | Matthew Ito, PharmD, FNLA<br>Lynne Braun, PhD, CNP, FNLA<br>Joyce Ross, MSN, CRNP, FNLA | |
| **General Panel Members** | Terry A. Jacobson (Chair)<br>Kevin Maki<br>Carl Orringer<br>Peter Jones | Harold Bays<br>W. Virgil Brown |

## ***New*** For National Lipid Association Annual Summary 2016

- 2016 Update of Content and References
- Links to NLA:
  - Updates
  - Audio files
  - Websites
  - Webcasts
  - Slide shows
  - Applications
  - Risk assessment tools
  - Continuing patient education
  - Patient education tools


# Keeping NLA Members Up-to-Date: Key Articles for the 2016 NLA Annual Summary

# Key Ongoing Trials in Clinical Lipidology

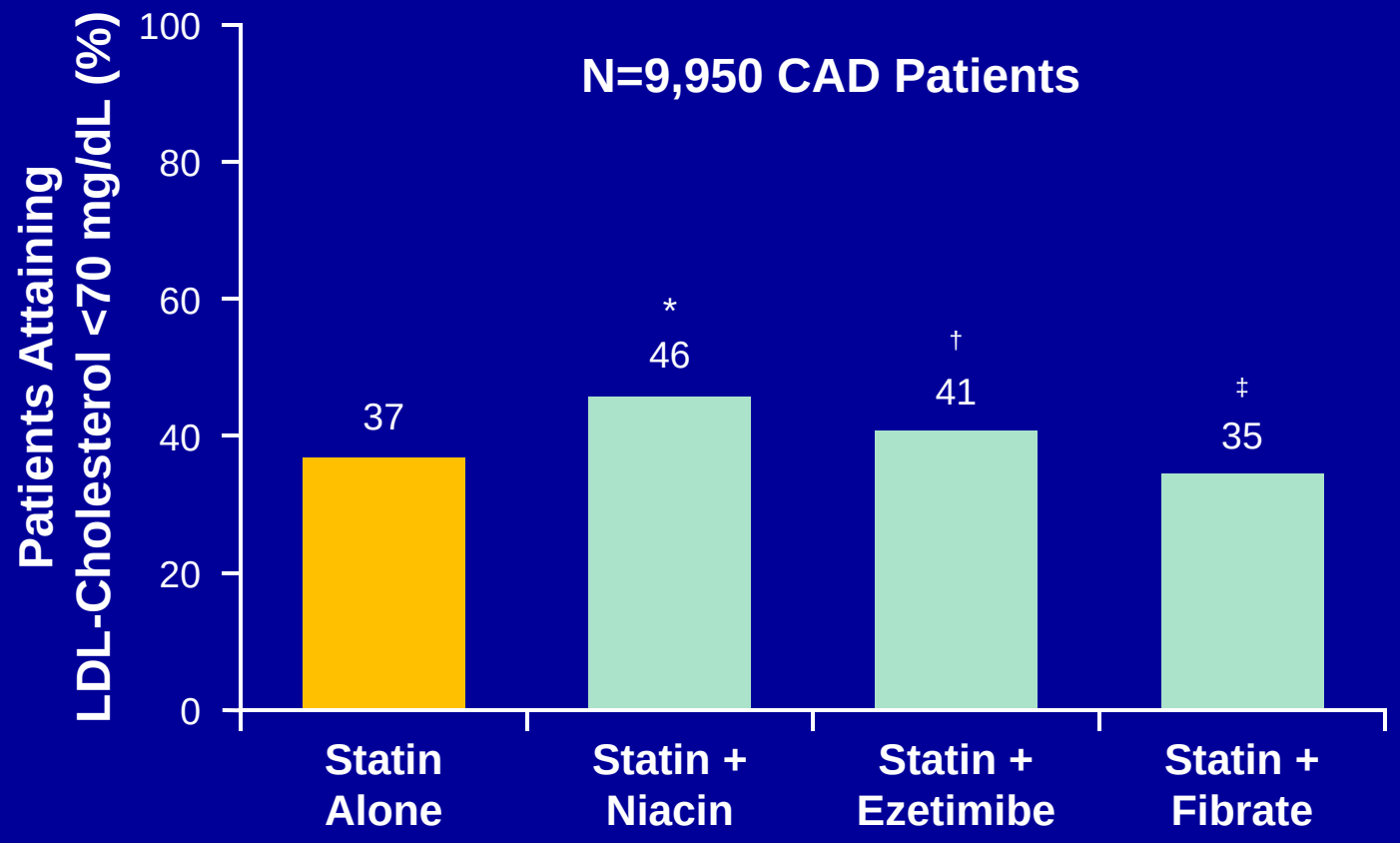
**Sergio Fazio, MD, PhD**
**William and Sonja Connor Professor of Preventive Cardiology**
**Professor of Medicine, Physiology & Pharmacology**
**Director, Center for Preventive Cardiology**
**Knight Cardiovascular Institute**
**Oregon Health and Science University**
**Portland, Oregon**

# Why do we need more drugs and more studies?

- High prevalence of statin intolerance (>10% of users).
- High prevalence of extreme hypercholesterolemia, difficult to treat with one drug only.
- Increasing certainty of the LDL hypothesis (more drugs needed)
- Increasing uncertainty of the HDL hypothesis (more targets needed)
- Decreasing uncertainty of the triglyceride hypothesis (more trials needed)

# LDL

# LDL-C Goals Are Hard to Reach for High-Risk Individuals




Karalis DG, et al. *Cholesterol*. 2012;2012:861924.

# Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

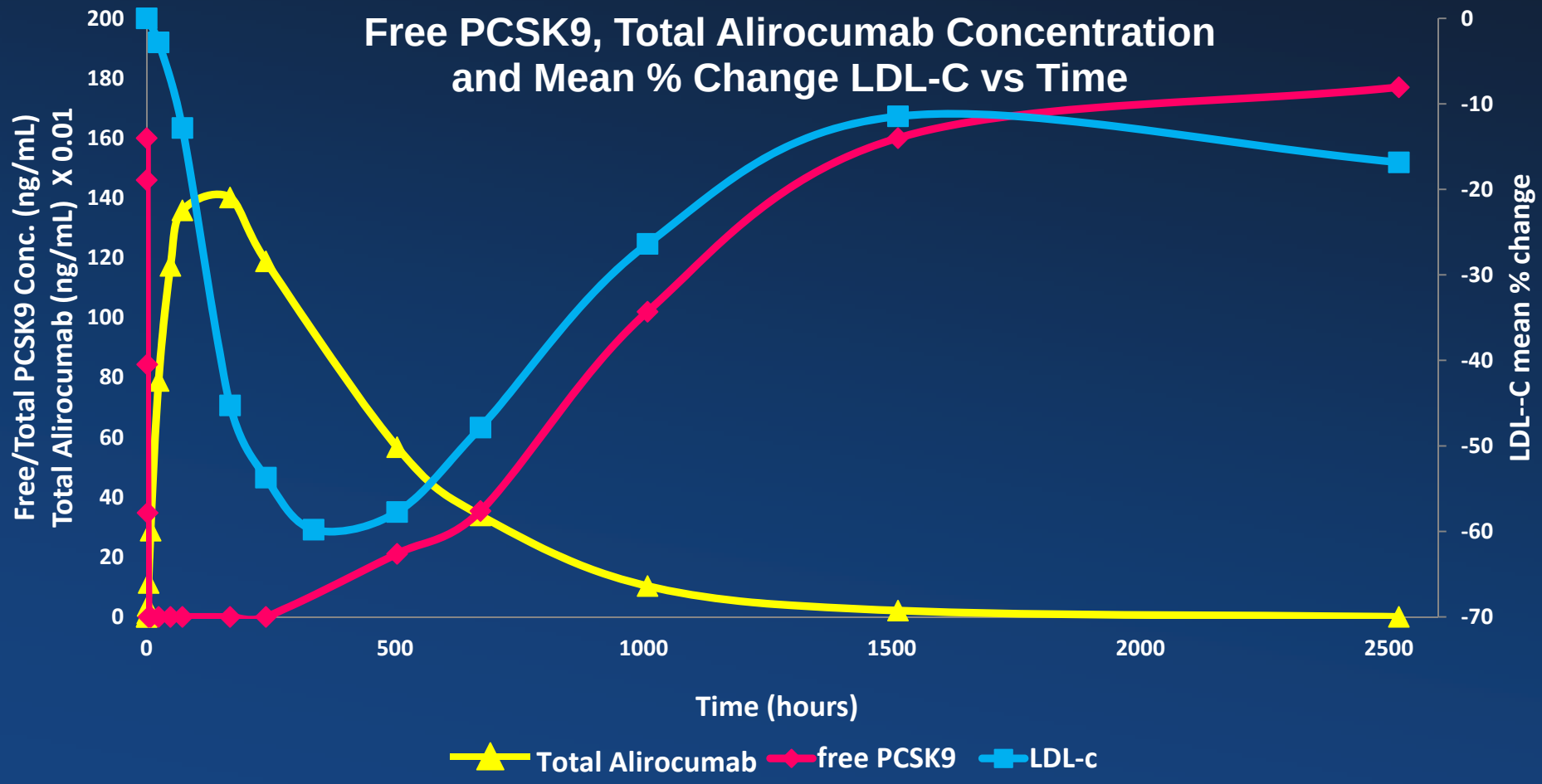
Proprotein convertases are proteolytic enzymes that activate precursor proteins into biologically active forms

**PCSK9:** A circulating protein that binds the LDL-R and targets it to lysosomal degradation, thus causing reduced LDL clearance and raised LDL levels. Other features include:

- It can bind other proteins (annexin, resistin, etc)
- It may target other lipoprotein receptors
- It is up-regulated by statins and insulin
- It is down-regulated by fasting
- It associates with LDL and Lp(a)

Abifadel M, et al. Curr Atheroscler Rep. 2014;16(9):439.

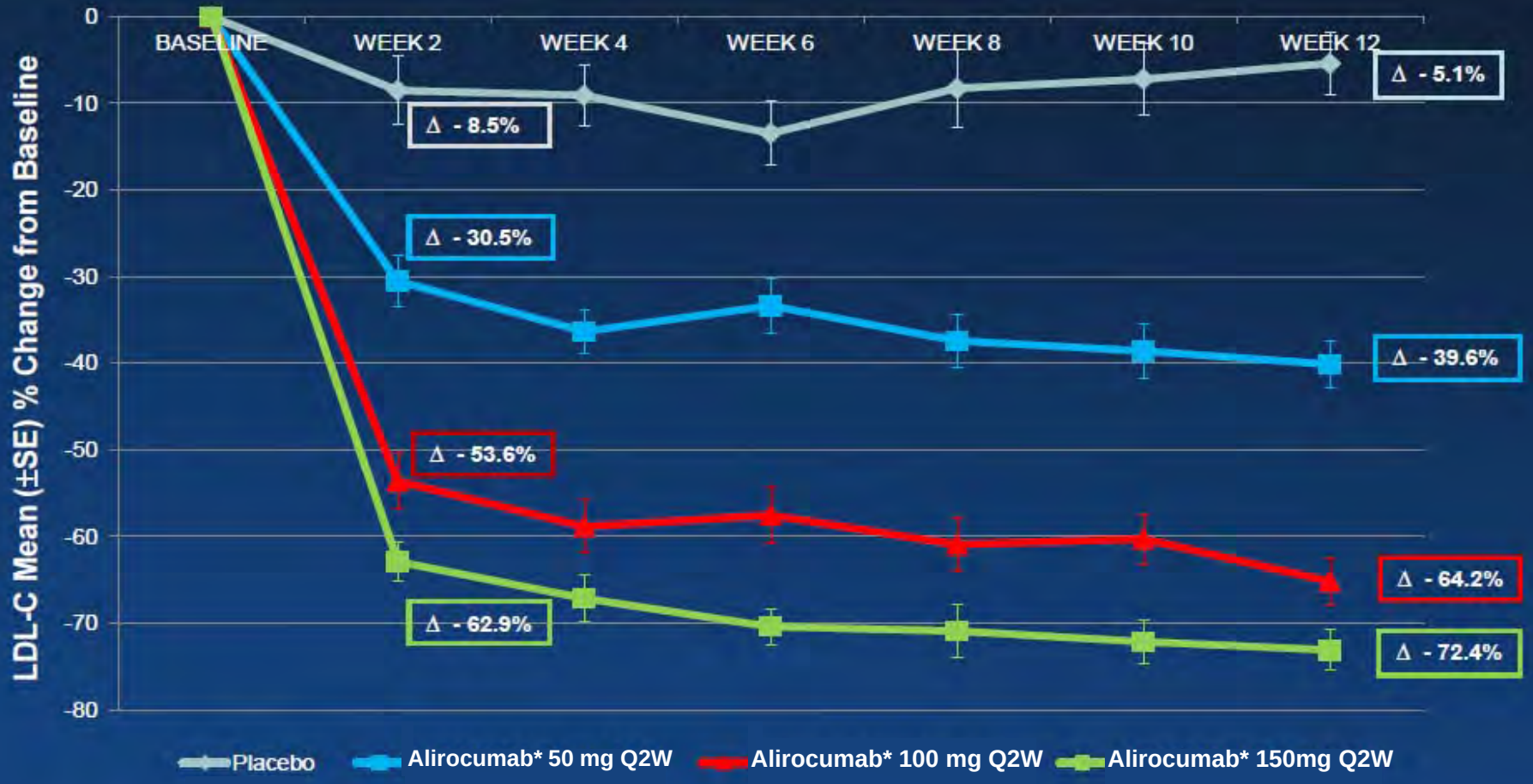
# Alirocumab*: Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C




***Alirocumab=SAR236553/REGN727**

Koren MJ, et al. Postgrad Med. 2015;127(2):125-32.

# Change in Calculated LDL-C at 2 Weekly Intervals from Baseline to Week 12

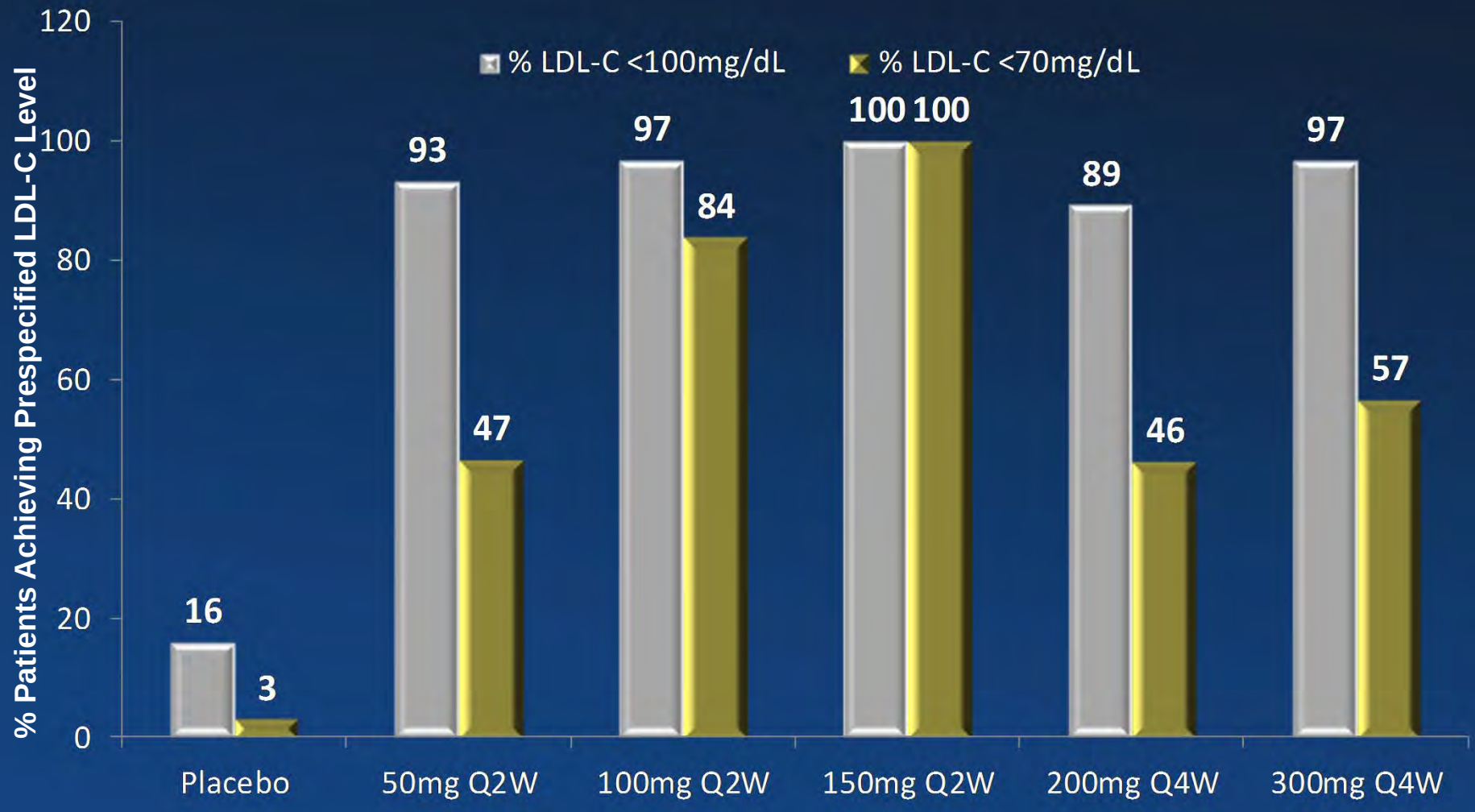



Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

*Alirocumab=SAR236553/REGN727.

McKenney JM, et al. *J Am Coll Cardiol.* 2012;59:2344-2353.

# Attainment of Pre-specified LDL-C Levels at Week 12 (mITT Population)

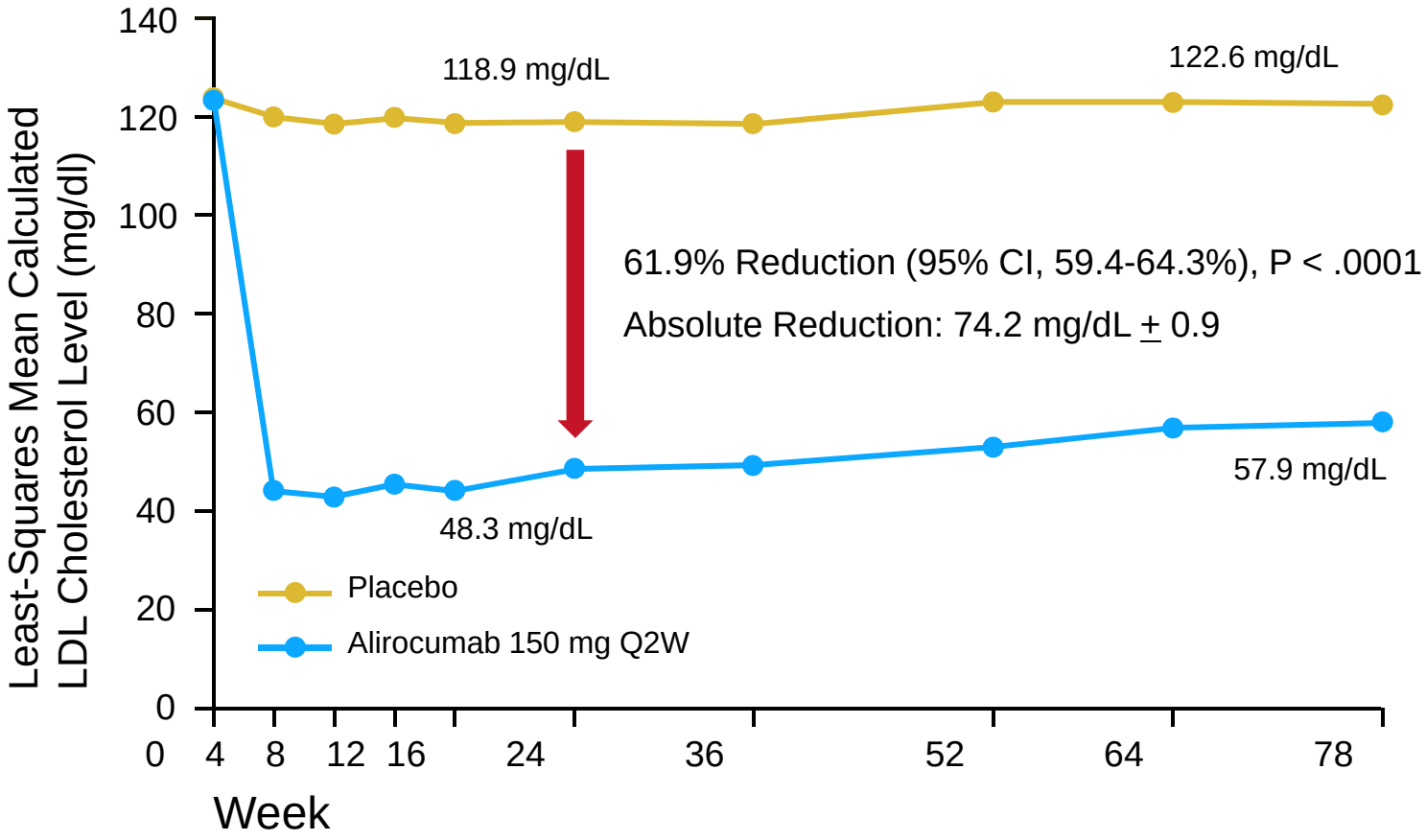



McKenney JM, et al. *J Am Coll Cardiol.* 2012;59:2344-2353.

# ODYSSEY LONG TERM:
# LDL-C Reduction Maintained Over 52 Weeks

## Achieved LDL-C Over Time

All patients on background of maximally-tolerated statin ± other lipid-lowering therapy

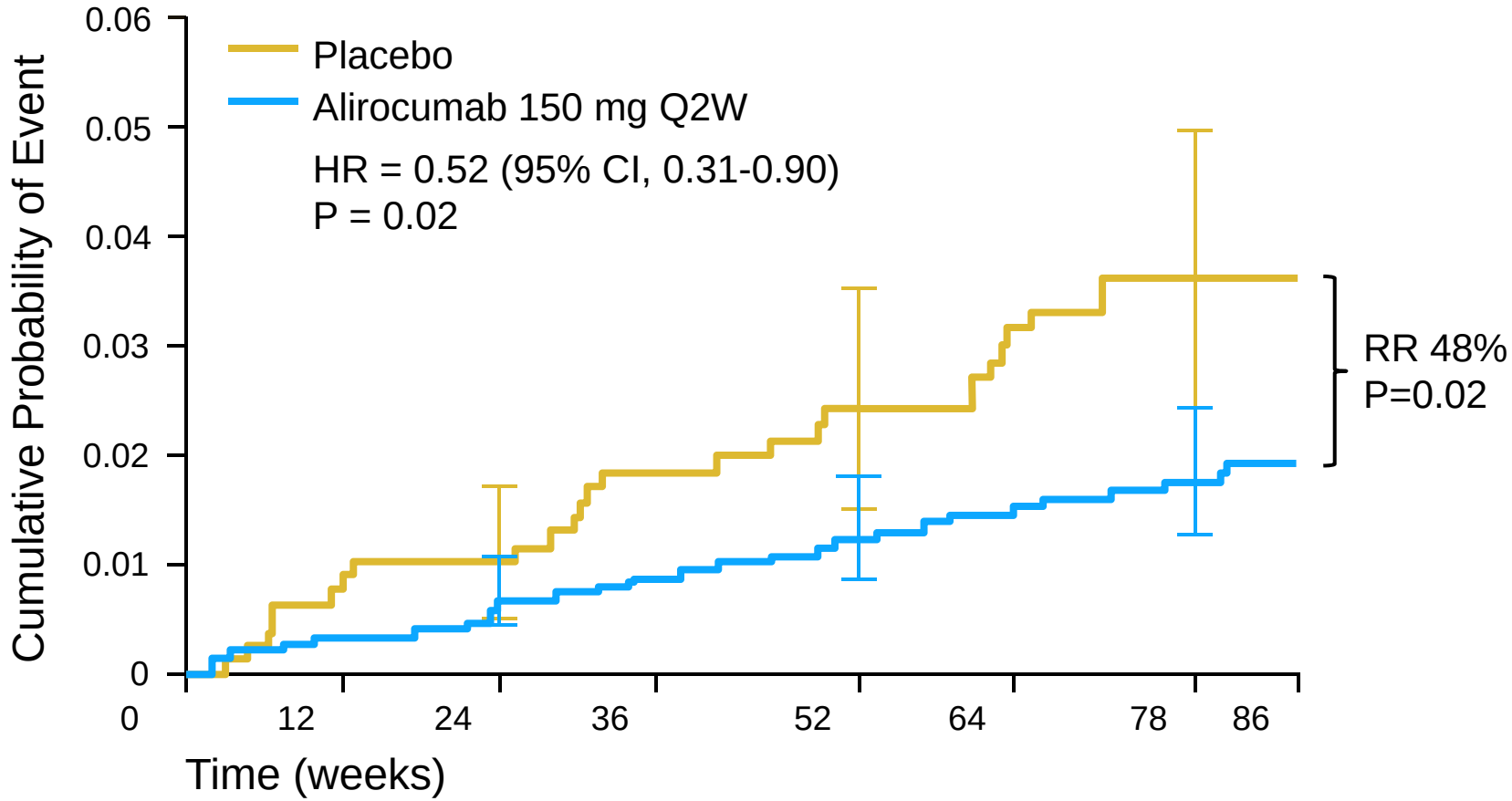



Intent-to-treat (ITT) analysis.

Robinson JG, et al. N Engl J Med. 2015;372:1489-99.

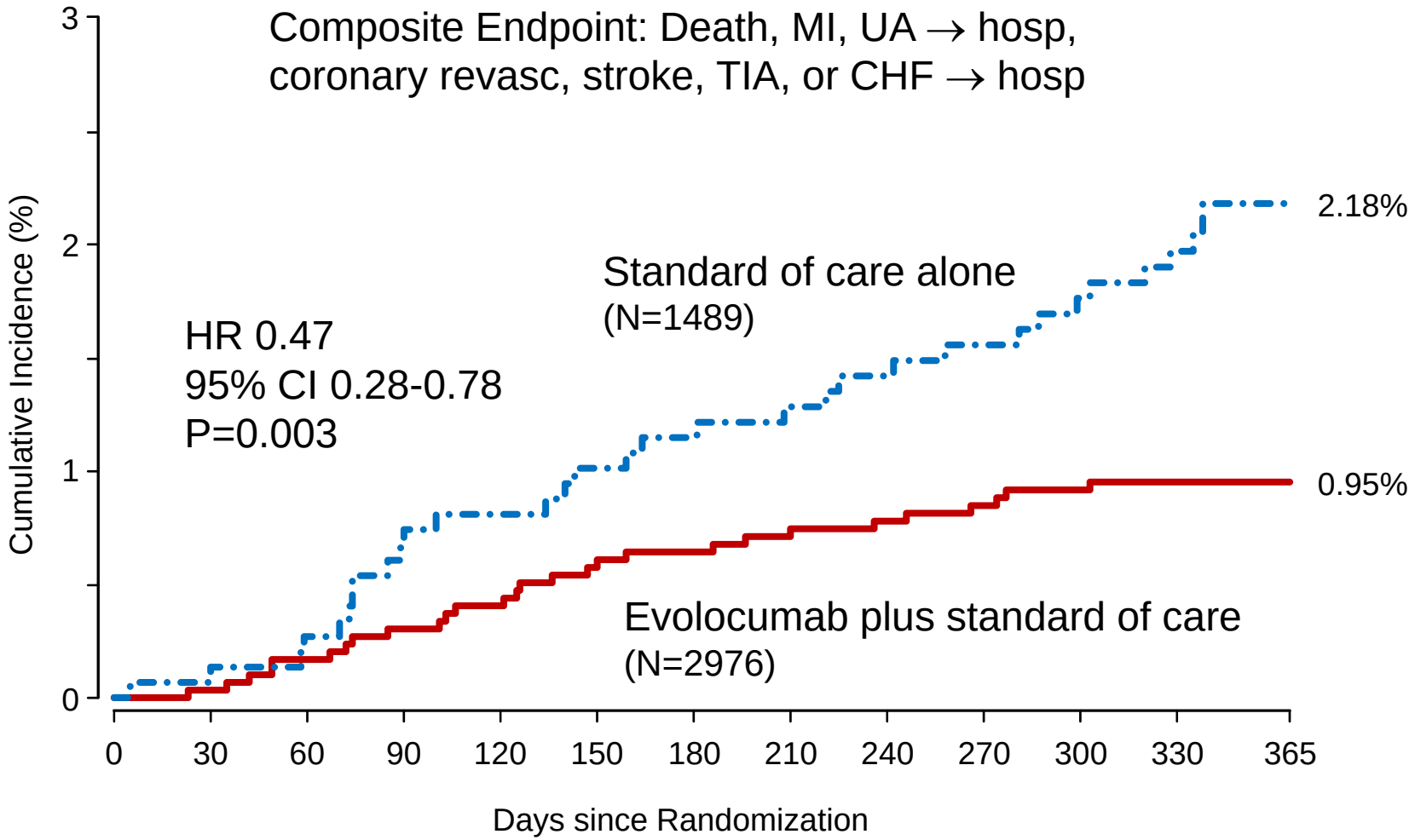
# ODYSSEY LONG TERM: Major Adverse Cardiovascular Events

**Composite endpoint: Death from coronary heart disease, nonfatal MI, fatal or nonfatal stroke, or unstable angina requiring hospitalization**




Robinson JG, et al. *N Engl J Med.* 2015;372:1489-1499.

# OSLER Program: Cardiovascular Outcomes with Evolocumab*




*Not FDA approved.

Sabatine MS, et al. *N Engl J Med.* 2015;372:1500-1509.

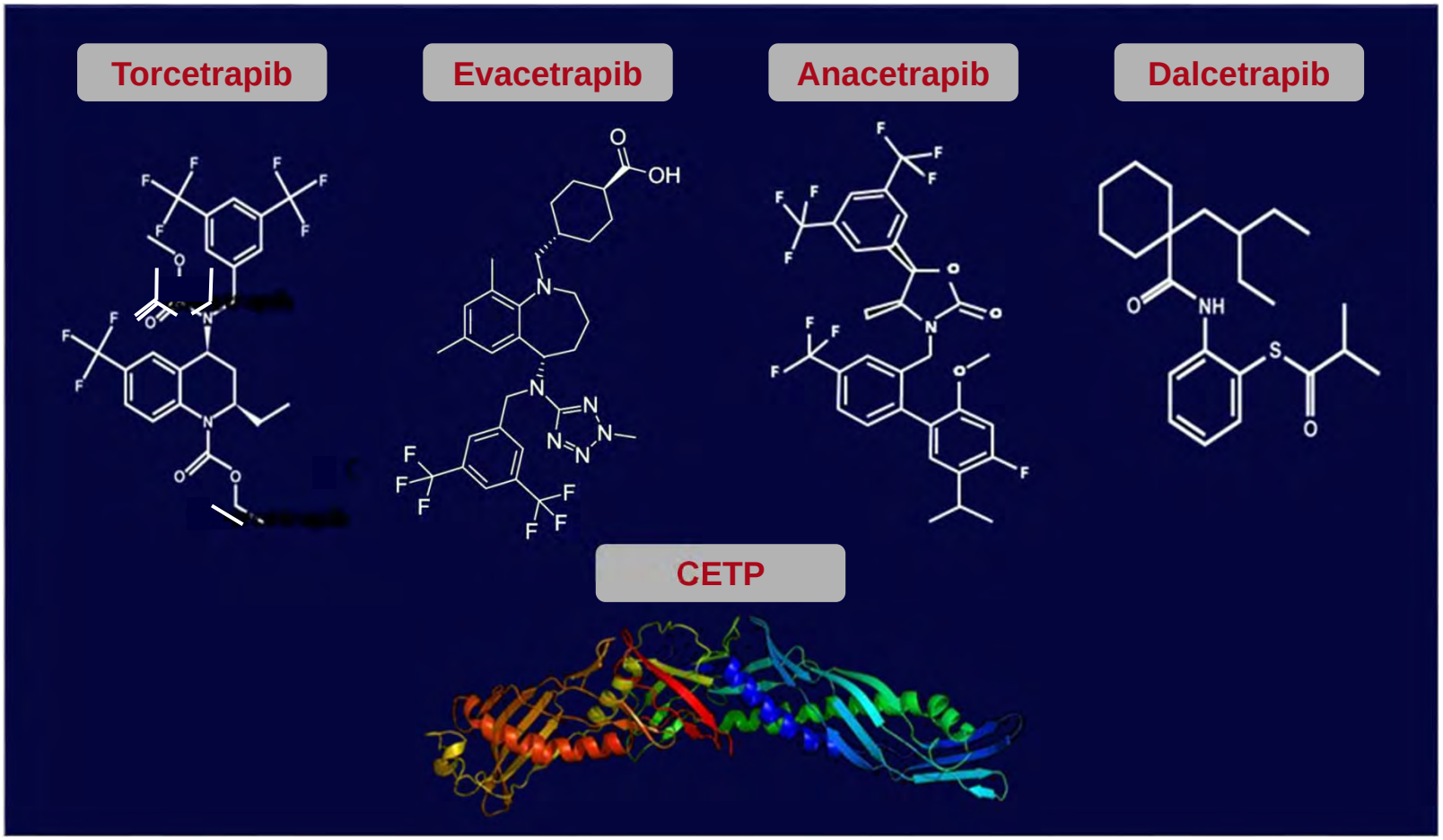
# PCSK9 Inhibitor Cardiovascular Outcomes Trials

| | **Evolocumab*** (AMG 145) | **Alirocumab** (SAR236553 / REGN727) | **Bococizumab*** (RN 316) | |
|---|---|---|---|---|
| **Sponsor** | Amgen | Sanofi / Regeneron | Pfizer | |
| **Trial** | **FOURIER** | **ODYSSEY Outcomes** | **SPIRE I** | **SPIRE II** |
| **Sample size** | 27,500 | 18,000 | 17,000 | 9,000 |
| **Patients** | MI, stroke or PAD | 4-52 wks post-ACS | High risk of CV event | |
| **Statin** | Atorva ≥20 mg or equiv | Evid-based med Rx | Lipid-lowering Rx | |
| **LDL-C mg/dL(mmol/L)** | ≥70 (≥1.8) | ≥70 (≥1.8) | 70-99 (1.8-2.6) | ≥100 (≥2.6) |
| **PCSK9i Dosing** | Q2W or Q4W | Q2W | Q2W | |
| **Endpoint** | 1°: CV death, MI, stroke, revasc or hosp for UA,<br>Key 2°: CV death, MI, or stroke | CHD death, MI, ischemic stroke, or hosp for UA | CV death, MI, stroke, or urgent revasc | |
| **Completion** | 12/2017 | 1/2018 | 8/2017 | |

*Not FDA approved.
*www.clinicaltrials.gov.*

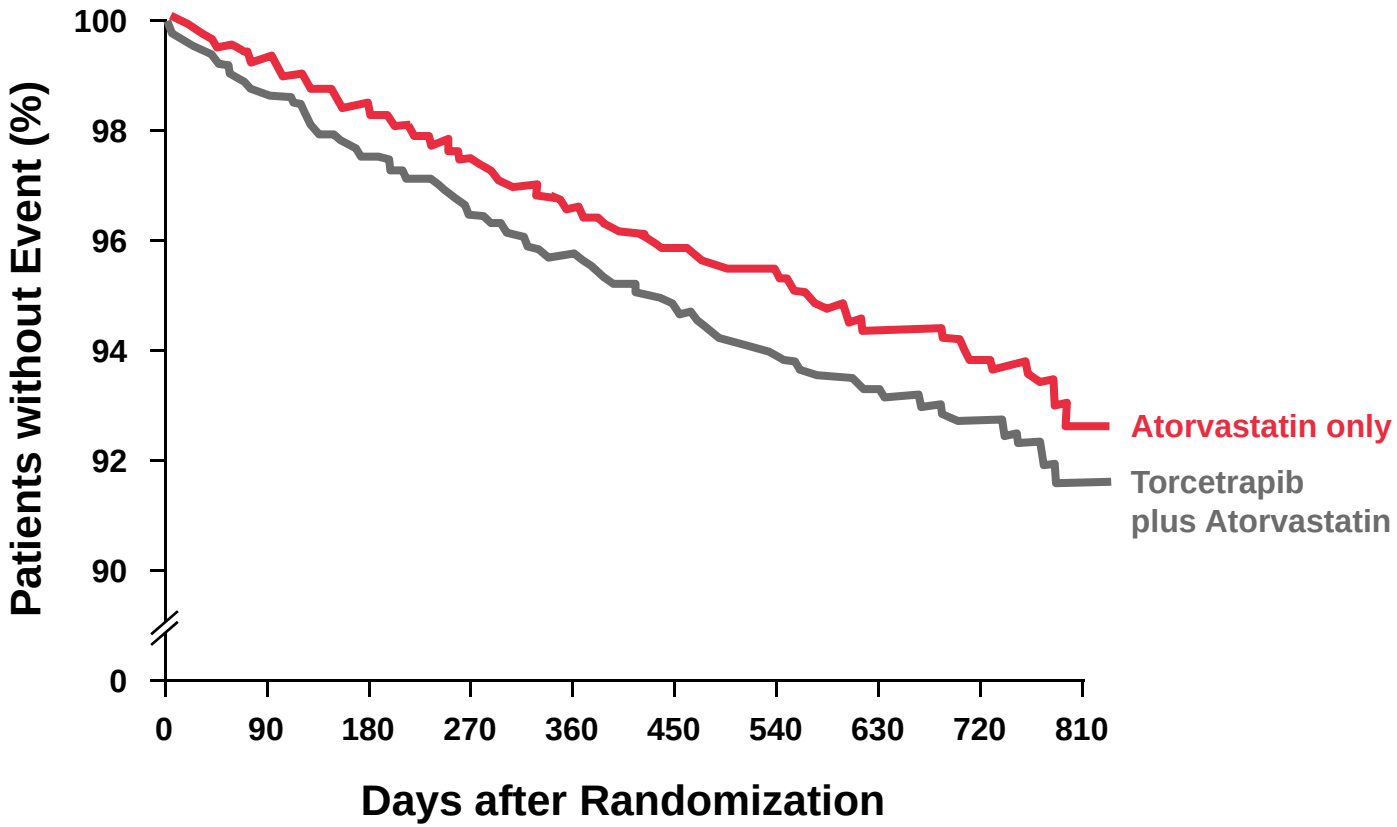
# HDL

# CETP Inhibitors and Modulators




**Barter PJ, et al. *N Engl J Med*. 2007;357(21):2109-2122;**
**Qiu X, et al. *Nat Struct Mol Biol*. 2007;14(2):106-112.**

# Torcetrapib: Increased Cardiovascular and Non-Cardiovascular Morbidity and Mortality




**Is the toxicity of torcetrapib related to the mechanism or the molecule?**

**Barter PJ, et al. *N Engl J Med.* 2007;357(21):2109-2122.**

# dal-HEART Program

## Dalcetrapib HDL Evaluation, Atherosclerosis, and Reverse Cholesterol Transport

**The dal-HEART Program tests a novel hypothesis that raising HDL through CETP inhibition will attenuate cardiovascular risk.**

### dal-OUTCOMES[1]

A double-blind, randomized, placebo-controlled study in 15,600 patients recently hospitalized for ACS

**Goal**: To evaluate the effect of dalcetrapib on CV outcomes

### dal-VESSEL[2]

A double-blind, randomized, placebo-controlled study in 450 patients with CHD or CHD risk equivalent

**Goal**: To evaluate the effect of dalcetrapib on endothelial function and blood pressure, measured by FMD and ABPM

### dal-PLAQUE[3]

A double-blind, randomized, placebo-controlled study in 130 patients with CHD

**Goal**: To evaluate the effect of dalcetrapib on inflammation, plaque size, and burden, measured by PET/CT and MRI

### dal-PLAQUE 2[4]

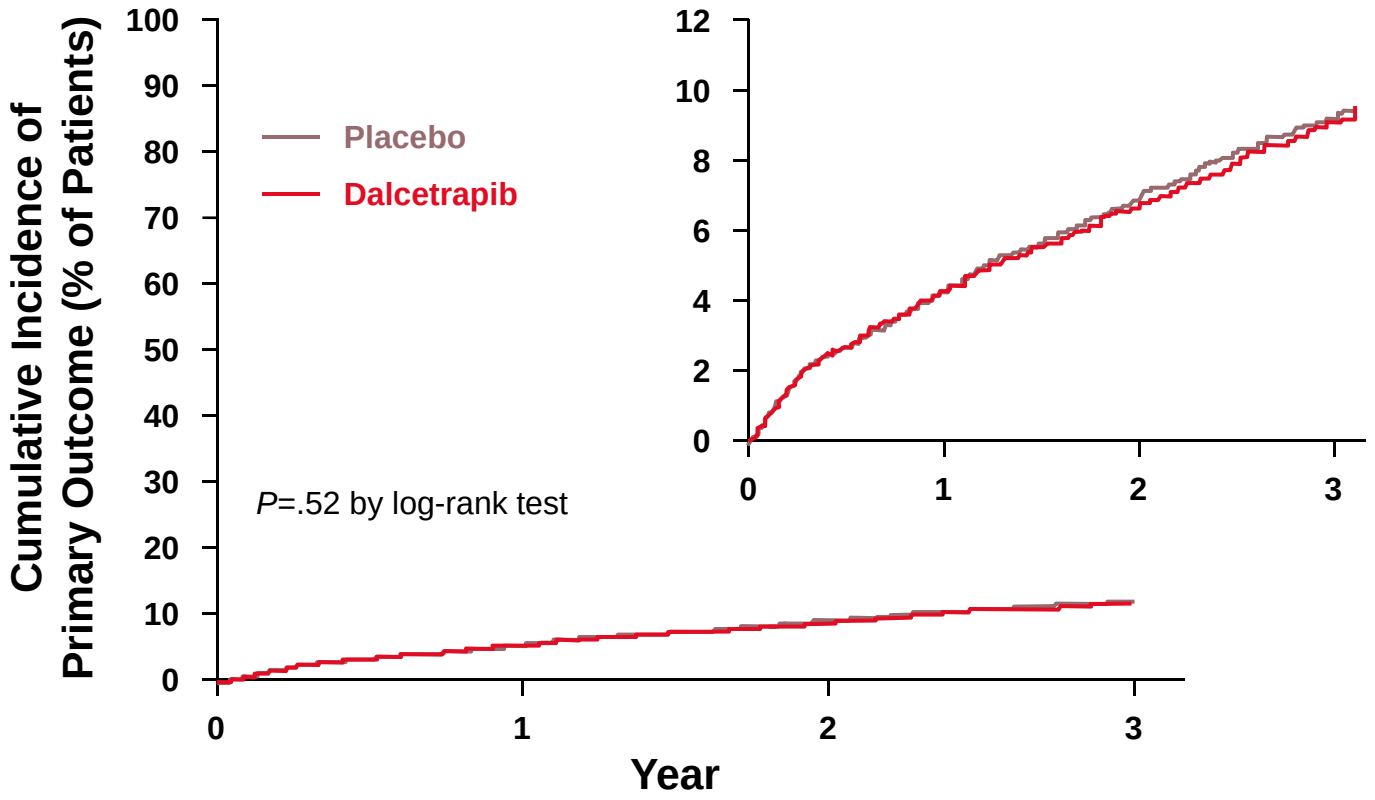
A double-blind, randomized, placebo-controlled study in 900 patients with CAD

**Goal**: To evaluate the effect of dalcetrapib on atherosclerotic progression, assessed by IVUS and carotid B-mode ultrasound

**dal-OUTCOMES = Dalcetrapib in Stable Coronary Heart Disease Patients with Recent Acute Coronary Syndrome; dal-VESSEL = Vascular Effects and Safety of Dalcetrapib in Patients with or at Risk of CHD; dal-PLAQUE = Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging.**

**[1]Schwartz GG, et al. *N Engl J Med.* 2012;367(22):2089-2099; [2]Luscher TF, et al. *Eur Heart J.* 2012;33(7):857-865; [3]Fayad ZA, et al. *Lancet.* 2011;378(9802):1547-1559; [4]Not yet published.**

# dal-OUTCOMES Results: No ↓CVD




**No. at Risk:**

| | | | | |
|---|---|---|---|---|
| **Placebo** | 7933 | 7386 | 6551 | 1743 |
| **Dalcetrapib** | 7938 | 7372 | 6495 | 1736 |

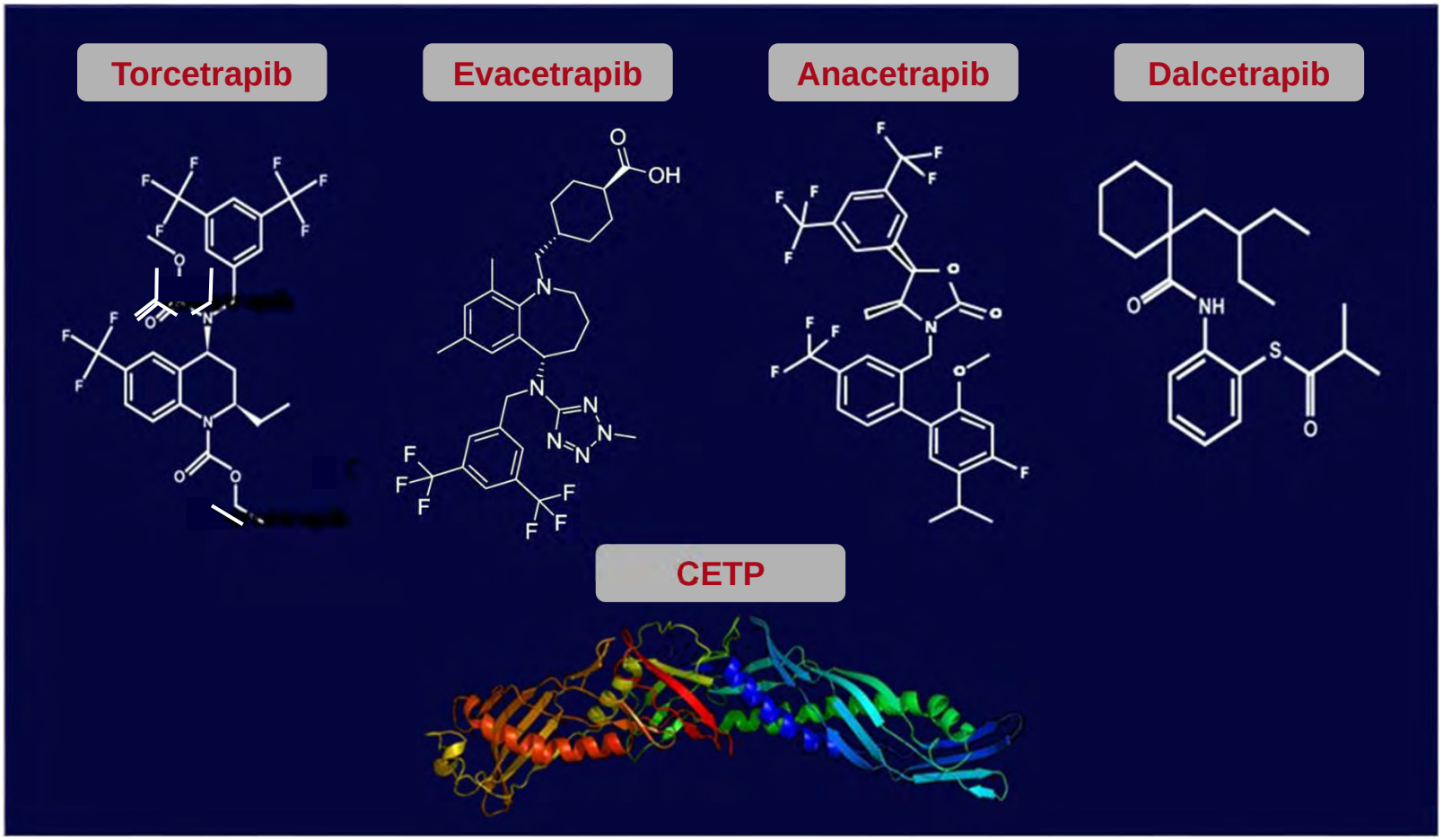
**Schwartz GG, et al. *N Engl J Med*. 2012;367(22):2089-99.**

# CETP Polymorphisms and Cardiovascular Risk in Humans

- A meta-analysis has been conducted of studies investigating relationships between CETP polymorphisms and cardiovascular disease in humans
- 46 studies had data on 27,196 coronary cases and 55,338 controls
- Those polymorphisms that were associated with lower CETP mass and lower CETP activity had higher levels of HDL-C and a significantly reduced coronary risk

**Thompson A, et al. *JAMA*. 2008;299(23):2777-2788.**

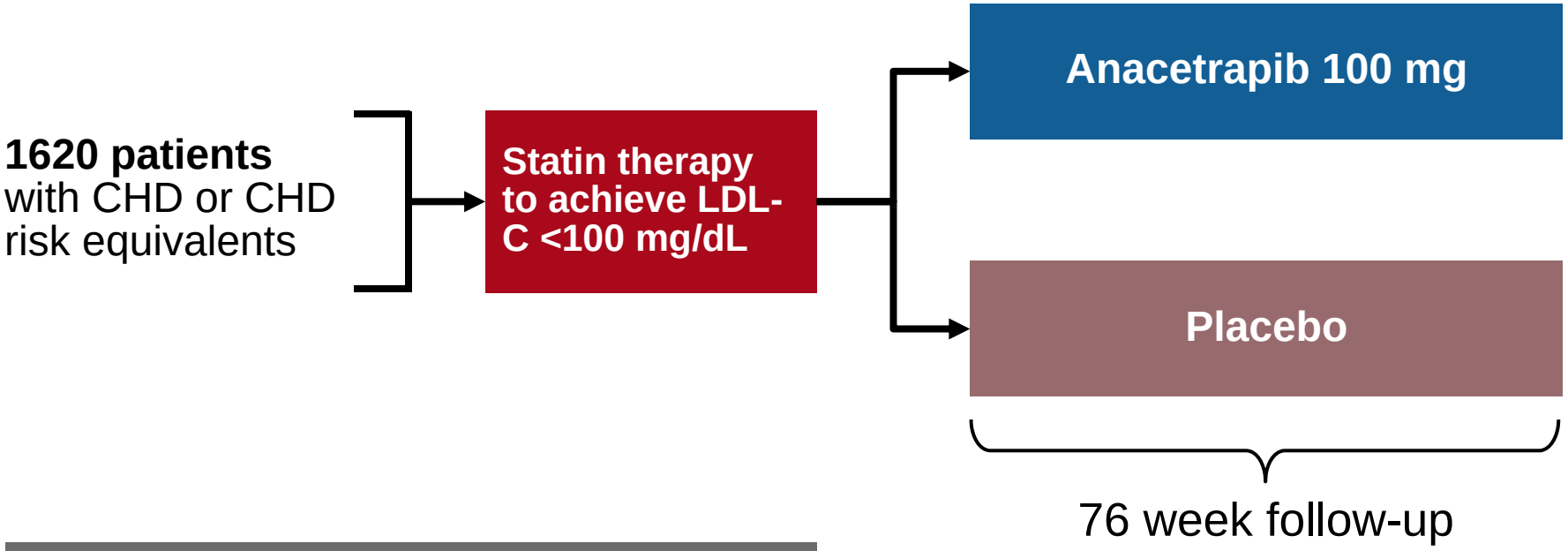
# CETP Inhibitors and Modulators




**Barter PJ, et al. *N Engl J Med*. 2007;357(21):2109-2122;**
**Qiu X, et al. *Nat Struct Mol Biol*. 2007;14(2):106-112.**

# DEFINE Trial

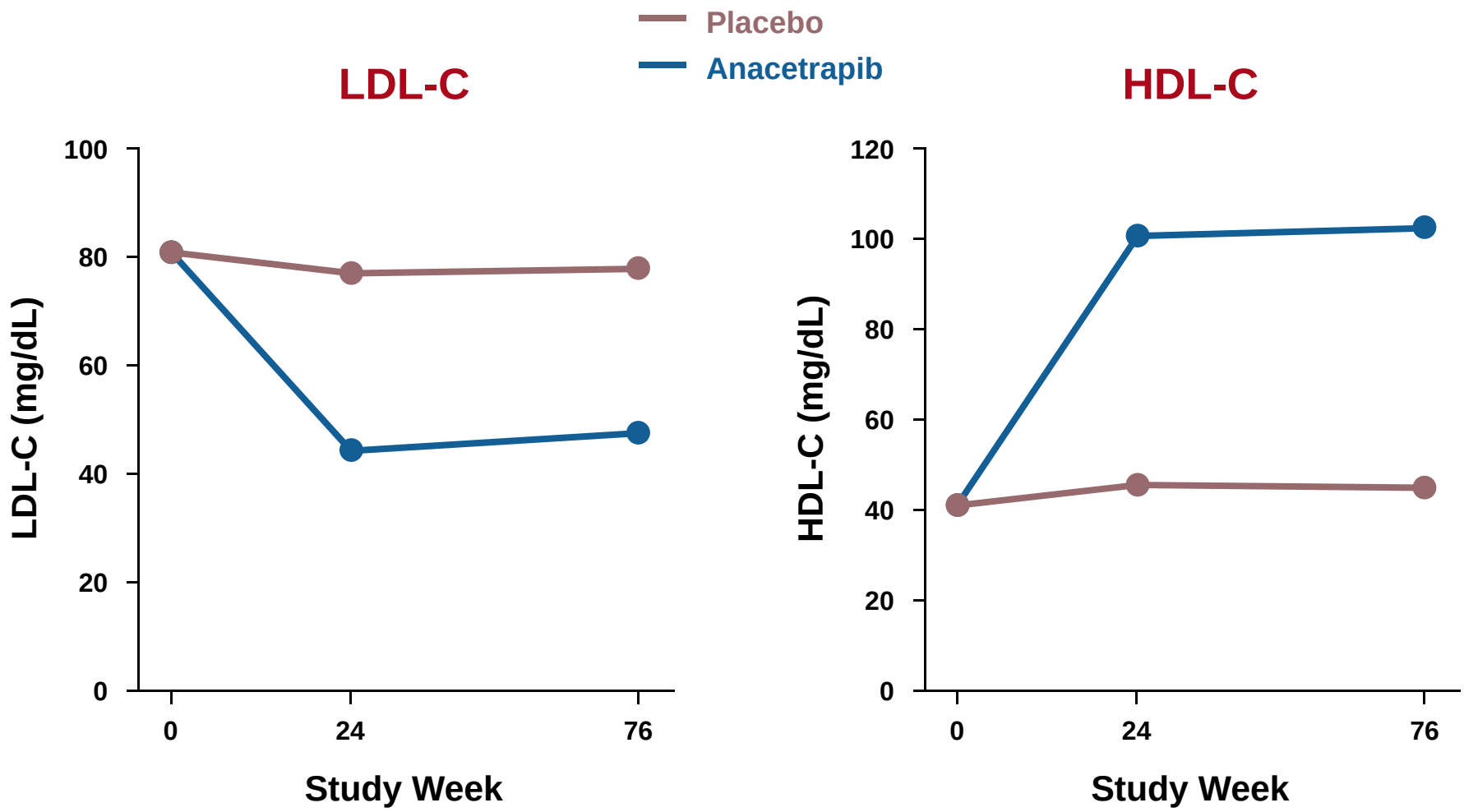
## Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib




**Primary End Point**
Lipid efficacy and the safety

**Cannon CP, et al. *NEJM*. 2010;363(25):2406-15.**

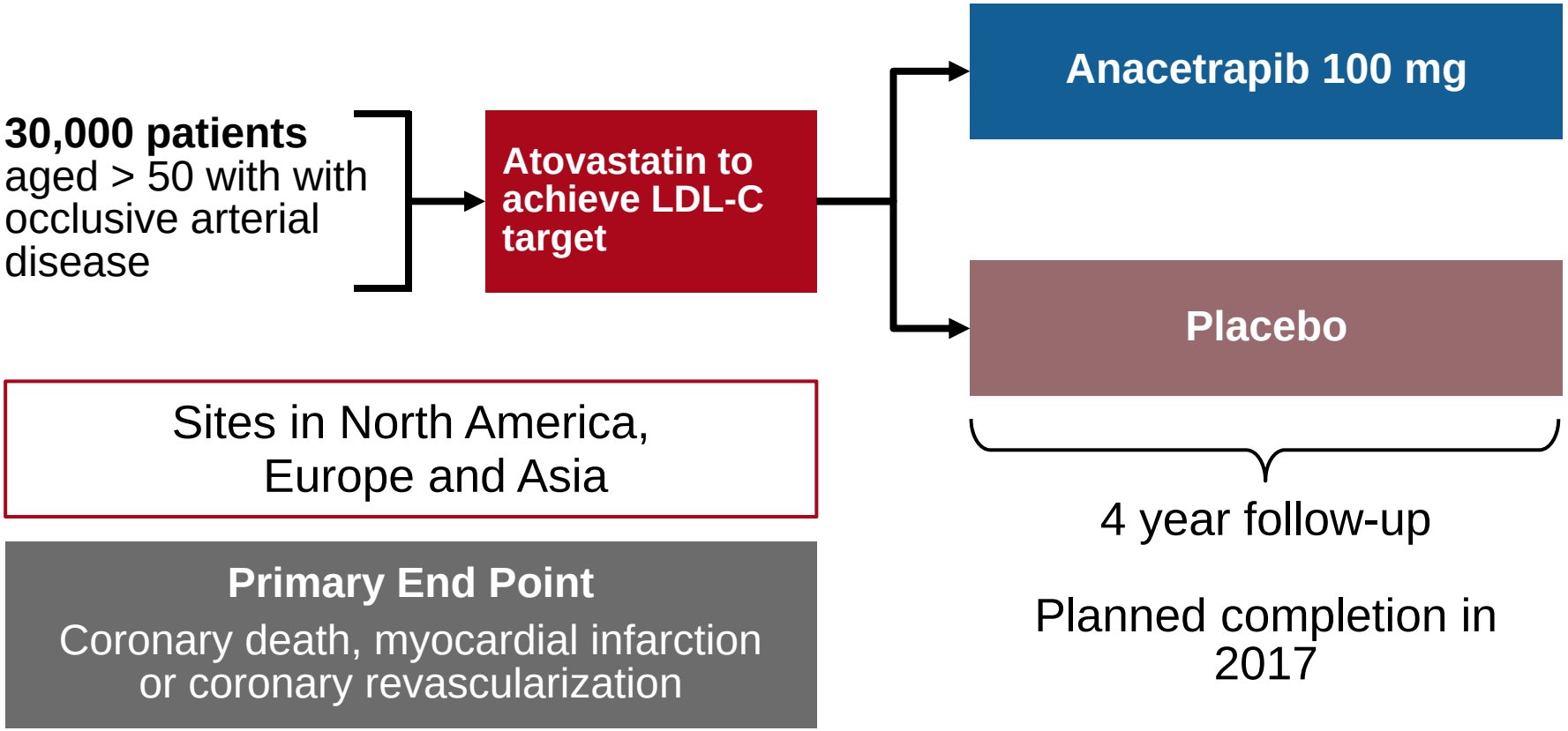
# DEFINE Trial




Cannon CP, et al. *NEJM*. 2010;363(25):2406-15.

# REVEAL Trial

## Randomized Evaluation of the Effects of Anacetrapib through Lipid-Modification




**University of Oxford. *Reveal.* www.revealtrial.org. Accessed November 2, 2014.**

ORIGINAL CONTRIBUTION

Scan for Author Video Interview

# Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination With Statins on HDL and LDL Cholesterol

## A Randomized Controlled Trial

Stephen J. Nicholls, MBBS, PhD
H. Bryan Brewer, MD, PhD
John J. P. Kastelein, MD, PhD
Kathryn A. Krueger, MD
Ming-Dauh Wang, PhD
Mingyuan Shao, MS
Bo Hu, PhD
Ellen McErlean, MSN
Steven E. Nissen, MD

**Context** Interest remains high in cholesteryl ester transfer protein (CETP) inhibitors as cardioprotective agents. Few studies have documented the efficacy and safety of CETP inhibitors in combination with commonly used statins.

**Objective** To examine the biochemical effects, safety, and tolerability of evacetrapib, as monotherapy and in combination with statins, in patients with dyslipidemia.

**Design, Setting, and Participants** Randomized controlled trial conducted among 398 patients with elevated low-density lipoprotein cholesterol (LDL-C) or low high-density lipoprotein cholesterol (HDL-C) levels from April 2010 to January 2011 at community and academic centers in the United States and Europe.

**Interventions** Following dietary lead-in, patients were randomly assigned to receive placebo (n=38); evacetrapib monotherapy, 30 mg/d (n=40), 100 mg/d (n=39), or 500 mg/d (n=42); or statin therapy (n=239) (simvastatin, 40 mg/d; atorvastatin, 20 mg/d; or rosuvastatin, 10 mg/d) with or without evacetrapib, 100 mg/d, for 12 weeks.

**Main Outcome Measures** The co–primary end points were percentage changes from baseline in HDL-C and LDL-C after 12 weeks of treatment.

**Results** The mean baseline HDL-C level was 55.1 (SD, 15.3) mg/dL and the mean baseline LDL-C level was 144.3 (SD, 26.6) mg/dL. As monotherapy, evacetrapib produced dose-dependent increases in HDL-C of 30.0 to 66.0 mg/dL (53.6% to 128.8%) compared with a decrease with placebo of –0.7 mg/dL (–3.0%; $P<.001$ for all compared with placebo) and decreases in LDL-C of –20.5 to –51.4 mg/dL (–13.6% to –35.9%) compared with an increase with placebo of 7.2 mg/dL (3.9%; $P<.001$ for all compared with placebo). In combination with statin therapy, evacetrapib, 100 mg/d, produced increases in HDL-C of 42.1 to 50.5 mg/dL (78.5% to 88.5%; $P<.001$ for all compared with statin monotherapy) and decreases in LDL-C of –67.1 to –75.8 mg/dL (–11.2% to –13.9%; $P<.001$ for all compared with statin monotherapy). Compared with evacetrapib monotherapy, the combination of statins and evacetrapib resulted in greater reductions in LDL-C ($P<.001$) but no greater increase in HDL-C ($P=.39$). Although the study was underpowered, no adverse effects were observed.

**Conclusions** Compared with placebo or statin monotherapy, evacetrapib as monotherapy or in combination with statins increased HDL-C levels and decreased LDL-C levels. The effects on cardiovascular outcomes require further investigation.

**Trial Registration** clinicaltrials.gov Identifier: NCT01105975

*JAMA. 2011;306(19):2099-2109* www.jama.com

THE DEVELOPMENT OF STATINS for reducing low-density lipoprotein cholesterol (LDL-C) has revolutionized cardiovascular disease prevention.[1-6] Nonetheless, cardiovascular disease remains the number one cause of death.[7] Accordingly, considerable efforts have focused on development of novel therapeutic agents designed to address residual cardiovascular risk. Because individuals from the general population with elevations of high-density lipoprotein cholesterol (HDL-C) have a reduced incidence of coronary heart disease,[8] it has been assumed that finding an appropriate therapy to increase HDL-C levels would yield substantial clinical benefit.

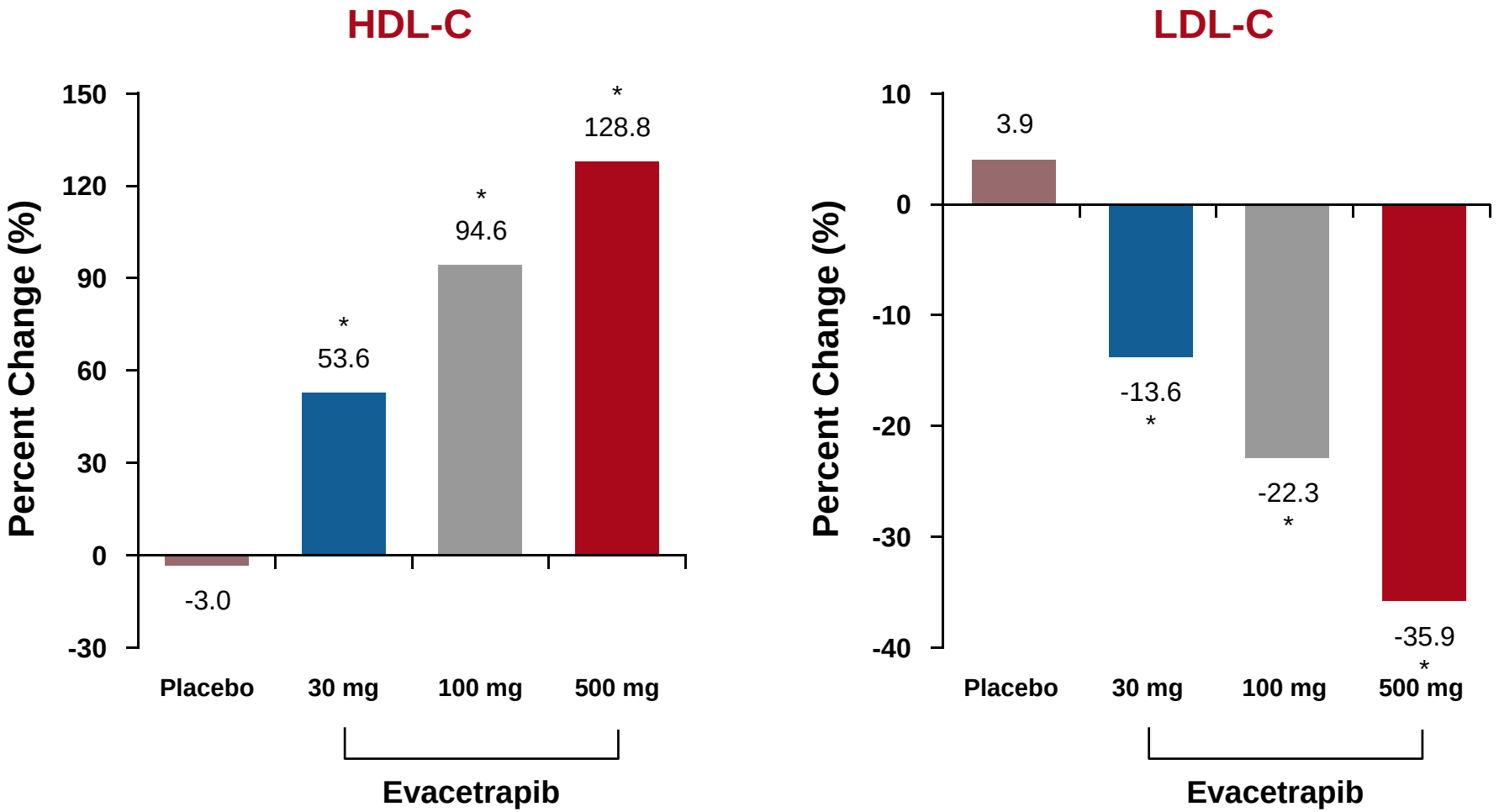
However, development of drugs that increase HDL-C levels has been challenging and fraught with failures, including the premature termination of

**For editorial comment see p 2153.**

**Author Video Interview available at www.jama.com.**

**Author Affiliations:** Cleveland Clinic Coordinating Center for Clinical Research (Drs Nicholls and Nissen, Mr Shao, and Ms McErlean) and Department of Quantitative Health Sciences (Dr Hu), Cleveland Clinic, Cleveland, Ohio; Medstar Research Institute, Washington, DC (Dr Brewer); Academic Medical Center, Amsterdam, the Netherlands (Dr Kastelein); and Eli Lilly, Indianapolis, Indiana (Drs Krueger and Wang).
**Corresponding Author:** Stephen J. Nicholls, MBBS, PhD, Department of Cardiovascular Medicine, Mail Code JJ-65, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195 (nichols1@ccf.org).

# Percent Change in HDL-C and LDL-C




****P*<.001 compared with placebo.**

**Nicholls SJ, et al. *JAMA*. 2011;306(19):2099-109.**

# ACCENTUATE Study

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
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Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail

Text Size

## A Study of Evacetrapib (LY2484595) in Participants With High Cholesterol (ACCENTUATE)

This study is currently recruiting participants. (see Contacts and Locations)

*Verified August 2015 by Eli Lilly and Company*

**Sponsor:**
Eli Lilly and Company

**Information provided by (Responsible Party):**
Eli Lilly and Company

**ClinicalTrials.gov Identifier:**
NCT02227784

First received: August 26, 2014
Last updated: August 21, 2015
Last verified: August 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

### Purpose

The purpose of the ACCENTUATE study is to evaluate whether the study drug known as evacetrapib is effective in treating participants with high cholesterol and atherosclerotic cardiovascular disease (ASCVD) and/or diabetes.

# Triglycerides

# Randomized Trials of n-3 Fatty Acids on CVD Endpoints

| Trials | Population/background fish or n-3 PUFA intake | Intervention | Duration of follow-up | Events | RR (95% CI) | Achieved power† |
|---|---|---|---|---|---|---|
| Alpha Omega Trial[27] | 4837 patients with a history of past (average ~4.3 years prior) MI | 376 mg/day EPA+DHA versus a combined control group receiving either placebo or ALA 1.9 g/day | 3.3 years | Major cardiovascular events, n=671<br>CHD deaths, n=138 | 1.01 (0.87–1.17)<br>0.98 (0.68–1.32) | 0.96<br>0.36 |
| OMEGA Trial[28] | 3851 patients with recent (≤2 weeks prior) MI | 840 mg/day EPA+DHA versus placebo | 1 year | Major cardiovascular events, n=331<br>Sudden deaths, n=57 | 1.21 (0.96–1.52)<br>0.95 (0.56–1.60) | 0.72<br>0.17 |
| SU.FOL.OM3[29] 2010 | 2501 patients with a history of past (average ~100 days prior) acute coronary or cerebral ischaemic event | 600 mg/day EPA+DHA versus a combined control group receiving either placebo or B vitamins (5-methyltetrahydrofolate, 560 μg; $B_6$, 3 mg and $B_{12}$, 20 μg) | 4.2 years | Major cardiovascular events, n=157<br>CHD deaths, n=40 | 1.08 (0.79–1.47)<br>Not reported | 0.4<br>0.14 |
| ORIGIN[14] | 12 536 patients at high risk for CVD and had IFG, IGT or diabetes | 900 mg/day EPA+DHA versus placebo | 6.2 years | CVD deaths, n=1155<br>Arrhythmia death‡, n=547 | 0.98 (0.87–1.10)<br>1.10 (0.93–1.30) | >0.99<br>0.87 |
| Risk and prevention study[2] | 12 513patients with multiple cardiovascular risk factors, or atherosclerotic vascular disease, but not MI | 850 mg/day EPA+DHA versus placebo | 5 years | CVD deaths, n=279<br>CHD deaths, n=158 | 1.03 (0.82, 1.30)<br>1.07 (0.78–1.46) | 0.61<br>0.38 |

*Adapted from Mozaffarian and Wu.[4]

# Are Omega 3 Fats Cardioprotective?: Why Have Trials Failed

**n-3 PUFA do not reduce CVD events**

**n-3 PUFA have little benefit on top of aggressive medical treatments including statins, anti-platelet agents, etc.**

**n-3 PUFA trials have been inadequately powered to detect a clinically meaningful effect on CHD deaths, the endpoint most likely to be effected based on both epidemiological and clinical trial data**

**n-3 PUFA background therapy has increased due to increased fish consumption and greater use of fish oil supplements**

**n-3 PUFA doses in clinical trials, have been too low (0.5- 1.0 g EPA and DHA) to effect long term plaque stabilization (2-4gms)**

**n-3 PUFA have a limited benefit on CHD deaths after a threshold intake has been reached of ≥ 250 mg/day.**

# Alpha Omega Trial: Results in Statin vs Non-Statin Users

**Table 3** Unadjusted and adjusted hazard rate ratios for major cardiovascular events among statin users and statin non-users randomized to *n*-3 fatty acid supplementation in the Alpha Omega Trial with the placebo group as reference

| | Statin users ($n = 3740$) | | | | | Statin non-users ($n = 413$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No./total (%) | HR (95% CI) | *P*-value | $HR^{a}_{adj}$ (95% CI) | Adj *P*-value | No./total (%) | HR (95% CI) | *P*-value | $HR^{a}_{adj}$ (95% CI) | Adj *P*-value |
| Placebo (reference) | 123/943 (13) | 1.00 | | 1.00 | | 20/113 (18) | 1.00 | | 1.00 | |
| EPA–DHA | 127/920 (14) | 1.06 (0.83, 1.36) | 0.65 | 1.05 (0.82, 1.34) | 0.72 | 16/102 (16) | 0.84 (0.44, 1.62) | 0.60 | 0.82 (0.42, 1.58) | 0.55 |
| ALA | 119/930 (13) | 0.98 (0.76, 1.27) | 0.89 | 0.98 (0.76, 1.26) | 0.87 | 17/102 (17) | 0.94 (0.49, 1.80) | 0.85 | 0.90 (0.47, 1.72) | 0.75 |
| EPA–DHA + ALA | 126/947 (13) | 1.02 (0.79, 1.31) | 0.89 | 1.02 (0.80, 1.31) | 0.88 | 9/96 (9) | 0.48 (0.22, 1.06) | 0.070 | 0.46 (0.21, 1.01) | 0.051 |

ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
[a]$HR_{adj}$, hazard rate ratio adjusted for age, gender, and diabetes mellitus types I and II.

Eussen S et al. Eur Heart Journal (2012) 33, 1582–1588

# Clinical Trials with EPA

| | MARINE (N=229) | ANCHOR (N=702) | REDUCE-IT (N≈8000) |
|---|---|---|---|
| Patients | Severe HTG | Mixed dyslipidemia on statin | Mixed dyslipidemia on statin |
| CV Risk | -- | High risk for CHD event | High risk for CHD event |
| TG Level | ≥500 to ≤2,000 mg/dL | 200 to <500 mg/dL | 200* to <500 mg/dL |
| Primary Endpoint | TG reduction | TG reduction | CV events |
| Timeline | 2009-2011 | 2009-2011 | 2011-ongoing |
| Status | FDA approved indication | sNDA under review | >7300 pts randomized |

# REDUCE-IT: Primary Objective

- In patients
  - with established CVD, or at high risk for CVD,
  - At LDL goal while on statin therapy,
  - And with hypertriglyceridemia
- To evaluate the effect of 4 g/day AMR101 for preventing first occurrence of a Major Adverse Cardiovascular Event (MACE)
  - MACE is composite endpoint that includes:
    - CV death
    - Nonfatal MI
    - Nonfatal stroke
    - Coronary revascularization
    - Unstable angina (caused by MI and requiring emergent hospitalization)

# REDUCE-IT: Secondary Objectives

- Effect of therapy on composite of :
  - CV death, nonfatal MI, coronary revascularization, unstable angina*****, nonfatal stroke, or peripheral vascular disease requiring intervention
- Effect of therapy on:
  - Arrhythmia requiring hospitalization
  - Cardiac arrest
  - Peripheral vascular disease requiring intervention
  - Total mortality

**** If determined to be caused by MI and requiring emergent hospitalization***

# STRENGTH Study

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
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Text Size

## Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH)

**This study is currently recruiting participants.** (see Contacts and Locations)

*Verified August 2015 by AstraZeneca*

**Sponsor:**
AstraZeneca

**Collaborator:**
The Cleveland Clinic

**Information provided by (Responsible Party):**
AstraZeneca

**ClinicalTrials.gov Identifier:**
NCT02104817

First received: April 2, 2014
Last updated: August 26, 2015
Last verified: August 2015
History of Changes

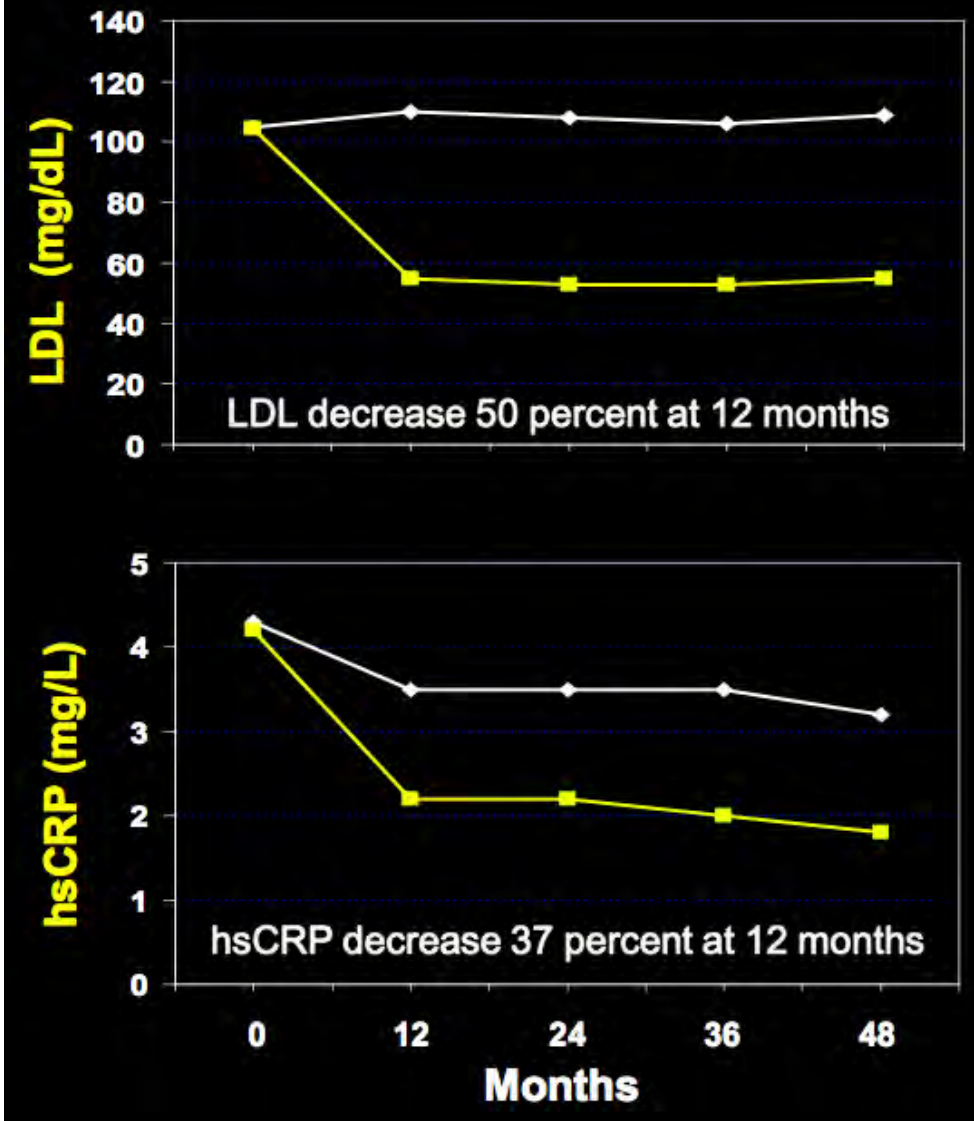
Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

### Purpose

The study is a randomized, double-blind, well-controlled (corn oil), parallel group design that will enroll approximately 13,000 patients with hypertriglyceridemia and high risk for CVD to be randomized 1:1 to either corn oil + statin or Epanova + statin, once daily, for approximately 3-5 years as determined when the number of MACE outcomes is reached.

# Inflammation

# JUPITER
## Achieved LDLC, Achieved hsCRP, or Both?



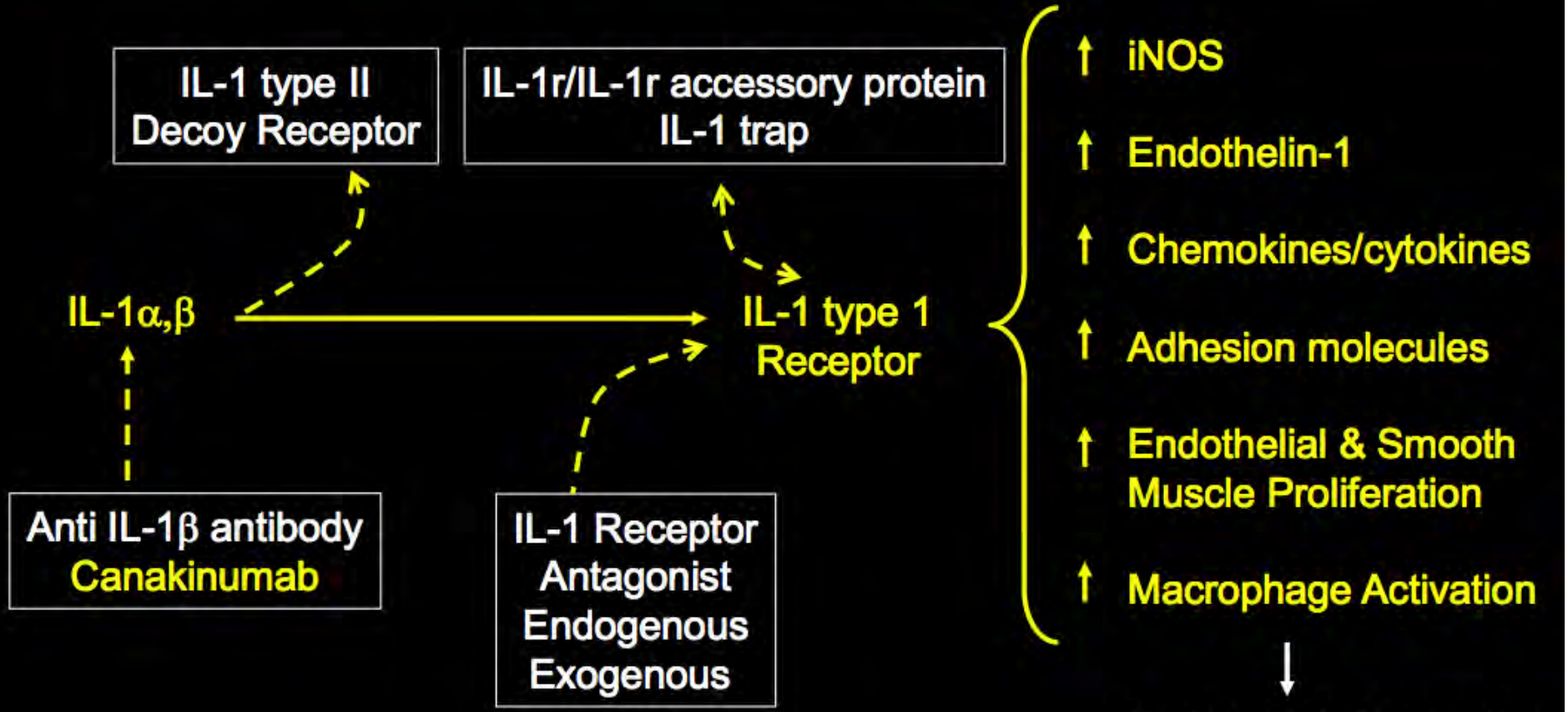

**The Real Controversy:**

**Is the large benefit observed in the JUPITER trial due to lipid lowering, to inflammation inhibition, or to a combination of these two processes?**

# Can targeted Anti-Inflammatory Therapy Reduce Cardiovascular Risk?

- Aspirin / Statins
- Direct CRP inhibitors
- DMARDs/ MTX
- TNF / IL-6 Inhibitors
- IL-1 antagonism
- 5-LO Inhibitors
- Leukotriene blockade
- Salsalate
- CCR2/CCR5
- Lp-PLA2 inhibition
- spLA inhibition
- RNAi / anti-sense
- Immunization strategies

# IL-1: Potential Roles in Atherogenesis and Methods of Inhibition

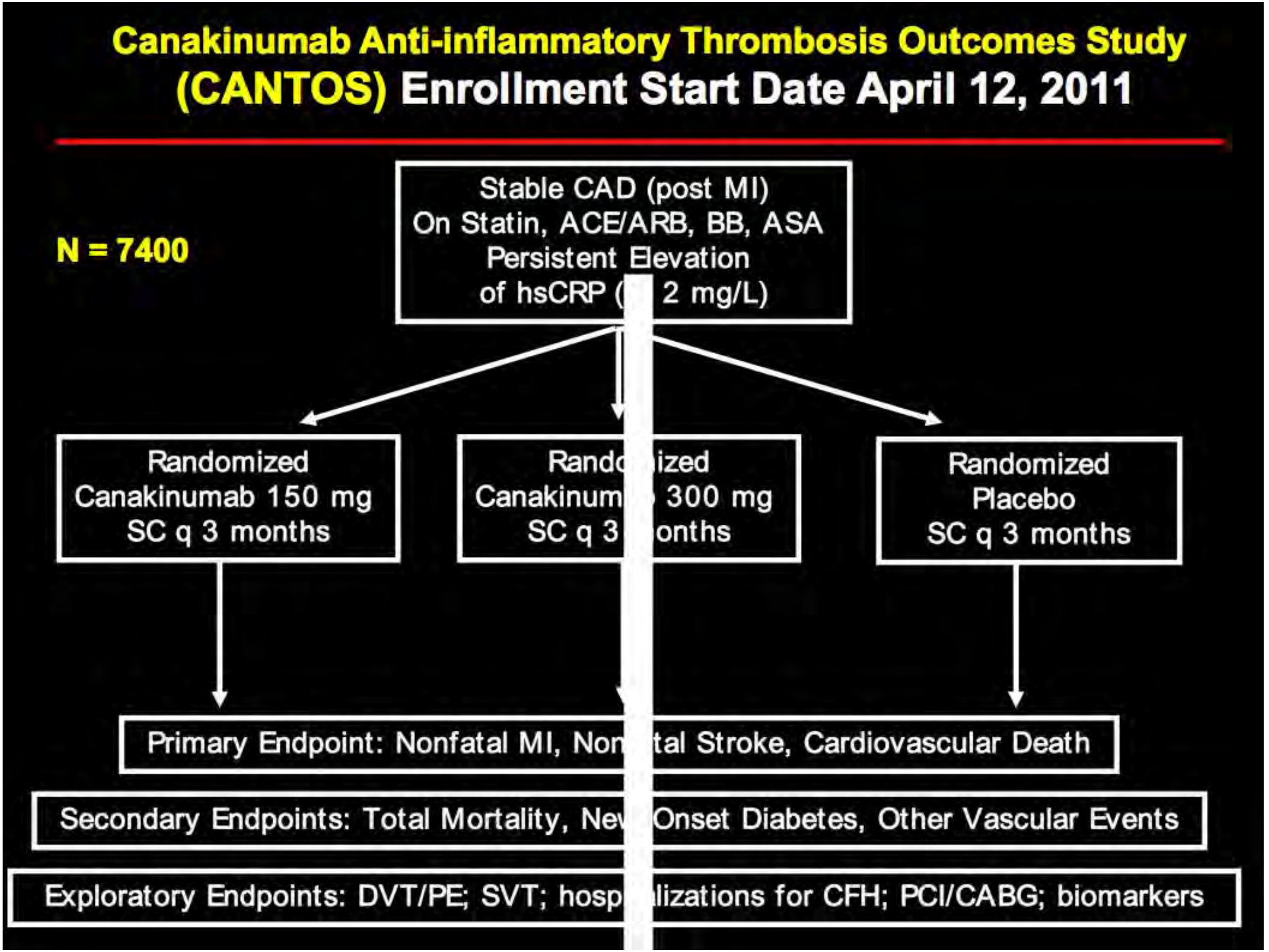



*Adapted from Fearon W, Fearon D. Circulation 2008;117:2577-9*

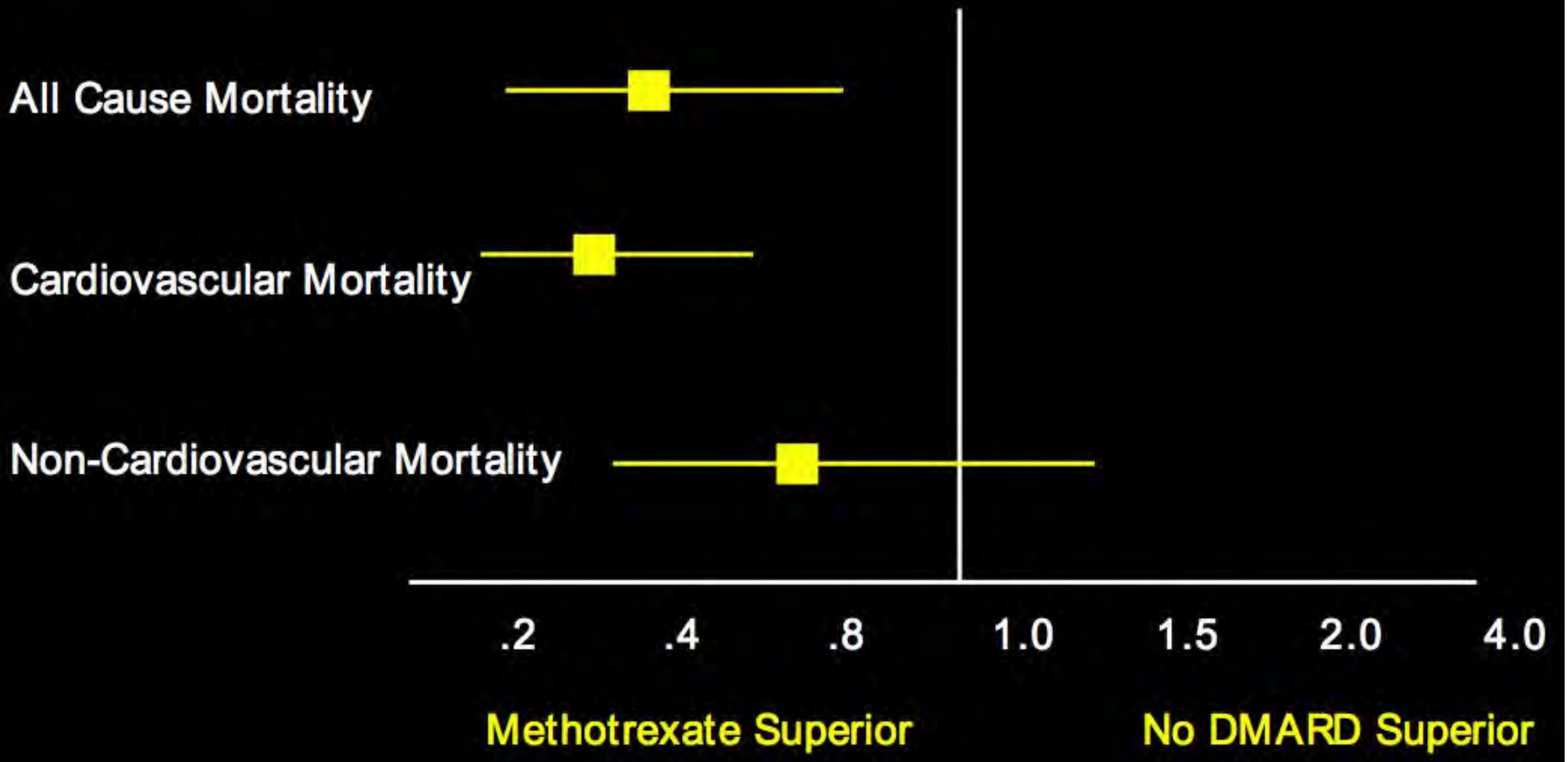
# Canakinumab (Ilaris, Novartis)

- high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)
- designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine
- long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months

# Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) Enrollment Start Date April 12, 2011

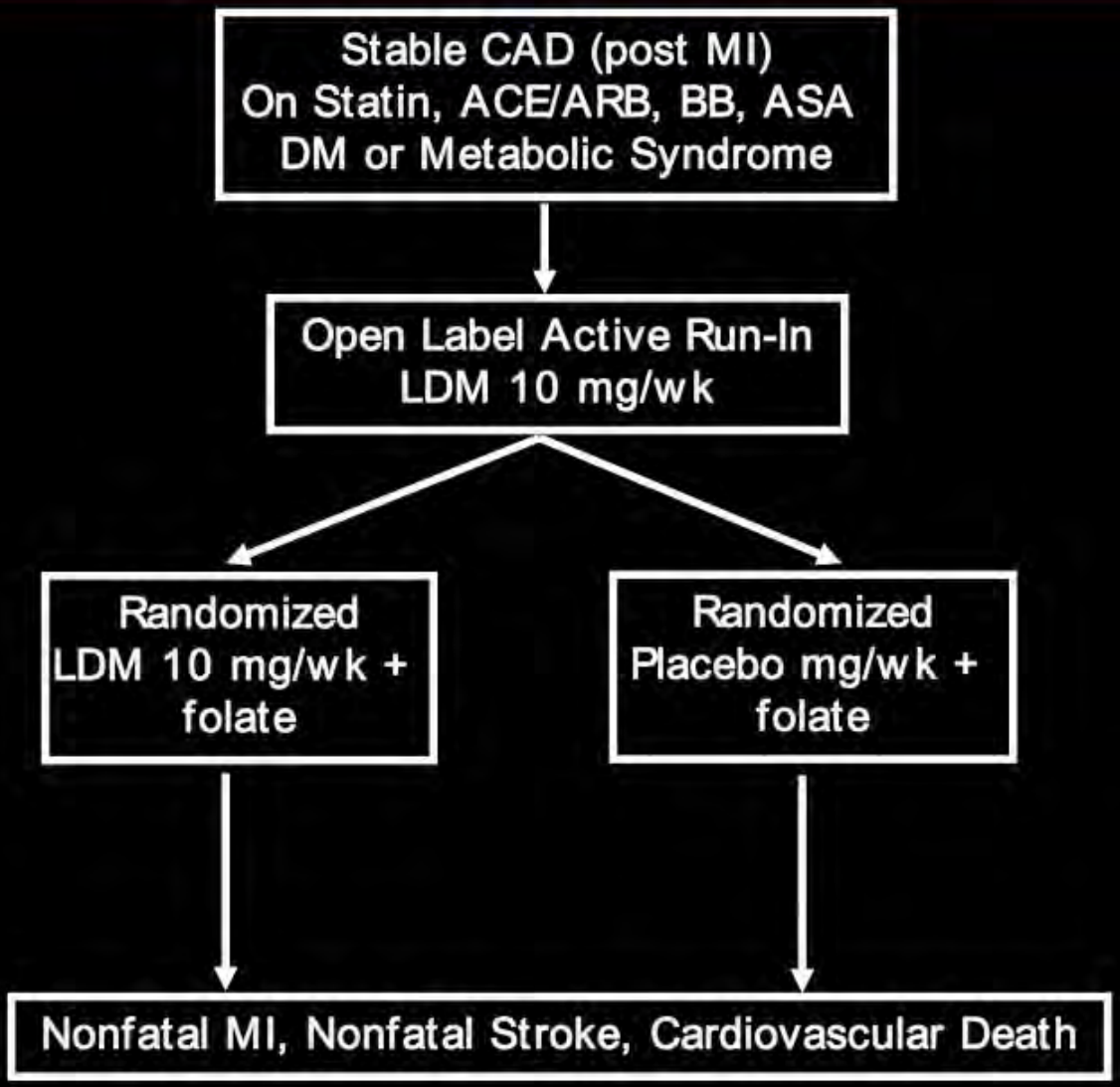


# Low Dose Methotrexate and Mortality in Patients with Rheumatoid Arthritis: Wichita Arthritis Study




Choi et al, Lancet 2002;359:1173-77

# Cardiovascular Inflammation Reduction Trial (CIRT)
# NHLBI




Ridker P. Thromb Haemost 2009

# Conclusions

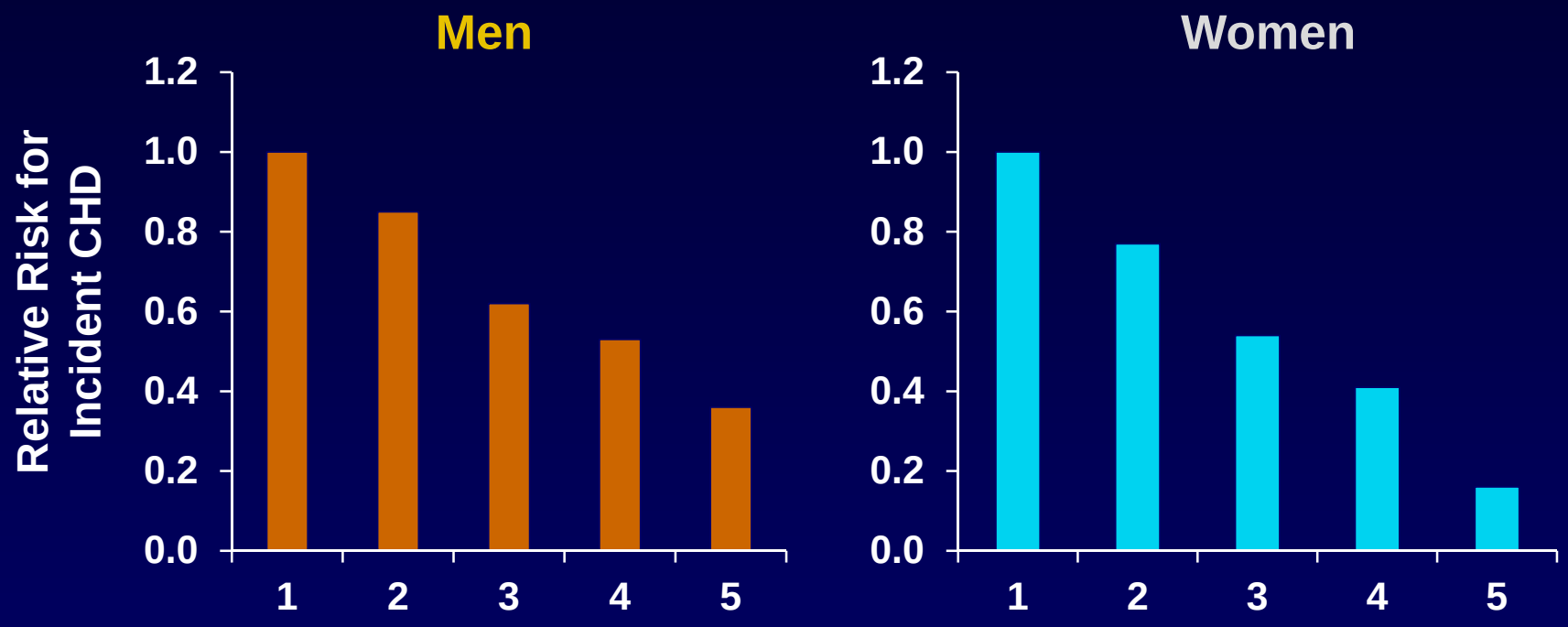
- Novel LDL lowering agents are entering the market.
- Triglyceride lowering agents need to prove their value in CVD risk reduction.
- HDL modulators have a long way to go and novel target and drugs may be needed to recalibrate the HDL hypothesis.
- Anti-inflammatory agents continue to be of promise.

# HDL Has Been an Elusive Target: The Focus Should Be on Atherogenic Lipoproteins and Proven Therapies

**Benjamin J. Ansell, MD FACC, FACP**
Atherosclerosis Research Unit
Professor of Medicine, Division of Cardiology
UCLA School of Medicine, Los Angeles, CA

UCLA DAVID GEFFEN SCHOOL OF MEDICINE

# Low HDL-C Is a Well-Established, Independent CHD Risk Factor: ARIC




**HDL-C Quintiles**

| | | | | | |
|---|---|---|---|---|---|
| mmol/L | 0.80 | 0.97 | 1.11 | 1.27 | 1.60 |
| mg/dL (median) | 31 | 38 | 43 | 49 | 62 |

**Adjusted for age and race, 12-year follow-up; N=12,339**


Sharrett AR et al. Circulation 2001;104:1108-1113.
Ballantyne CM. Eur Heart J Suppl. 2003;5 (Suppl D):D17-D25.


# Lipid Lowering and Plaque Regres
# Combination Therapy St

| Study | Treatment group: Regimen | Treatment group: LDL | Δ% Stenosis (*P*) | % Eve reducti |
|---|---|---|---|---|
| CLAS I | D + R + N | ↓43 | — | 25 |
| POSCH (5y) | D + PIB ± R | ↓42 | — | 35 (62) |
| Lifestyle | V + M + E | ↓37 | ↓2.2 (0.001) | — |
| FATS (N+C) | D + R + N | ↓32 | ↓0.9 (0.005) | 80 |
| FATS (L+C) | D + R + L | ↓46 | ↓0.7 (0.02) | 70 |
| CLAS II | D + R + N | ↓40 | — | 43 |
| USCF-SCOR | D + R + N ± L | ↓39 | ↓1.5 (0.04) | — |
| SCRIP | D+(R+N+L+F)+E, BP | ↓21 | — | 50 |
| HARP | D+P+N+C+F | ↓41 | ↑2.1 | 33 |
| Post-CABG | D+L+C | ↓37-40 | ↓0.054 | 29 |

C=cholestyramine; D=diet; E=exercise program; F=fibrate-type drug; L=lovastatin; M=relaxation techniques; N=nicotinic acid; P= pravastatin; PIB=partial ileal bypass; R=resin; V=vegetarian diet.

Levine GN et al. *N Engl J Med.* 1995;332
Brown BG, Fuster V. In: Fuster V et al, eds. *Atherosclerosis and Coronary Arte*
Philadelphia, Lippincott-Rav

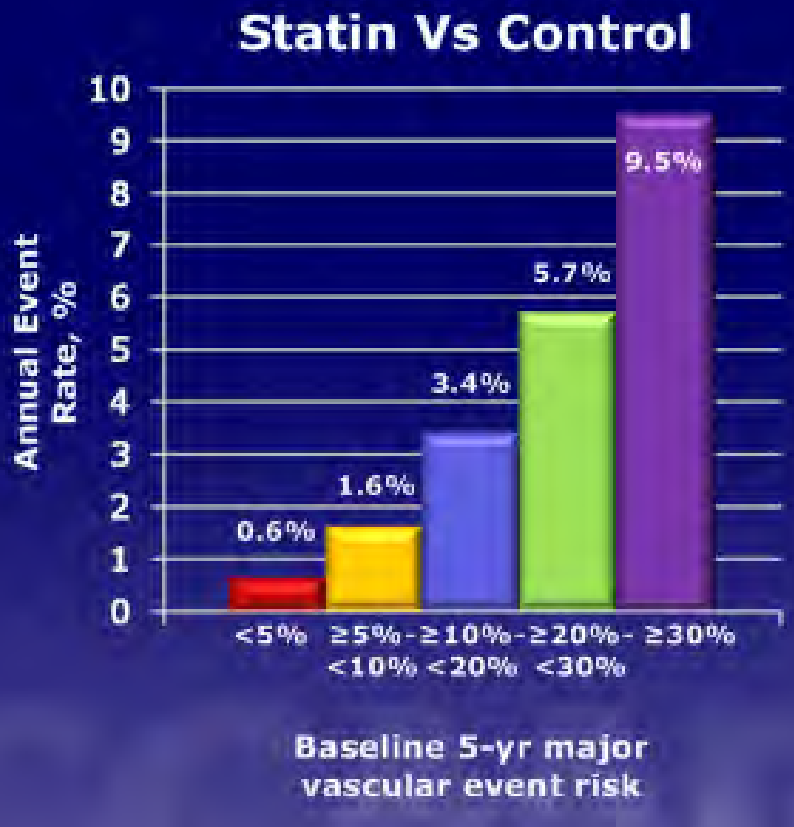
Committee on Cardiovascular and Metabolic Diseases

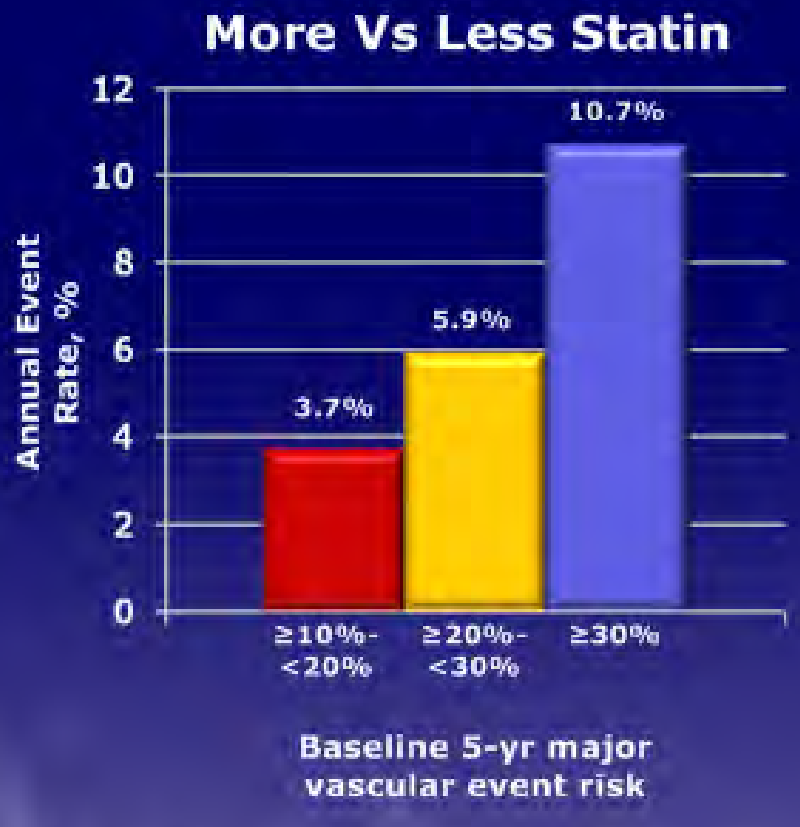
CCMD

CCMDweb.org



# CTT Meta-Analysis: Net Effects of Statins for LDL-C Lowering in Primary Prevention: Vascular Event Rate




CTT=Cholesterol Treatment Trialists'

Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2012;380:581-590.

Committee on Cardiovascular and Metabolic Diseases

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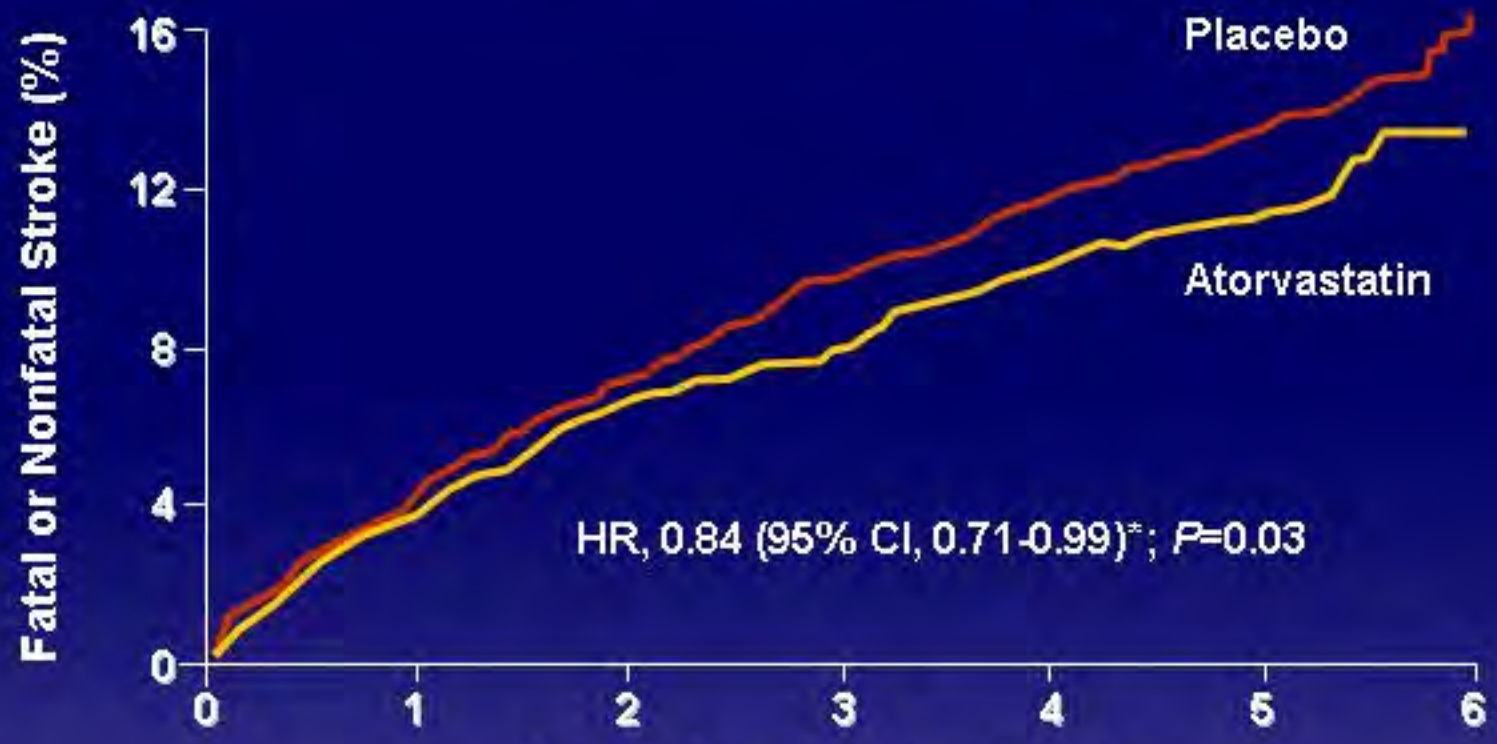
CCMDweb.org

# SPARCL Primary Outco
# Fatal or Nonfatal St




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Atorvastatin | 2365 | 2208 | 2106 | 2031 | 1935 | 922 | 126 |
| Placebo | 2366 | 2213 | 2115 | 2010 | 1926 | 887 | 137 |

SPARCL=Stroke Prevention by Aggressive Reduction in Cholesterol Levels

*Prespecified adjustment for baseline factors.

SPARCL Investigators. *N Engl J Med*. 2006;355

American College of Cardiology 2015

# ODYSSEY LONG TERM
## Post-Hoc Analysis: Major Adverse Cardiovascular Events With Alirocumab Vs Placebo

48% lower risk of MACE with alirocumab vs placebo

| | Alirocumab (n=1,550) | Ezetimibe (n=788) |
|---|---|---|
| Adjudicated MACE | 1.7% (27) | 3.3% (26) |
| | HR=0.452 (0.31, 0.90)<br>nominal *P*=0.02 | |

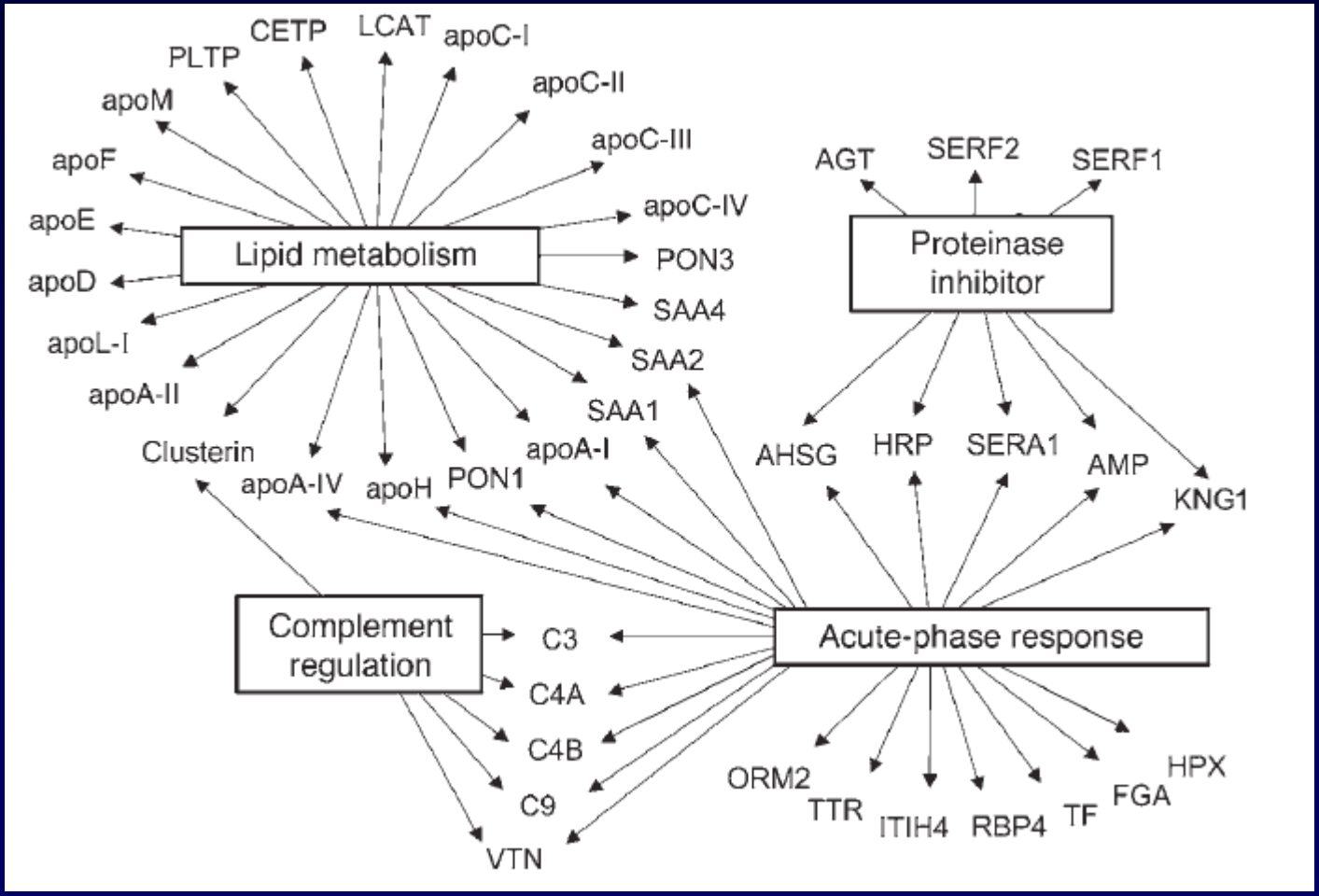
Major adverse cardiovascular events: CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, unstable angina requiring hospitalization

All subjects on maximally tolerated statin ± other lipid-lowering therapy

Alirocumab is an investigational agent; not yet FDA approved

Robinson JG, et al. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1501031.

# HDL – Proteomic Domains




Vaisar T et al. *J. Clin. Invest. 2007:*117;746–756.

# HDL-Based Therapies: Questions

- What is the right therapy for low HDL-C?
  - One that raises low HDL-C (or HDL-P)?
  - One that targets HDL composition and/or function?
  - One that benefits patients with low HDL-C independent of HDL, e.g., LDL-C/non-HDL-C-lowering?
- Is HDL-C raising necessary (vs. lowering LDL-C and/or improving HDL function)?
- Focus needs to be on impacting CVD

# Drugs That Raised HDL-C with Increased CVD

1. **Estrogen/progestin: WHI**
   - HDL-C increased by 7.3% (vs. placebo)
   - CHD risk increased by 29%
   - Stroke risk increased by 41%
2. **Torcetrapib: ILLUMINATE**
   - ↑HDL-C by 70% and ↓LDL-C by 25% (vs. placebo)
   - CHD risk increased by 21%
   - Stroke risk increased by 8%
   - All-cause mortality increased by 58%

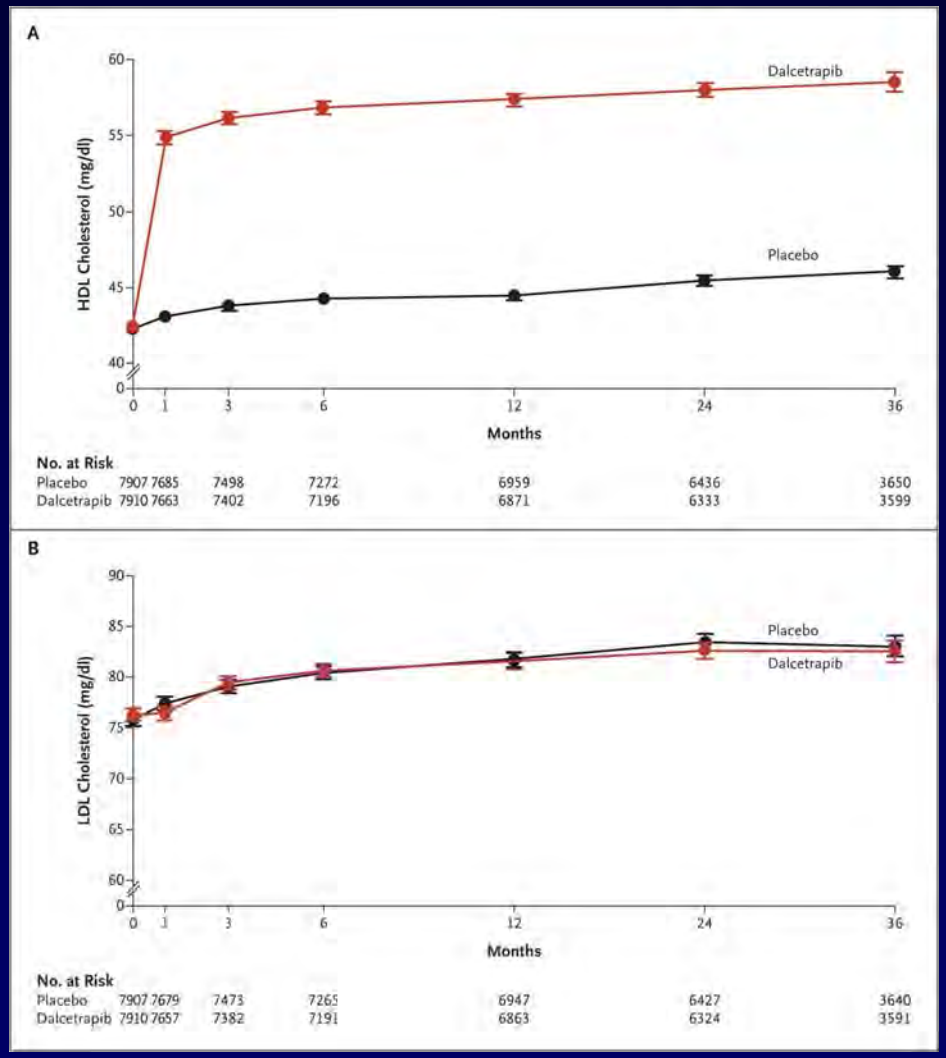
Writing Group for the WHI Investigators. JAMA 2002;288:321–333.
Barter PJ et al. N Engl J Med 2007;357:2109–2122.

# ILLUMINATE: Mortality by Treatment Assignment

| Event | Atorvastatin Only (N = 59) | Torcetrapib plus Atorvastatin (N = 93) |
|---|---|---|
| | *no. of patients* | |
| Any cardiovascular cause | 35 | 49 |
| Sudden death | 25 | 26 |
| Fatal myocardial infarction (not procedure-related) | 6 | 8 |
| Fatal stroke | | |
| Hemorrhagic | 0 | 4 |
| Ischemic | 0 | 2 |
| Embolic | 0 | 0 |
| Not classified | 0 | 0 |
| Fatal heart failure | 1 | 2 |
| Other vascular-related cause | 2 | 1 |
| Fatal myocardial infarction (procedure-related) | 0 | 2 |
| Other cardiac-related cause | 1 | 4 |
| Any noncardiovascular cause | 20 | 40 |
| Cancer | 14 | 24 |
| Infection | 0 | 9 |
| Trauma | 3 | 3 |
| Suicide or homicide | 1 | 0 |
| Other cause | 2 | 4 |
| Reason unknown | 4 | 4 |

Barter PH et al. *N Engl J Med.* 2007;357:2109-22.

# DAL-Outcomes: Recent ACS Patients

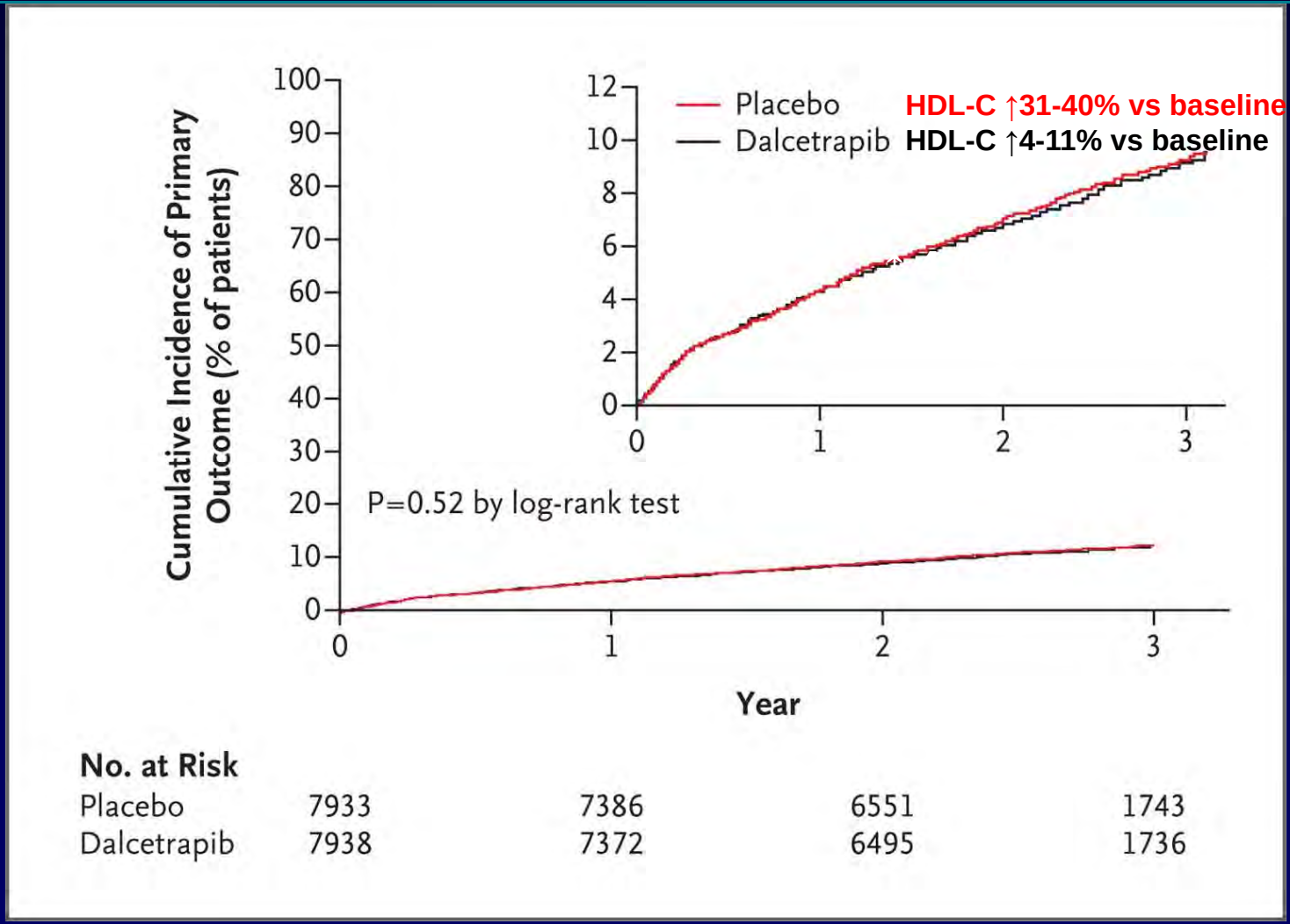



↑ **31-40% vs baseline**

↑ **4-11% vs baseline**

Schwartz GG et al. N Engl J Med 2012;367:2089-2099

# Dal-Outcomes: Primary Endpoint



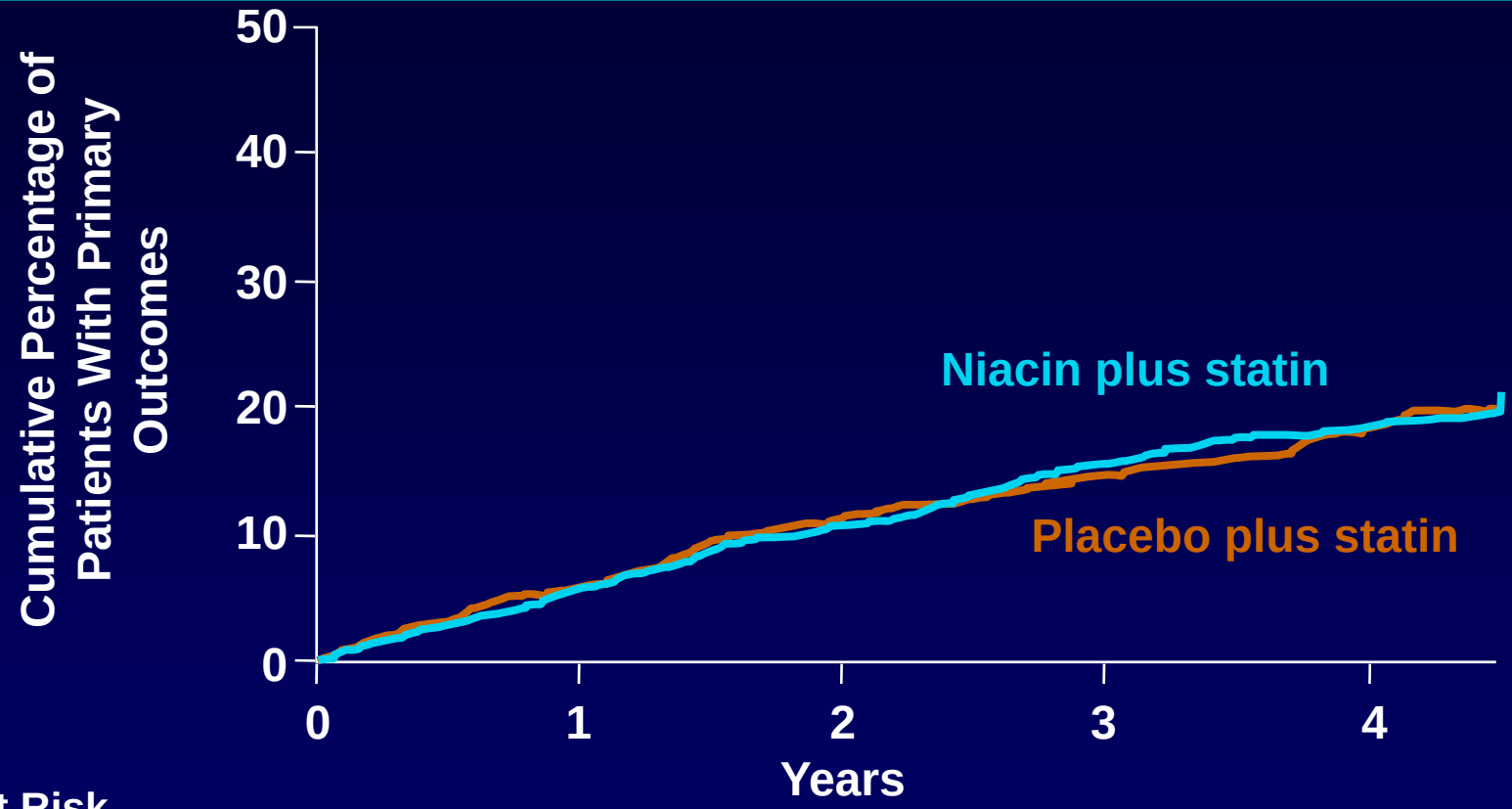

Schwartz GG et al. N Engl J Med 2012;367:2089-2099

# CETP Inhibitors

- HDL raising-effect on outcomes appears to be neutral at best (dalcetrapib)
- Have raised BP in 2/2 CV endpoint trials (results neutral for anacetrapib to date)
- Raised hs-CRP in dalOUTCOMES, DEFINE
- Anacetrapib and evacetrapib in Phase III
- Role (?) as LDL-lowering agent(s) to be defined

Schwartz GG et al., *N Engl J Med* 2012: 367:2089-2099.

# AIM-HIGH: Primary Endpoint

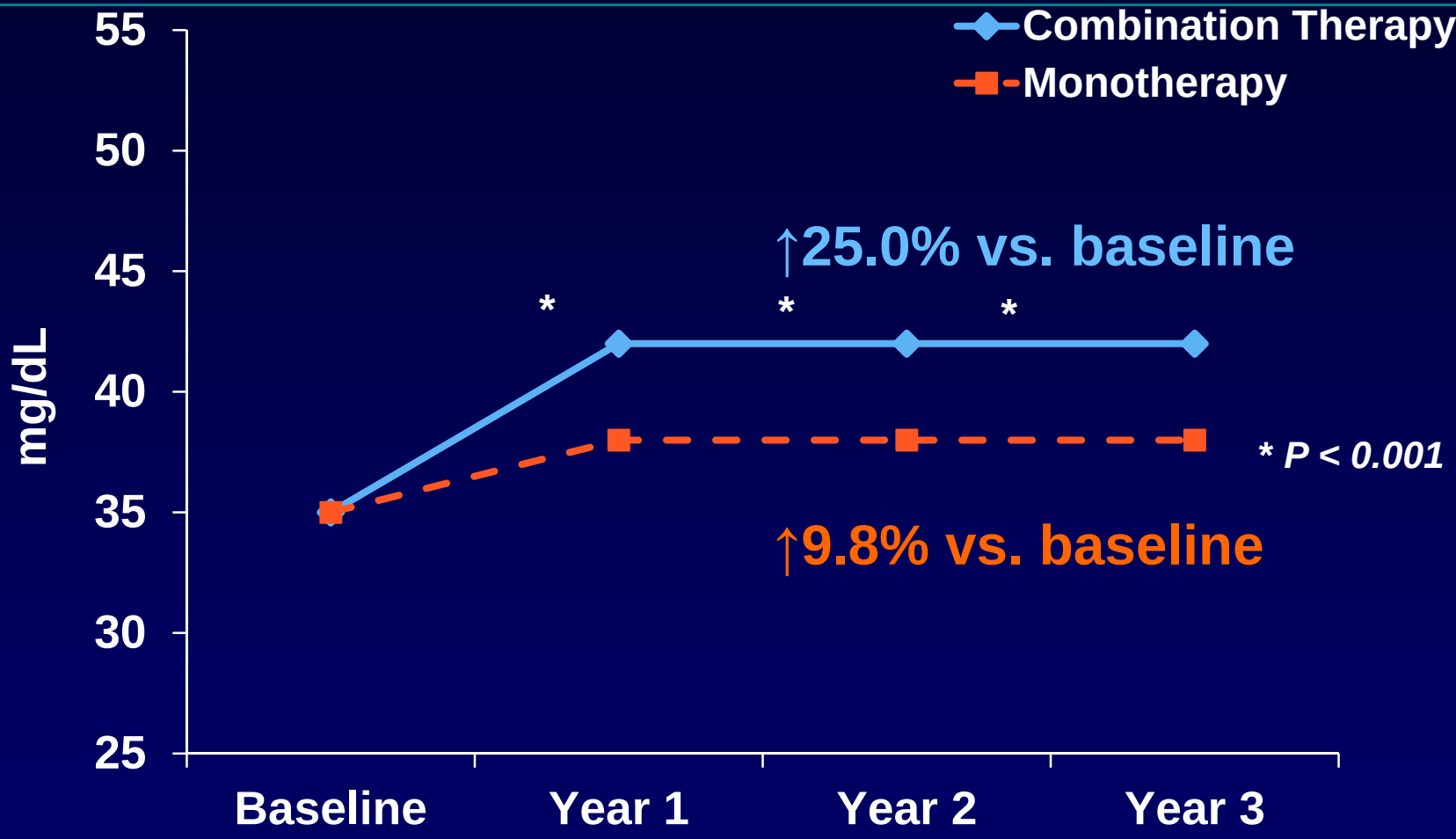



| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Placebo plus statin | 1696 | 1581 | 1381 | 910 | 436 |
| Niacin plus statin | 1718 | 1606 | 1366 | 903 | 428 |

P=0.79 by log-rank test

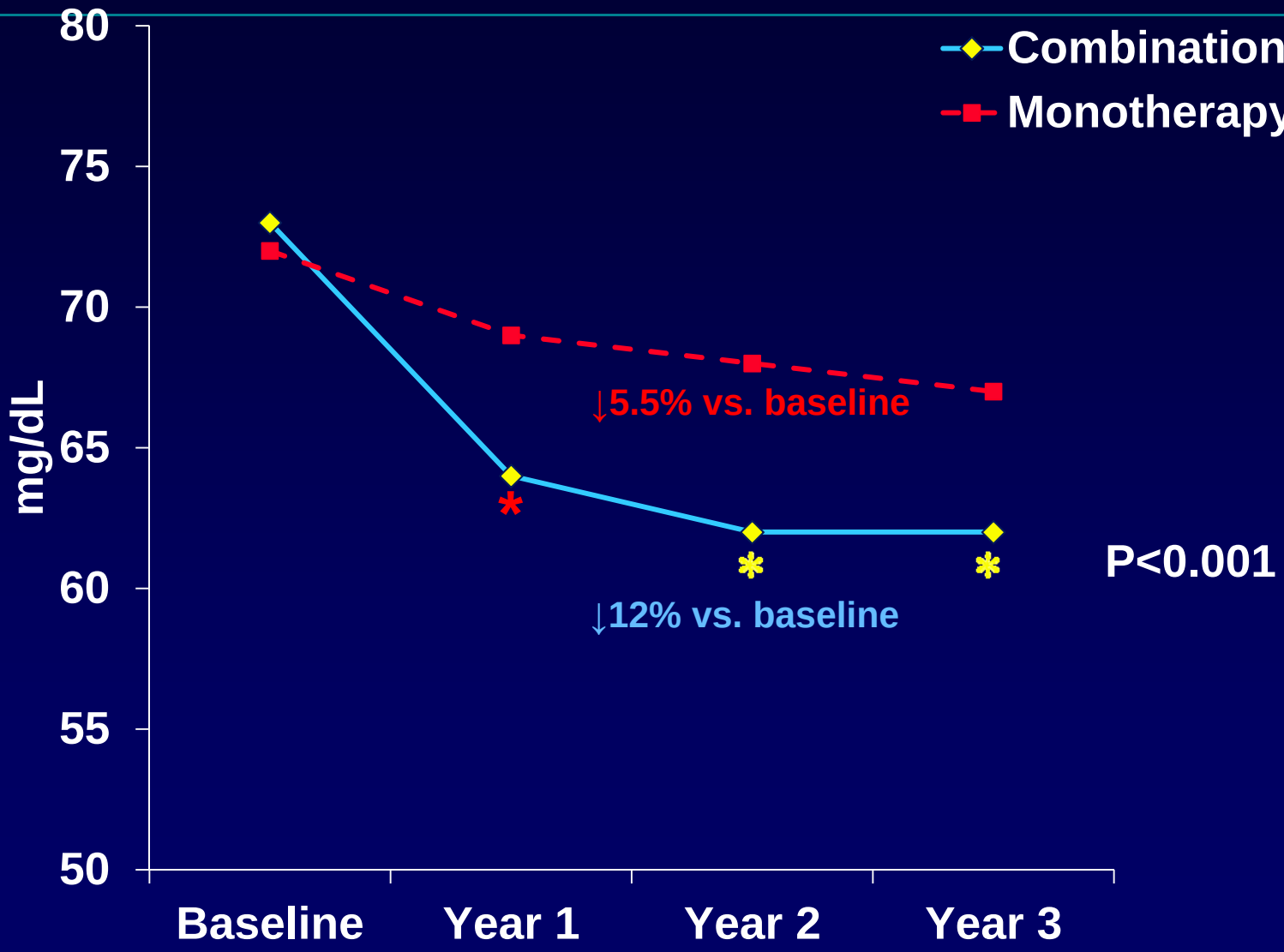
AIM-HIGH Investigators. N Engl J Med. 2011; 265(24):2255-2267.

# AIM-HIGH: HDL-C Results



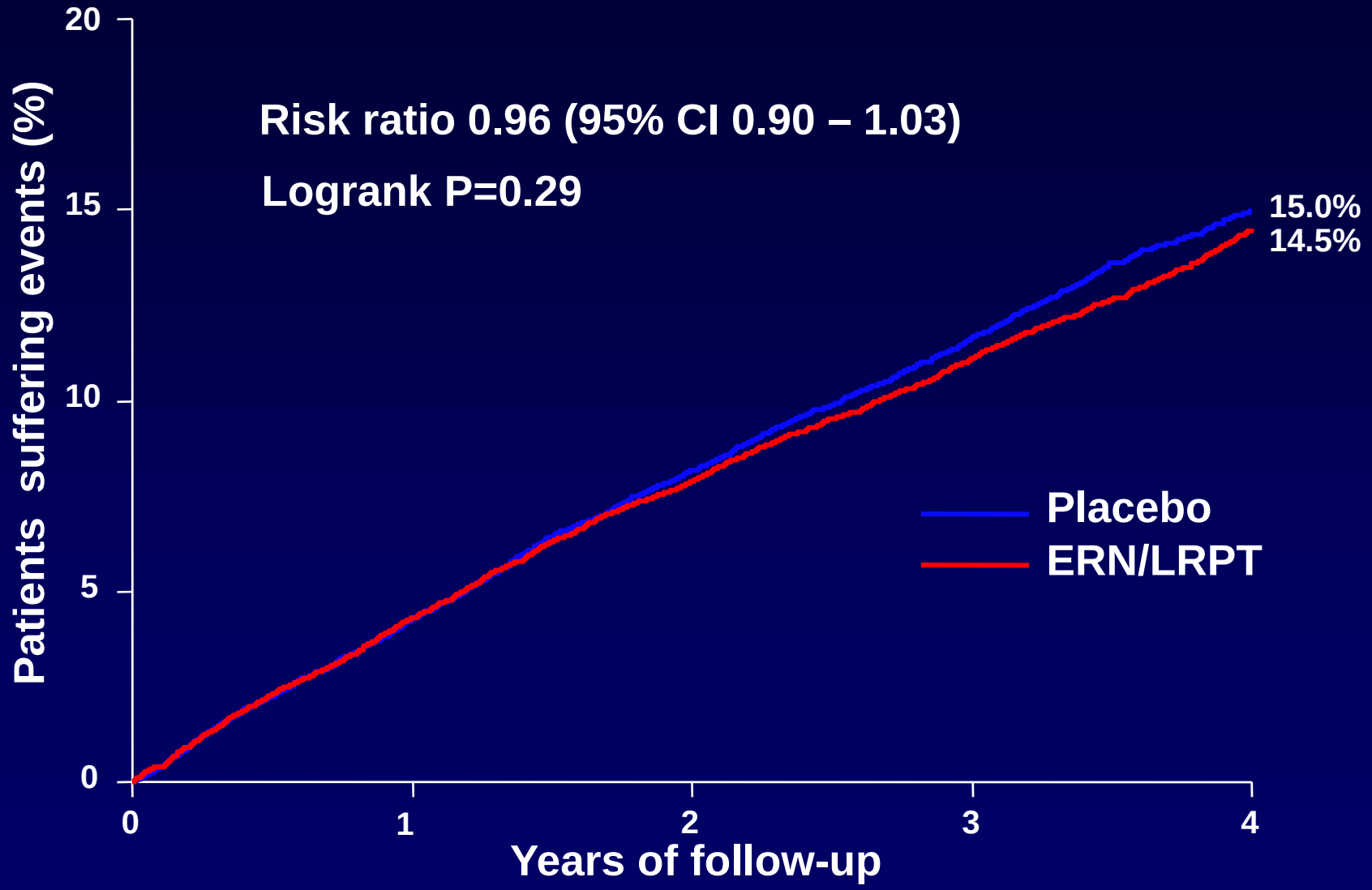

AIM-HIGH Investigators. N Engl J Med. 2011; 265(24):2255-2267.

# AIM-HIGH: LDL-C Results




AIM-HIGH Investigators. *N Engl J Med.* 2011; 265:2255-67.

# HPS-2/THRIVE: Effect of ERN/LRPT on Major Vascular Events




http://www.hps2-thrive.org/docs_prof.htm. Accessed 3/1/2015.

# Summary: LDL vs HDL-Based Approaches

- Not all genetic variants and therapies that raise HDL-C have reduced CHD events.
- Raising HDL-C (or HDL-P) may neither be necessary nor sufficient to improve HDL-mediated CVD risk; function *may* be more important.
- Reducing LDL and related atherogenic lipoproteins has consistently reduced atherosclerotic risk.
- Optimizing statin/LDL-based therapies and lifestyle practices should remain the primary focus.

“It's what we think we know that keeps us from learning.”

-Claude Bernard (1811-1873)

An Introduction to the Study of Experimental Medicine

# HDL Therapeutics: The Start of a New Era

**Robert S. Rosenson, MD, FACC, FACP, FAHA,**
**Director, Cardiometabolic Disorders**
**Mount Sinai Heart**
**Professor of Medicine (Cardiology)**
**Mount Sinai School of Medicine**
**New York, New York**

# Major Anti-Atherosclerotic Functional Roles of HDL With Available Clinical Measures

- Macrophage cholesterol efflux
- Anti-oxidative effects
- Anti-inflammatory effects
- Endothelial function
- Glucose homeostasis

*Rosenson RS, Brewer Jr. HB, Ansell B, Barter PJ, Chapman MJ, Heinecke J, Kontush A, Tall A, Webb N. Circulation 2013*128(11):1256-67.

# HDL/ApoA-I Proteome – Structure & Function

- **Myeloperoxidase-mediated modifications**
  - **Methionine oxidation and site-specific chlorination of Tyr192 on apoA-I impairs ABCA1-dependent efflux and LCAT activity**
  - **3-chlorotyrosine and 3-nitrotyrosine modifications of apoA-I in the arterial wall impair ABCA1-dependent efflux and activate NF-kB**
- **Serum Amyloid A protein (SAA)**
  - **Enrichment of the HDL proteome with SAA1 and SAA2 reduce cholesterol efflux from J774 macrophage cells**
- **Paraoxonase**
  - **Loss of PON1 and PON3 decreases the antioxidant protection from peroxidation of LDL particles**
  - **Reduction in efficient hydrolysis of proinlmammtory fragment short-chain phospholipids and phospholipid hydroperoxides increases proinflammtory cytokine production**

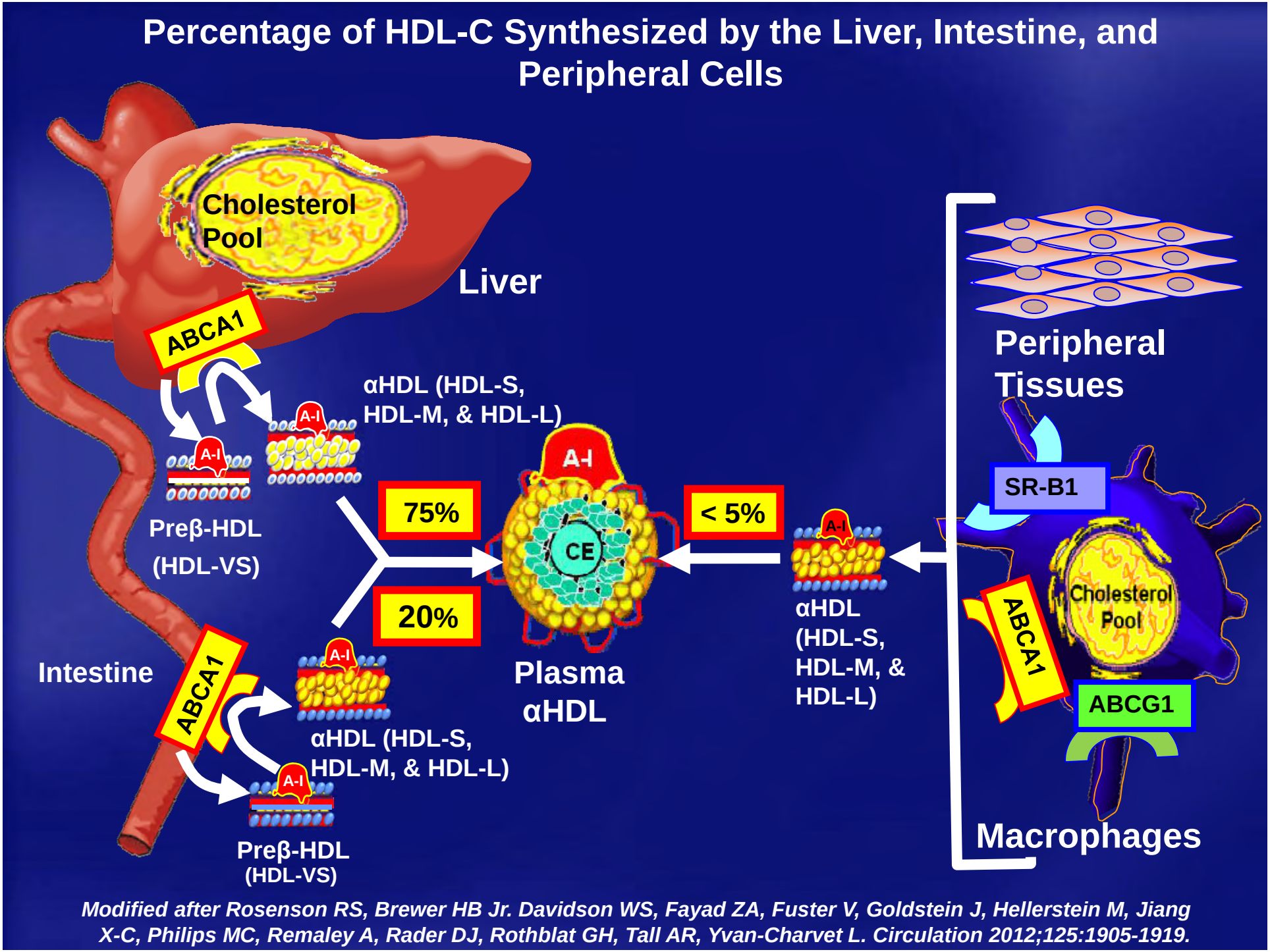
Rosenson RS, Brewer HB, Ansell B, Barter P, Chapman MJ, Heinecke JW, Kontush A,
Tall AR, Webb NR. Nature Card Reviews 2015 (in press)

# HDL/ApoA-I Lipidome – Structure & Function

- **Group IIA secretory phospholipase $A_2$**
  - **Increases rates of apoA-I catabolism**
- **Triglyceride Enrichment**
  - **Impairs HDL stability and enhances apoA-I catabolism**
- **Phospholipid Oxidation of Acyl Chains**
  - **Increased polarity of the lipid domains that allows water to penetrate into the hydrophobic cellular lipid membrane, which alters the binding and orientation of apo A-I**
  - **Alterations in the orientation of apoA-I results in reduced capacity to stimulate the activity of PON1 and LCAT**

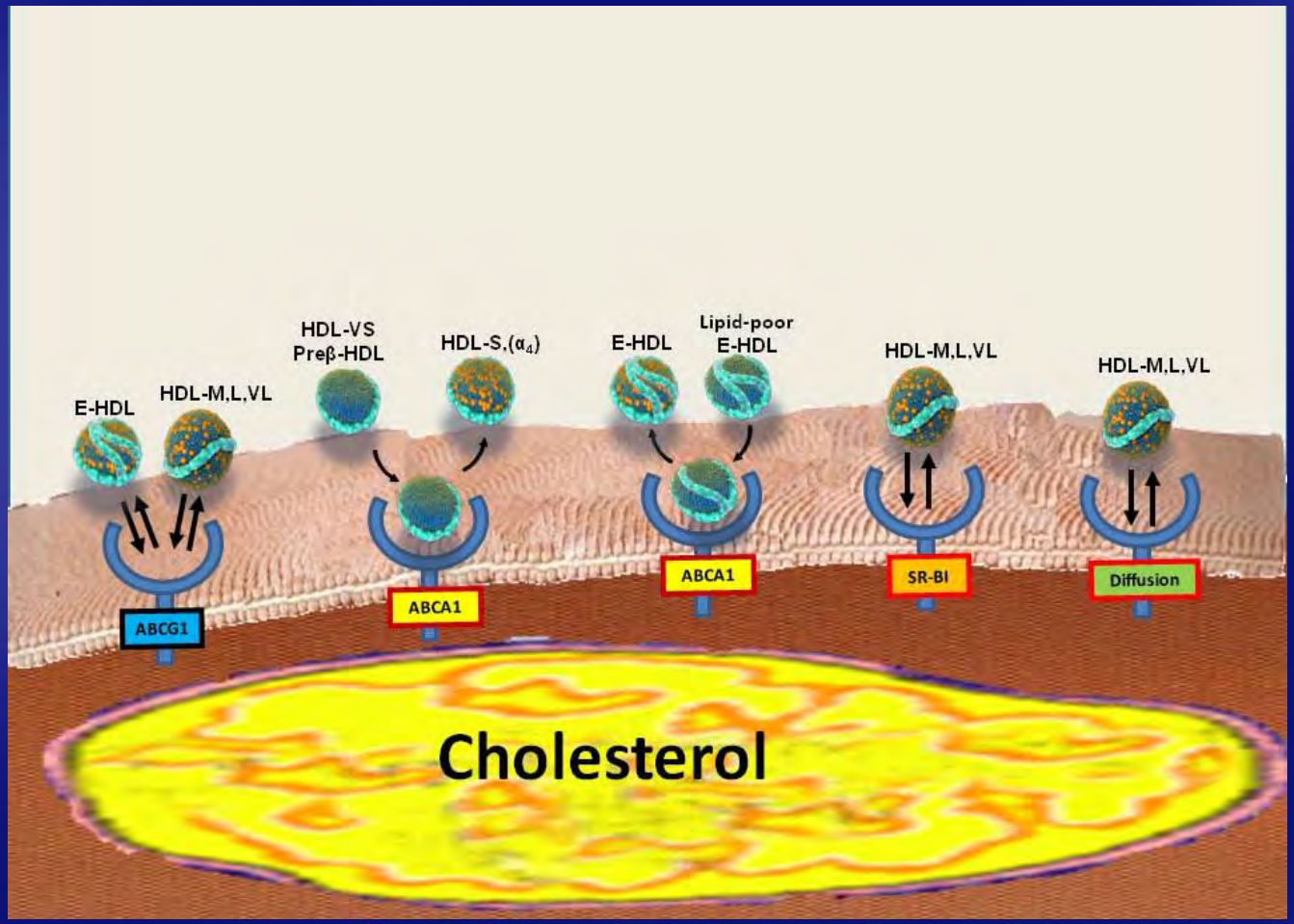
Rosenson RS, Brewer HB, Ansell B, Barter P, Chapman MJ, Heinecke JW, Kontush A, Tall AR, Webb NR. Nature Card Reviews 2015 (in press)

# Percentage of HDL-C Synthesized by the Liver, Intestine, and Peripheral Cells



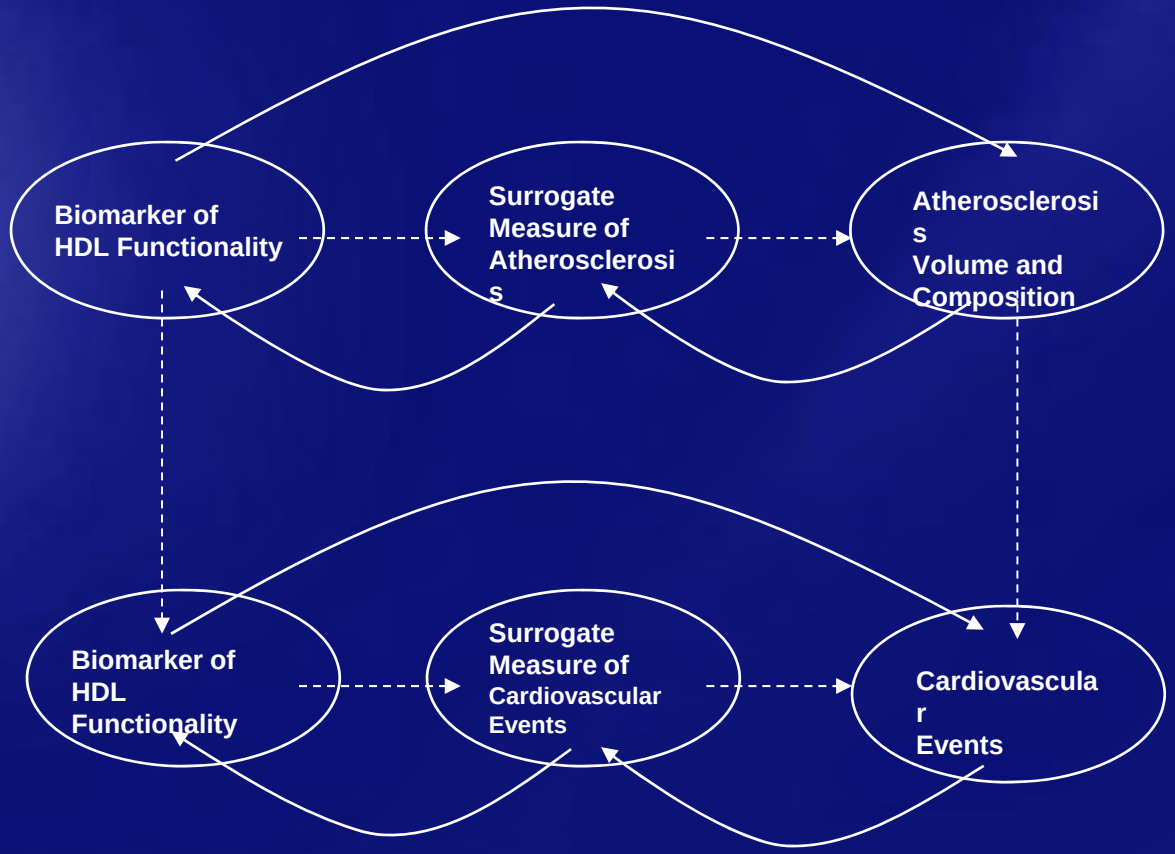

*Modified after Rosenson RS, Brewer HB Jr. Davidson WS, Fayad ZA, Fuster V, Goldstein J, Hellerstein M, Jiang X-C, Philips MC, Remaley A, Rader DJ, Rothblat GH, Tall AR, Yvan-Charvet L. Circulation 2012;125:1905-1919.*

# HDL Particle Subclasses And Cholesterol Efflux From Cholesterol-Loaded Cells




*Rosenson RS, Brewer HB, Jr., Davidson WS, Fayad ZA, Fuster V, Goldstein J, Hellerstein M, Jiang XC, Phillips MC, Rader DJ, Remaley AT, Rothblat GH, Tall AR, Yvan-Charvet L. Circulation. 2012;125(15):1905-1919. Copyright © 2012, Wolters Kluwer Health.*

# Validation of HDL Functional Measures in the Evaluation of Atherosclerosis and Cardiovascular Events




Rosenson RS, Brewer Jr. HB, Ansell B, Barter PJ, Chapman MJ, Heinecke J, Kontush A, Tall A, Webb N. Circulation 2013;128:1256-67

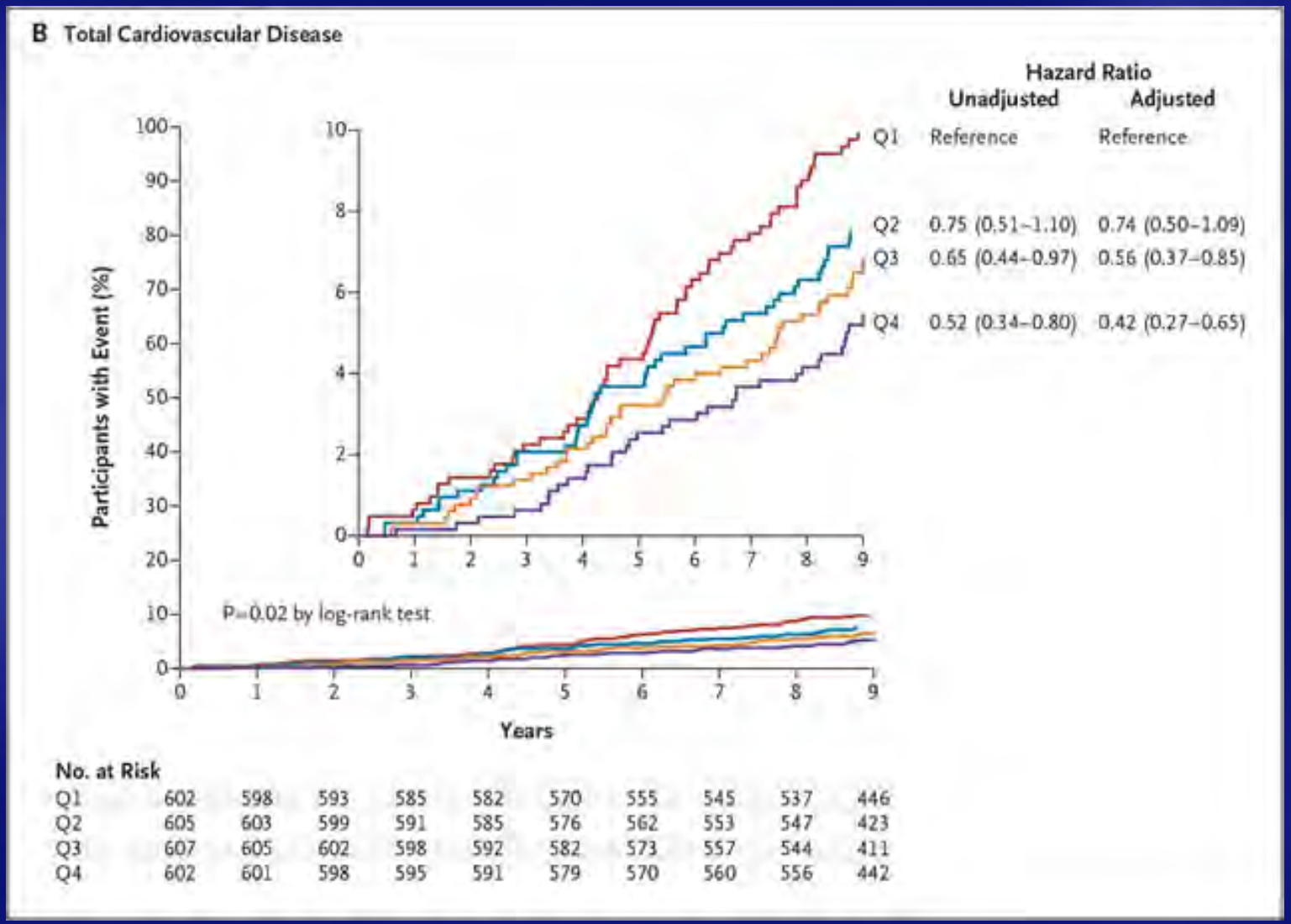
# Odds Ratios for CAD According to the Efflux Capacity and Selected Risk Factors

**The logistic-regression model also was adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.**

| Risk Factor | Odds Ratio (95% CI) | *P* Value |
|---|---|---|
| Diabetes | 1.92 (1.26–2.93) | 0.003 |
| Hypertension | 1.80 (1.31–2.47) | < 0.001 |
| Smoking | 1.10 (0.95–1.73) | 1.78 |
| LDL cholesterol | 1.01 (0.86–1.18) | 0.93 |
| HDL cholesterol | 0.85 (0.70–1.03) | 0.09 |
| Efflux capacity | 0.75 (0.63–0.90) | 0.002 |


1. Khera AV, et al. *N Engl J Med*. 2011;364(2):127-135. Copyright © 2011 Massachusetts Medical Society.
2. de la Llera-Moya M, et al. *Arterioscler Thromb Vasc Biol*. 2010;30(4):796-801.

# Kaplan–Meier Curves and Hazard Ratios for Cardiovascular Events, According to Quartile of Cholesterol Efflux Capacity




Rohatgi A et al. N Engl J Med 2014;371:2383-2393

# Cholesterol Efflux Capacity and Incident CHD Events in EPIC-Norfolk

**Nested case-control sample within a prospective study of 25,639 individuals aged 40-79 years examined in 1993-1997 and followed up to 2009**

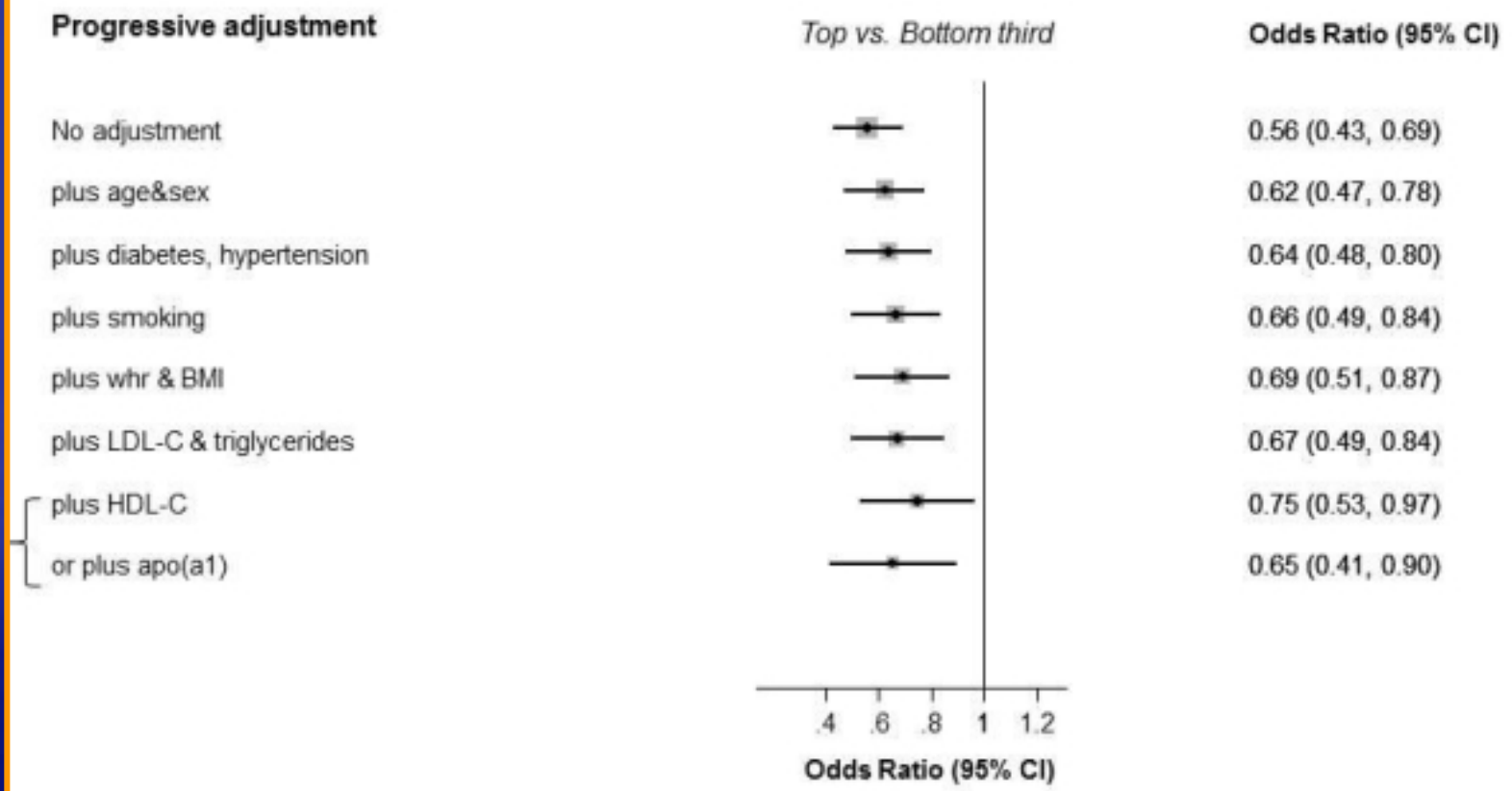
**Efflux capacity was quantified in 1,895 incident CHD cases and 2,474 control participants free of any cardiovascular disorders**

**Validated ex vivo radiotracer assay that involved incubation of J774 macrophages with apoB-depleted serum from study participants**

***Saleheen D, et al. Lancet Endocrin Diabetes 2015***

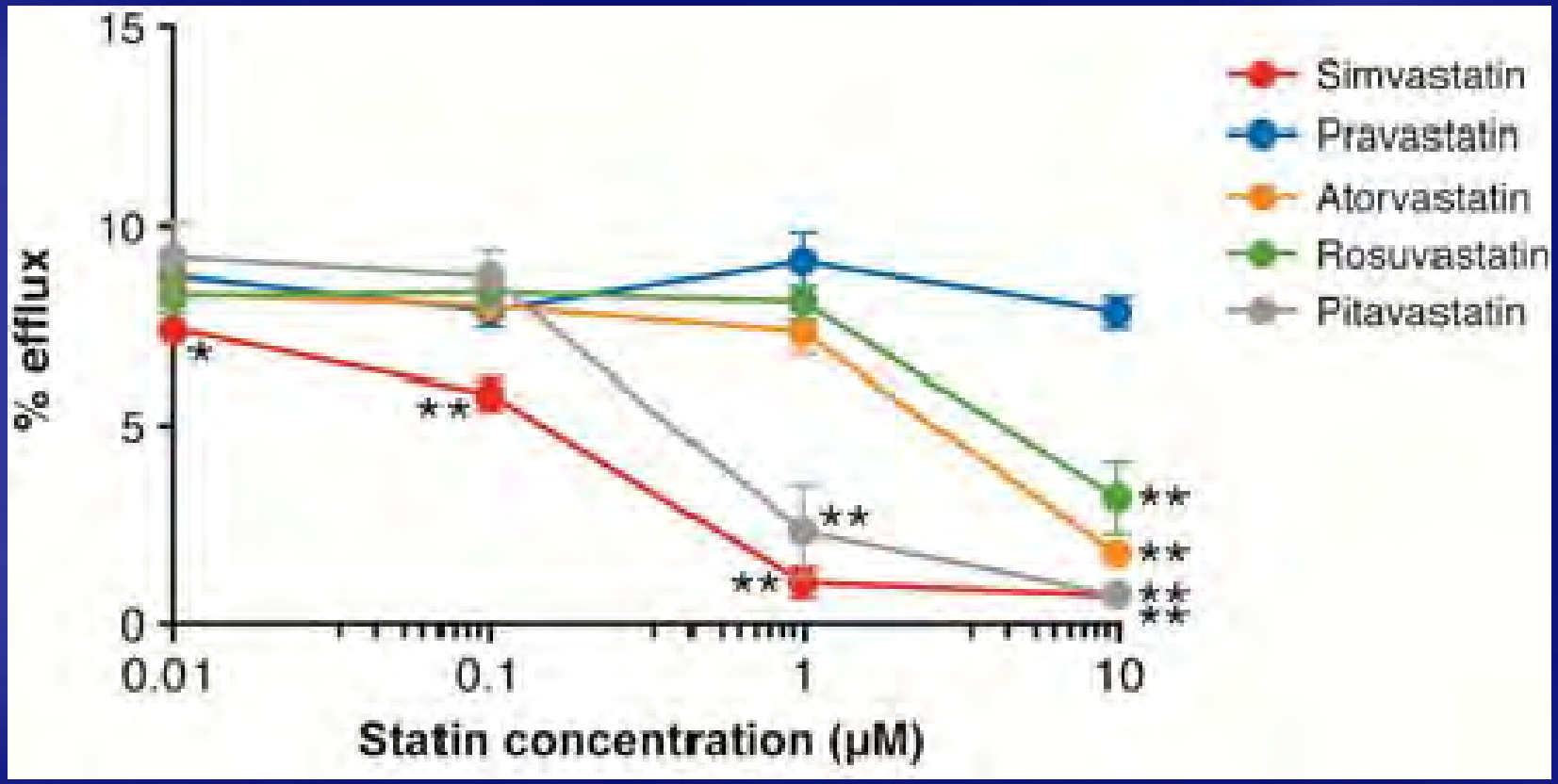
# Association of Cholesterol Efflux and Incident CHD Events – EPIC Norfolk

**Figure.** Association of cholesterol efflux levels in association with incident CHD events (1895 cases & 2474 controls)




***Saleheen D, et al Lancet Endorinol Diabetes 2015***

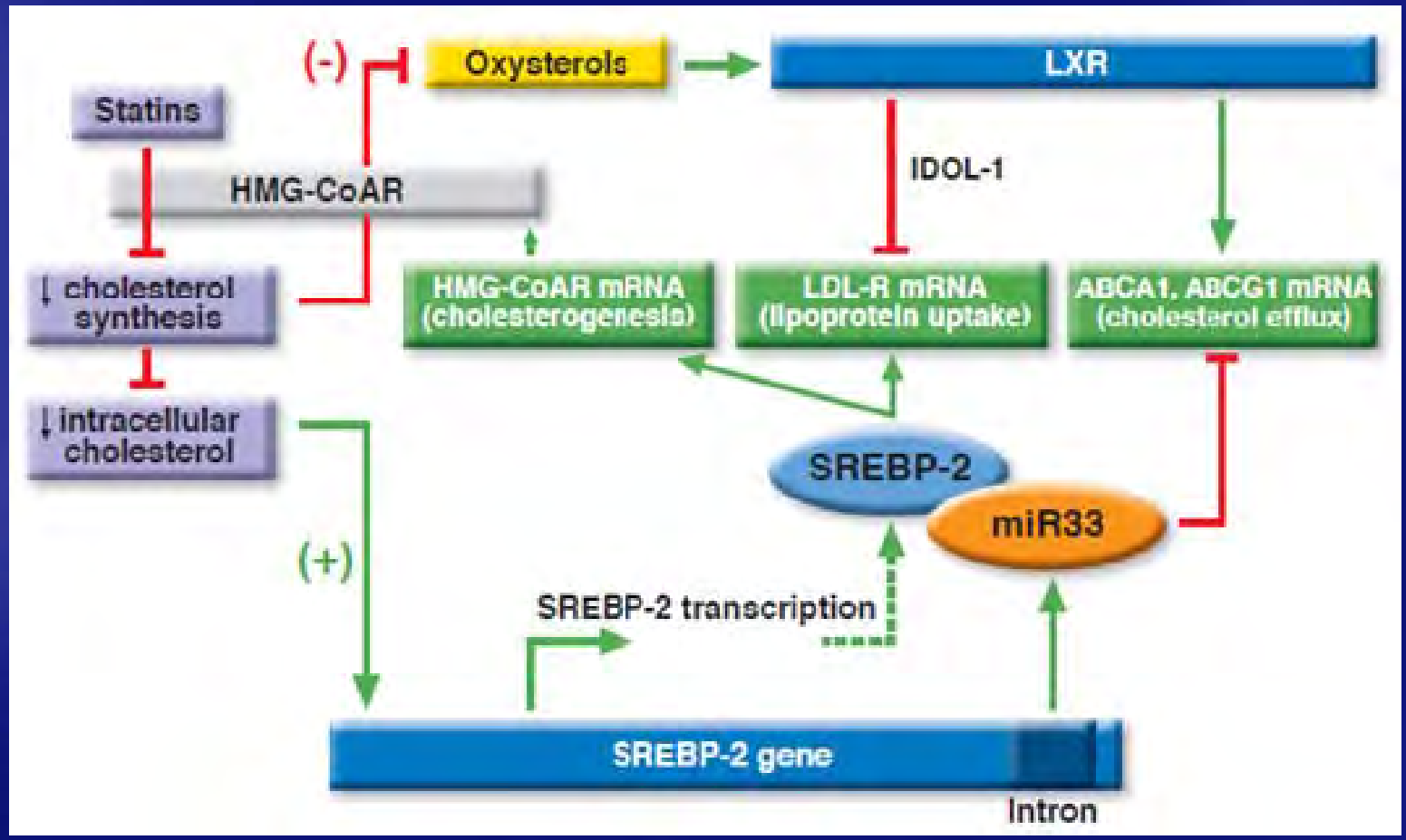
# Effect of Different Statins on ABCA1-Mediated Cholesterol Efflux from J774A.1 Macrophages




*P < 0.05; **P < 0.01 vs. no statin.
Values are mean ± SD (triplicate).

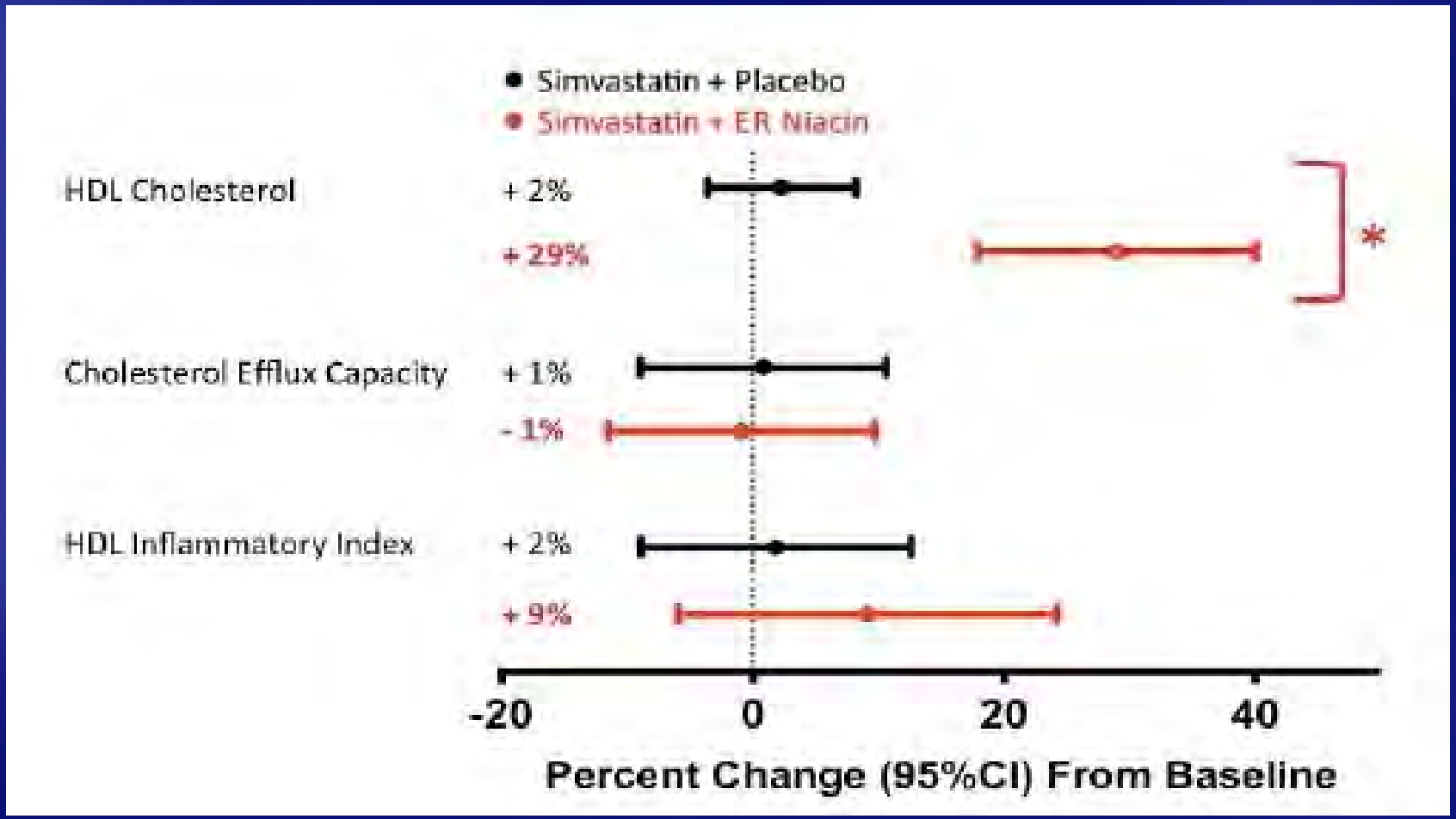
*Niesor, E, et al. Cardiovasc Drugs Ther 2015*

# Unified paradigm for cholesterol homeostasis




*Niesor, E, et al. Cardiovasc Drugs Ther 2015*

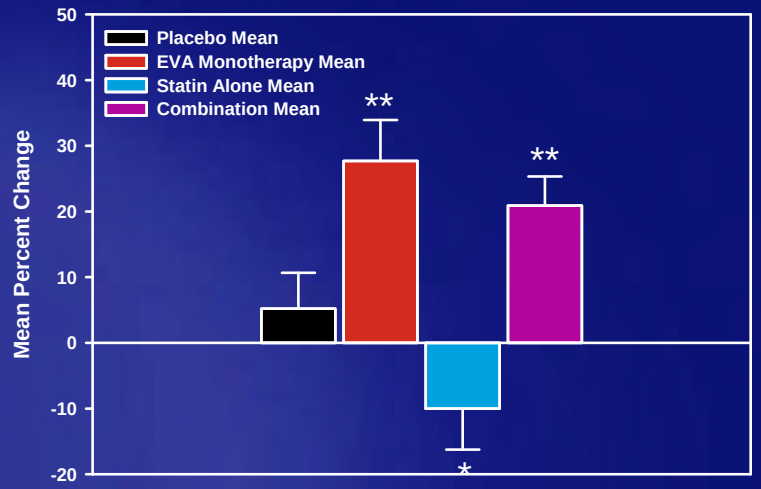
# Functionality of HDL in AIM-HIGH



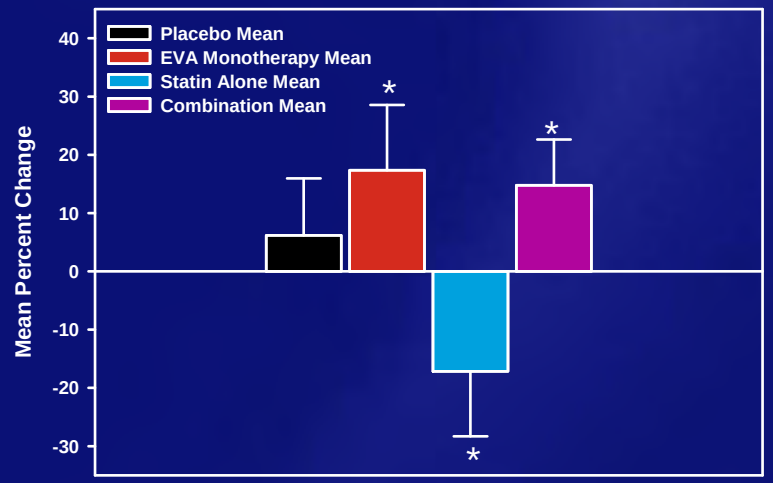

Khera AV, et al . J Am Coll Cardiol 2013

# Percent Change in Cholesterol Efflux by Treatment

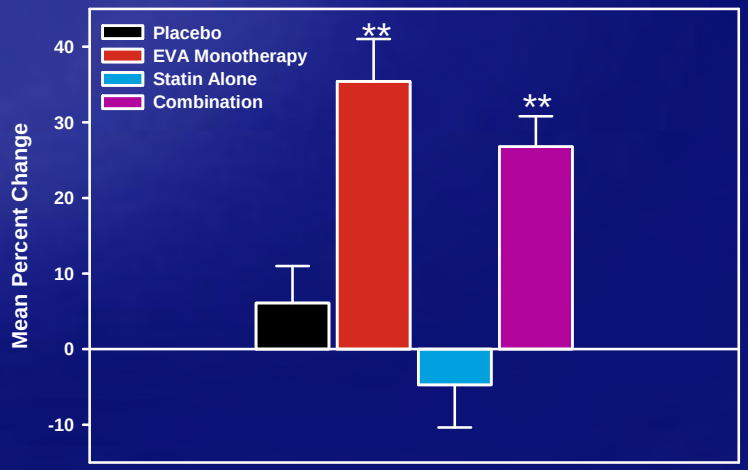
**Percent Change in Global Cholesterol Efflux by Treatment**




**Percent Change in ABCA1 Mediated Cholesterol Efflux by Treatment**




**Percent Change in Non-ABCA1 Mediated Cholesterol Efflux by Treatment**



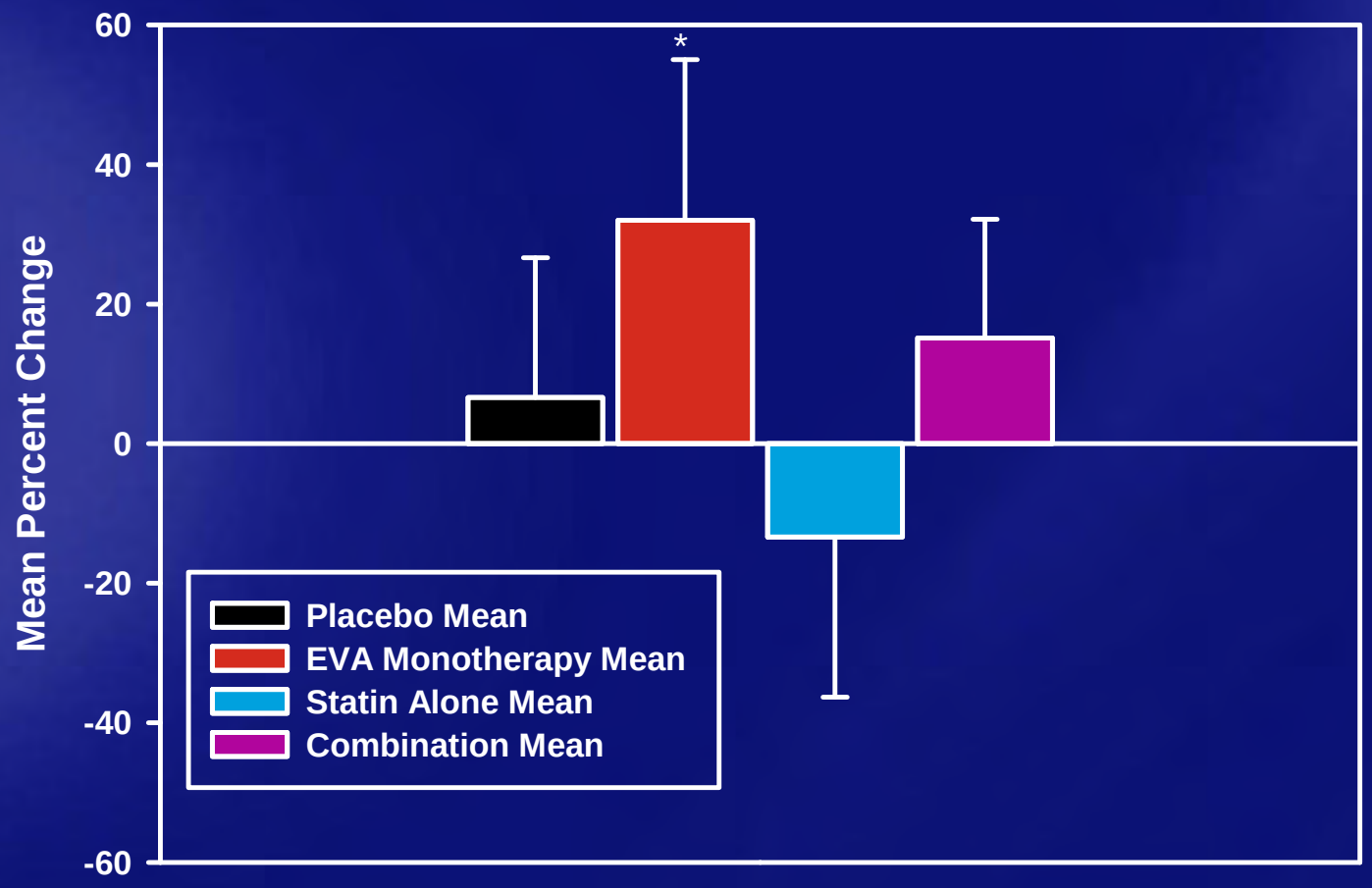

Error bars represent 90% CI

*p<.05 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group
**p<.001 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

Abbreviations: ABCA1=ATP Binding Cassette transporter A1 pathway; CI=confidence interval, EVA=evacetrapib

Nicholls et al. Presented AHA Scientific Sessions 2014

# Percent Change in Prebeta-1 HDL by Immunofixation



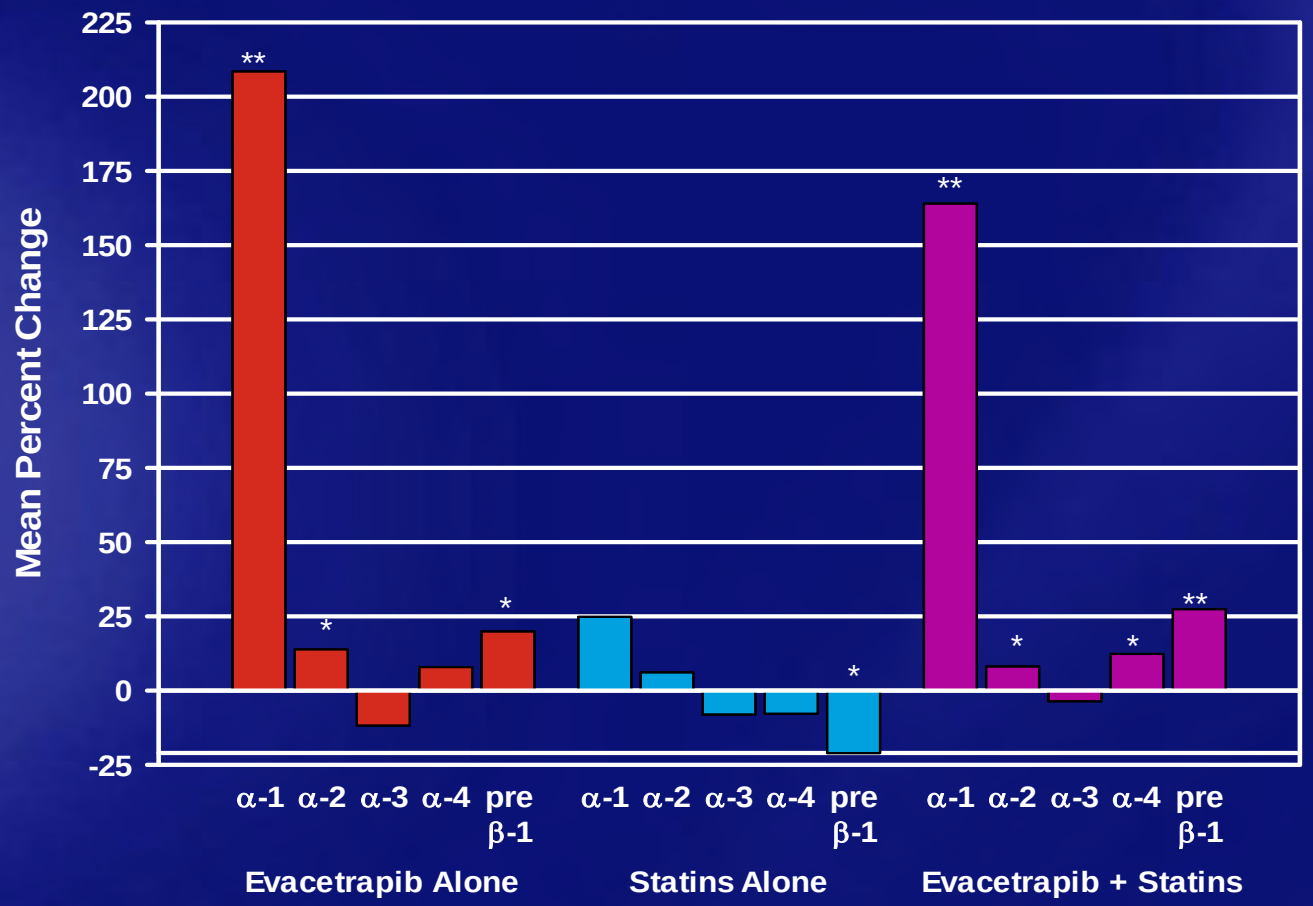

Error bars represent 90% CI

*p<.05 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

Abbreviations: CI=confidence interval; EVA=evacetrapib; HDL=high-density lipoprotein

Nicholls et al. Presented AHA Scientific Sessions 2014

# Percent Change in HDL Subclasses by 2D-gel




*p<.05 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

**p<.001 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

Abbreviations: 2D=two dimensional; EVA=evacetrapib; HDL=high-density lipoprotein; preβ-1=prebeta-1

Nicholls et al. Presented AHA Scientific Sessions 2014

# LOCATION TRIAL

- **Using zirconium-89 labeled CER-001, CER-001, pre-beta HDL mimetic, preferentially targets atherosclerotic plaques as evaluated by PET/CT scanning.**
- **CER-001 infusion increased plasma mediated cholesterol efflux capacity. After one hour of CER-001 infusion, plasma mediated cholesterol efflux increased by 13.8% and mean plasma apoA-I levels increased by 9.9 mg/dL.**

Stroes E, et al. ESC 2015
Cerenis Therapeutics press release

.

# Conclusions

- Therapeutic interventions directed towards increaed cholesterol loading of the HDL particle have been based on epidemiological studies that have established HDL-C as a biomarker of CVD risk
- The advent of clinical tools to assess HDL functionality has changed the paradigm for HDL therapeutics
- Key mechanistic criteria for clinical outcomes tirals with an HDL –based therapy include the generation of HDL particles that improve the efficiency of macrophage cholesterol efflux, and compositional change in the proteome and lipdome of the HDL particle that improves anti-oxidant and anti-inflammatory properties

# Treatment Intensity vs. Treatment Targets

# AHA/ACC Guideline – Why?

Patrick E. McBride, MD, MPH
Professor, Departments of Medicine & Family Medicine
Associate Director, Preventive Cardiology
University of Wisconsin

# Required by EBM of IOM to use RCTs / SMA as Evidence

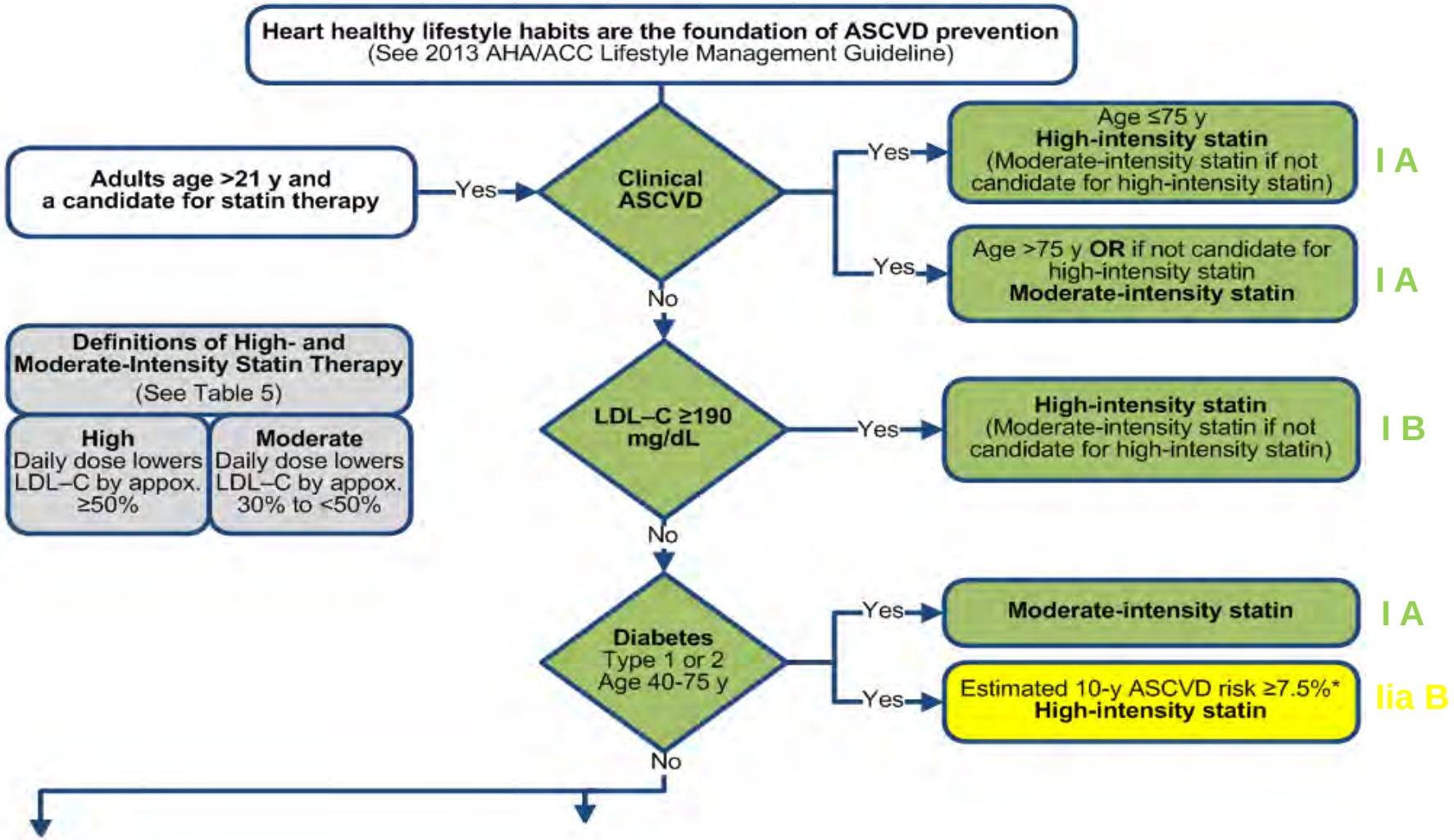
- **Not a single RCT used LDL targets for determining treatment goals**
- **All RCTs were based on treatment INTENSITY – the dose of a statin or other medication**
- **This guideline was based on *LDL Cholesterol ONLY by* design of the NIH**
- **Design was due to the complexity of the EBM evidence model**
- **NICE / ESC and AHA/ACC guidelines – targets not justified by evidence**

# Benefits of Intensity of Treatment vs. LDL-C Targets

- Evidence – based and cost effective
- Potential for greater risk reduction benefit
- Simplification for clinicians – not tied to multiple lab tests; not adding medications when cholesterol near goal and treating to evidence
- Calculated LDL not highly accurate, esp. low LDL
- Non-HDL and other targets not used in trials
- Not penalized for treating by evidence
- Pay for performance is clinician based and not penalized for lack of patient adherence
- Potential for fewer adverse effects and drug-drug interactions

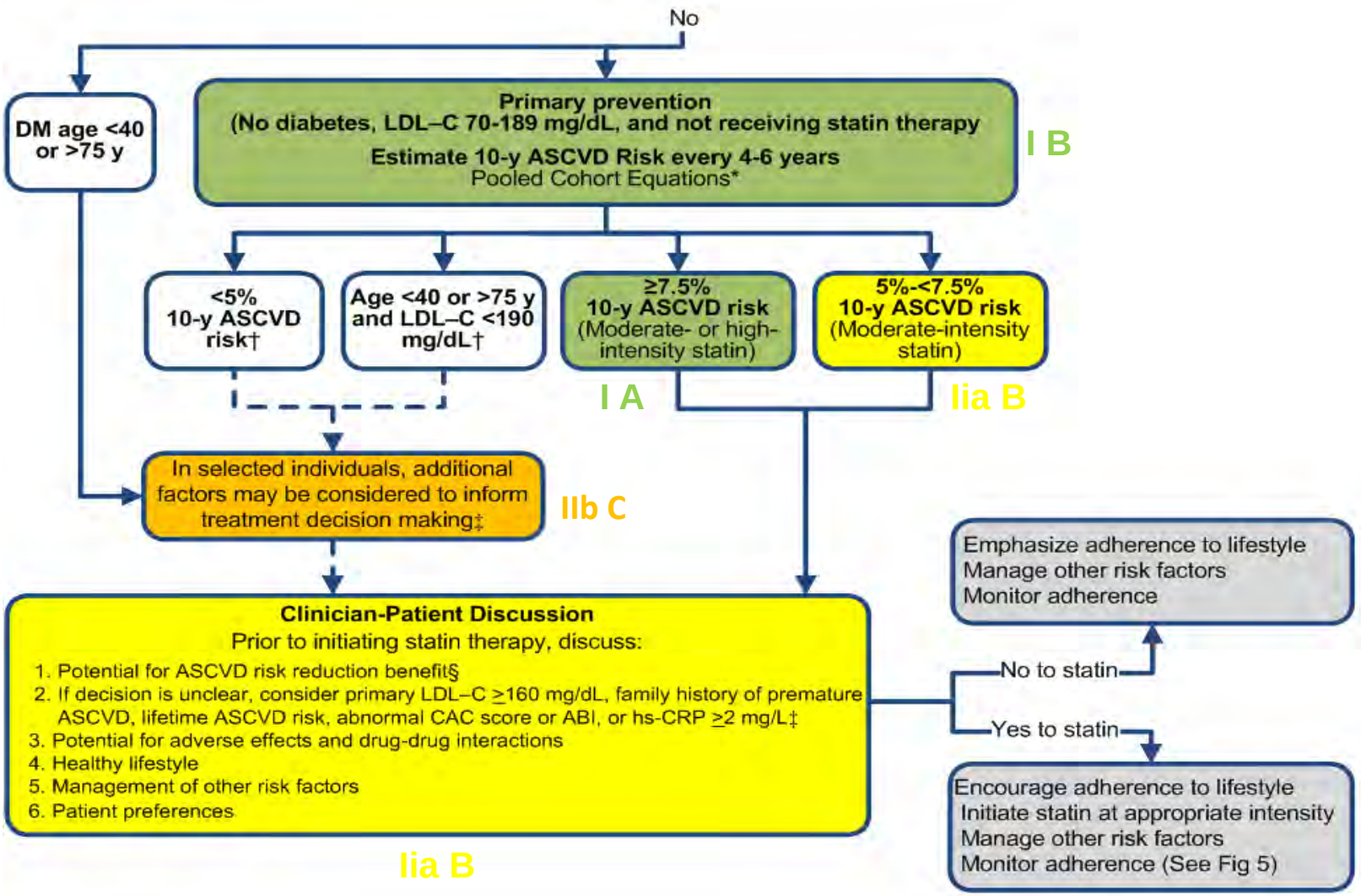
# What the 2013 ACC/AHA Cholesterol Guideline to Reduce ASCVD Risk Says

## Major recommendations for *initiating* statin therapy



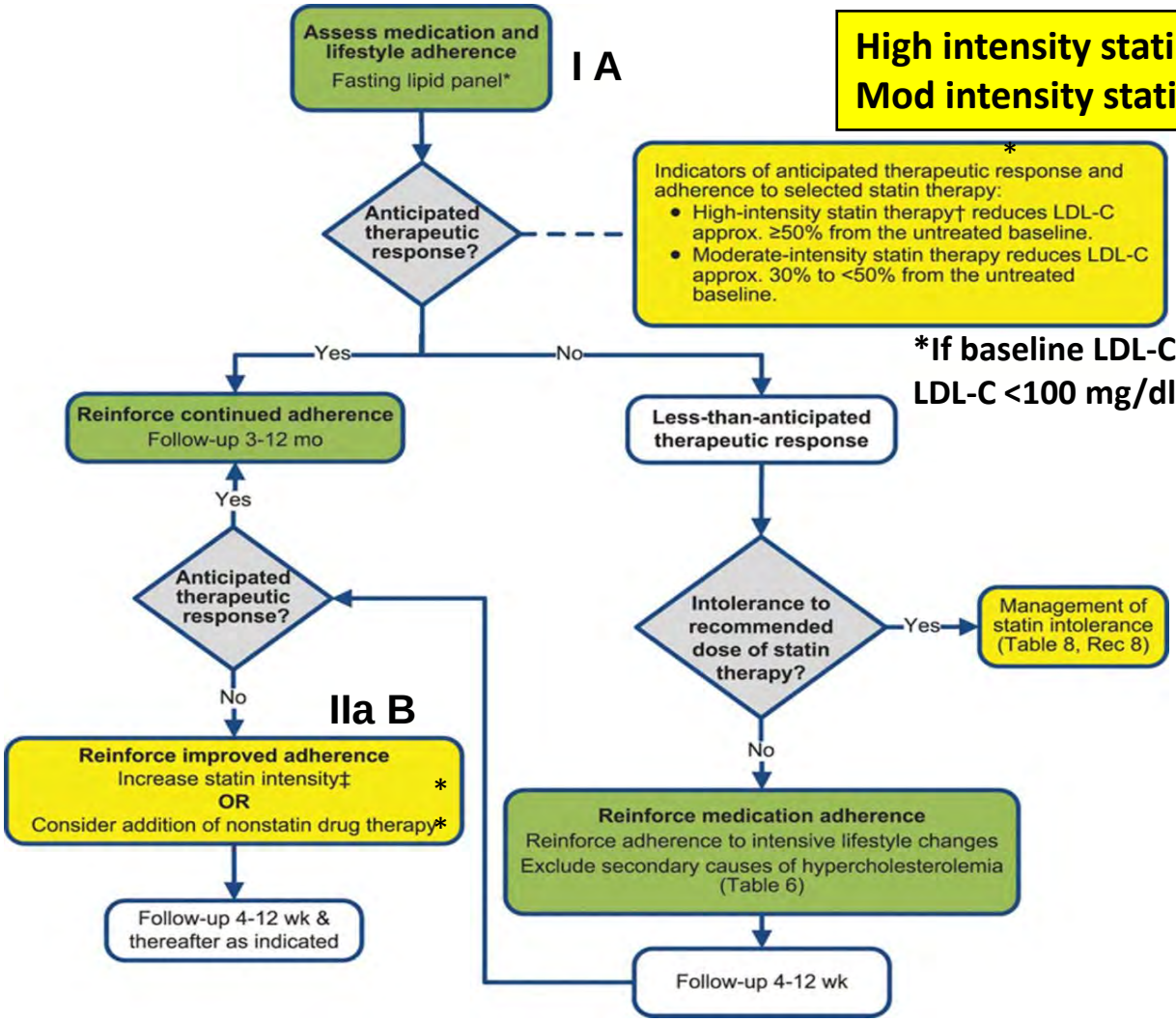
# What the 2013 ACC/AHA Cholesterol Guideline to Reduce ASCVD Risk Says

## Major recommendations for *initiating* statin therapy (cont)



# What the 2013 ACC/AHA Cholesterol Guideline to Reduce ASCVD Risk Says

## ***Monitoring*** Therapeutic Response and Adherence




**High intensity statin ≥50% ↓LDL-C**
**Mod intensity statin 30-<50% ↓LDL-C**

***If baseline LDL-C unknown, may use LDL-C <100 mg/dl**

****Nonstatin shown to reduce ASCVD events in RCTs preferred**

American Heart Association.

Stone NJ, Robinson JG, Lichtenstein AH, et al.. *J Am Coll Cardiol.* 2014;63(25, Part B):2889-2934

# Testing the new paradigm: 2013 ACC/AHA cholesterol guideline outperforms NCEP ATP 3

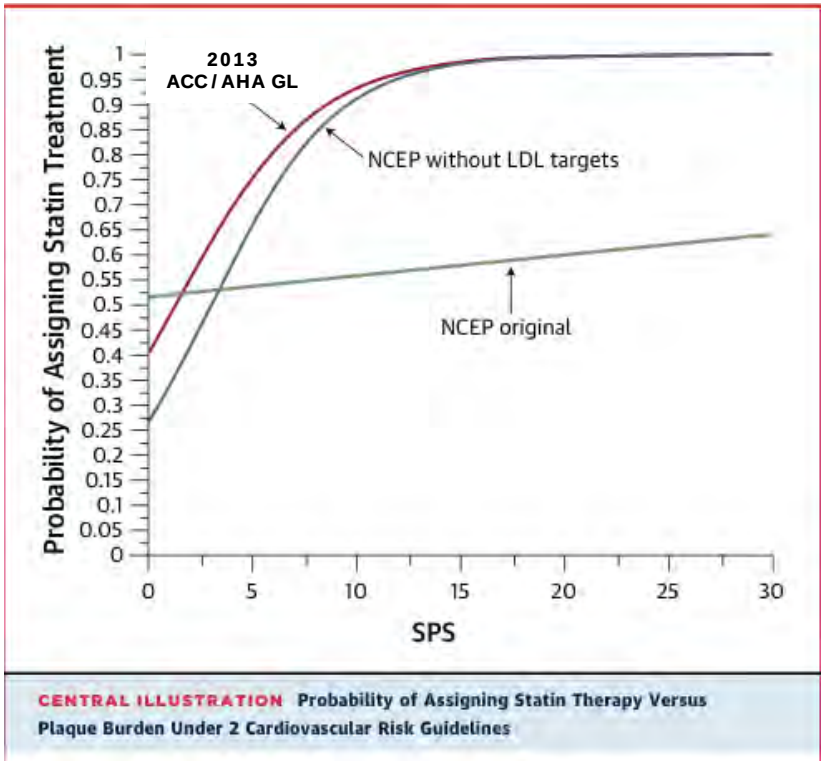
## LDL-C cut-points are the main problem with ATP3

✓**2013 ACC/AHA - Will prevent more CVD events**

- **Dallas Heart Study – identified more high risk patients**
- **U.S. NHANES – would prevent 450,000 more ASCVD events/10 years**

✓**Why? No correlation LDL-C levels with plaque (CTA)**

- **Removing LDL-C cut-points improves accuracy NCEP ATP 3**



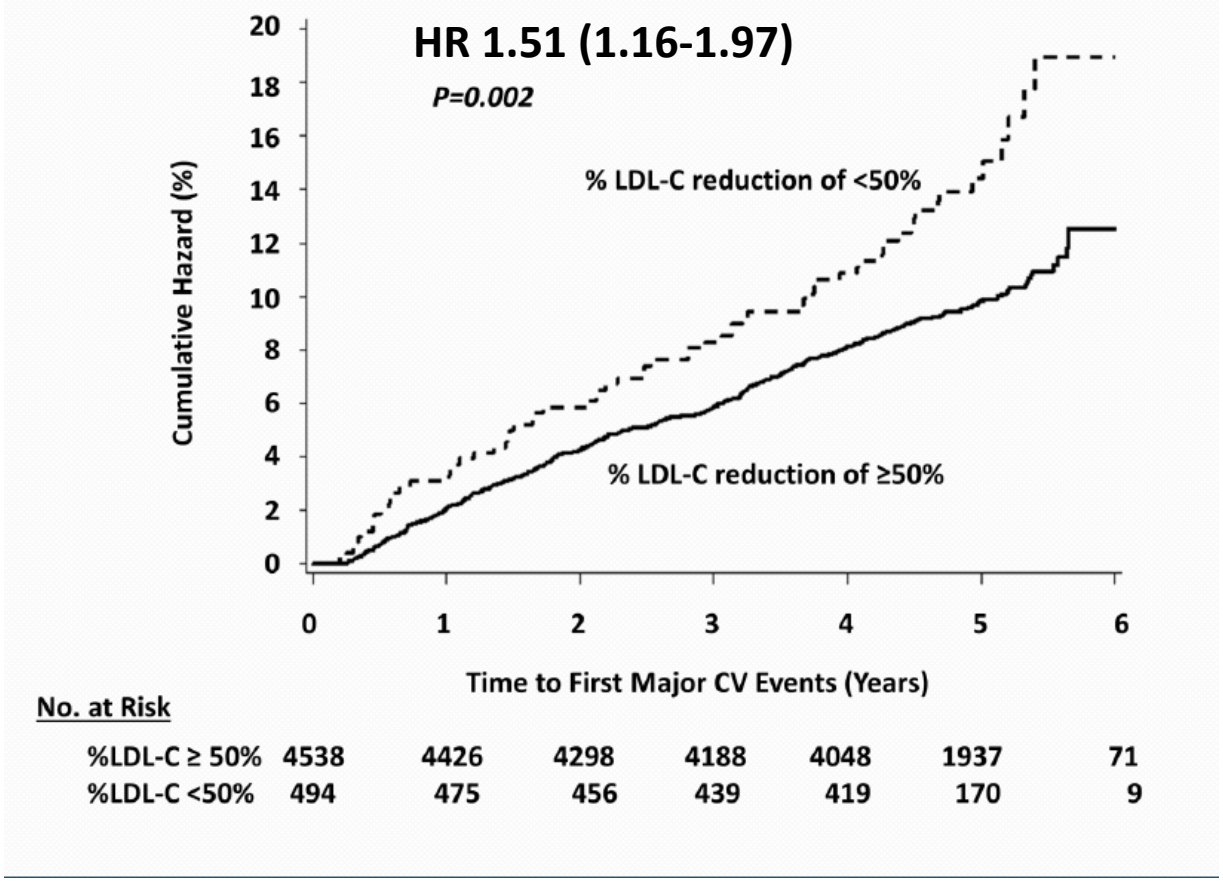

CENTRAL ILLUSTRATION Probability of Assigning Statin Therapy Versus Plaque Burden Under 2 Cardiovascular Risk Guidelines

Paixo ARM, et al. Circ Cardiovasc Qual Outcomes online ahead-of-print Aug 5, 2014; Pencina MJ, et al. *NEJM.* 2014;370(15):1422-1431. Johnson KM et al. JACC 2014; 64: 910-919; Pursani A, et al. Atherosclerosis 2014; 237-314-318; Karmali KN, et al. JACC 2014; 64: 959-968

# Reducing ≥50% LDL-C prevents more ASCVD events than achieved LDL-C <70 mg/dl

## TNT-IDEAL-SPARCL pooled analysis

**Patients with LDL-C <70 mg/dl**




Bangalore S, et al. Presented at ACC.15, San Diego CA. March 16, 2015.

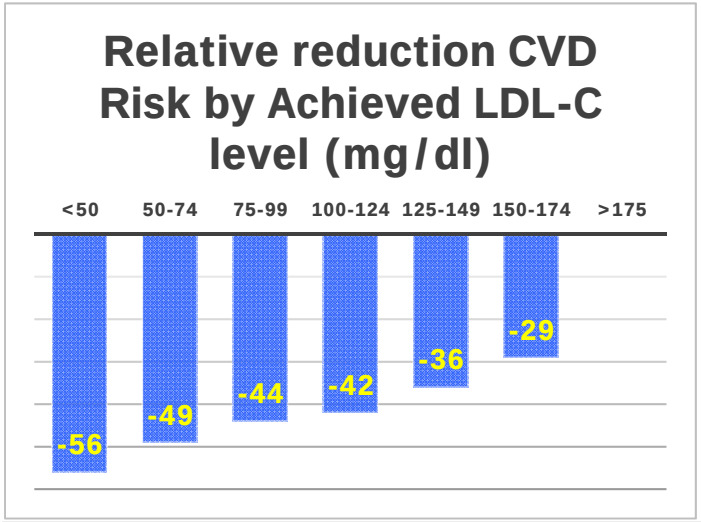
# LDL-C goal approach & under-treatment

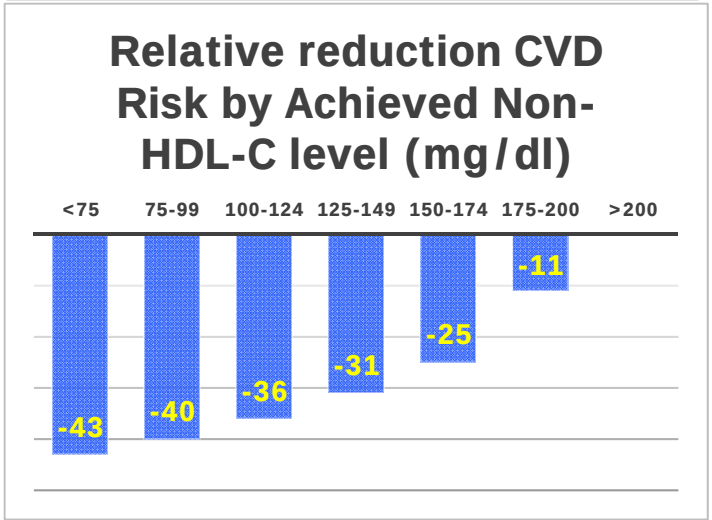
- **ASCVD patients (N > 45,000)**
  - **Large managed care (Optum) database 2004 to 2012**
- **Any lipid therapy: 61% → 68% (>30% no RX)**
  - **LDL-C <70 mg/dl: 11% → 26%**
  - **LDL-C <100 mg/dl: 50% → 70%**
  - **High potency statin: 8% → 18% (Few on HPS**)**
    - *****Atorvastatin 40-80 mg, rosuvastatin 20-40 mg, simvastatin 80 mg**
- **Conclusion: Treatment should occur according to treatment guidelines – High Intensity RX**

Rodriguez F, et al. Am J Cardiol 2015; 115: 190-195

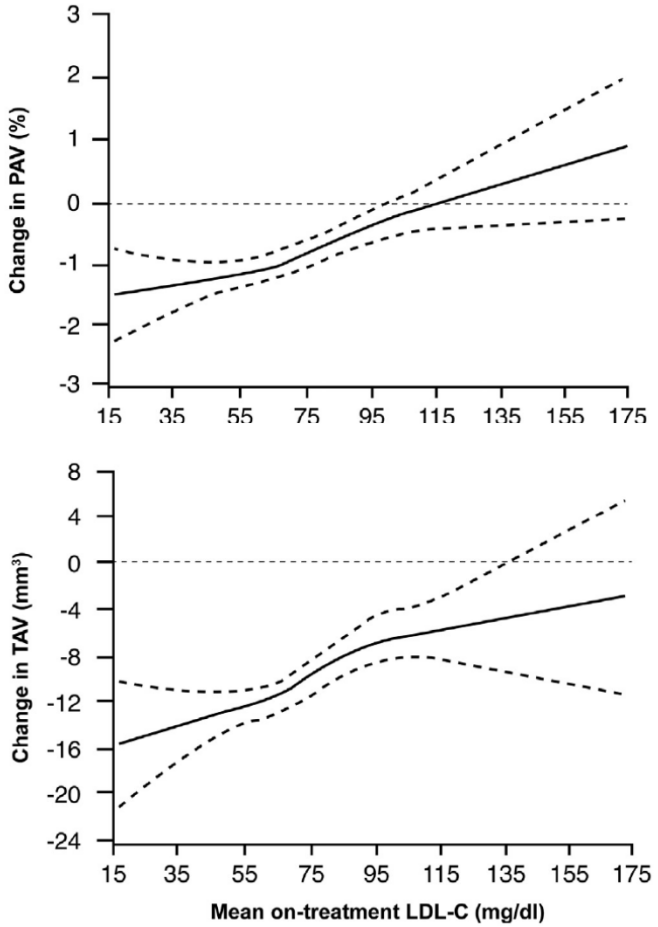
# Why stop at 100 or 70 mg/dl?

## No lower LDL-C limit for ASCVD risk reduction




*Individual level meta-analysis adjusted for sex, age, smoking, diabetes, SBP, HDL-C
Personal communication: Associations persist after further adjustment for baseline LDL-C




18-24 months rosuvastatin 40 mg or atorvastatin 80 mg (n=1881)

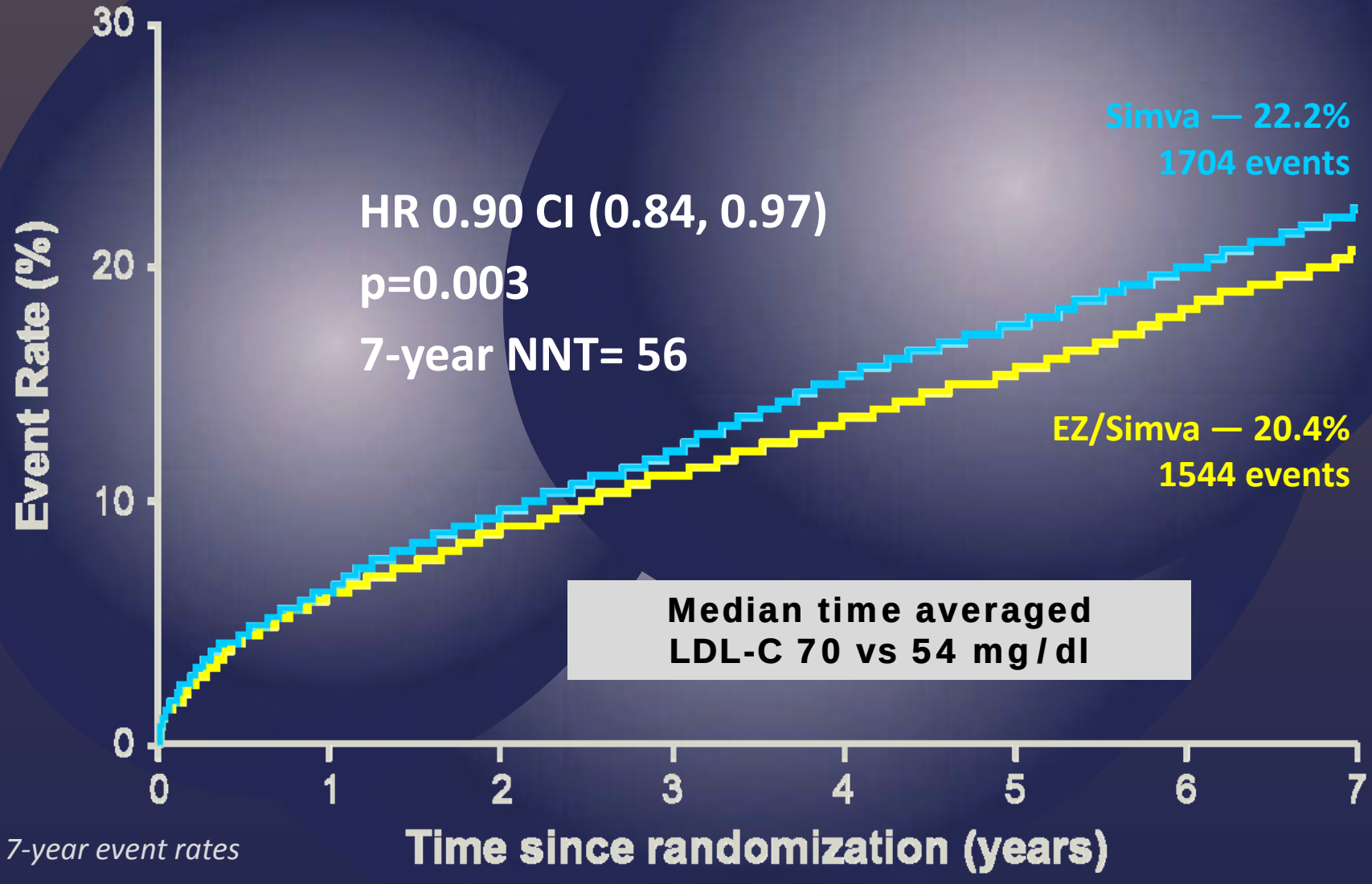
Boekholdt SM, et al. JACC 2014; 64:485-494; Puri R, Nissen SE, et al. Am J Cardiol 2014; 114: 1465-1472

# Benefits of Intensity of Treatment vs. LDL-C Targets

- Evidence – based and cost effective***
- Potential for greater risk reduction benefit
- Simplification for clinicians – not tied to multiple lab tests; not adding medications when cholesterol near goal and treating to evidence
- Calculated LDL not highly accurate, esp. low LDL
- Non-HDL and other targets not used in trials
- Not penalized for treating by evidence
- Pay for performance is clinician based and not penalized for lack of patient adherence
- Potential for fewer adverse effects and drug-drug interactions

# Interpreting IMPROVE-IT

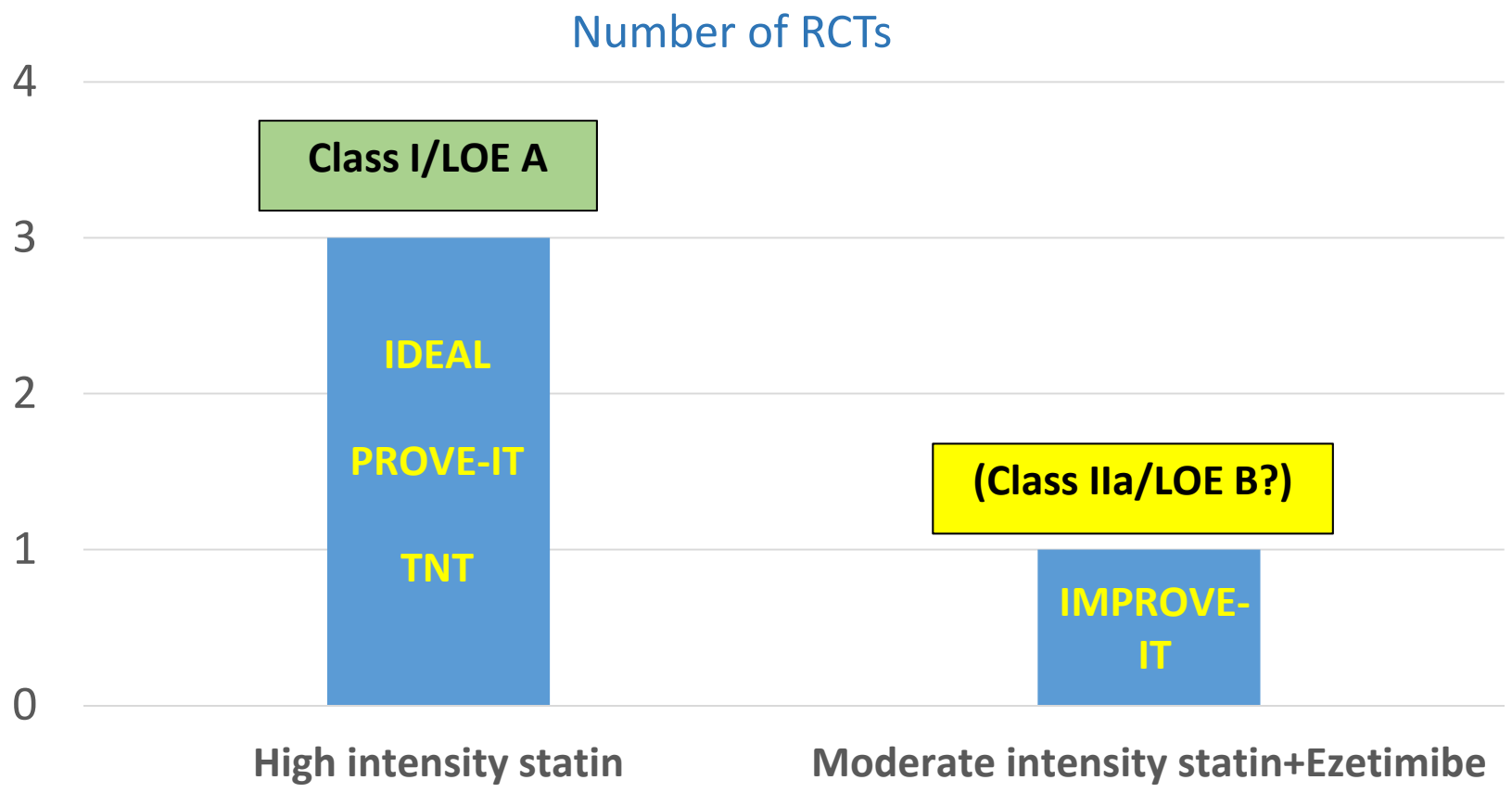
CV Death, Non-fatal MI, or Non-fatal Stroke




*7-year event rates*

Cannon C, et al. Presented at AHA Scientific Sessions 2014, Chicago IL Nov 17, 2014.

# Based on ACC/AHA Recommendation Class/Level of Evidence Approach: Moderate intensity statin + Ezetimibe an alternative to High intensity statin



National Lipid Association

Fall Clinical Lipid Update

Pittsburgh, PA

August 31, 2015

# Lipoprotein Goals and Monitoring are of Value in Patient Care

W. Virgil Brown, MD

Emory University

Atlanta , GA, USA

# Patients always question your preparation and your ability in the art of MEDICINE

Why is the doctor prescribing this?

Will it work?
Is it safe?

Did it work?

# Guidelines Serve the ART of Medicine

- Guidelines should contain answers to the following:

  What is your objective?

  PREVENT VASCULAR DISEASE

  What are you treating?

  TARGET THAT IS CAUSAL

  How intensely should you treat?

  GOAL OF THERAPY

# Defining the target should use the Scientific Method

- Science uses evidence to build and then challenge a theory.
  - It is the theory that describes what we can observe.
  - Facts without theory mean nothing. [*Albert Einstein*]
- The test of a sound theory is its ability to predict observations and outcome of experiments with a high probability.
- It must withstand the challenge of different interventions in different systems
- There is a sound theory of atherogenesis built on 100 years of experiments.
- Elevated apoB containing lipoproteins cause atherosclerosis and should be a target of therapy.

# TARGETS -
# APO-B CONTAINING LIPOPROTEINS

How do we assess the TARGET?

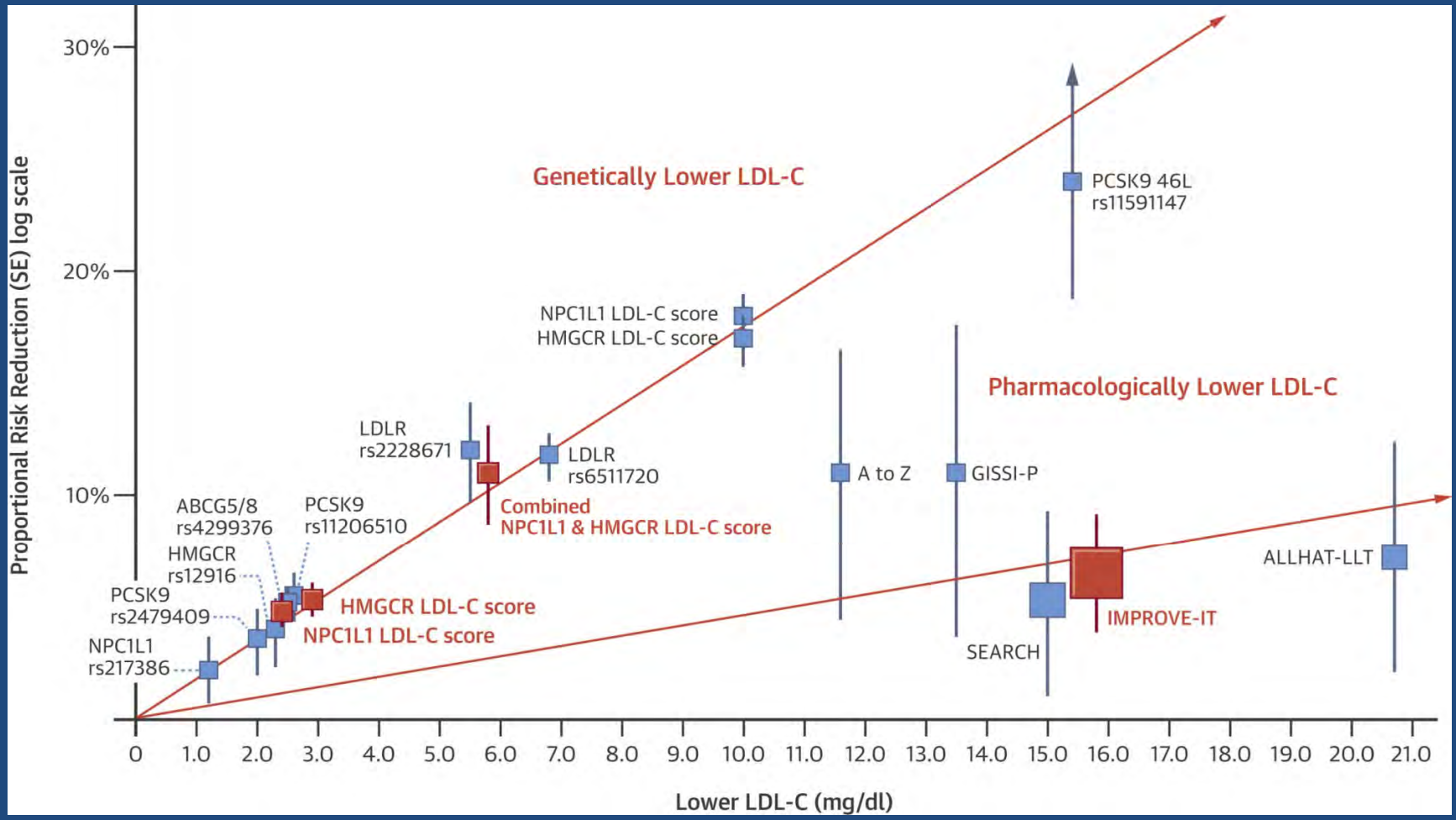
LDL- cholesterol

Non-HDL cholesterol (Total C – HDL-C)

<u>Good candidates supported by modern science :</u>

Apo B or LDL particle number

# Effect of Naturally Random Allocation to Lower LDL-C on Risk of CHD Mediated by Polymorphisms in NPC1L1, HMGCR, or Both: A 2 × 2 Factorial Mendelian Randomization Study

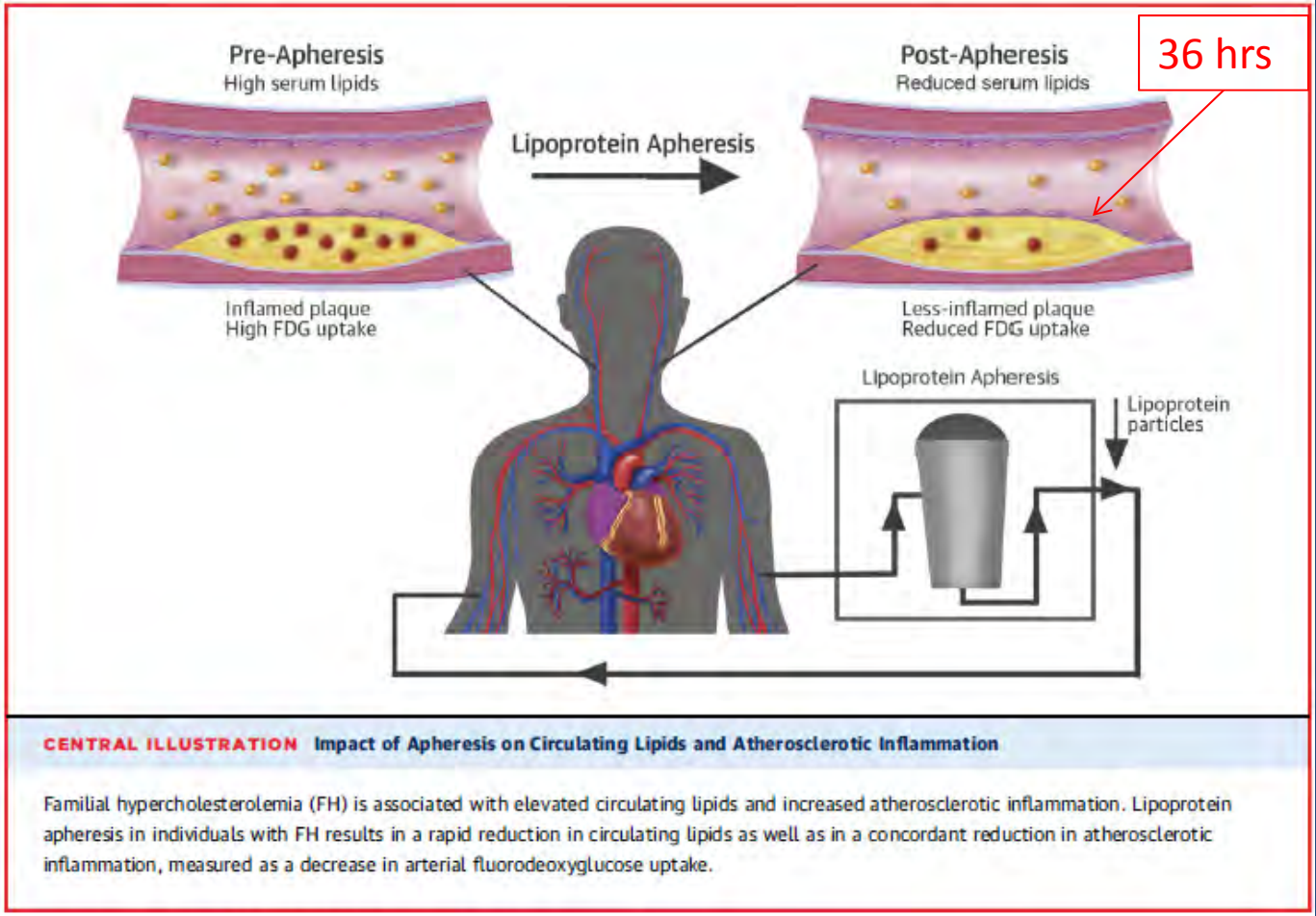



Ference BA et al. *J Am Coll Cardiol.* 2015;65:1552-1561.

JACC Journals

# Physical removal of apoB-Lp by Apheresis reduces inflammation in arteries

[18F-flurodeoxyglucose positron emission tomography]




**CENTRAL ILLUSTRATION** **Impact of Apheresis on Circulating Lipids and Atherosclerotic Inflammation**

Familial hypercholesterolemia (FH) is associated with elevated circulating lipids and increased atherosclerotic inflammation. Lipoprotein apheresis in individuals with FH results in a rapid reduction in circulating lipids as well as in a concordant reduction in atherosclerotic inflammation, measured as a decrease in arterial fluorodeoxyglucose uptake.

Wijk, Sjouke, Figurroa, et al. JACC (2014) 64:1918

ACC/AHA Guidelines:

Goals are not recommended because they have not been tested in randomized clinical trials.

Question:

Can goal usage in clinical practice be developed from randomized clinical trials?

# Goals are Tools for use in the ART of MEDICINE.

Based on the observed relationship between LDL-C (or nonHDL-C) and the incidence of ASCVD and informed by scientific observation and randomized clinical trials.

The range of safe values are determined by knowledge of lipoprotein metabolism and by the safety and efficacy of the therapeutic options available.

They are tested and modified by experience with patients and by observation of the populations affected.

They will change overtime with new observational data

# • Evidence Based Medicine:

- Hypotheses: my statin is better than placebo, my statin is better than your statin, big dose is better than little dose, statins benefit those with diabetes, high blood pressure , CVD, no CVD,and those with high LDL or lower LDL.

| **Randomize** | **Observe and record** | **Count endpoints and analyze** |
|---|---|---|
| STATIN therapy → | Mysterious and wonderful things happen. → | Statistically fewer endpoints |
| Placebo or comparator → | No mysterious and wonderful things. → | Lots of endpoints |

Result: An "INDICATION" granted by the FDA

# Clinical Trials are not models of the Art

- The intervention is predetermined by a hypothesis. (not patient needs.)
- Clinical criteria are selected for thousands of individuals to best fit the hypothesis
- Many patients are excluded based on preselected criteria.
- Procedures and schedule of visits are preset and occur at regular intervals
- Goals of the therapy have no relevance to treatment during the trial.
- Investigator and patient agree to remain blinded to the therapeutic results
- Patients adhere based on faith in the staff, the consistency of procedures and the perceived absence of adverse reactions to the intervention.

Success : Measured by statistical tests (large numbers).

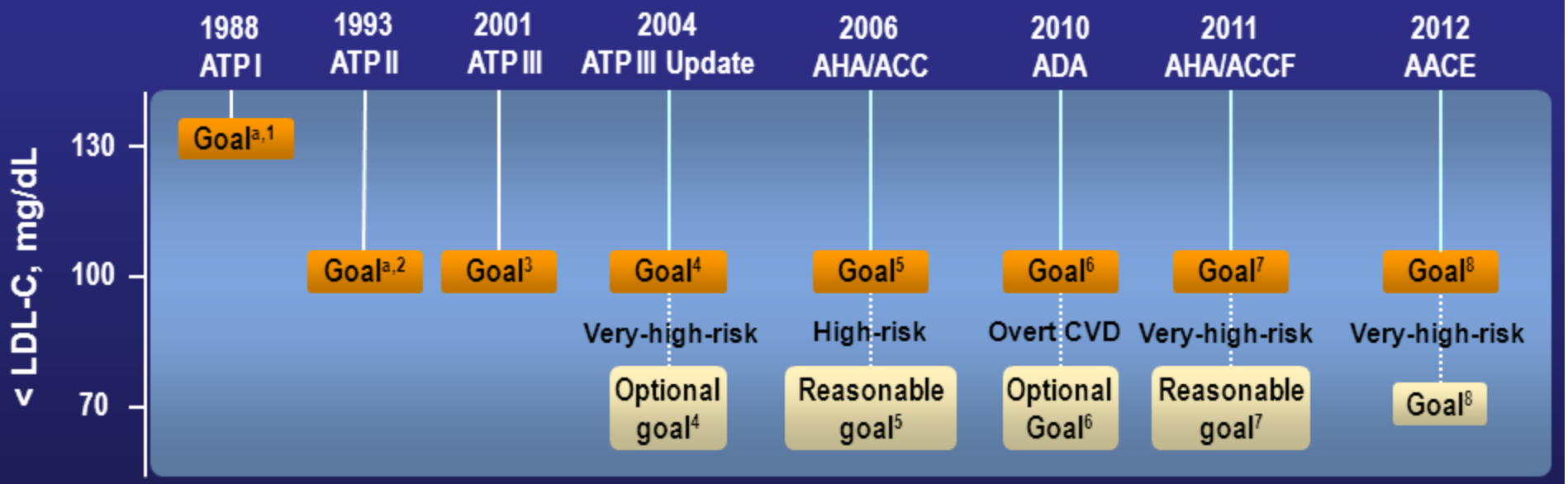
# In Medical Practice :

- The problem is presented by one individual
- Clinical care  uncovers and accepts other problems (often many)
- The physician must choose what to treat (i.e. selects targets – often several)
- Explain the objective (prevent heart attack or stroke)
- Explain how you plan to do it (define the target and set the goals)
- Choose laboratory tests and procedures to fit targets and time constraints
- Monitor based on patient's needs but limited by the practice and third party payers.
- Adherence is  based on faith in you, achievement of goals, cost and lack of adversity.

Success:
A patient at goals of therapy with a stable or improving clinical status.

# LDL-C Goals for High-Risk Patients Have Become More Intensive Over Time

As part of therapeutic lifestyle changes, including diet, LDL-C treatment goals for high-risk patients have been lowered over time




[a]Goal is ≤LDL-C value.

ATP = Adult Treatment Panel; AHA = American Heart Association; ACC = American College of Cardiology; ADA = American Diabetes Association; ACCF = American College of Cardiology Foundation; AACE = American Association of Clinical Endocrinologists.

**1.** NCEP ATP I. *Arch Intern Med.* 1988;148:36–69; **2.** NCEP ATP II. *JAMA.* 1993;269:3015–3023; **3.** NCEP ATP III. *JAMA.* 2001;285:2486–2497; **4.** Grundy SM et al. *Circulation.* 2004;110:227–239; **5.** Smith SC Jr et al. *Circulation.* 2006;113:2363–2372; **6.** ADA. *Diabetes Care.* 2010;33(suppl 1):S11–S61. **7.** Smith SC Jr et al. *Circulation.* 2011;124:2458–2473. **8.** Jellinger PS et al. *Endocr Pract.* 2012;18(suppl 1):1–78.

# Traditionally goals are not single values. Goal Setting is Range Setting

- < 100 mg/dL does not mean 100 mg/dL

  It means 99 to 0 mg/dL.

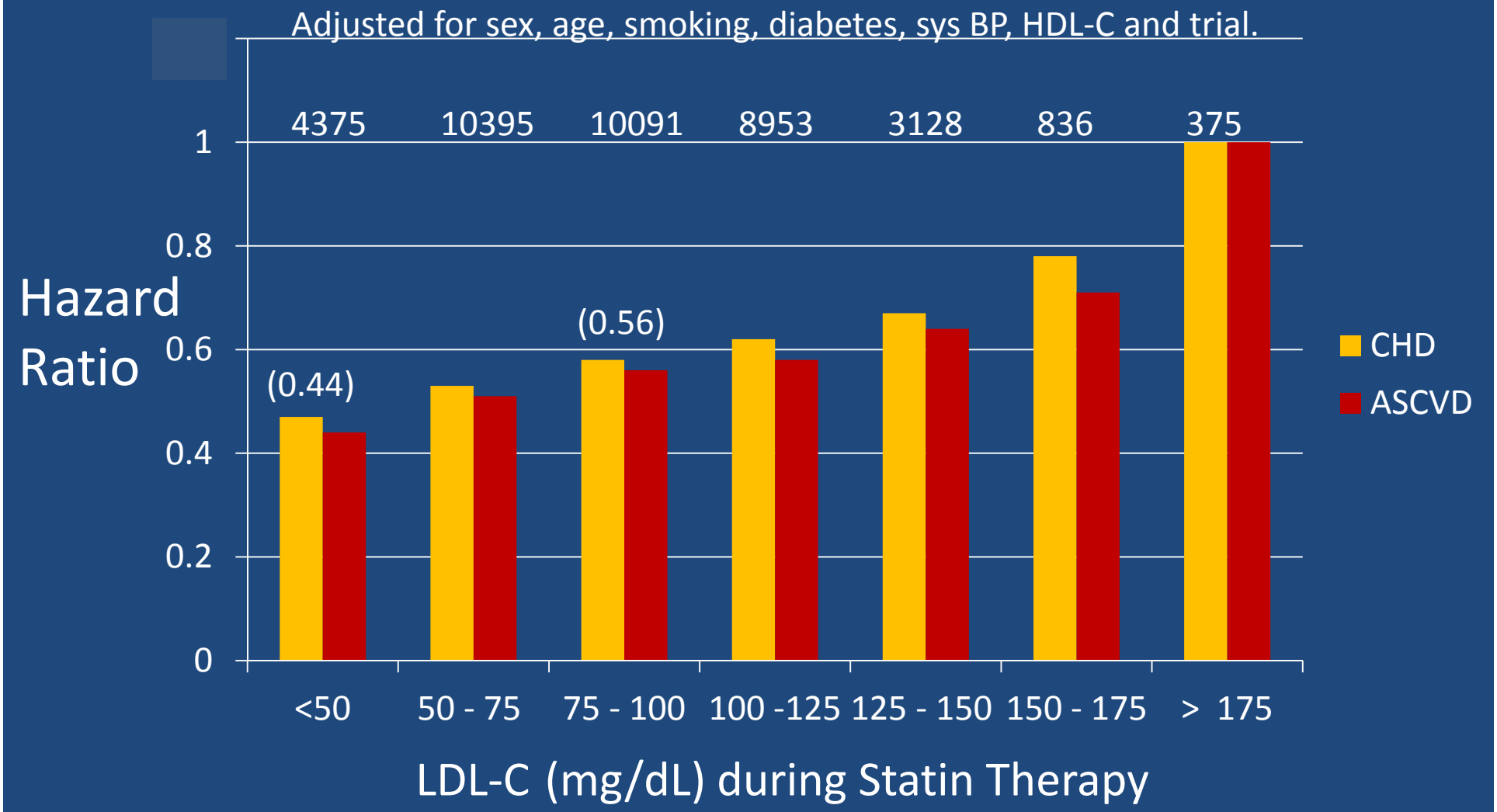
- ≤70 mg/dL does not mean 70 mg/dL

  It means 69 to 0 mg/dL.

- There is no recommended lower limit.

# LDL-C: Residual Risk on Statins

N= 38,253 from 14 DRBCTs

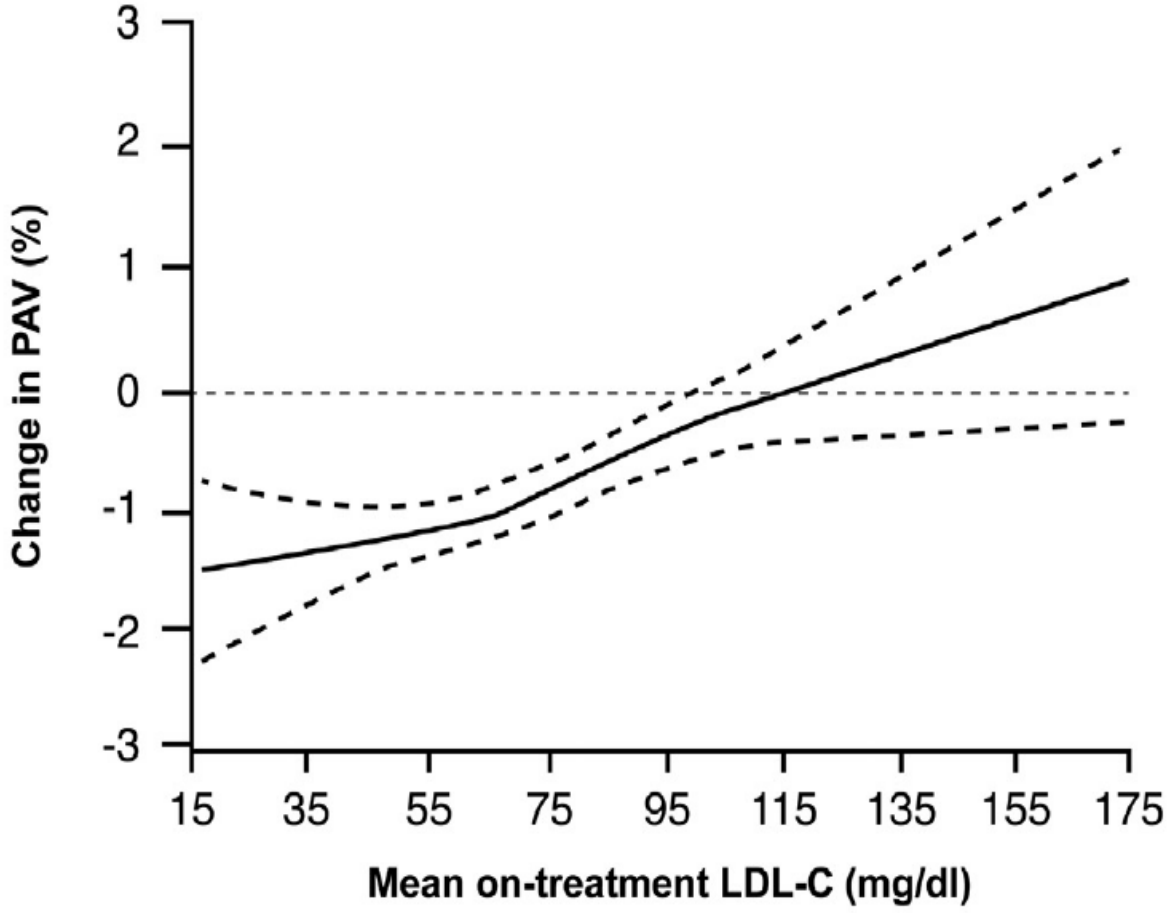



Boekholdt et al. JACC August 5, 2014

# Changes in Percent Atheroma Volume by IVUS:

## In 8 trials with 1881 patients treated with rosuvastatin 40mg or atorvastatin 80 mg for 18 to 24 months.

Puri, Nissen, Shao, et.al. Am J of Cardio (2014) 114:1465 - 1472



# Evidence based or Science based?

In practicing the art of medicine, randomized double blind controlled clinical trials with only one intervention (statin) are not appropriate for scientifically setting targets of therapy or for setting goals of that therapy.

# Art of Medicine is Science Based

- The Art of Medicine and its advancement depends on having a well based theory.
- THE theory defines appropriate TARGETS for therapy
- The GOALS for the targets are informed by RCTs but GOALS come from observations and their performance in practice
- An expert in the art uses all effective tools for achievement of GOALS consistent with the theory
- The theory guides development of new treatments.

  [EZETIMIBE, PCSK-9 INHIBITION, antiC3 ASO, CETP INHIBITION
- It relieves the confinement of “evidence based medicine” - to simply copying the behavior observed in clinical trials.

# Summary:

- Guidelines must serve the ART of medicine.
- They should help in explaining what you are treating – the TARGET.
- Provide for GOALS -- interim milestones that allow assurance to doctor and patient that the therapy is working.

# ACC/AHA Guidelines: Introduction

The Expert Panel acknowledges that our process did not provide for a comprehensive approach to the detection, evaluation, and treatment of lipid disorders as was done in the prior ATP III Report .

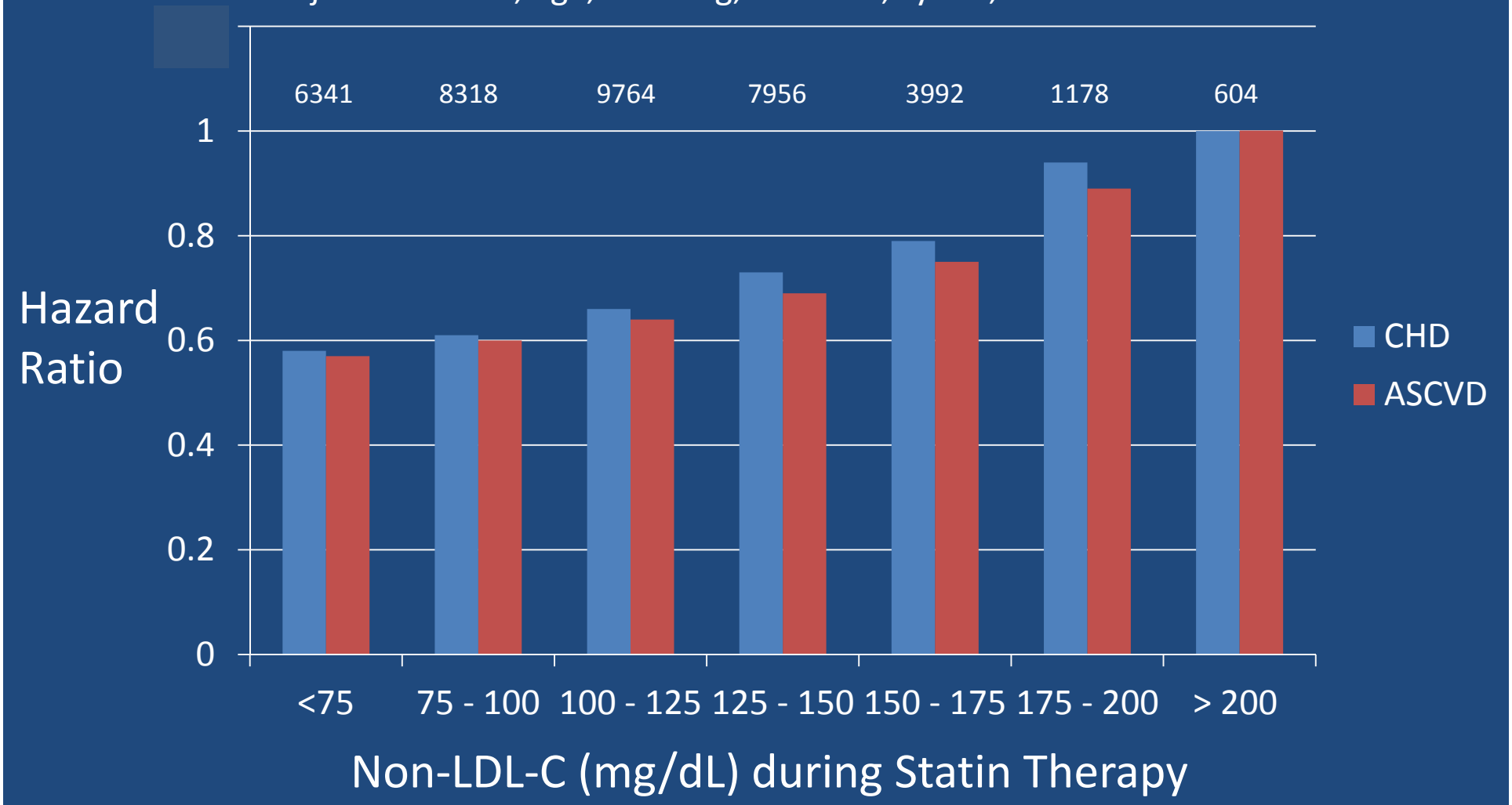
- A limited number of expert opinion recommendations were made only when RCT evidence was not present and after a thorough consideration of what the Expert Panel had learned from the RCTs.

- For the many questions regarding complex lipid disorders that were beyond the scope of our systematic evidence review, or for which little or no RCT data are available, it is anticipated that clinicians with lipid expertise can contribute to their management.

# Non-HDL-C: Residual Risk on STATINS

N= 38,253

Adjusted for sex, age, smoking, diabetes, sys BP, HDL-C and trial.

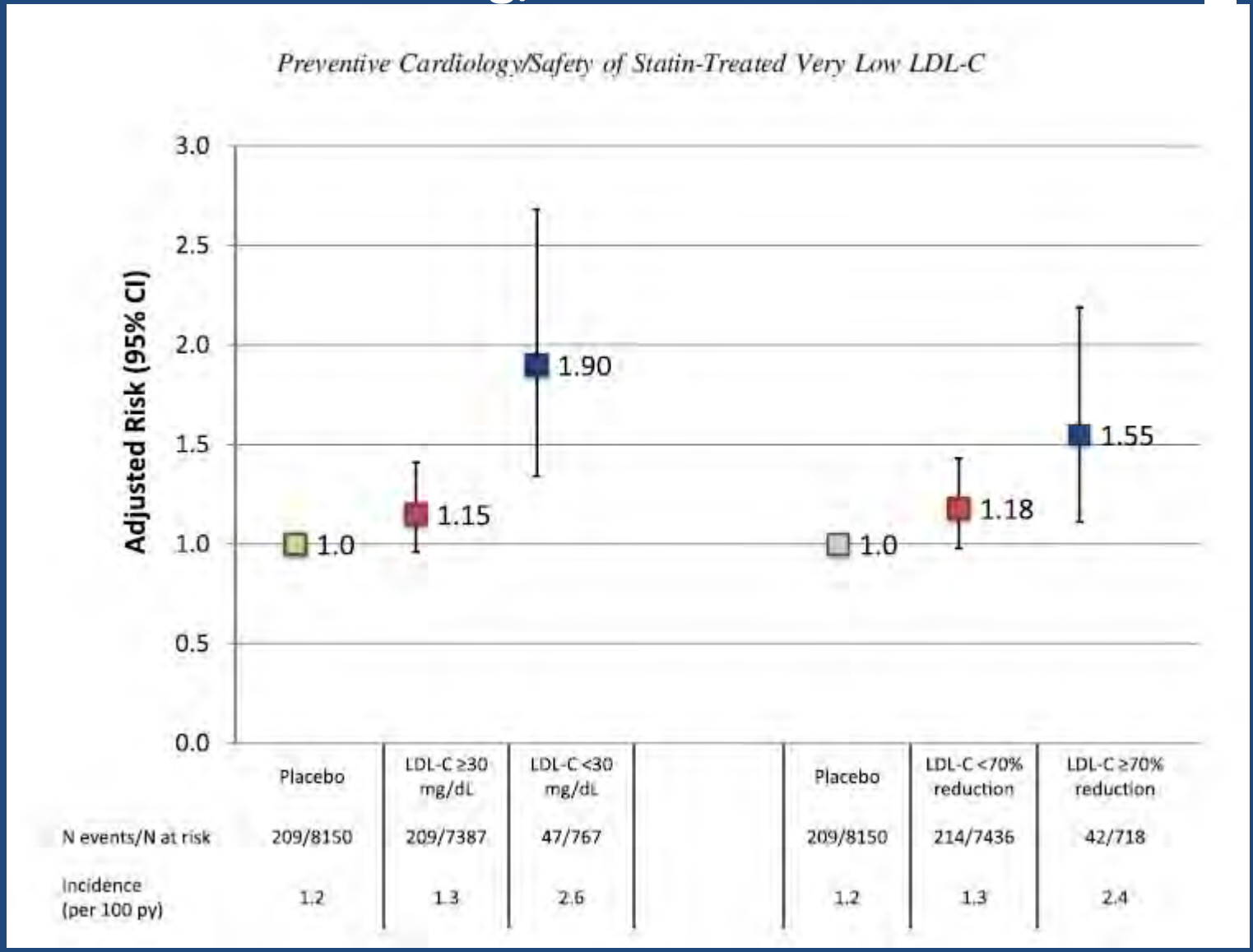



Boekholdt et al. JACC August 5, 2014

# Organizations Recommending Goal Setting (Partial List)

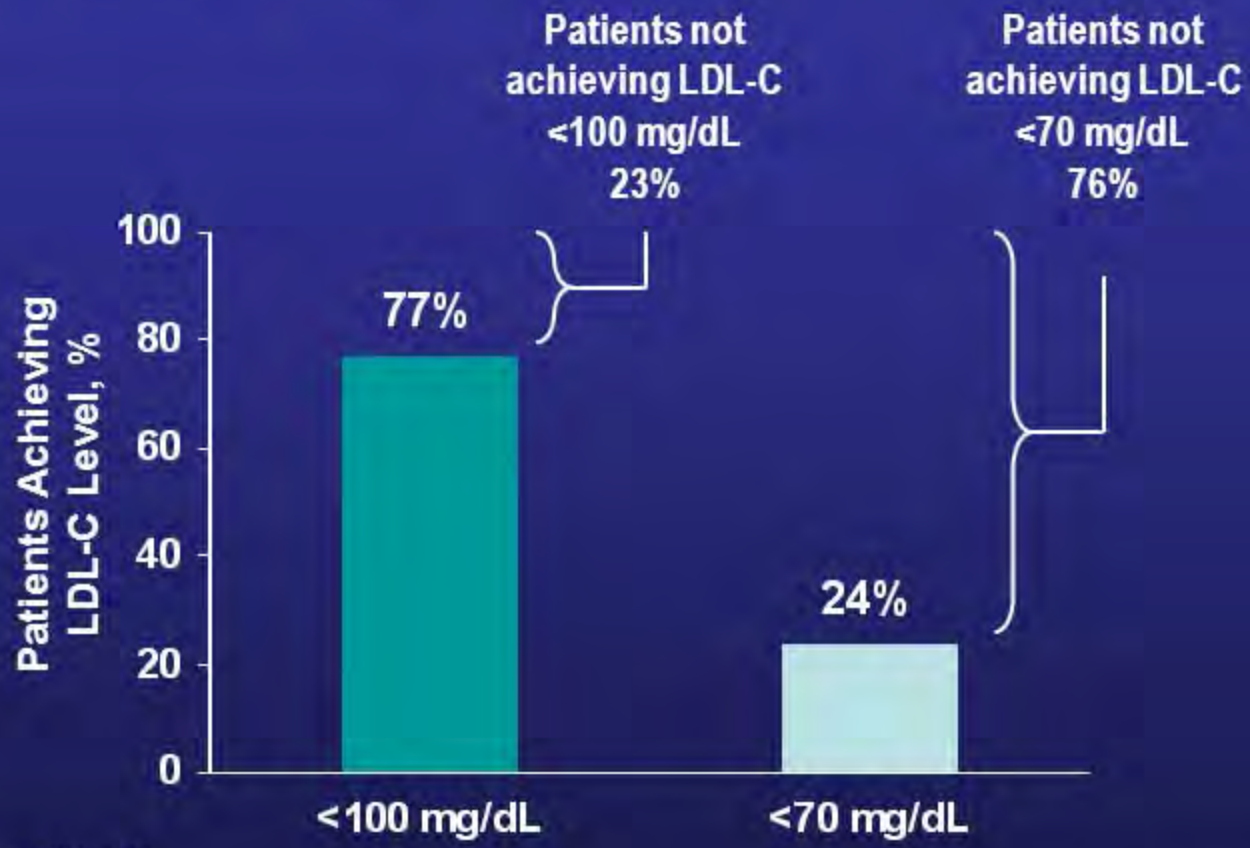
- American Association of Clinical Endocrinologists
- American Diabetes Association
- American Association of Clinical Endocrinologists
- Canadian Cardiovascular Society
- European Atherosclerosis Society
- European Society of Cardiology; HDL-C
- IAS, International Atherosclerosis Society
- JAS, Japan Atherosclerosis Society
- National Collaborating Centre for Primary Care
- National Lipid Association

# Jupiter: Diabetes presenting in subpopulations with LDL-C <30 mg/dL or with LDL-C reduced ≥ 70%




Everette, BM et al. Am J Cardiol (2014) 2014;114:1682-1689

# NHANES 2007–2008: Many High-risk Patients Were Not at LDL-C Levels <100 mg/dL or <70 mg/dL[1,a]




Adapted with permission from Jones PH et al.[1]

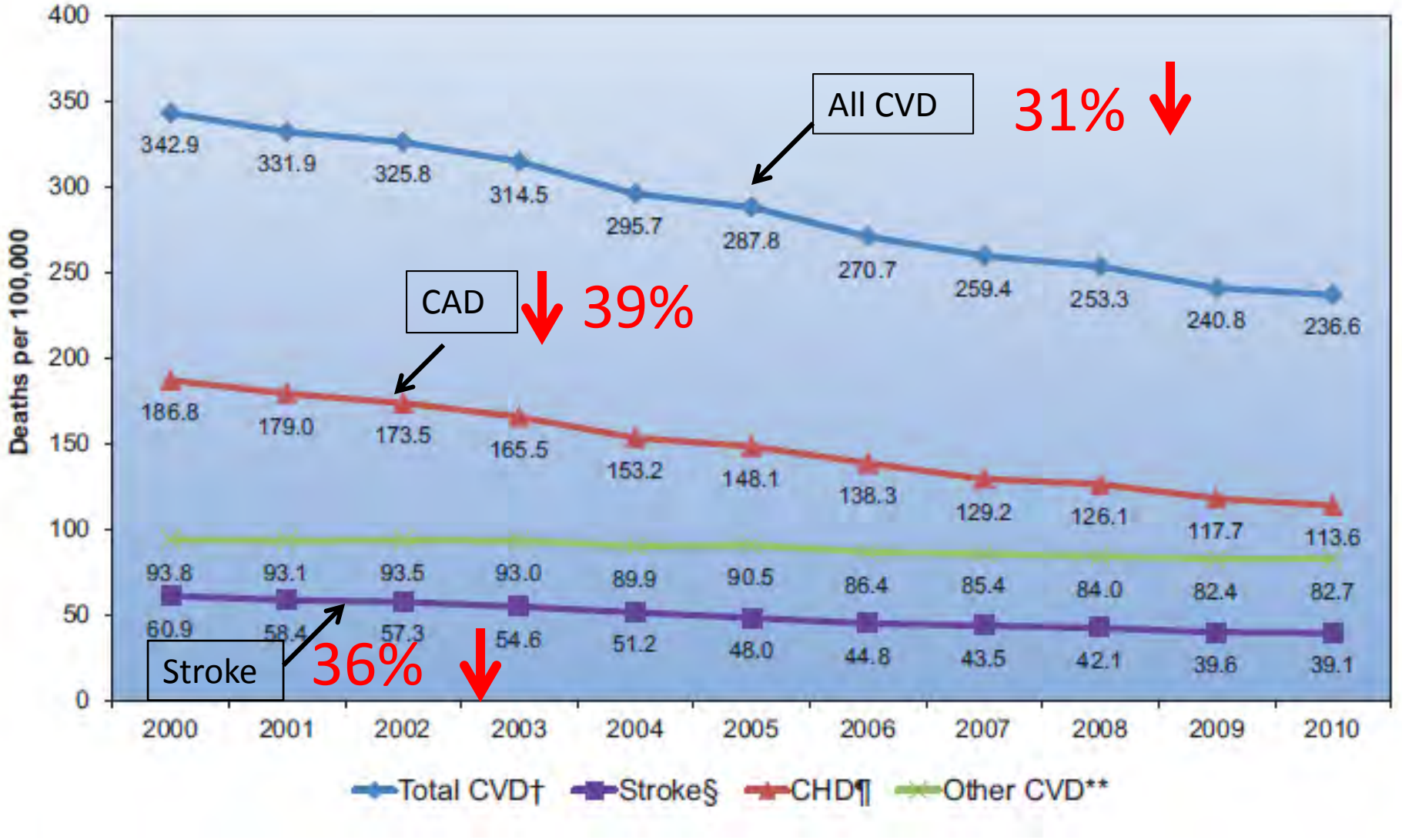
[a]Using a projected US population of 218.4 million adults ≥18 years of age with a measured lipid panel, 16.3% (projected 35.5 million adults) of whom were treated with lipid-modifying therapy. Among these, 49.3% (projected 17.5 million adults) were at high cardiovascular risk (CHD or CHD risk equivalents). Of these high-risk patients, 59.4% (projected 10.4 million adults) were treated with statin monotherapy for >90 days at the time of the lipid panel.

NHANES = National Health and Nutrition Examination Survey.

**1.** Jones PH et al. *J Am Heart Assoc.* 2012;1:e001800 doi: 10.1161/JAHA.112.001800.

# Mortality from ASCVD In USA (2000 through 2010)

National Center for Health Statistics



Why change a system that seems to be working?

Why change a system that has worldwide endorsement?

Does one not need evidence to introduce a new approach to such an important disease?

Thank you for listening!

# Statin compliance over time


**Figure 2** Barriers to statin compliance.[9] This figure is part of the National Lipid Association Toolkit and is also included in a supplement in the Fall 2013 issue of the National Lipid Association's Lipid Spin. SE, side effects.

Cohen, et al. J Clinical Lipidology (2013) 7:573

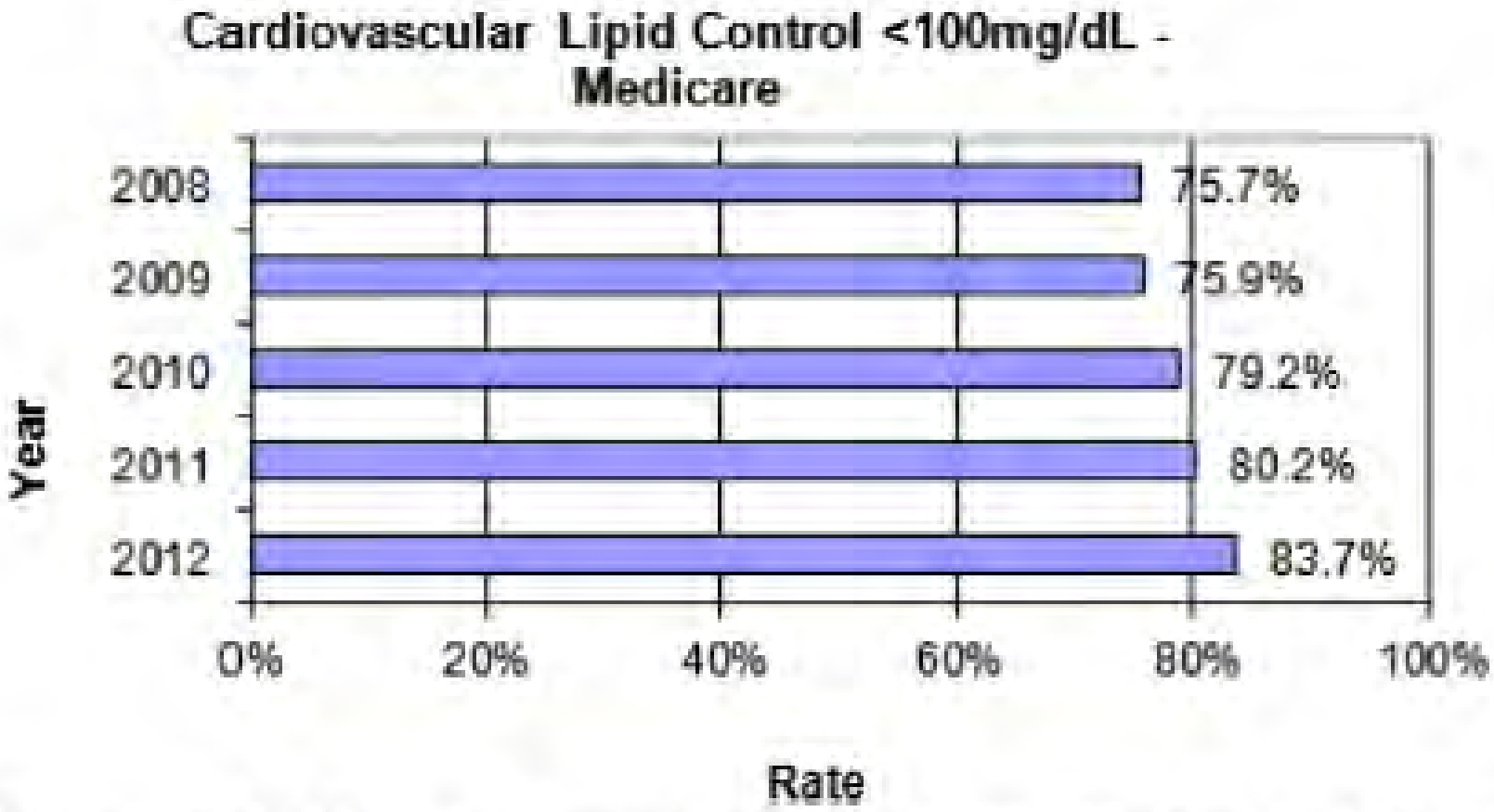
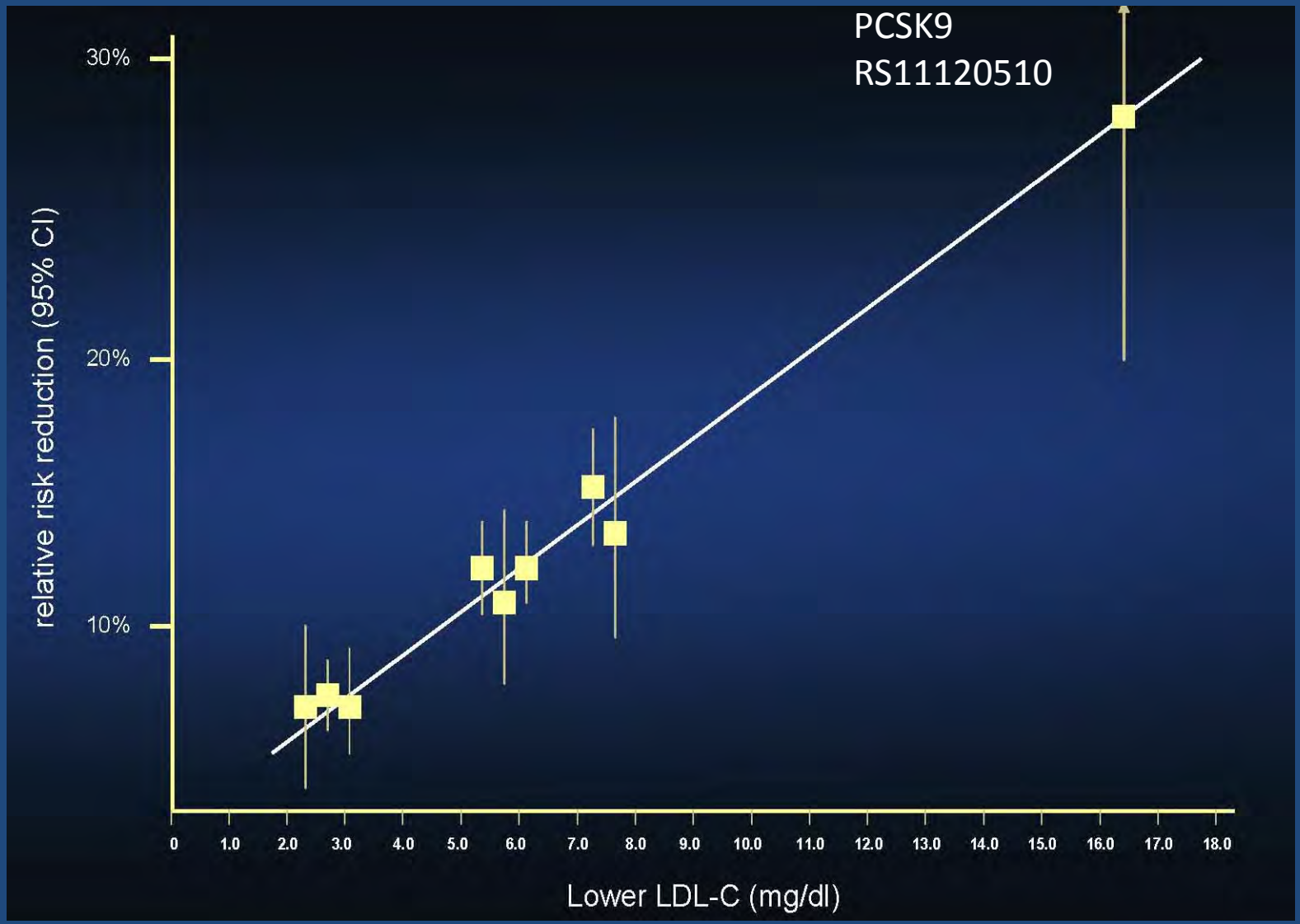



**Figure 10** Kaiser Permanente Southern California LDL-C <100 mg/dL among Medicare members with cardiovascular conditions, Healthcare Effectiveness Data and Information Set. LDL-C, low-density lipoprotein cholesterol.

Cohen, et al. J Clinical Lipidology (2013) 7:573

# Linear Effect on CHD (per unit lower LDL-C)




Ference BA et al. J Am Coll Cardiol. 2012;60:2631-9

# Genetic Variants and Statin Resistance

Z. Reiner Nutrition, Metabolism & Cardiovascular Diseases (2014) 24, 1057–1066

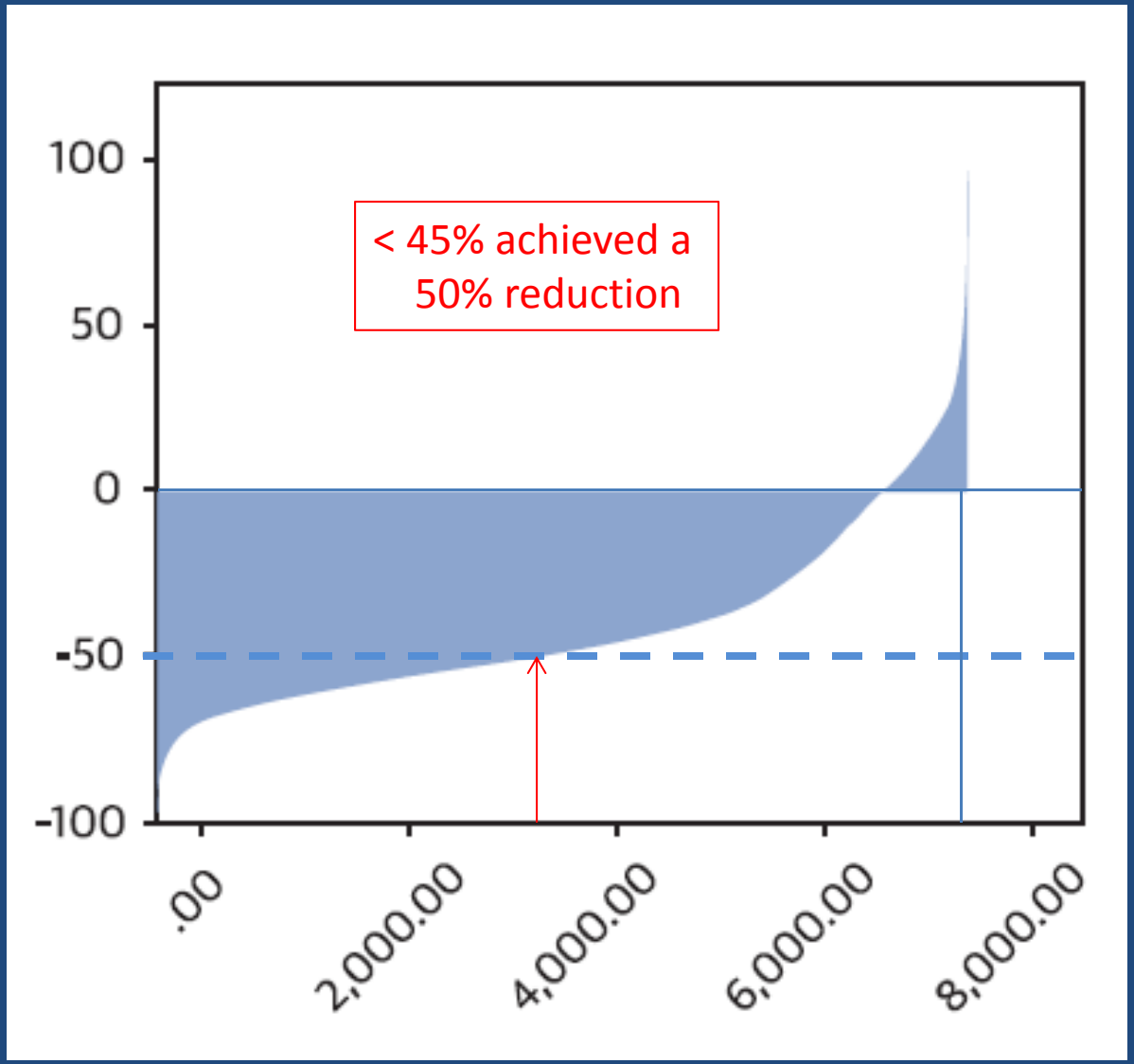
**Table 1** Possible genetic factors causing a reduced lipid-lowering response to statins.

| Gene | Mutation or polymorphism | Reference |
|---|---|---|
| MRP1 | c.3435T | [17] |
| MRP2 | c.1446G | [18] |
| ABCB1 | 2677T | [19] |
| OATP2B1 | c.3886 and c.521C | [24] |
| NPC1L1 | non-2/2 haplotype | [26] |
| HMG-CoA-R | heterozygous for SNP12, SNP2a | [10] |
| CYP7A1 | A 204C | [29] |
| PCSK9 | Gain-of-function | [35] |
| LDL-R | Ava II and Pvu II | [36] |
| ApoE | $E_2$ | [32] |
| CETP | rs1532624 | [42] |
| RHOA | H3B haplotype, rs 11716445 | [25] |
| TNF-α | C-857T | [43] |
| LPA | rs 10455872 | [32] |

# Rosuvastatin (20 mg) in Jupiter:

% LDL-C

Change with one year of treatment




Boekholdt et al.
JACC August 5, 2014

# How intensively do you treat? (Beyond RCTs)

- Answer:
- Reduce LDL-C by at least 50%.

  - Going below 40 mg/dL may not be a good idea.

  - In effect, a goal range :

    Treat if over 70 but not below 40 mg/dL

A concept not tested in RDBCTs. Expert opinion?

# Answer in ACC/AHA Guidelines

"Using goal setting for LDL-C or non-HDL-C has not been tested in randomized clinical trials".

"In these guidelines, we can not recommend using goals of therapy".

---

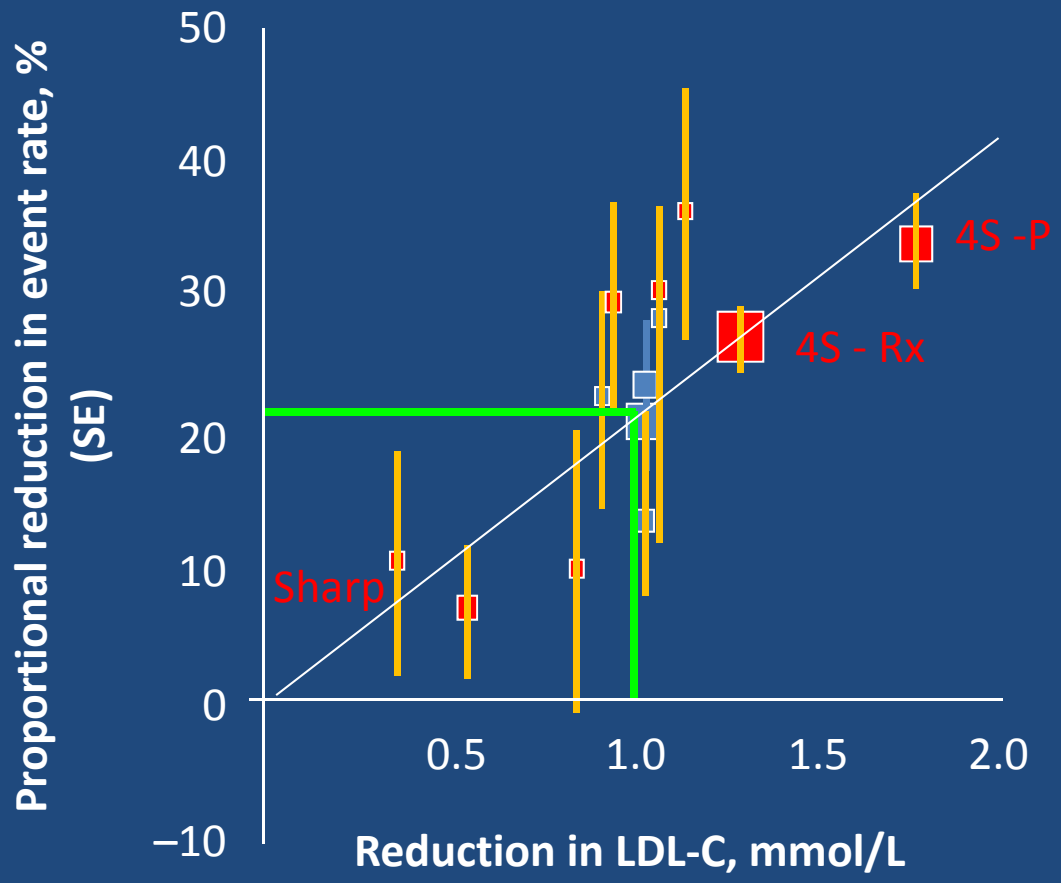
*Summary of recommendation:*

*Treat those with LDL-C > 190 mg/dL.*

*Treat patients represented in successful clinical trials.*

*Give as much statin as the patient will tolerate and that is within FDA approved dosing schedules.*

# Reduction in Major Vascular Events with Statin Therapy: Meta-Analysis of 14 Trials (n=90,056)




22% risk reduction per mmol/L (38.5 mg/dL)

P<0.0001

CTT Collaborators. *Lancet* 2005;366:1267–1278.

JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING

HNRCA

# Dietary Cholesterol Restriction: *Much Hype about Nothing*

Alice H. Lichtenstein, D.Sc.
Gershoff Professor of Nutrition Science and Policy
Tufts University, Boston, MA

Tufts UNIVERSITY

# Introduction

- Early work suggested that dietary cholesterol increases plasma total cholesterol and later LDL cholesterol concentrations in animal models and humans.
- Elevated total and LDL cholesterol concentrations are associated with increased CVD risk, hence, since the 1960's dietary guidelines have consistently recommended limiting food sources of cholesterol.
- Comfortable logic – dietary cholesterol translates directly to dietary cholesterol.

# Introduction

- More recent data suggests the effect of dietary cholesterol on lipoprotein profiles is mixed.
- Concern raised that some of the original findings may have been confounded by covarying with saturated fat and body weight, and very high levels of dietary cholesterol (600 mg to 900 mg/day).
- Current intakes are approaching recommended levels.

# Dietary Cholesterol (females)

| Dietary Reference Intake Group | Day 1: Mean | Day 1: SE |
|---|---|---|
| Females: 1-3 | 170 | (5.1) |
| Females: 4-8 | 182 | (5.3) |
| Females: 9-13 | 208 | (8.0) |
| Females: 14-18 | 203 | (7.9) |
| Females: 19-30 | 218 | (8.1) |
| Females: 31-50 | 238 | (6.0) |
| Females: 19-50 | 231 | (4.7) |
| Females: 51-70 | 228 | (8.2) |
| Females: 71 and over | 189 | (4.7) |
| Females: 50 and over | 217 | (5.2) |
| Females: 19 and over | 225 | (4.1) |

# Dietary Cholesterol (males)

| Dietary Reference Intake Group | Day 1: Mean | Day 1: SE |
|---|---|---|
| Males: 1-3 | 171 | (7.7) |
| Males: 4-8 | 195 | (6.3) |
| Males: 9-13 | 241 | (10.2) |
| Males: 14-18 | 303 | (11.9) |
| Males: 19-30 | 344 | (10.6) |
| Males: 31-50 | 374 | (9.3) |
| Males: 19-50 | 363 | (7.5) |
| Males: 51-70 | 339 | (7.2) |
| Males: 71 and over | 274 | (10.2) |
| Males: 50 and over | 323 | (5.8) |
| Males: 19 and over | 348 | (5.1) |

# Introduction

- Caveat;
  - Recommendations for the general population, not for individuals at very high risk of CVD

# Dietary Cholesterol

- 2013 AHA/ACC Lifestyle guideline committee concluded;

  *"There is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C."*

# Dietary Cholesterol

- 2015 Dietary Guidelines Advisory Committee concluded;

  *"The 2015 DGAC will not bring forward this recommendation [≤300 mg/day] because available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol, consistent with the conclusions of the AHA/ACC."*

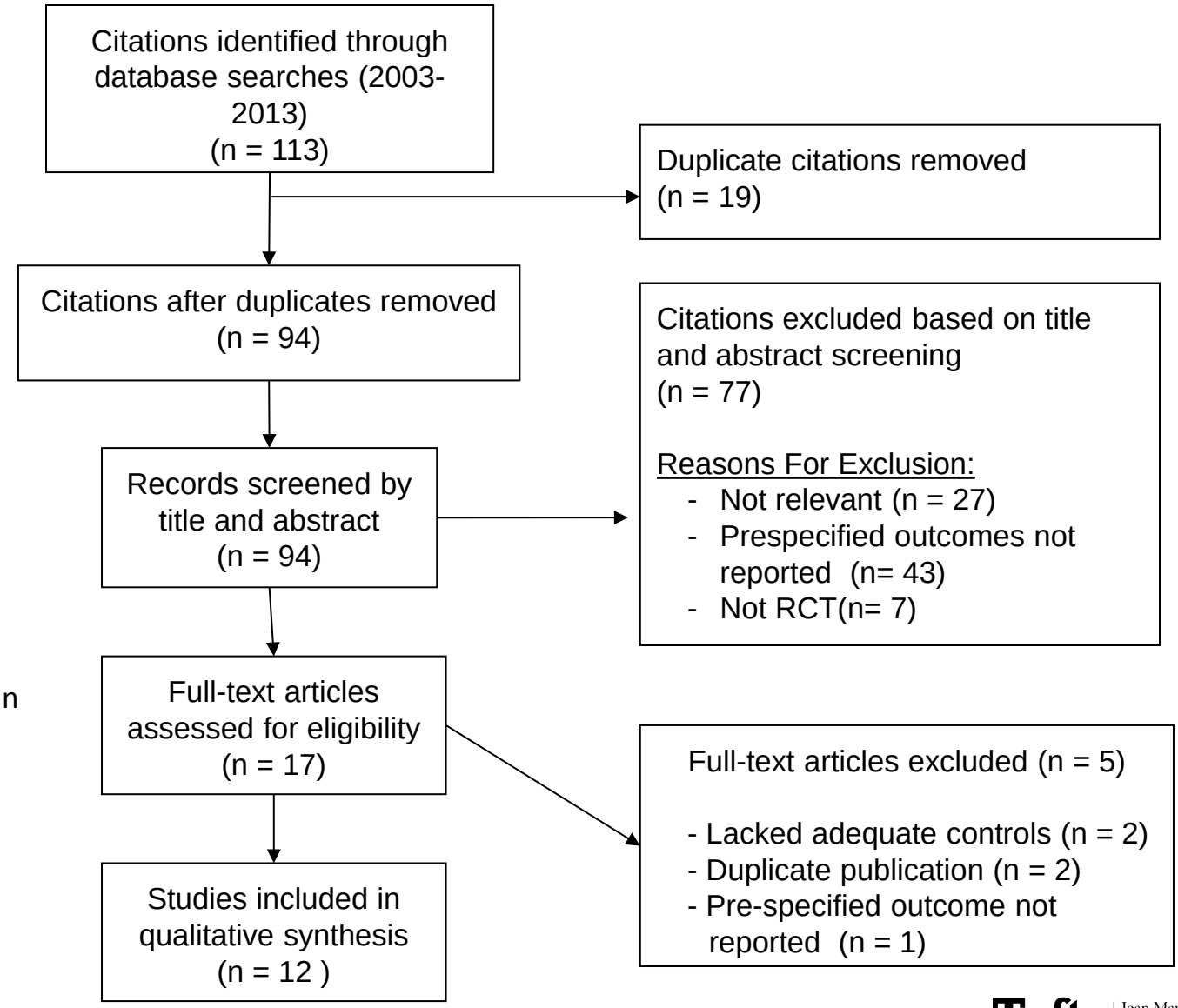
  "Cholesterol is not a nutrient of concern for overconsumption."

# Dietary Cholesterol and Lipoprotein Profiles

- Intervention studies (2003-2013);
  - Wide range study designs
  - Wide range inclusion criteria (age, weight status, insulin sensitivity)
  - Isocaloric, hypocaloric
  - Range intervention periods broad, 4-12 weeks
  - Range cholesterol intakes broad, 1-3 eggs/day
  - When findings significant, data were stratification on basis of cholesterol responsiveness or ABCG5 genotype

Griffin JD and Lichtenstein AH. Curr Nutr Rep 2013; 2:274

# Dietary Cholesterol




Griffin JD, Lichtenstein AH. Curr Nutr Rep 2013;2:274

# Dietary Cholesterol

- Strikingly high degree of variability in background diet, subject characteristics and study design.
- Within the context of current levels of dietary cholesterol intake, the effect on plasma lipids concentrations, with primary interest in LDL-C cholesterol concentrations, was modest and limited to population subgroups.

# Dietary Cholesterol

- For subgroups who are responsive, restrictions in dietary cholesterol intake are likely warranted.
- The biological determinants of inter-individual variability remains a relatively understudied area.

# Dietary Cholesterol

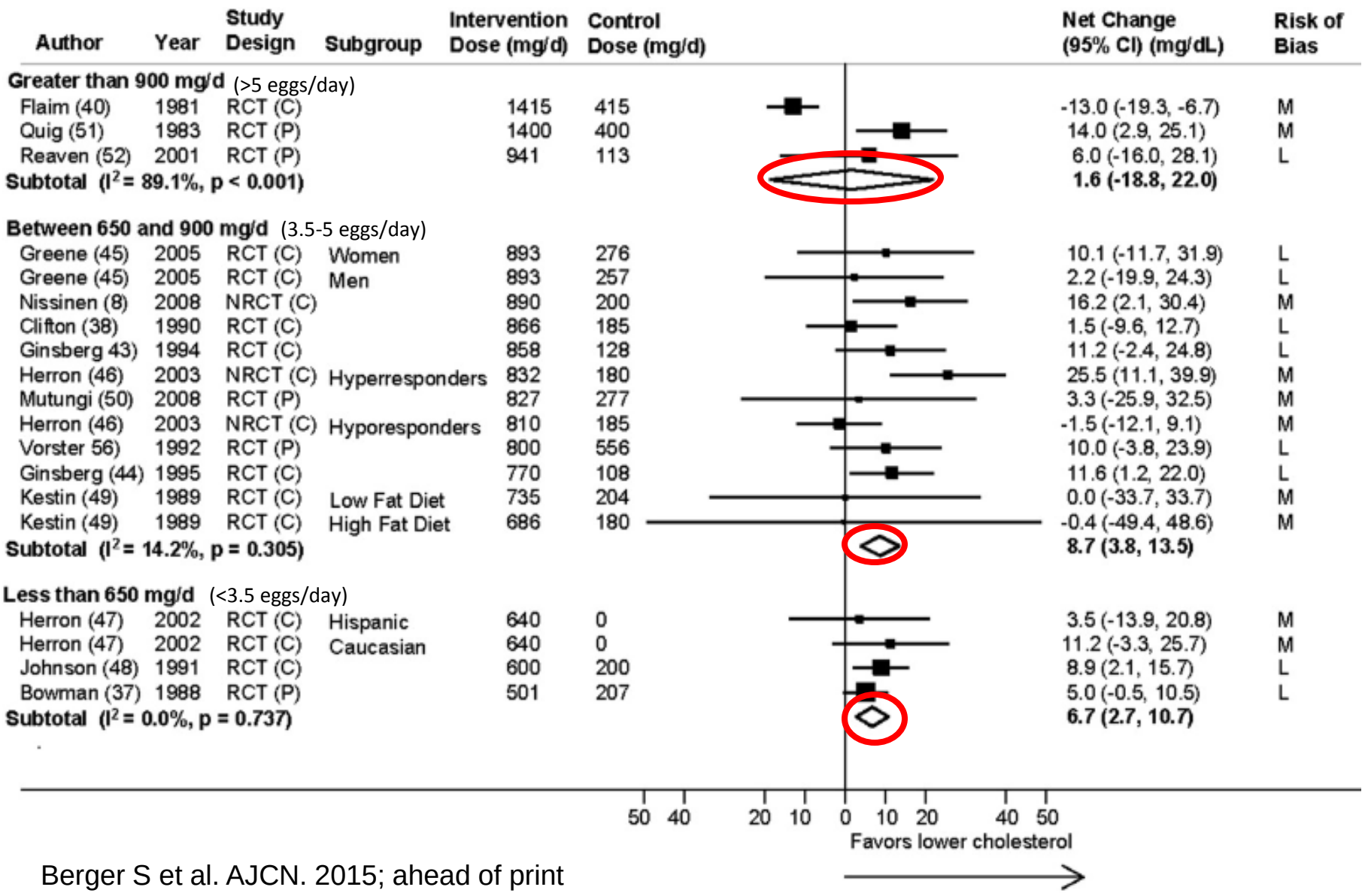
**AJCN. First published ahead of print June 24, 2015 as doi: 10.3945/ajcn.114.100305.**

## Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis[1–3]

*Samantha Berger,[4] Gowri Raman,[4] Rohini Vishwanathan,[5] Paul F Jacques,[5] and Elizabeth J Johnson[5]**

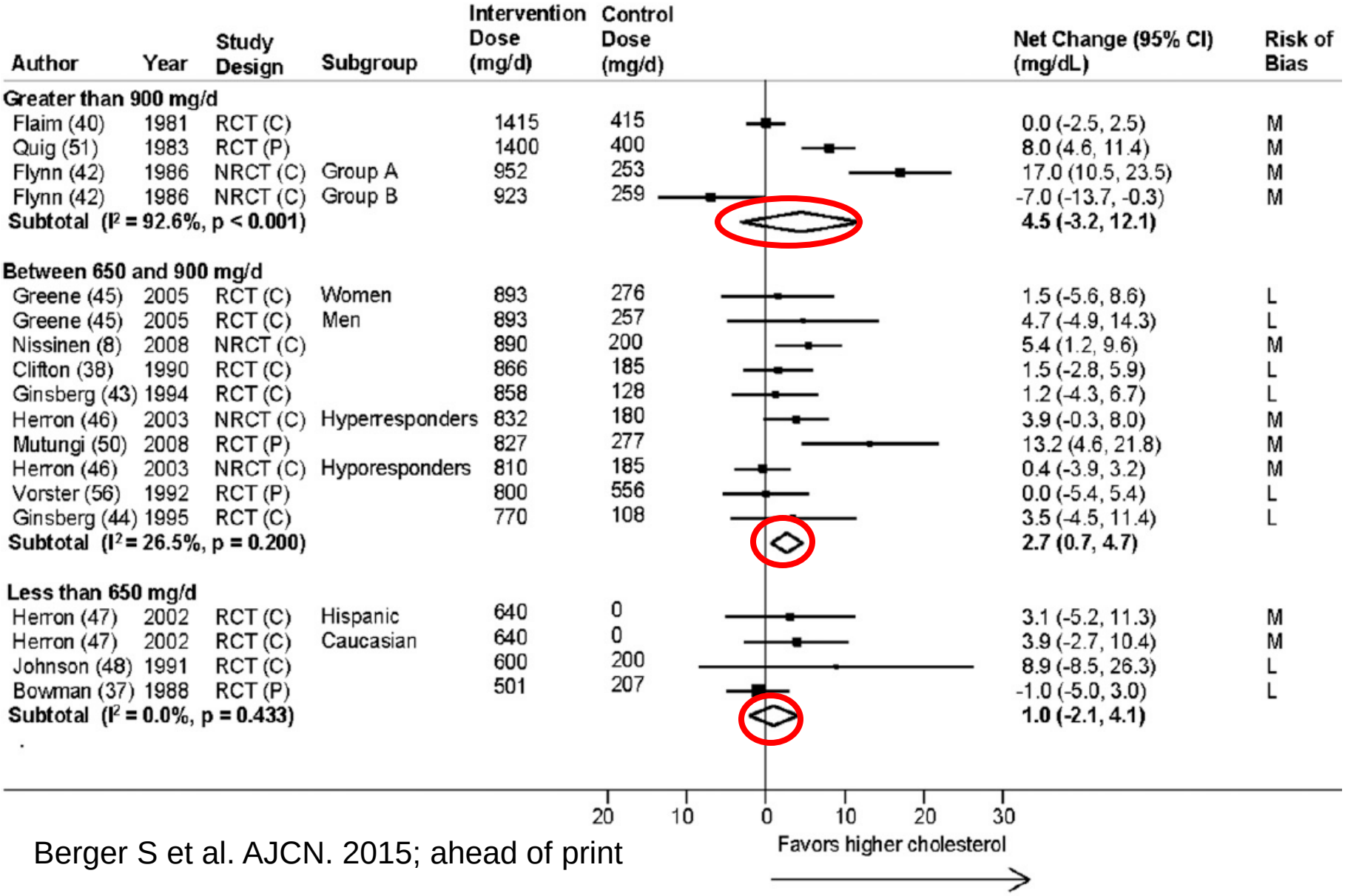
[4]Tufts Clinical Evidence Synthesis Center, Tufts Medical Center, Boston, MA, and [5]Jean Mayer USDA Human Nutrition, Research Center on Aging at Tufts University, Boston, MA

# Dietary Cholesterol – LDL-C



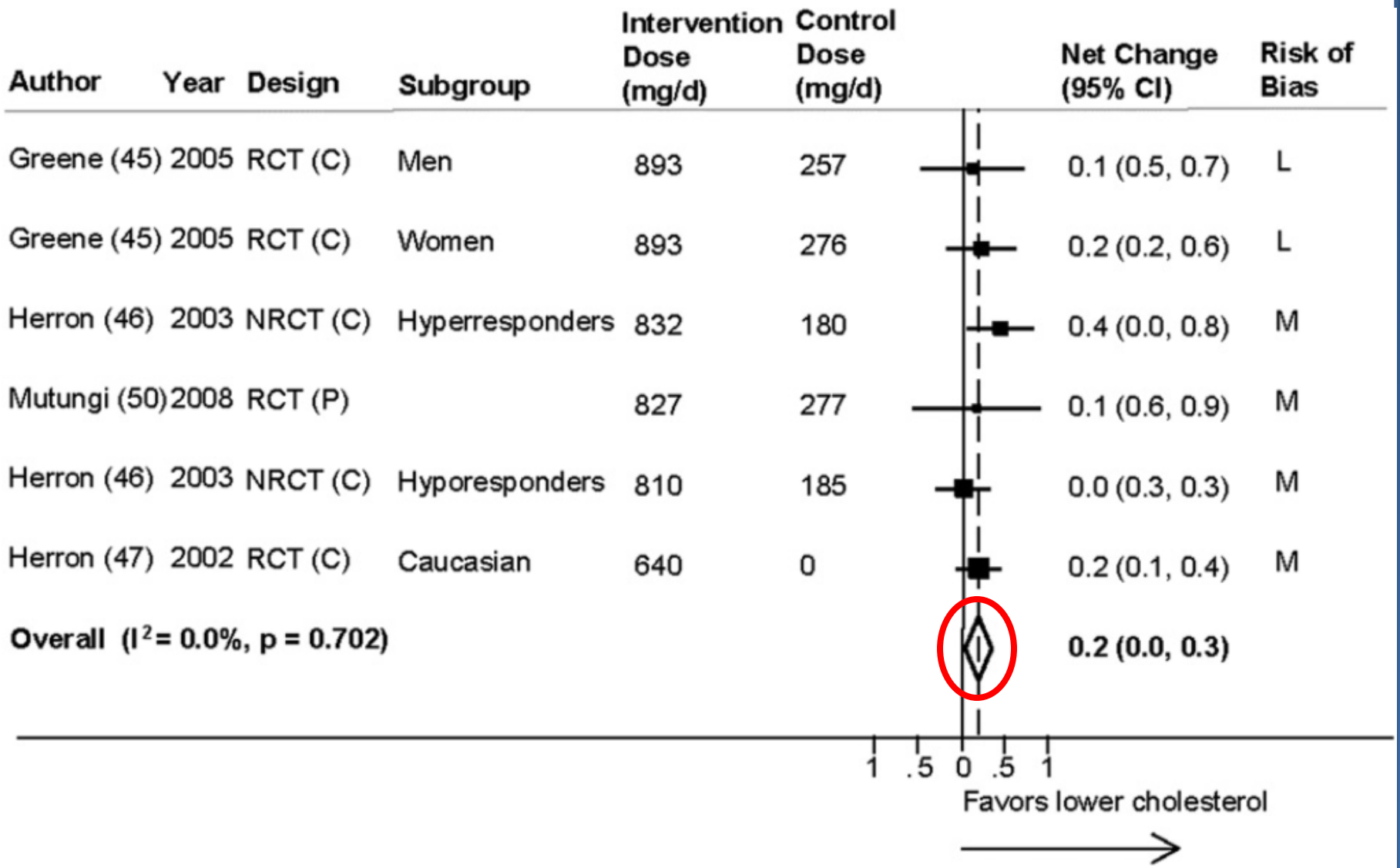

Berger S et al. AJCN. 2015; ahead of print

# Dietary Cholesterol – HDL-C




Berger S et al. AJCN. 2015; ahead of print

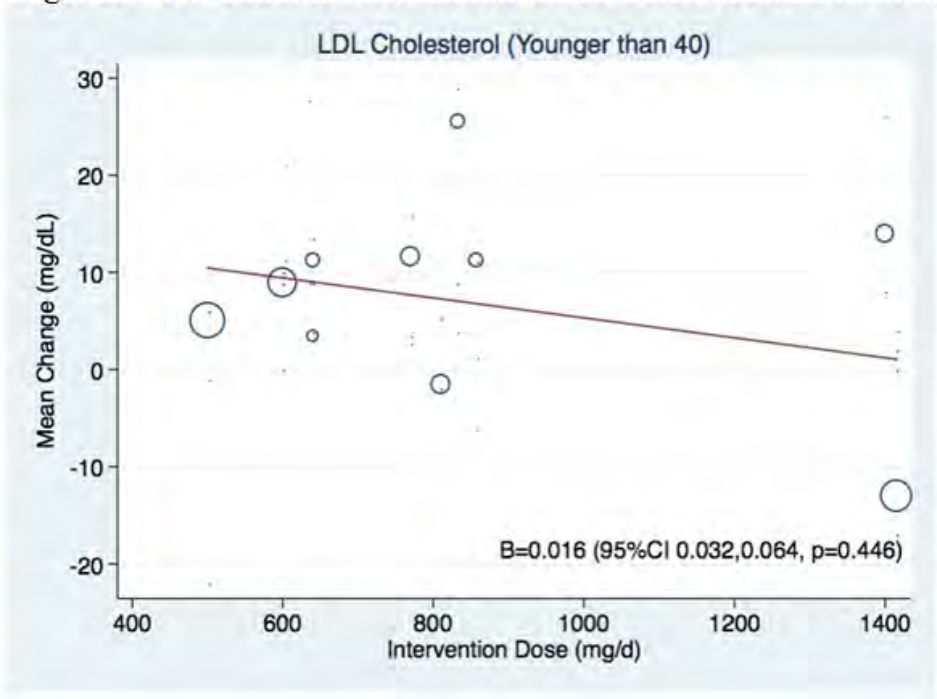
# Dietary Cholesterol – TC/HDL-C

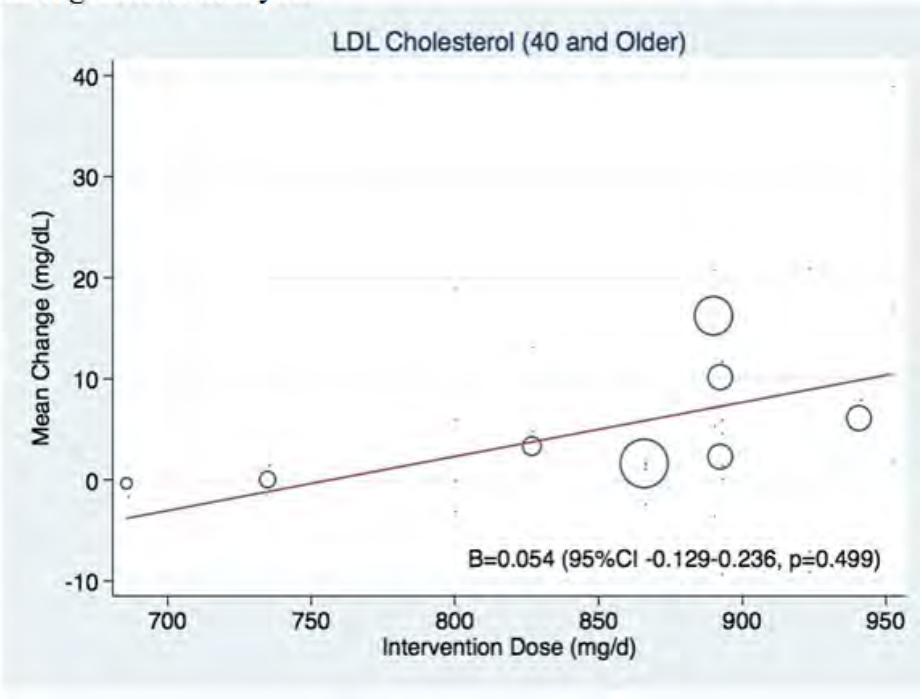



Berger S et al. AJCN. 2015; ahead of print

# Dietary Cholesterol – LDL-C

**Supplemental Figure 6.** Meta-regression of dietary cholesterol dose and mean change in LDL cholesterol stratified by age
Legends: *All extreme intervention doses were excluded from meta-regression analysis

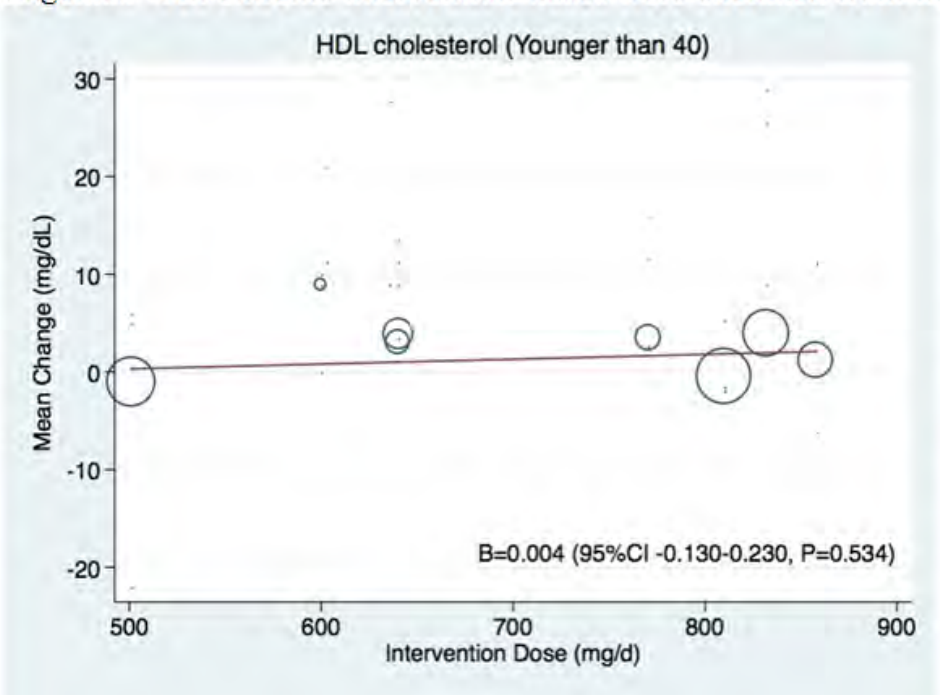


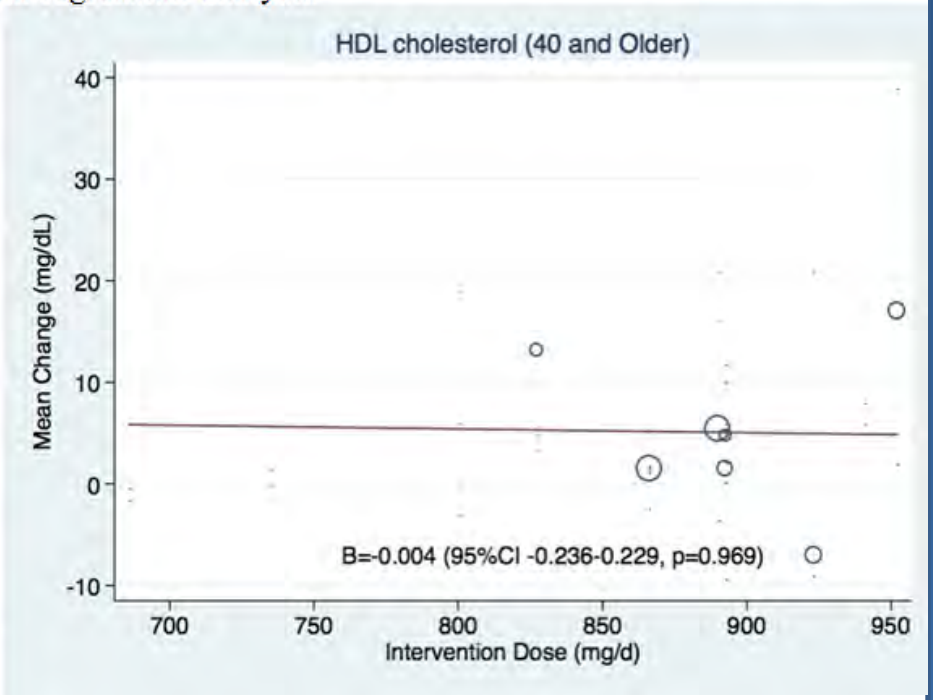




Berger S et al. AJCN. 2015; ahead of print

# Dietary Cholesterol – LDL-C

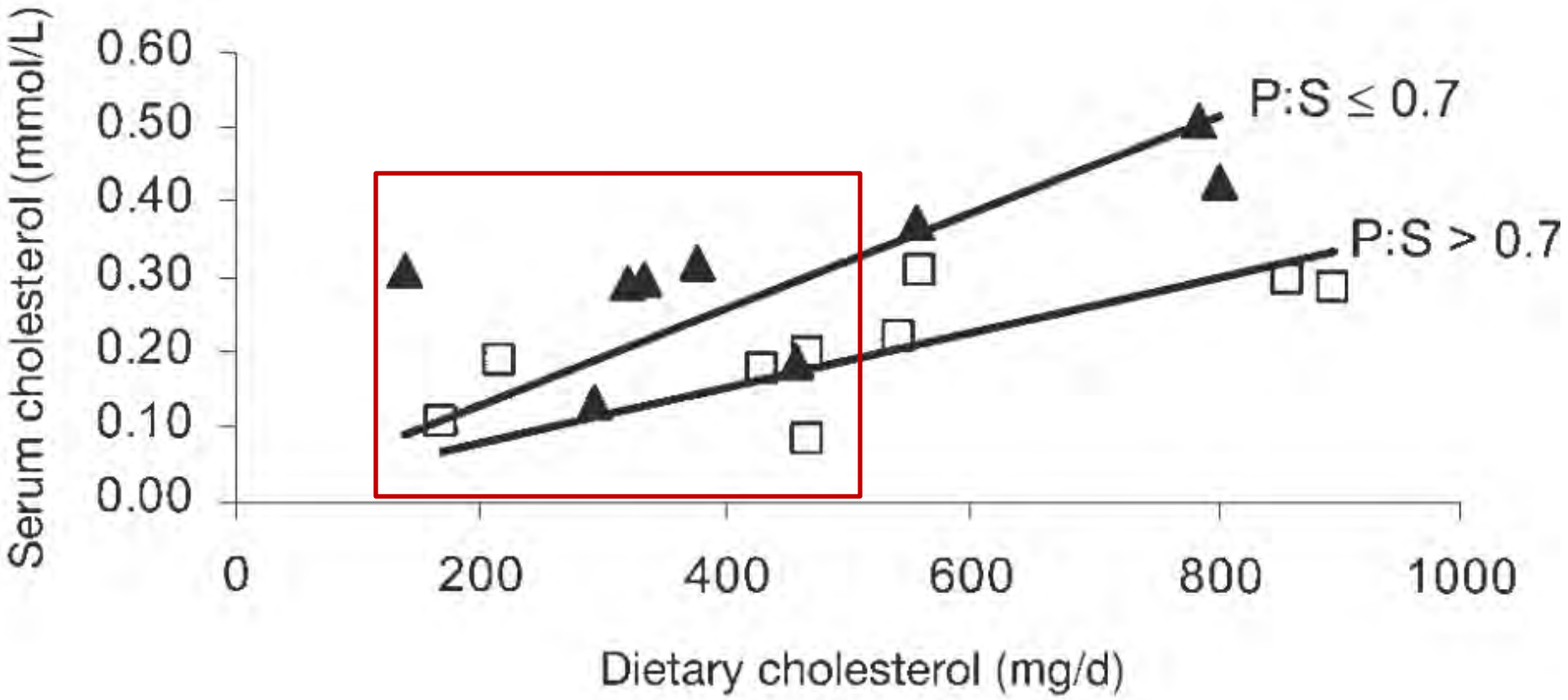
**Supplemental Figure 7.** Meta-regression of dietary cholesterol dose and mean change in HDL cholesterol stratified by age
Legends: *All extreme intervention doses were excluded from meta-regression analysis



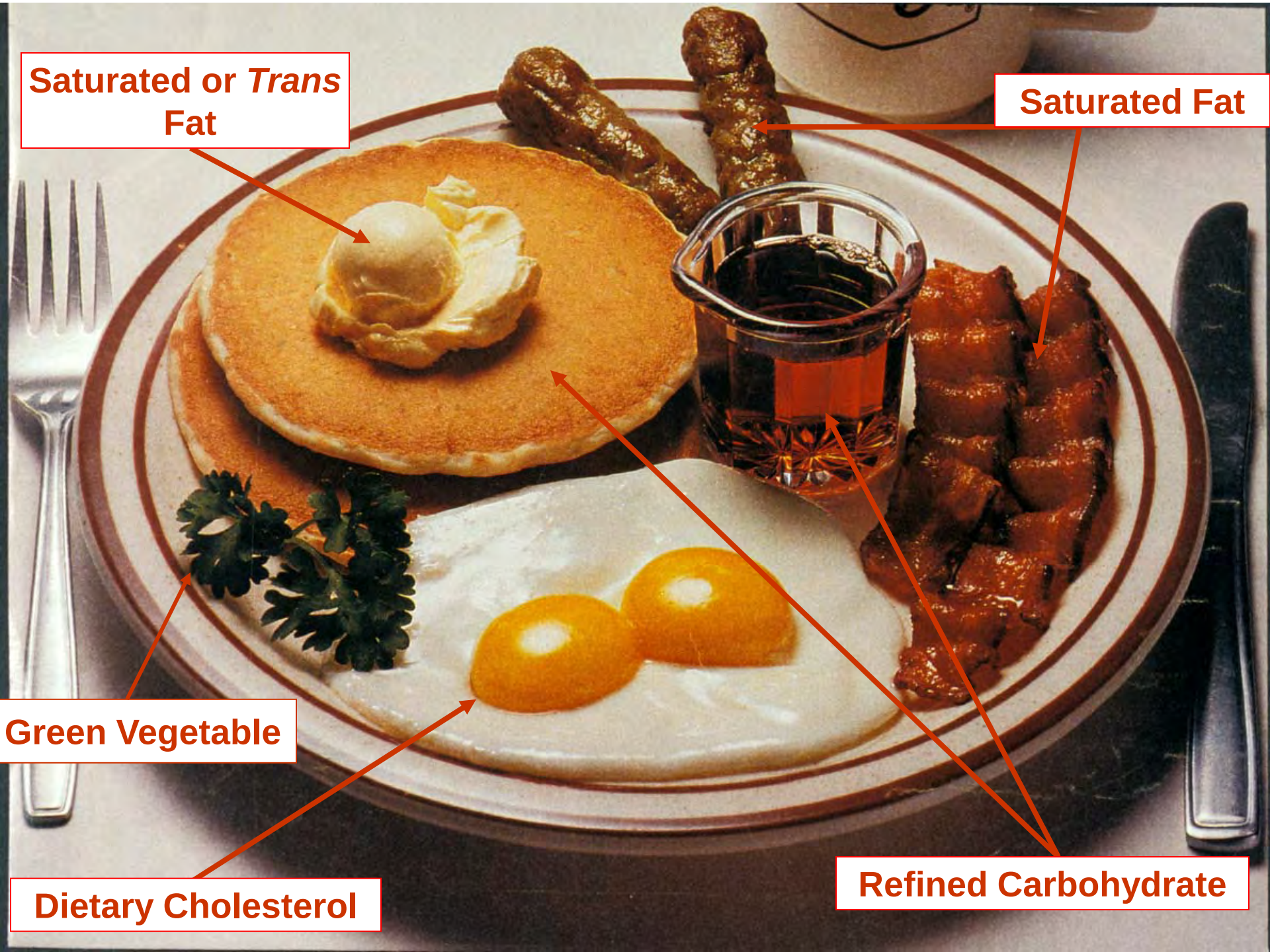

Berger S et al. AJCN. 2015; ahead of print

# Dietary Cholesterol – LDL-C




2 large eggs = ~372 mg cholesterol

Weggemans RM, Zock PL, Katan MB J Clin Nutr 2001;73:885


Saturated or *Trans* Fat
Saturated Fat
Green Vegetable
Dietary Cholesterol
Refined Carbohydrate

# Dietary Cholesterol – Summary

- Within the context of current dietary cholesterol intakes, the effect on LDL and HDL cholesterol concentrations modest, and appears to be limited to population subgroups.
- In these cases, restrictions in dietary cholesterol, *in addition to* achieving and maintaining a healthy body weight and adhering to a heart health diet  warranted.

# LOW CHOLESTEROL COOKING

• STEP • BY • STEP •


ULTRA HOLD
CHOLESTEROL
Conditioning Styling Gel

The Span of Clinical Lipidology: Bridging the Gap Between Research and Clinical Application

# Dietary Cholesterol Restriction is Still Important


Penny M. Kris-Etherton, PhD, RD, CLS, FNLA
Department of Nutritional Sciences
Penn State University

# Outline

- Dietary cholesterol recommendations
- Evidence to support dietary cholesterol restriction
  - Clinical Studies
  - Epidemiologic Studies (for persons with diabetes)
- Increasing prevalence of diabetes in the U.S.
- Food sources of dietary cholesterol
- Summary




# Recommendations for Dietary Cholesterol

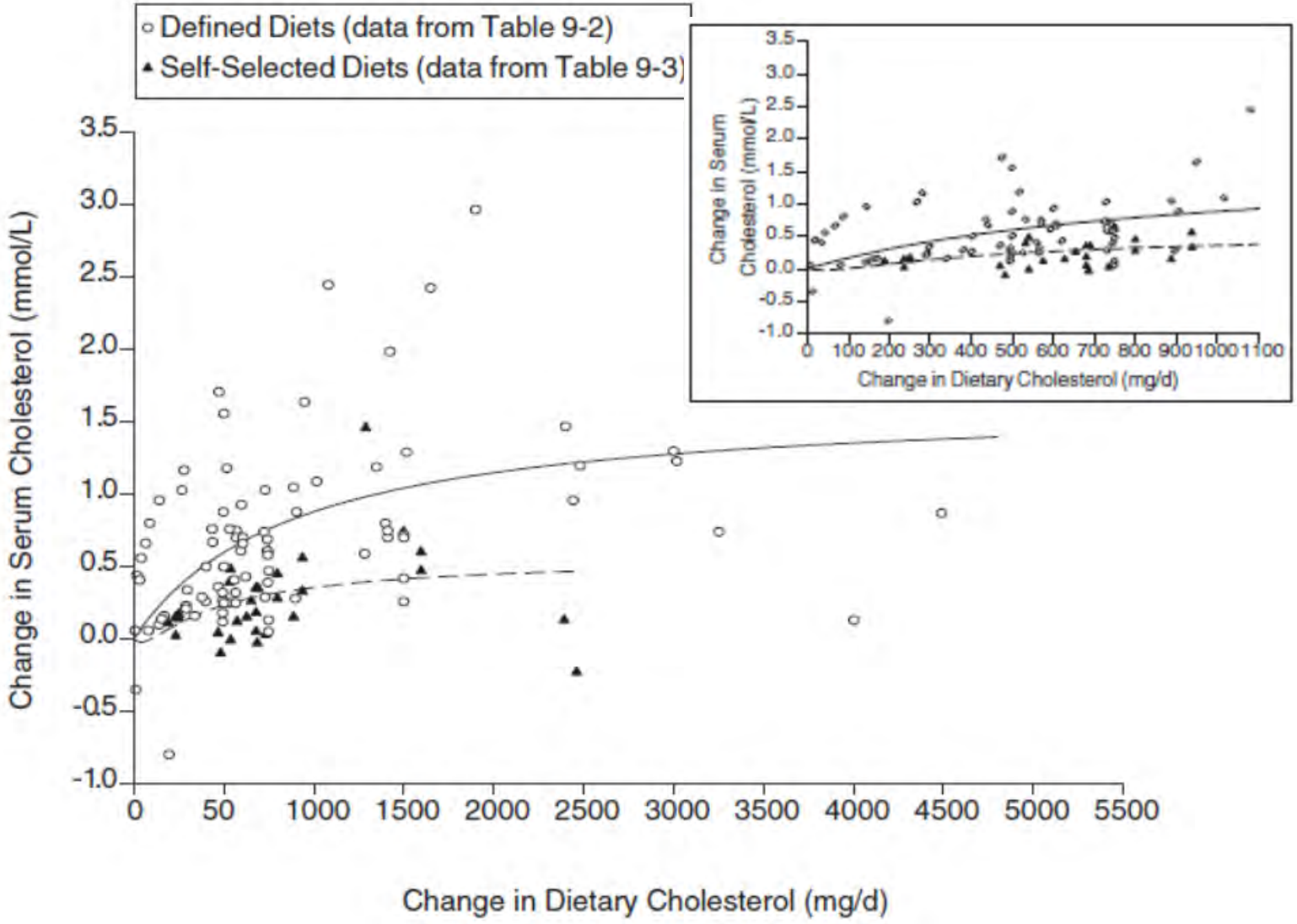
| Recommendations | Strength | Quality |
|---|---|---|
| The cardioprotective eating pattern should limit cholesterol intake to < 200 mg/day to lower levels of atherogenic cholesterol (LDL-C and non-HDL-C). | B | Moderate |
| There are individuals who are hyper-responders to dietary cholesterol because of genetic or other reasons. For known or suspected hyper-responders, further reduction in dietary cholesterol beyond the <200 mg/day that is recommended as part of the cardioprotective eating pattern for the management of dyslipidemia may be considered. Consumption of very low intakes of dietary cholesterol (near 0 mg/day) may be helpful for such individuals. | B | Low |

# Recommendations for Dietary Cholesterol

| Country | Organization | Cholesterol Recommendation |
|---|---|---|
| Australia | Heart Foundation | No cholesterol recommendations or upper limit. |
| International | WHO | **<300 mg** dietary cholesterol/day |
| International | International Atherosclerosis Society | **<200 mg** dietary cholesterol/day |
| United States | National Lipid Association | **<200 mg** dietary cholesterol/day |
| United States | American Diabetes Association (2013) | **<300 mg** dietary cholesterol/day |
| United States | 2010 Dietary Guidelines for Americans | Consuming **< 300 mg/day** can help maintain normal blood cholesterol levels.<br>Consuming **< 200 mg/day** can further help individuals at high risk of cardiovascular disease. |
| Canada | Heart and Stroke Foundation | Recommendation for healthy individuals is **300 mg of dietary cholesterol /day** with <7% of calories from SFA.<br>People with heart disease or diabetes are advised to limit themselves to **200 mg of dietary cholesterol/day** with < 7% of calories from SFA. |
| Europe | European Society for Cardiology | The cholesterol intake in the diet should ideally be **<300 mg/day** |

# Evidence to Support Recommendations to Restrict Dietary Cholesterol

## Clinical Studies



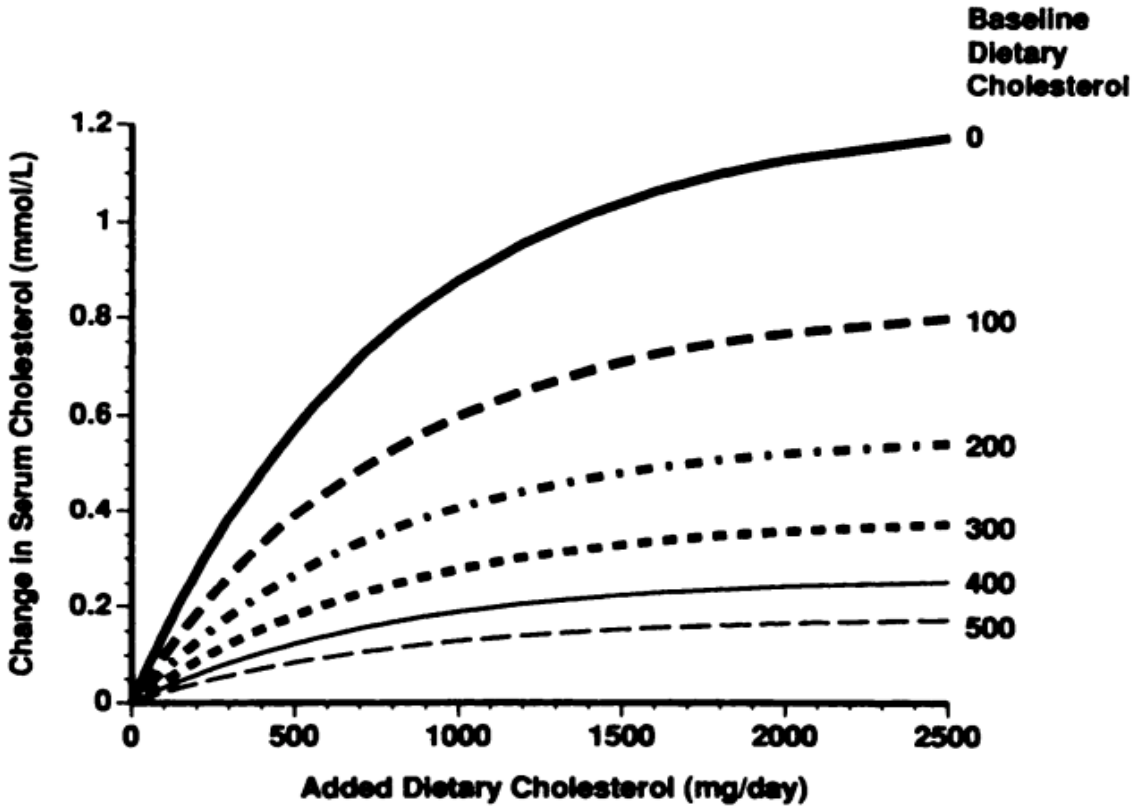

Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press; 2002/2005.

# Institute of Medicine

↑ Dietary cholesterol → ↑ LDL ≈ 2 mg/dL
100 mg/d (0.05 mmol/L)

- Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press; 2002/2005.

# Meta-Analysis: Dietary Cholesterol and Serum Cholesterol




Hopkins PN. Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. Am J Clin Nutr. 1992;55:1060-1070.

# A Dose-Response Study of the Effects of Dietary Cholesterol on Fasting and Postprandial Lipid and Lipoprotein Metabolism in Healthy Young Men

*Henry N. Ginsberg, Wahida Karmally, Maliha Siddiqui, Steve Holleran, Alan R. Tall, Steven C. Rumsey, Richard J. Deckelbaum, William S. Blaner, and Rajasekhar Ramakrishnan*

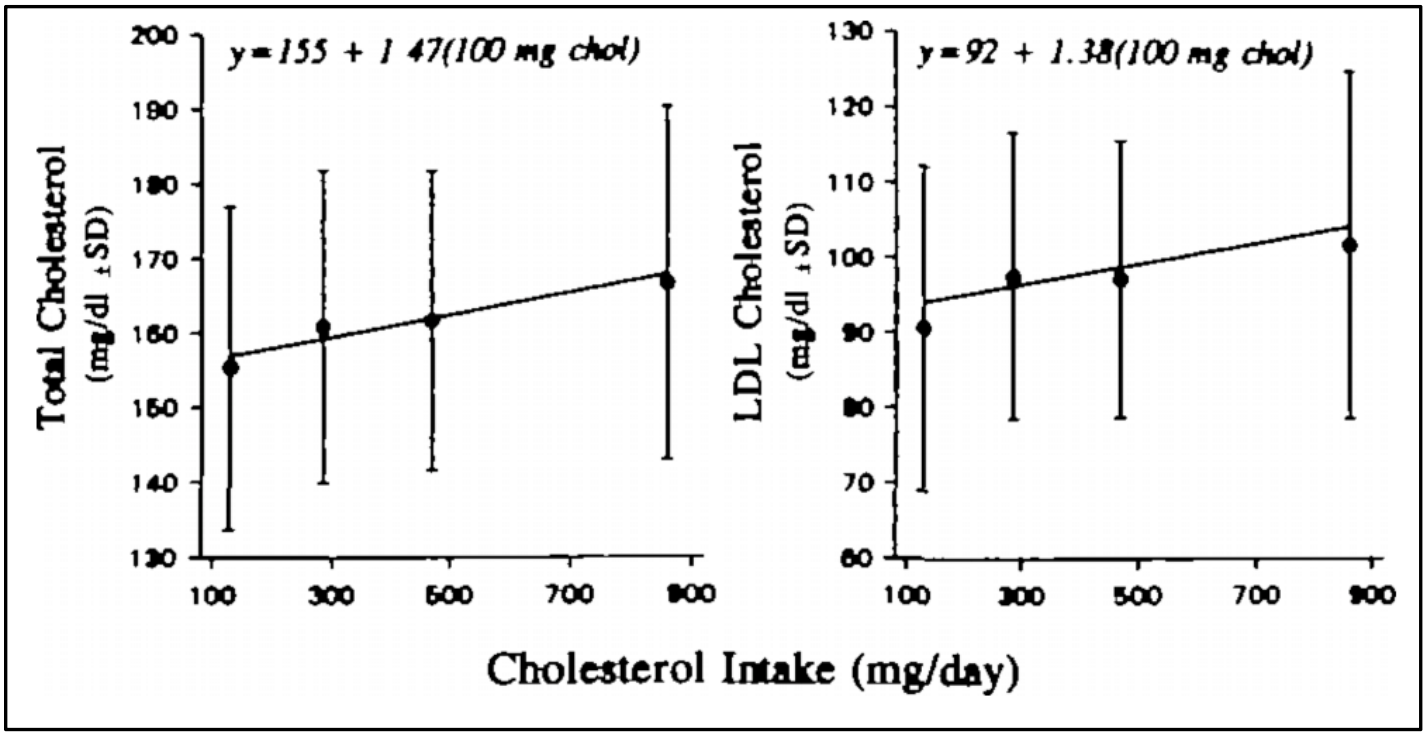
*Arterioscler Thromb*
*Volume 14:576-586*
*April 1994*

# Increases in Dietary Cholesterol Are Associated With Modest Increases in Both LDL and HDL Cholesterol in Healthy Young Women

*Henry N. Ginsberg, Wahida Karmally, Maliha Siddiqui, Steve Holleran, Alan R. Tall, William S. Blaner, and Rajasekhar Ramakrishnan*

*Arterioscler Thromb Vasc Biol*
*Volume 15:169-178*
*February 1995*

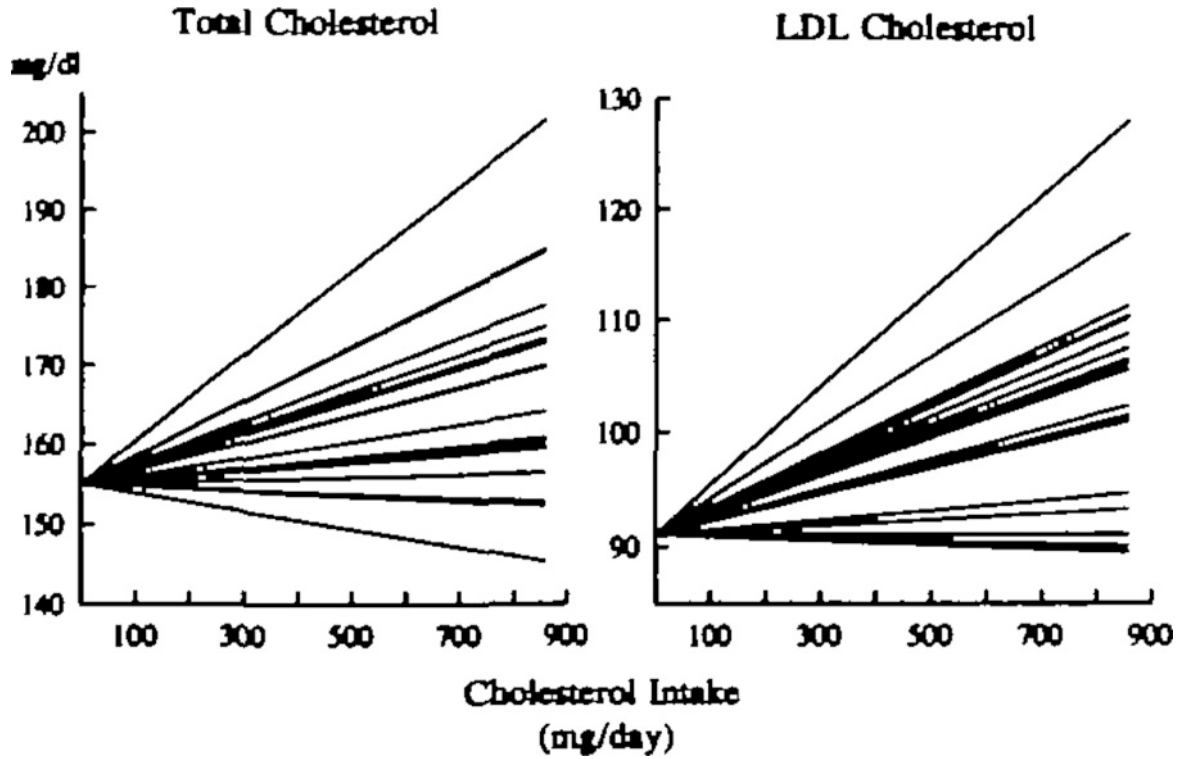
# Responses of Plasma Total (Left) and LDL-C (Right) to Increasing Dietary Cholesterol in Men




- 4 period controlled feeding crossover study of 20 healthy men
- Average total-C and LDL-C increased by 1.47 mg/dL and 1.38 mg/dL, respectively, for each 100 mg/day increase in dietary cholesterol.
- HDL-C also increased by 0.29 mg/dL per 100 mg/day of dietary cholesterol

Ginsberg et al. Arterioscler Thromb. 1994;14:576-86.

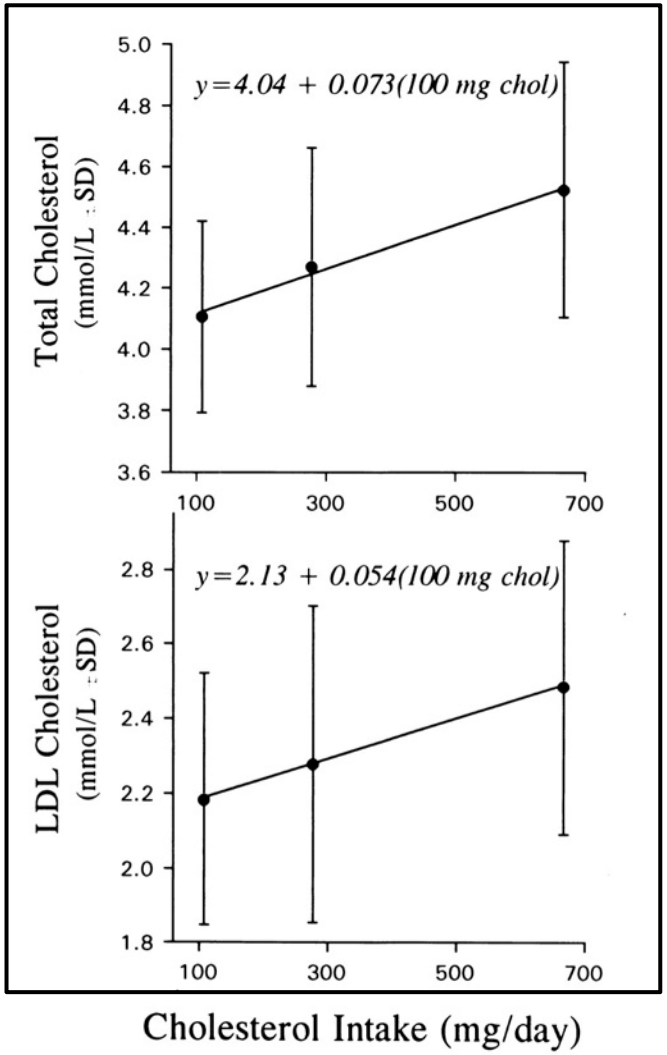
# Individual Variability in Dose-Response Relationship for Total-C and LDL-C with Increasing Dietary Cholesterol

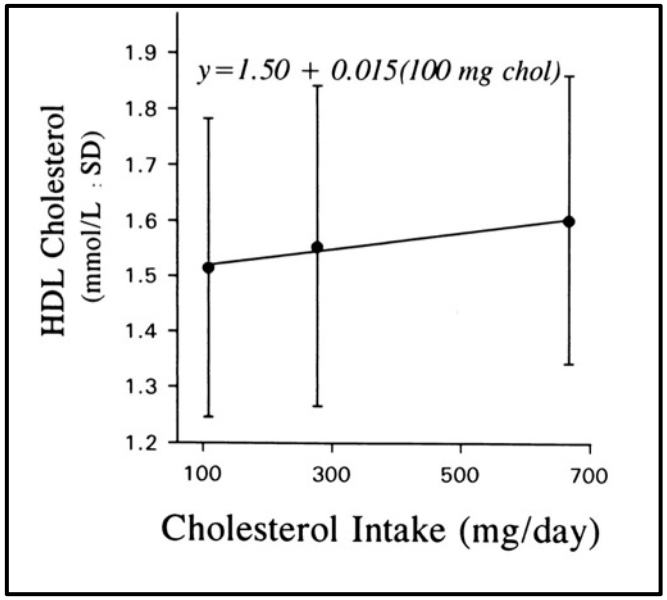



- The results indicate that there was a wide range of mostly positive responses to dietary cholesterol.
- However, three subjects actually had negative cholesterol responses to increasing eggs, while several responded at more than twice the mean.

Ginsberg et al. Arterioscler Thromb. 1994;14:576-86.

# Responses of Plasma Total, LDL-C And HDL-C to Increasing Dietary Cholesterol in Women




- Total fasting cholesterol concentrations increased by 2.81 mg/dL per 100 mg dietary cholesterol added to the diet per day (*P*=.001).
- LDL-C increased by 2.08 mg/dL per 100 mg/d dietary cholesterol (*P*=.003).
- HDL-C concentrations increased by 0.57 mg/dL per 100 mg/d dietary cholesterol (*P*<.04).

Ginsberg et al. Arterioscler Thromb Vasc Biol. 1995;15:169-178.

# Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis[1–3]

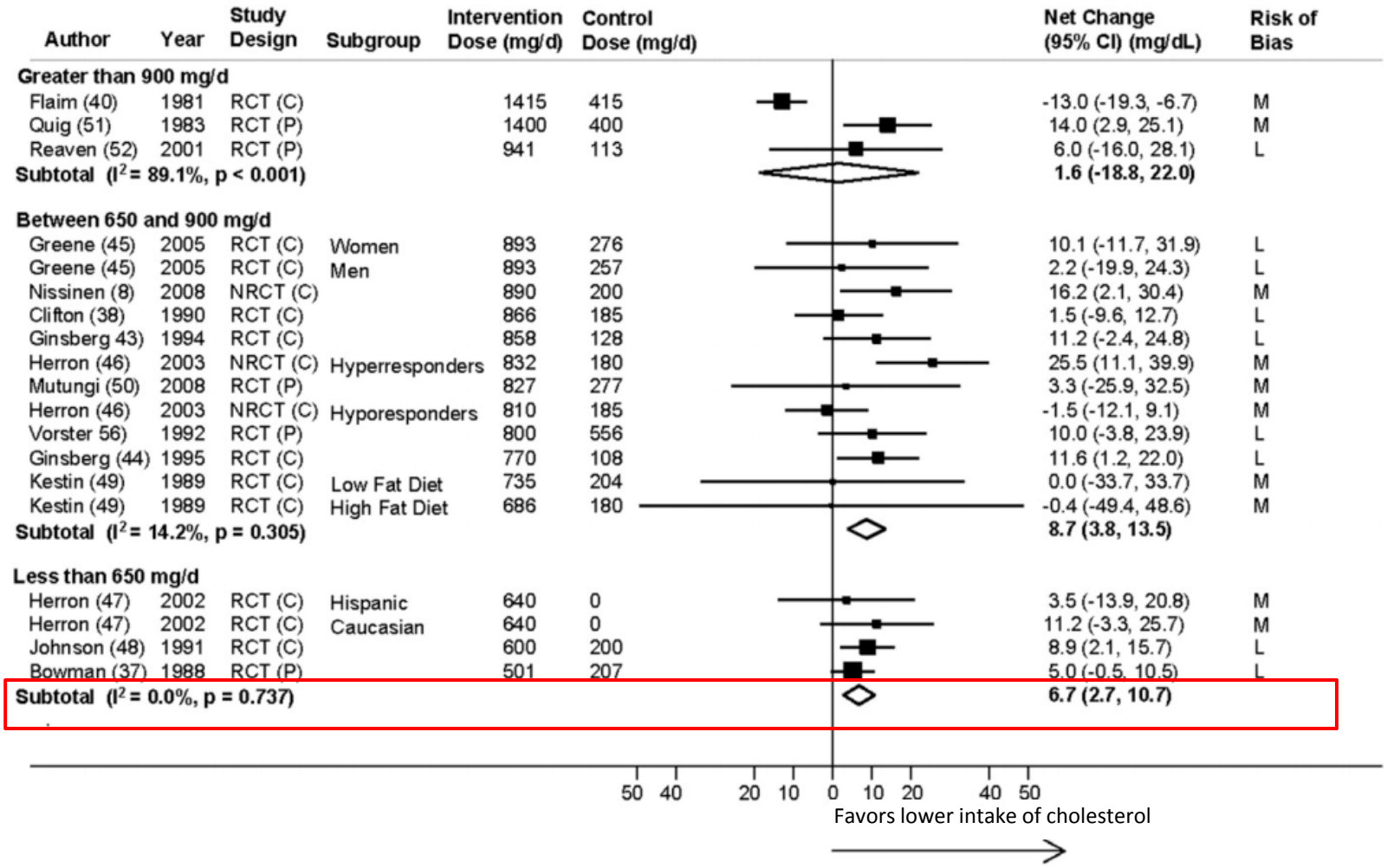
*Samantha Berger,[4] Gowri Raman,[4] Rohini Vishwanathan,[5] Paul F Jacques,[5] and Elizabeth J Johnson[5]**

[4]Tufts Clinical Evidence Synthesis Center, Tufts Medical Center, Boston, MA, and [5]Jean Mayer USDA Human Nutrition, Research Center on Aging at Tufts University, Boston, MA

- Forty studies (17 cohorts in 19 publications with 361,923 subjects and 19 trials in 21 publications with 632 subjects) published between 1979 and 2013 were included.
- Dietary cholesterol was not significantly associated with coronary artery disease, ischemic stroke or hemorrhagic stroke.
- Dietary cholesterol significantly increased both serum total cholesterol and LDL-C.
- Dietary cholesterol also significantly increased HDL-C and the LDL-C:HDL-C ratio.

Berger et al. Am J Clin Nutr. 2015;102:276-294.

# Meta-Analysis: Effect of Dietary Cholesterol on LDL-C by Strata of Intervention Dose



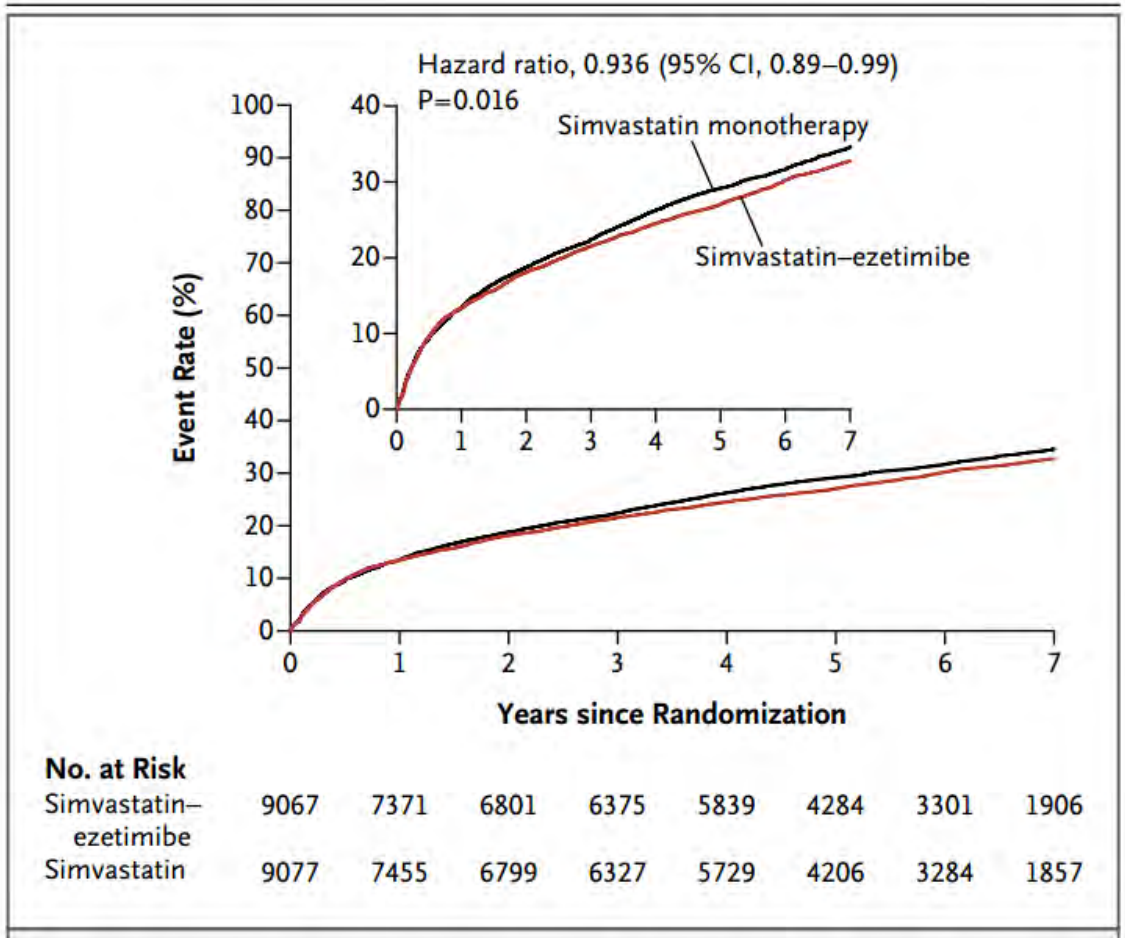

Berger et al. Am J Clin Nutr. 2015;102:276-294.

# Why do Some Studies Show Increased CVD Risk with Egg Consumption and Others do not?

"…most of the included studies were conducted in Western countries that traditionally have a relatively high-cholesterol diet. Thus, it is likely that the background cholesterol concentration among these participants was already high, so that changes in their cholesterol concentrations might not be sensitive to egg consumption."

Shin et al. Am J Clin Nutr 2013;98:146–59.

# Beneficial Effect of Ezetimibe + Simvastatin Compared with Simvastatin Alone on CVD Events in Patients with Diabetes (IMPROVE-IT)




- The median time-weighted average LDL-C level during the study was 53.7 mg/dL in the simvastatin–ezetimibe group, vs. 69.5 mg/dL in the simvastatin alone group (P<0.001).
- The Kaplan–Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, vs. 34.7% in the simvastatin alone group.

Cannon et al. N Engl J Med. 2015;372:2387-2397.

# Summary of Clinical Studies

- Dietary cholesterol increases LDL-C. For every 100 mg/day of dietary cholesterol, LDL-C increases ≈2 mg/dL.
- The increase in LDL-C is related to the baseline cholesterol intake. The lower the intake, the greater the response.
- There is marked variability in the response to dietary cholesterol.
- Small reductions in LDL-C decrease CVD events (in patients with diabetes).

# Evidence to Support Recommendations to Restrict Dietary Cholesterol

# Epidemiological Studies

# Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis[1–3]

*Jang Yel Shin, Pengcheng Xun, Yasuyuki Nakamura, and Ka He*

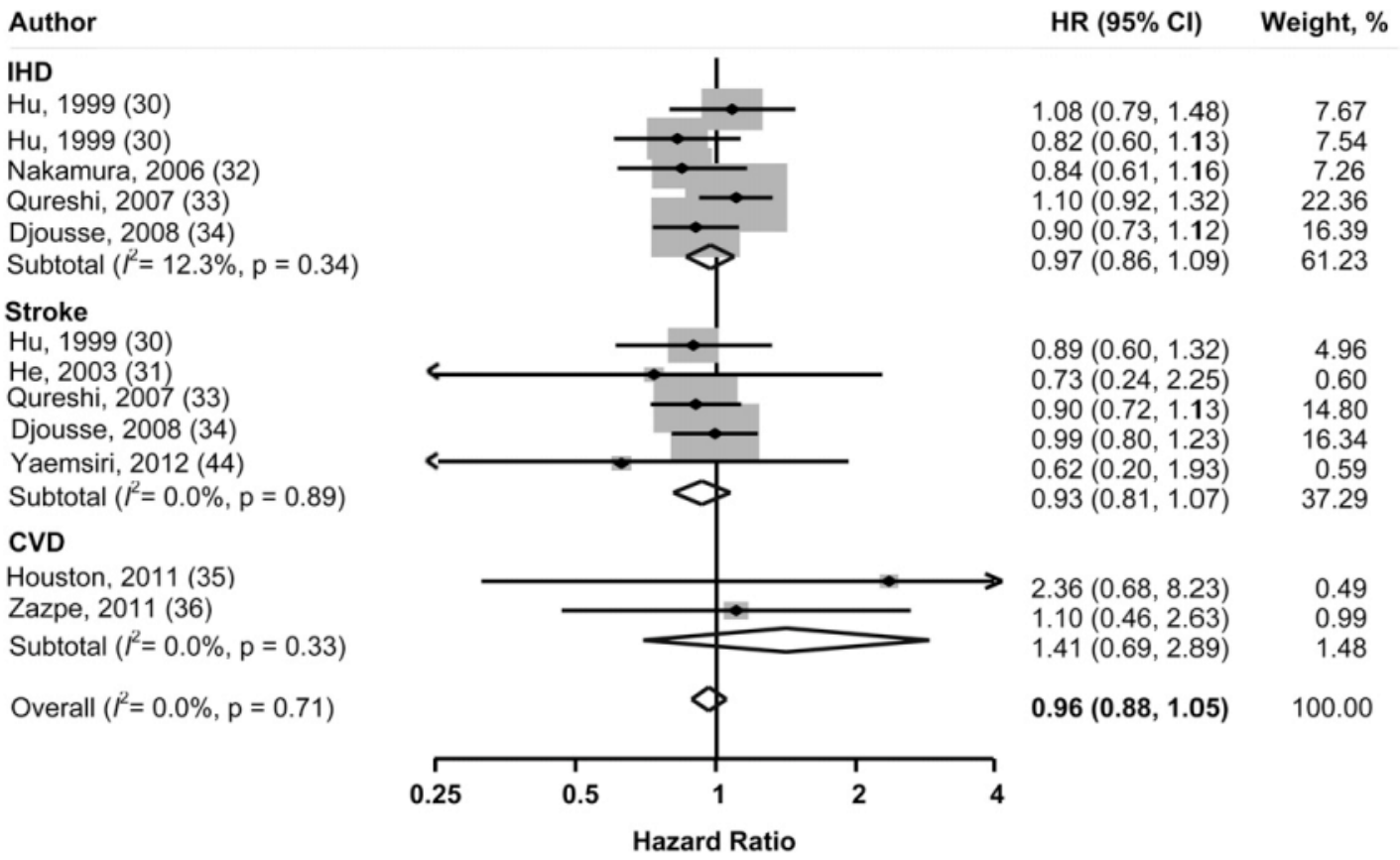
- A total of 22 independent cohorts from 16 studies were identified, including participants ranging in number from 1600 to 90,735 and in follow-up time from 5.8 to 20 years.
- Comparison of the highest category (≥ 1 egg/d) of egg consumption with the lowest (<1 egg/wk or never)

- **Conclusion**: egg consumption is not associated with the risk of CVD and cardiac mortality in the general population. However, egg consumption may be associated with an increased incidence of type 2 diabetes among the general population and CVD comorbidity among diabetic patients.

Shin et al. Am J Clin Nutr. 2013;98:146–59.

# Egg Consumption is not Associated with the Risk of CVD and Cardiac Mortality in the General Population

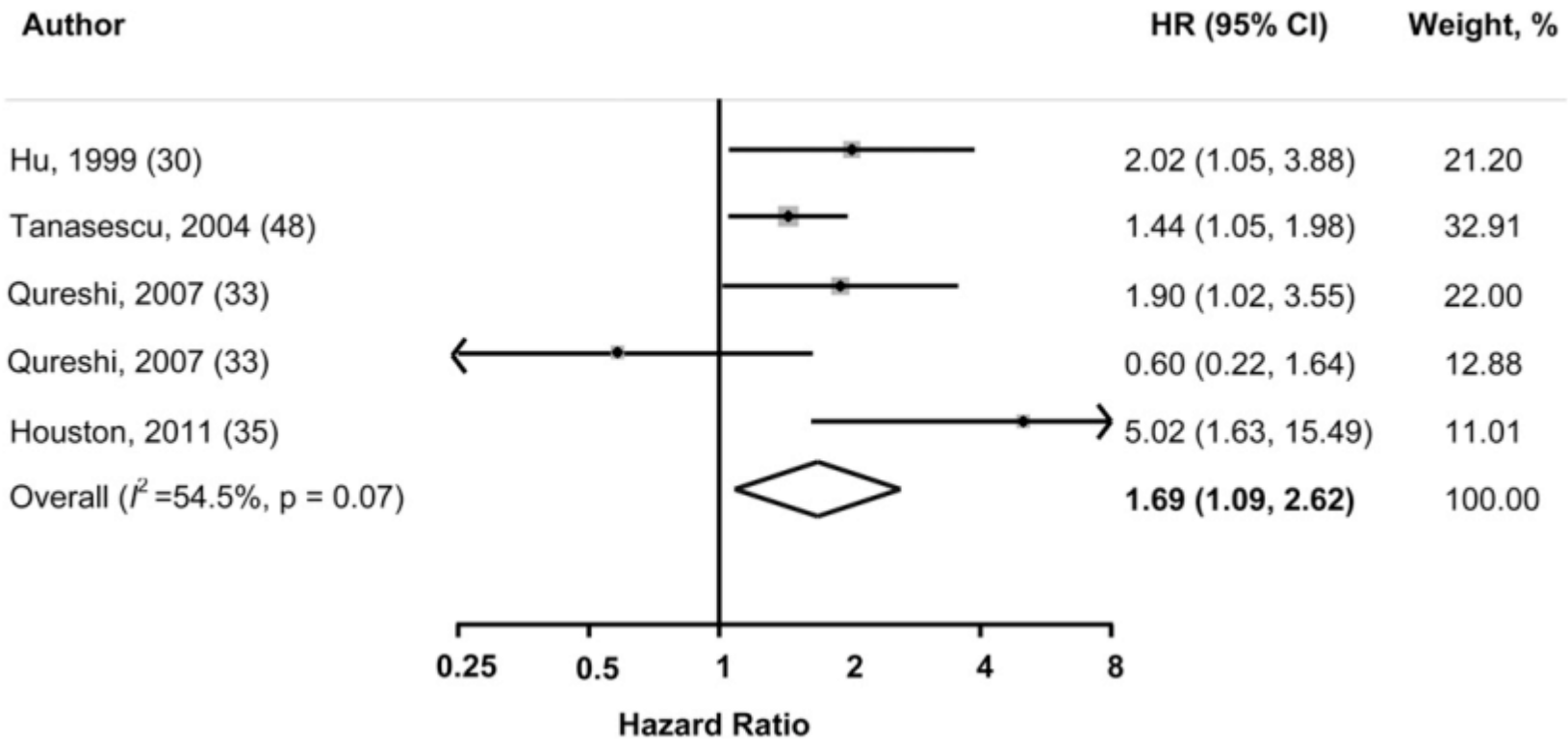
Pooled HRs and 95% Cis for Incident IHD, Stroke, and Overall CVD




Shin et al. Am J Clin Nutr. 2013;98:146–59.

# Egg Consumption May be Associated with Increased CVD Comorbidity Among Persons with Diabetes

Patients with diabetes who ate eggs more than once per day had a **69%** increased risk of developing CVD than were those who never ate eggs or ate eggs less than once per week




Shin et al. Am J Clin Nutr. 2013;98:146–59.

# A Prospective Study of Egg Consumption and Risk of Cardiovascular Disease in Men and Women

Frank B. Hu, MD
Meir J. Stampfer, MD
Eric B. Rimm, ScD
JoAnn E. Manson, MD
Alberto Ascherio, MD
Graham A. Colditz, MD
Bernard A. Rosner, PhD
Donna Spiegelman, ScD
Frank E. Speizer, MD
Frank M. Sacks, MD
Charles H. Hennekens, MD
Walter C. Willett, MD

- Two prospective cohort studies, the Health Professionals Follow-up Study (1986-1994) and the Nurses' Health Study (1980-1994) were evaluated.
- In an analysis of subgroups, there was an association between egg consumption and CVD in subjects with diabetes.
  - In men with diabetes, greater than 1 egg per day increased relative risk for CHD was **102%.**
  - In women, the increase in relative risk was **49%**.

Hu et al. JAMA. 1999;281(15):1387-1394.

# A Higher Intake of Dietary Cholesterol was Related to Increased CVD Risk Among Women (N=5672) with Type 2 Diabetes from The Nurses' Health Study

Each increase of 200 mg cholesterol/1000 kcal was associated with a **37%** increased risk of CVD, which was a composite of fatal CHD, nonfatal MI, and stroke

| | Q1 | Q2 | Q3 | Q4 | Q5 | P for trend |
|---|---|---|---|---|---|---|
| Median (mg/1000 kcal) | 139.6 | 175.9 | 203.6 | 236.5 | 298.2 | |
| RR | | | | | | |
| Age-adjusted | 1.00 | 0.96 (0.73, 1.26) | 1.18 (0.91, 1.53) | 1.24 (0.96, 1.60) | 1.63 (1.28, 2.09) | <0.001 |
| Multivariate* | 1.00 | 0.99 (0.74, 1.31) | 1.19 (0.91, 1.54) | 1.18 (0.89, 1.57) | 1.47 (1.10, 1.95) | 0.003 |
| Adjusted for fatty acids** | 1.00 | 0.96 (0.72, 1.27) | 1.16 (0.88, 1.54) | 1.14 (0.85, 1.53) | 1.39 (1.04, 1.88) | 0.01 |

* Adjusted for age, smoking, postmenopausal hormone use, parental history of myocardial infarction before 60 y of age (yes or no), alcohol intake, moderate/vigorous activities, BMI, total caloric intake, protein intake, fiber intake, multivitamin use, vitamin E supplement use, and medication use

** After additional adjustment for trans and monounsaturated fats

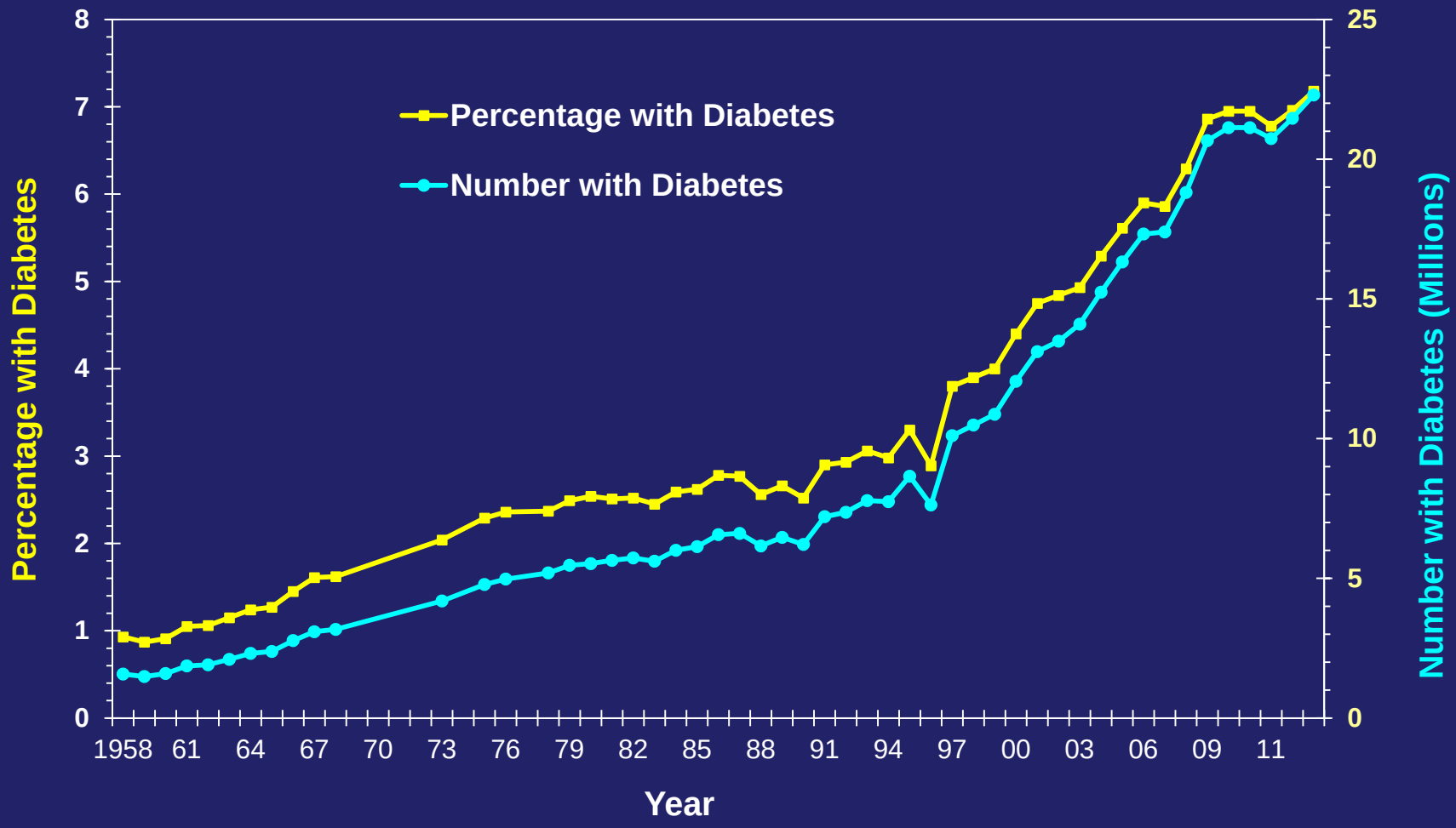
Tanasescu et al. Am J Clin Nutr. 2004;79:999-1005.

# Summary of Epidemiological Studies

- Egg consumption is not associated with the risk of CVD and cardiac mortality in the general, healthy population.

- In persons with diabetes, egg consumption and dietary cholesterol significantly increase risk of CVD.

# Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2013




CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

# Trends in Prevalence of Prediabetes in the US, 1988 and 1999-2010

| Definitions of prediabetes | Prevalence (± SE), % | | |
|---|---|---|---|
| | NHANES 1988-1994 (n=15,578) | NHANES 1999-2004 (n=12,726) | NHANES 2005-2010 (n=15,135) |
| Calibrated $HbA_{1c}$ of 5.7% - 6.4% | 5.8 ± 0.35 | 11.9 ± 0.47 | 12.4 ± 0.42 |
| Fasting subsample | | | |
| FPG level of 5.6-6.9 mmol/L (100-125 mg/dL) | 25.2 ± 0.84 | 26.3 ± 1.14 | 28.7 ± 0.87 |
| $HbA_{1c}$ level of 5.7% - 6.4% | 6.0 ± 0.40 | 11.9 ± 0.56 | 12.4 ± 0.50 |

In 2012, 86 million Americans age 20 and older had prediabetes; this is up from 79 million in 2010.

# Current Intake of Dietary Cholesterol in the US, NHANES 2011-2012

| Gender | Cholesterol Intake |
|---|---|
| Males 20+ | 338 mg/day |
| Females 20+ | 229 mg/day |
| Combined | 282 mg/day |

DATA SOURCE: What We Eat in America, NHANES 2011-2012.

# Top Food Sources of Dietary Cholesterol based on NHANES, 2005-2006

| Food Item | Contribution to intake (%) | Cumulative Contribution |
|---|---|---|
| Eggs and egg mixed dishes | 24.6 | 24.6 |
| Chicken and chicken mixed dishes | 12.5 | 37.1 |
| Beef and beef mixed dishes | 6.4 | 43.6 |
| Burgers | 4.6 | 48.2 |
| Regular cheese | 4.2 | 52.4 |
| Sausage, franks, bacon, and ribs | 3.9 | 56.3 |
| Other fish and fish mixed dishes | 3.4 | 59.7 |
| Grain-based desserts | 3.3 | 63.0 |
| Dairy desserts | 3.2 | 66.3 |
| Pasta and pasta dishes | 3.1 | 69.3 |
| Pizza | 2.9 | 72.2 |
| Mexican mixed dishes | 2.9 | 75.1 |
| Cold cuts | 2.7 | 77.8 |

http://appliedresearch.cancer.gov/diet/foodsources/cholesterol/table1.html

# Conclusions

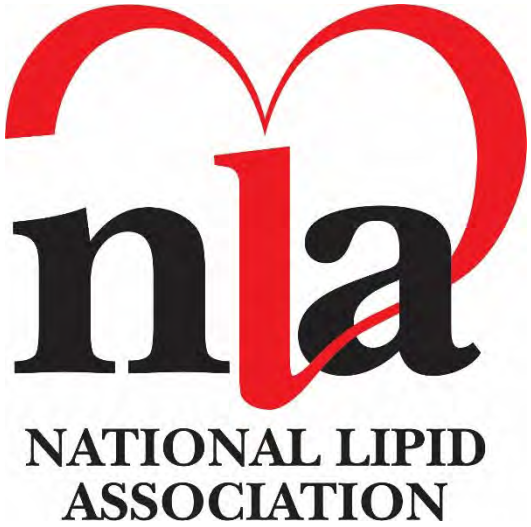
- Scientific evidence supports NLA recommendation for <200 mg/day of dietary cholesterol
- Variability in response to dietary cholesterol makes it difficult to identify hyper-responders
- Even small reductions in LDL-C have CVD benefits
- The growing prevalence of diabetes is a further justification for restriction of dietary cholesterol


Thank You!

NATIONAL LIPID ASSOCIATION

# NLA Recommendations for Patient-Centered Management of Dyslipidemia

## Part 2




# NLA Expert Panel Steering Committee

**Terry A. Jacobson, MD (Chair)**
**Kevin C. Maki, PhD**
**Carl E. Orringer, MD**
**Peter H. Jones, MD**

**On Behalf of the NLA Part 2**
**Recommendations Expert Panel Working Group**

# NLA Expert Panel Working Group*

**Judith Aberg, MD**
**Harold Bays, MD**
**Piers Blackett, MD**
**Julie Bolick, MS, RDN**
**Lynne Braun, PhD, CNP**
**W. Virgil Brown, MD**
**Jonathon S. Coblyn, MD**
**Jeffrey Curtis, MD, MS, MPH**
**Stephen Daniels, MD, PhD**
**Martha Daviglus, MD, PhD**
**Thomas Dayspring, MD**
**Prakash Deedwania, MD**
**Sarah DeFerranti, MD**
**Carl J. Fichtenbaum, MD**
**Mary R. Dicklin, PhD**
**Keith Ferdinand, MD**
**Catherine McNeal, MD, PhD**
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**Ralph La Forge, MSc**
**Rae-Ellen W. Kavey, MD, MPH**
**Katherine Liao, MD, MPH**
**Christopher T. Longenecker, MD**
**J. Antonio G. Lopez, MD**
**Brian McCrindle, MD**
**James McKenney, PharmD**
**Pamela Morris, MD**
**Merle Myerson, MD**
**E. Turner Overton, MD**
**Amber Pirzada, MD**
**Jorge Plutzky, MD**
**Katherine Rhodes, PhD, RDN**
**Carlos Jose Rodriguez, MD, MPH**
**Joyce Ross, MSN, CRNP**
**Geeta Sikand, MA, RDN**
**Nancy T. Smith, MS, RDN**
**Daniel Solomon, MD, MPH**
**James A. Underberg, MS, MD**
**Elaine Urbina, MD**
**Kris Vijay, MD**
**Robert Wild, MD, MPH, PhD**
**Don Wilson, MD**

*Listed in alphabetical order.

# NLA Expert Panel Section Chairs

**Nutrition**
Penny Kris-Etherton, PhD, RD
Geeta Sikand, MA, RDN, CLS
Kevin C. Maki, PhD, CLS

**Exercise/Physical Activity**
Ralph LaForge, MSc
Kevin C. Maki, PhD, CLS

**Children and Adolescents**
Don Wilson, MD
Stephen Daniels, MD, PhD

**Women's Health**
Pamela Morris, MD

**From Pregnancy to Menopause**
Robert Wild, MD, MPH, PhD, NCMP

**Older Patients**
Carl Orringer, MD
Scott Grundy, MD, PhD

**Hispanics/Latinos**
Martha Daviglus, MD, PhD

**African Americans**
Keith Ferdinand, MD

**South Asians**
Kris Vijay, MD
Prakash Deedwania, MD

**American Indians/ Alaska Natives**
Kevin C. Maki, PhD
Ralph La Forge, MSc

**Patients Infected with HIV**
Judith Aberg, MD

**Patients with Rheumatoid Arthritis**
Katherine Liao, MD, MPH

**Patients with Residual Risk Despite Statin and Lifestyle Therapy**
Peter Jones, MD
James McKenney, PharmD

**Patient Adherence**
Joyce Ross, MSN, CRNP
Lynne Braun, PhD, CNP

**Team-Based Collaborative Care**
Lynne Braun, PhD, CNP
Matthew Ito, PharmD
Joyce Ross, MSN, CRNP

# Major Categories of the NLA Part 2 Recommendations

Lifestyle Therapies

- Nutrition
- Exercise/Physical Activity

Groups with Special Considerations

Improving Patient Outcomes

- Patient Adherence
- Team-based Collaborative Care

# Groups with Special Considerations

**The Lifespan - Children to Seniors**

- Children and Adolescents
- Women's Health
- From Pregnancy to Menopause
- Older Adults

**Ethnic and Racial Groups**

- Hispanics/Latinos
- African Americans
- South Asians
- American Indians/Alaska Natives

**High Risk Conditions and Residual Risk**

- Patients Infected with HIV
- Patients with Rheumatoid Arthritis
- Residual Risk Despite Statin and Lifestyle Therapy

# Major Categories of the NLA Part 2 Recommendations

- Lifestyle Therapies
  - Nutrition
  - Exercise/Physical Activity
- Groups with Special Considerations
- Improving Patient Outcomes
  - Patient Adherence
  - Team-based Collaborative Care

# Lifestyle Therapies: Nutrition

- The National Lipid Association (NLA) Expert Panel supports a cardioprotective eating pattern for the management of dyslipidemia and overall cardiovascular health that includes **<7% of energy from saturated fat, with minimal intake of *trans* fatty acids** to lower levels of atherogenic cholesterol (low-density lipoprotein cholesterol [LDL-C] and non-high-density lipoprotein cholesterol [non-HDL-C]).

- The cardioprotective eating pattern should **limit cholesterol intake to <200 mg/day** to lower levels of atherogenic cholesterol (LDL-C and non-HDL-C).

- There are individuals who are hyper-responders to dietary cholesterol because of genetic or other reasons. For known or suspected hyper-responders, further reduction in dietary cholesterol beyond the <200 mg/day that is recommended as part of the cardioprotective eating pattern for the management of dyslipidemia may be considered. Consumption of very low intakes of dietary cholesterol (near 0 mg/day) may be helpful for such individuals.

# Lifestyle Therapies: Nutrition

- The NLA Expert Panel recommends any of the following **healthy dietary patterns, including an emphasis on a variety of plant foods and lean sources of protein** for managing dyslipidemia: Dietary Approaches to Stop Hypertension (DASH), United States Department of Agriculture (USDA) (healthy U.S.-style), American Heart Association (AHA), Mediterranean-style, and vegetarian/vegan. However, the dietary pattern should be individualized based on the patient's specific dyslipidemia. Also, patients' cultural and food preferences are important for guiding food selection to maximize dietary adherence. Nutritional counseling and follow-up/monitoring by a registered dietitian nutritionist is recommended whenever possible to individualize a patient's dietary pattern. Nutrition therapy should be included in those with other medical conditions, including diabetes.

- **If alcohol is consumed as part of a healthy dietary pattern, this should be in moderation** (≤7 drinks per week for women and ≤14 drinks per week for men; consumed in a non-binge pattern). One drink is equivalent to 12 oz. beer, 5 oz. wine, or 1.5 oz. distilled spirits.

# Lifestyle Therapies: Nutrition

- **Dietary saturated fat may be partially replaced with unsaturated fats** (mono- and polyunsaturated fats), as well as proteins, to reach a goal of <7% of energy from saturated fats. This can be achieved, in part, by incorporating foods high in unsaturated fats, such as liquid vegetable oils and vegetable oil spreads, nuts and seeds, as well as lean protein foods, such as legumes, seafood, lean meats, and non- or low-fat dairy products, into the diet as replacements for foods high in saturated fats.

- **Weight loss of 5-10% body weight is generally recommended for overweight or obese** individuals to lower atherogenic lipoprotein lipids and improve other atherosclerotic cardiovascular disease (ASCVD) risk factors. A variety of dietary approaches can be implemented for weight loss. Any dietary approach will result in weight loss if energy intake is reduced. An energy-reduced healthy dietary pattern that meets nutrient needs is recommended for patients who are overweight or obese. Several healthy dietary patterns, such as the Mediterranean-style, DASH, USDA, and vegetarian diets, can be tailored to personal and cultural food preferences and appropriate calorie needs for weight control.

# Lifestyle Therapies: Nutrition

- Eating patterns that contain a moderate quantity of carbohydrate, lower glycemic index and load, and higher protein, have been associated with modest benefits for weight loss and maintenance.

- **Plant sterols and stanols (~2 g/day) are recommended for cholesterol lowering, as well as viscous fibers (5 to 10 g/day or even greater, if acceptable to the patient), as adjuncts to other lifestyle changes**. However, individuals with phytosterolemia (sitosterolemia) should avoid foods that are fortified with stanols and sterols.

- **For patients with triglyceride (TG) levels ≥150 mg/dL, lifestyle therapy is indicated, including weight loss, if overweight or obese, physical activity, and restriction of alcohol, and sugars and refined starches**. Partial replacement of sugars and refined starches with a combination of unsaturated fats, proteins, and high-fiber foods may help to reduce TG and non-HDL-C concentrations.

# Lifestyle Therapies: Nutrition

- **For patients with TG levels ≥1000 mg/dL (and selected patients with TG 500-999 mg/dL), a low-fat diet (<15% of energy) and alcohol abstinence are recommended initially to minimize chylomicronemia**. In patients with hypertriglyceridemia and diabetes, dietary carbohydrate should not be substantially increased to avoid worsening glycemia when reducing fat intake. Medium-chain TG oil may be used as a source of energy that will not induce chylomicron production. For patients without lipoprotein lipase deficiency, dietary fat may be liberalized with monitoring of the TG response once the TG concentration is <500 mg/dL.

- **Therapeutic dosages of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) for TG reduction are 2.0 to 4.0 g/day. Use of these dosages of long-chain omega-3 fatty acids for TG-lowering should be done only under the supervision of a qualified clinician**. Clinicians are encouraged to educate patients on the importance of the amount of EPA + DHA in each capsule of dietary supplement or prescription products, and to take the appropriate number of capsules daily to achieve therapeutic levels. At present, prescription forms of EPA and EPA + DHA concentrates are only indicated for treatment of very high TG (≥500 mg/dL) to reduce the risk of pancreatitis.

# Lifestyle Therapies: Nutrition

- For primary and secondary prevention of ASCVD, consuming ≥2 servings/week of fish/seafood (preferably oily) is recommended. One serving is equal to 3.5 to 4 oz. and should ideally not be prepared using deep-frying.

- For patients with known ASCVD, suggestive, but not conclusive, evidence from randomized controlled trials is available for a benefit of long-chain omega-3 fatty acid supplementation at ~1 g/day EPA + DHA on cardiac mortality, but not non-fatal ASCVD events. EPA + DHA supplements may be considered for such patients, especially those who do not consume the recommended intakes of EPA + DHA from dietary sources.

- For patients with heart failure, 1 g/day of EPA + DHA is recommended as an adjunct to heart failure therapy.

- An alpha-linolenic acid intake of 0.6 to 1.2% of energy is recommended.

# Lifestyle Therapies: Nutrition

- **Consumption of at least three 1-oz. equivalent servings per day of fiber-rich whole grains is recommended**.

- **Consumption of ≥4 servings/week (1 oz. per serving) of nuts (including the legume, peanuts) is recommended**, because nut consumption has been consistently associated with reduced ASCVD risk. Nuts may be included in the diet as a protein food and as a source of healthy fat (predominantly unsaturated fatty acids).

- **Soy protein foods are one source of plant protein, among others** (e.g., nuts, legumes), that may be used as a substitute for protein foods high in saturated fat as part of a cardioprotective eating pattern.

# Lifestyle Therapies: Nutrition

- **Nutrition education/medical nutrition therapy (MNT) by a registered dietitian nutritionist with follow-up and monitoring are recommended to promote long-term dietary adherence**. Clinicians should, when feasible, refer patients to a registered dietitian nutritionist for MNT to individualize a cardioprotective dietary pattern and promote successful lifestyle modifications.

# Key References – Lifestyle Therapies: Nutrition


- 2015 Dietary Guidelines Advisory Committee, Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Scientific Report of the 2015 Dietary Guidelines Advisory Committee http://www.health.gov/dietaryguidelines/2015-scientific-report/PDFs/Scientific-Report-of-the-2015-Dietary-Guidelines-Advisory-Committee.pdf

- Eckel RH, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk *J Am Coll Cardiol.* 2013:S0735-S1097.

- Griffin JD, Lichtenstein AH. Dietary Cholesterol and Plasma Lipoprotein Profiles: Randomized-Controlled Trials *Curr Nutr Rep.* 2013;2:274-282.

# Major Categories of the NLA Part 2 Recommendations

- Lifestyle Therapies
  - Nutrition
  - Exercise/Physical Activity
- Groups with Special Considerations
- Improving Patient Outcomes
  - Patient Adherence
  - Team-based Collaborative Care

# Lifestyle Therapies: Exercise/Physical Activity

- The recommended minimal quantity of exercise for supporting cardiovascular health and improving the lipid profile (lowering TG and sometimes raising HDL-C) is **150 min per week of moderate to higher intensity aerobic activity**. This level of physical activity is consistent with public health recommendations.

- **To enhance the effects on TG and HDL-C, and produce reductions in LDL-C, as well as loss of body fat and weight, ≥2000 kcal per week of energy expenditure (generally 200 to 300 min per week)** of moderate or higher intensity physical activity is recommended.

- Resistance exercise is also recommended to play a supportive role in maintaining strength, balance, and bone density.

# Key References – Lifestyle Therapies: Exercise/Physical Therapy


- Gordon D, et al. The Effects of Exercise Training on the Traditional Lipid Profile and Beyond *Curr Sports Med Rep*. 2014;13:253-259.
- Haskell WL, et al. Physical Activity and Public Health: Updated Recommendation for Adults from the American College of Sports Medicine and the American Heart Association *Med Sci Sports Exerc*. 2007;39:1423-1434.
- Mann S, et al. Differential Effects of Aerobic Exercise, Resistance Training and Combined Exercise Modalities on Cholesterol and the Lipid Profile: Review, Synthesis and Recommendations *Sports Med*. 2014;44:211-221.
- American College of Sports Medicine. *Guidelines for Exercise Testing and Prescription,* 9th Edition. 2013.
- Eckel RH, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk *J Am Coll Cardiol.* 2013:S0735-S1097.

# Groups with Special Considerations

**The Lifespan - Children to Seniors**

- Children and Adolescents
- Women's Health
- From Pregnancy to Menopause
- Older Adults

**Ethnic and Racial Groups**

- African Americans
- Hispanics/Latinos
- South Asians
- American Indians/Alaska Natives

**High Risk Conditions and Residual Risk**

- Patients Infected with HIV
- Patients with Rheumatoid Arthritis
- Residual Risk Despite Statin and Lifestyle Therapy

# Groups with Special Considerations: Children and Adolescents

- **Universal lipid screening of all children, regardless of general health or the presence or absence of ASCVD risk factors, is recommended between 9-11 years of age, with repeat lipid screening at 20 years of age, or earlier if dyslipidemia is present**.

- **If a child or adolescent patient is screened and has a fasting or non-fasting non-HDL-C level ≥145 mg/dL, then additional follow-up is recommended**. Two fasting lipid profiles should be obtained and the results averaged for evaluation of the most appropriate course of action.

# Groups with Special Considerations: Children and Adolescents

- Children at least 2 years of age with the following characteristics should be screened for dyslipidemia:
  - One or both biological parents are known to have hypercholesterolemia, or are receiving lipid-lowering medications
  - Have a family history of premature ASCVD in an expanded first degree pedigree (i.e., to include not only parents and siblings, but also aunts, uncles, and grandparents) in men <55 or women <65 years of age
  - Consideration should also be given to screening for those in whom family history is unknown (e.g., adopted)

- Children should be regularly screened for major risk factors and conditions associated with increased ASCVD risk, but there are no validated methods for risk scoring in patients <20 years of age.

# Groups with Special Considerations: Children and Adolescents

- Decisions on target levels during treatment are a matter of clinical judgment, but age-appropriate, percentile-based cutpoints from the 2011 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: **National Heart, Lung, and Blood Institute should be considered as the *upper limits* for therapeutic atherogenic cholesterol goal ranges for managing children and adolescents:**
  - **Non-HDL-C: 144 mg/dL**
  - **LDL-C: 129 mg/dL**

- **Cascade screening and reverse cascade screening are recommended to enhance detection of individuals at risk for familial hypercholesterolemia (FH).**

- An alternate treatment goal for pediatric FH patients in whom it may not be possible to achieve an LDL-C level of 130 mg/dL, is a 50% reduction in LDL-C.

# Groups with Special Considerations: Children and Adolescents

- Diet and other lifestyle interventions, including increased physical activity and weight management when overweight/obesity is present, are recommended for lowering elevated LDL-C, non-HDL-C, and TG in children and adolescents. Dietary management strategies should be guided by a registered dietitian nutritionist whenever feasible.

- Children ≥8 years of age are potential candidates for pharmacologic treatment for lipid lowering. The following treatment plans can be considered:
  - **Administer pharmacologic agents, primarily statins, when LDL-C level is ≥190 mg/dL and/or non-HDL-C is ≥220 mg/dL**.
  - Consider additional risk factors in addition to elevated LDL-C and/or non-HDL-C and follow the treatment algorithm from the 2011 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: National Heart, Lung, and Blood Institute.

# Groups with Special Considerations: Children and Adolescents

- **Statins and bile acid sequestrants are pharmacologic agents with evidence for efficacy and safety in children and adolescents. There is limited evidence on the safety and efficacy of cholesterol absorption inhibitors in children and adolescents**.

- Consideration should be given to measurement of pretreatment fasting glucose or glycated hemoglobin levels, liver enzymes, and creatine kinase in pediatric patients for whom a statin is prescribed.

- Potential side effects with lipid-altering pharmacotherapy should be monitored in pediatric patients according to the recommendations from the respective 2014 NLA statin safety task force.

# Groups with Special Considerations

**Throughout the Lifespan**

- Children and Adolescents
- Women's Health
- From Pregnancy to Menopause
- Older Adults

**Ethnic and Racial Groups**

- Hispanics/Latinos
- African Americans
- South Asians
- American Indians/Alaska Natives

**High Risk Conditions and Residual Risk**

- Patients Infected with HIV
- Patients with Rheumatoid Arthritis
- Residual Risk Despite Statin and Lifestyle Therapy

# Groups with Special Considerations: Women's Health

- In general, women should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015) with the following special considerations.

- **First-line cholesterol-lowering drug therapy, unless contraindicated, is moderate- to high-intensity statin**. The statin dosage may be increased or the patient switched to a more efficacious agent, if goal levels of atherogenic cholesterol are not achieved. Statin therapy should be a consideration for patients at very high risk (i.e., ASCVD or diabetes mellitus with ≥2 major ASCVD risk factors), even if the pre-treatment levels of atherogenic cholesterol are below the treatment goals.

# Groups with Special Considerations: Women's Health

- Non-statin drug therapy with cholesterol absorption inhibitor, bile acid sequestrant, fibric acid, nicotinic acid, or long-chain omega-3 fatty acid concentrates (the latter currently indicated only for very high TG) may be considered for women with contraindications for, or intolerance to, statin therapy, or in combination with statin therapy for patients who need additional lowering of atherogenic cholesterol to achieve treatment goals.

- **Women taking statins may be at increased risk for certain adverse events, particularly myalgia**. Variations between men and women observed in clinical studies of statin-related myalgia incidence may have been related to differences in age, comorbidities, body composition, and polypharmacy.

# Groups with Special Considerations

**Throughout the Lifespan**

- Children and Adolescents
- Women's Health
- From Pregnancy to Menopause
- Older Adults

**Ethnic and Racial Groups**

- Hispanics/Latinos
- African Americans
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- American Indians/Alaska Natives

**High Risk Conditions and Residual Risk**

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# Groups with Special Considerations: From Pregnancy to Menopause

- **Women should be screened for dyslipidemia before pregnancy or as part of the routine obstetrical laboratory examination**.

- **For women taking lipid-lowering medications prior to pregnancy, all, except bile acid sequestrants, should be stopped when the woman becomes pregnant, or is trying to become pregnant**.

- **Women should be educated on the importance of pregnancy avoidance when lipid-altering therapies other than bile acid sequestrants are used**.

- **Total cholesterol and TG levels in women with normal pregnancies should not exceed 250 mg/dL**. If they do, the clinician should consider and evaluate preexisting or acquired medical or obstetrical conditions, including hypothyroidism, chronic kidney disease, liver disease, uncontrolled diabetes mellitus, or preeclampsia.

# Groups with Special Considerations: From Pregnancy to Menopause

- **Hypercholesterolemia during pregnancy and breast feeding, especially in women with FH, may be treated with bile acid sequestrants.**

- **Women with FH may be treated with LDL apheresis during pregnancy and breast feeding.**

- Very high TG (≥500 mg/dL) may be treated during pregnancy with diet/lifestyle management plus prescription omega-3 fatty acids; fenofibrate or gemfibrozil may be administered beginning early in the second trimester, based on clinical judgment. These agents may be used during breast feeding.

# Groups with Special Considerations: From Pregnancy to Menopause

- **Polycystic ovarian syndrome (PCOS) is a high-risk condition for dyslipidemia, metabolic syndrome, and obstetrical complications of preeclampsia, hypertension, diabetes, and premature delivery**. All patients with PCOS, regardless of age, should undergo initial lipid and diabetes screening and more frequent follow-up screening is recommended, even if initial values are normal.

- The approach to risk stratification and atherogenic cholesterol treatment goals for women with PCOS should be the same as described for all patients with dyslipidemia in the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015).

- Therapeutic management of dyslipidemia in PCOS should focus on diet, exercise, and lipid-lowering medication, if needed. Use of metformin should also be considered to lower TG and reduce insulin resistance.

# Groups with Special Considerations: From Pregnancy to Menopause

- **Contraceptive choice impacts dyslipidemia**. Combined oral contraceptives should generally not be used by women ≥35 years of age who smoke because of additive stroke and myocardial infarction (MI) risk.

- Sex hormone therapy (HT) should not be used for prevention or treatment of ASCVD.

- Menopausal sex HT is an option for treatment of significant menopause symptoms during menopause transition for women at minimal risk for ASCVD.

# Groups with Special Considerations

**Throughout the Lifespan**

- Children and Adolescents
- Women's Health
- From Pregnancy to Menopause
- Older Adults

**Ethnic and Racial Groups**

- Hispanics/Latinos
- African Americans
- South Asians
- American Indians/Alaska Natives

**High Risk Conditions and Residual Risk**

- Patients Infected with HIV
- Patients with Rheumatoid Arthritis
- Residual Risk Despite Statin and Lifestyle Therapy

# Groups with Special Considerations: Older Adults

- Primary prevention strategies in patients 65-79 years of age should be managed in accordance with the NLA Recommendations for the Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015).

- **For patients age ≥65 to <80 years of age with ASCVD or diabetes mellitus, moderate or high intensity statin therapy should be considered after a careful consideration of the risk-benefit ratio**.

- **For secondary prevention in patients ≥80 years of age, moderate intensity statin therapy should be considered based upon a provider-patient discussion of the risks and benefits of such therapy, consideration of drug-drug interactions, polypharmacy, concomitant medical conditions including frailty, cost considerations, and patient preference**.

# Groups with Special Considerations: Older Adults

- Risk calculators such as the American College of Cardiology(ACC)/AHA Pooled Cohort Risk Calculator or the Adult Treatment Panel (ATP) III Framingham Risk Calculator can be used in select older individuals with one additional risk factor to further assess risk, using the thresholds for high risk of:
  - ≥15% 10-year risk for a hard ASCVD event (MI, stroke, or death from coronary heart disease [CHD] or stroke) with the Pooled Cohort Equations; and
  - ≥10% 10-year risk for a hard CHD event (MI or CHD death) using the ATP III Framingham Risk Calculator.

  **However, these risk calculators have several limitations for use in older patients, since advanced age is often the predominate driver of increased ASCVD risk, and this may result in overtreatment of lower risk older individuals**.

# Groups with Special Considerations: Older Adults

- Older, primary prevention patients who are statin-eligible should undergo a patient-centered discussion with their provider about the risks and benefits of statin therapy so that they can make a more informed decision about taking statins over the long term.

- If the older primary prevention patient is unable to achieve atherogenic cholesterol goals after a minimum 3-6 month trial on lifestyle modification, the provider should discuss the pros and cons of drug therapy and, if feasible, prescribe moderate intensity statin therapy, particularly for patients with one or more ASCVD risk factor aside from age, with risk exceeding the high risk threshold using the Pooled Risk Equation or ATP III Framingham Risk Calculator.

- **Coronary artery calcium (CAC) scoring may be useful to further assess risk in older patients for whom questions remain about whether to prescribe drug therapy**.

# Groups with Special Considerations: Older Adults

- If statin intolerance is an issue, consideration should be given to the use of alternate statin regimens such as low intensity statin therapy or non-daily moderate intensity statin therapy, low dose statin combination therapy with ezetimibe, bile acid sequestrants, or niacin, or non-statin monotherapy (i.e., ezetimibe or bile acid sequestrant) or their combination, with a goal of at least a 30% reduction in LDL-C.

# Groups with Special Considerations

**Throughout the Lifespan**

- Children and Adolescents
- Women's Health
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- Older Adults

**Ethnic and Racial Groups**

- Hispanics/Latinos
- African Americans
- South Asians
- American Indians/Alaska Natives

**High Risk Conditions and Residual Risk**

- Patients Infected with HIV
- Patients with Rheumatoid Arthritis
- Residual Risk Despite Statin and Lifestyle Therapy

# Ethnic and Racial Groups

- Hispanics/Latinos
- African Americans
- South Asians
- American Indians/Alaska Natives

# Groups with Special Considerations: Hispanics/Latinos

- In general, patients of Hispanic/Latino ethnicity should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015) with the following special considerations.

- **Clinicians should be aware that Hispanics/Latinos in the United States are a diverse population group tracing their ancestry to Mexico, the Caribbean (Puerto Rico, Cuba, and the Dominican Republic), Central America (El Salvador and Guatemala), and South America. ASCVD risk factor burden varies widely among individuals of Hispanic/Latino descent, depending on their country of origin**.

# Groups with Special Considerations: Hispanics/Latinos

- **Hispanics/Latinos tend to have a greater prevalence of high TG and low HDL-C than non-Hispanic whites (NHWs), leading to higher levels of non-HDL-C, and an increased likelihood for discordance between LDL-C and non-HDL-C concentrations**. LDL-C levels tend to be higher in Hispanic men compared with NHW men.

- **Hispanics/Latinos have higher prevalence of type 2 diabetes mellitus, obesity, and metabolic syndrome compared to NHWs, particularly among women**.

- Some cardiovascular risk equations (e.g., Framingham equations) may overestimate risk in Hispanic/Latino individuals.

# Ethnic and Racial Groups

- Hispanics/Latinos
- African Americans
- South Asians
- American Indians/Alaska Natives

# Groups with Special Considerations: African Americans

- In general, African Americans (AAs) should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015) with the following special considerations.

- Clinicians should be aware that AAs as a group are at increased risk for ASCVD.

- **Because attributable ASCVD risk in AAs is less driven by dyslipidemia than in NHWs, particular attention should be given to assessing non-lipid risk factors, such as hypertension, overweight and obesity, type 2 diabetes mellitus, and physical inactivity, when ascertaining ASCVD risk**.

- **AAs have a lower incidence of metabolic syndrome than NHWs, due to lower prevalence of high TG and low HDL-C. However, the incidence of type 2 diabetes mellitus is higher in AAs**.

# Groups with Special Considerations: African Americans

- **Because AA race/ethnicity is included in the 2013 ACC/AHA Pooled Cohort Equations for estimating 10-year ASCVD risk, this may be the preferable risk calculator to use in patients of AA race/ethnicity**.

- **Because lipoprotein (a) [Lp(a)] levels tend to be higher in AA patients, measuring Lp(a) for risk refinement may be considered in AA patients, particularly in those with a family history of premature ASCVD not explained by other risk factors**.

- **Clinicians should not withhold statin therapy from at risk AA patients with asymptomatic creatine kinase levels that exceed, but are <3.0 times, the standard upper limits of normal**. When practical, normative upper limits for creatine kinase that are adjusted for age, race, and sex should be used.

# Ethnic and Racial Groups

- Hispanics/Latinos
- African Americans
- South Asians
- American Indians/Alaska Natives

# Groups with Special Considerations: South Asians

- In general, patients of South Asian (SA) ethnicity should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015) with the following special considerations.

- **Clinicians should be aware that SAs (including individuals who trace their ancestry to Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka; and also members of the SA diaspora – past generations of SAs who originally settled in other parts of the world, including Africa, Canada, the Caribbean, Europe, the Middle East, and other parts of Asia and the Pacific Islands) as a group are at increased risk for ASCVD**.

- **Patients of SA descent in the United States have a greater prevalence of insulin resistance than NHWs, and some of the metabolic disturbances that accompany this condition include high TG, low HDL-C, and dysglycemia**.

# Groups with Special Considerations: South Asians

- SAs have increased prevalence of metabolic syndrome compared to NHW Americans. **Clinicians should be aware that Asians have different waist circumference cutpoints for defining overweight/obesity for definition of the metabolic syndrome than those recommended for Caucasian populations (≥37 inches [≥94 cm] for men and ≥32 inches [≥80 cm] for women).**

- Clinicians should be aware that risk assessment methods may under- or over-estimate ASCVD risk when used in populations different from those in which they were developed. ASCVD risk equations may underestimate risk for SAs in particular, although the degree of underestimation is uncertain. Clinicians should consider this when making decisions about risk stratification and treatment.

# Groups with Special Considerations: South Asians

- Due to the possibility of genetic variation in drug metabolism (as demonstrated mainly in studies of Chinese and Japanese patients), starting with a moderate intensity statin dosage and titrating upward to reach atherogenic cholesterol goals, or downward if intolerance occurs, is recommended for patients of Asian ethnicity.

- Because SAs are at increased risk for diabetes, vigilant monitoring for the potential of new-onset diabetes with statin treatment is warranted.

# Ethnic and Racial Groups

- Hispanics/Latinos
- African Americans
- South Asians
- American Indians/Alaska Natives

# Groups with Special Considerations: American Indians/Alaska Natives

- **Clinicians should be aware that American Indians (AIs)/Alaska Natives (ANs) have higher prevalence and incidence rates for ASCVD, and that certain ASCVD risk factors (e.g., obesity, metabolic syndrome, diabetes mellitus, and cigarette smoking) are more common among AIs/ANs than NHWs**, whereas prevalence values for hypertension and hypercholesterolemia are comparable or slightly elevated compared to NHWs.

- In general, clinicians should screen for and manage dyslipidemia in AI/AN patients using the approach outlined in the NLA Expert Panel Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015). **Because of the high frequencies of obesity, metabolic syndrome, and diabetes mellitus in AI/AN populations, strong emphasis should be on lifestyle therapies**.

# Groups with Special Considerations: American Indians/Alaska Natives

- Clinicians should generally assess risk in AI/AN patients using the risk assessment approach outlined in the NLA Expert Panel Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015).

# Groups with Special Considerations

**Throughout the Lifespan**

- Children and Adolescents
- Women's Health
- From Pregnancy to Menopause
- Older Adults

**Ethnic and Racial Groups**

- Hispanics/Latinos
- African American
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**High Risk Conditions and Residual Risk**

- Patients Infected with HIV
- Patients with Rheumatoid Arthritis
- Residual Risk Despite Statin and Lifestyle Therapy

# Groups with Special Considerations: Patients Infected with HIV

- **Clinicians should be aware that patients with human immunodeficiency virus (HIV) are at increased risk for ASCVD. The association between HIV infection and ASCVD risk is independent of the risk associated with major established ASCVD risk factors**.

- A fasting lipid panel should be obtained in all newly identified HIV-infected patients before and after starting antiretroviral therapy.

- For primary prevention of ASCVD, HIV infection may be counted as an additional ASCVD risk factor for risk stratification.

# Groups with Special Considerations: Patients Infected with HIV

- Risk stratification is based on the NLA Recommendations for the Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015) with initial risk stratification based on the number of major ASCVD risk factors (with the caveat that the presence of **HIV infection may be counted as an additional risk factor**), the use of risk prediction tools, such as the ATP III Framingham Risk Score or the ACC/AHA Pooled Cohort Equations if two risk factors are present, and the use of other clinical indicators to help inform clinical judgment, if needed.

- The non-HDL-C and LDL-C goals described in the NLA Part 1 Recommendations should be followed for HIV-infected patients (Jacobson 2015). Atherogenic cholesterol goals may not be attainable in all patients, but there is incremental benefit to lowering non-HDL-C and LDL-C to approach these goal levels.

# Groups with Special Considerations: Patients Infected with HIV

- Elevated TG ≥500 mg/dL that is refractory to lifestyle modification or changes in antiretroviral therapy (if an option) should generally be treated with either a fibrate (fenofibrate preferred) or prescription omega-3 fatty acids. After TG is lowered (<500 mg/dL), non-HDL-C and LDL-C should be reassessed for appropriate management.

- **Statin therapy is first line for elevated LDL-C and non-HDL-C; however, interactions between statins and antiretroviral agents and other medications must be considered prior to initiating lipid-lowering therapy**. The NLA Expert Panel recommends using atorvastatin, rosuvastatin, or pitavastatin as the generally preferred agents in HIV-infected patients.

# Groups with Special Considerations: Patients with Rheumatoid Arthritis

- **Clinicians should be aware that patients with rheumatoid arthritis (RA) are at increased risk for ASCVD**. The association of RA and systemic lupus erythematosus with ASCVD risk raises concern that other inflammatory conditions may also be associated with increased ASCVD risk. However, **only RA has been studied sufficiently to accurately quantify the degree to which it increases ASCVD risk**.

- The association between RA and ASCVD risk is independent of the risk associated with major established ASCVD risk factors. **For primary prevention of ASCVD, RA may be counted as an additional ASCVD risk factor for risk stratification**.

# Groups with Special Considerations: Patients with Rheumatoid Arthritis

- Risk stratification is based on the NLA Recommendations for the Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015) with initial risk stratification based on the number of major ASCVD risk factors (with the caveat that the presence of RA may be counted as an additional risk factor), the use of risk prediction tools, such as the ATP III Framingham Risk Score or the ACC/AHA Pooled Cohort Equations if two risk factors are present, and the use of other clinical indicators to help inform clinical judgment, if needed.

- Clinicians should be vigilant in ensuring that RA patients are routinely assessed for cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes, family history of early-onset ASCVD, and smoking. Calculation of lifetime ASCVD risk can be considered for patients age 20-59 years.

# Groups with Special Considerations: Patients with Rheumatoid Arthritis

- **Statins are generally the first-line treatment for dyslipidemia in RA**.
- At this time, atherogenic cholesterol treatment goals for patients with RA and other inflammatory diseases are the same as described in the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015).
- **If an RA patient has had lipid levels checked during an RA flare, it is recommended that the lipids be re-checked when their disease is controlled**.

# Groups with Special Considerations: Patients with Residual Risk Despite Statin and Lifestyle Therapy

- **For patients not at goal levels for atherogenic cholesterol on maximally tolerated statin therapy, consideration should be given to adding non-statin lipid-altering therapy to ongoing statin therapy for further lowering of atherogenic cholesterol, as long as the patient has sufficient ASCVD risk to warrant it, and the expected treatment benefit outweighs the risk for adverse consequences**.

- Recommended statin combination therapies to consider for further lowering of atherogenic cholesterol are, in the following order: first – ezetimibe 10 mg every day, second – colesevelam 625 mg 3 tablets twice a day (or 3.75 g powder form every day or in divided doses), and third – extended release niacin titrated to a maximum of 2000 mg, daily.

# Groups with Special Considerations: Patients with Residual Risk Despite Statin and Lifestyle Therapy

- **Until the CV outcomes trials are completed with PCSK9 inhibitors, these drugs should be considered primarily in: 1) patients with ASCVD who have LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy; and 2) heterozygous FH patients without ASCVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥160 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy**.

- **In addition, PCSK9 inhibitor use may be considered for selected high risk patients with ASCVD (e.g., recurrent ASCVD events) who have atherogenic cholesterol levels below the specified values, but above their treatment goals (i.e., LDL-C ≥70 mg/dL [non-HDL-C ≥100 mg/dL]).** Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.

# Groups with Special Considerations: Patients with Residual Risk Despite Statin and Lifestyle Therapy

- **PCSK9 inhibitor use may also be considered in selected high or very high risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid lowering therapies**. Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.

- **Fibrates and prescription omega-3 fatty acids are first-line drug choices for patients with TG ≥500 mg/dL, although consideration may be given to using statin therapy as a first-line drug in patients with TG 500-999 without a history of pancreatitis**.

# Major Categories of the NLA Part 2 Recommendations

- Lifestyle Therapies
  - Nutrition
  - Exercise/Physical Activity
- Groups with Special Considerations
- Improving Patient Outcomes
  - Patient Adherence
  - Team-based Collaborative Care

# Improving Patient Outcomes: Patient Adherence

- **The provider should assess adherence to both lifestyle and atherogenic cholesterol-lowering medications at every patient encounter**.

- **A multidisciplinary health care team (such as the patient's primary health care provider; nurses; nurse practitioners; pharmacists; physician assistants; registered dietitian nutritionists, including certified diabetes educators in some practices; exercise specialists; social workers; community health workers; and licensed professional counselors, psychologists, and health educators) is desirable to identify medication non-adherence and to facilitate strategies to improve adherence by helping patients overcome real (or perceived) barriers to adherence**.

# Improving Patient Outcomes: Patient Adherence

- **The multi-faceted approach should be employed by clinicians to improve medication adherence, including: a) simplify the regimen; b) provide clear education using visual aids and simple, low-literacy educational materials; c) engage patients in decision-making, addressing their specific needs, values, and concerns; d) address perceived barriers of taking medication; e) identify suboptimal health literacy and use "teach-back" techniques to increase patient understanding of those behaviors needed to be successful; f) screen and eliminate drug-drug and drug-disease interactions leading to low adherence or drug discontinuation; and g) praise and reward successful behaviors**.

# Major Categories of the NLA Part 2 Recommendations

- Lifestyle Therapies
  - Nutrition
  - Exercise/Physical Activity
- Groups with Special Considerations
- Improving Patient Outcomes
  - Patient Adherence
  - Team-based Collaborative Care

# Improving Patient Outcomes: Team-Based Collaborative Care

- **Health care teams for optimal lipid and ASCVD risk management may include, where available: the patient; the patient's primary health care provider; nurses; nurse practitioners; pharmacists; physician assistants; registered dietitian nutritionists, including certified diabetes educators in some practices; exercise specialists; social workers; community health workers; and licensed professional counselors, psychologists, and health educators**.

- Health care team members should coordinate care support among various team members, use evidence-based guidelines/recommendations for dyslipidemia management, establish a structured plan for monitoring patient progress, and provide patients with a variety of tools and resources to improve their own care.

- Team-based collaborative care may be incorporated into the Patient Centered Medical Home as a strategy to address shortfalls in patient health care quality, access, continuity, and cost.

# Background – Improving Patient Outcomes: Team-Based Collaborative Care

- Agency for Healthcare Research and Quality. Patient Centered Medical Home Resource Center. http://pcmh.ahrq.gov/page/defining-pcmh

- Proia K, et al. Team-based Care and Improved Blood Pressure Control: a Community Guide Systematic Review *Am J Prev Med*. 2014;47:86-99.

# Abbreviations/Acronyms Used

- **AA** = African American
- **ACC** = American College of Cardiology
- **AHA** = American Heart Association
- **AI** = American Indian
- **AN** = Alaska Native
- **ART** = antiretroviral therapy
- **ASCVD** = atherosclerotic cardiovascular disease
- **ATP** = Adult Treatment Panel
- **CAC** = coronary artery calcium
- **CHD** = coronary heart disease
- **DASH** = Dietary Approaches to Stop Hypertension
- **DHA** = docosahexaenoic acid
- **EPA** = eicosapentaenoic acid
- **FH** = familial hypercholesterolemia
- **HDL-C** = high-density lipoprotein cholesterol
- **HIV** = human immunodeficiency virus
- **HT** = hormone therapy
- **LDL-C** = low-density lipoprotein cholesterol
- **Lp(a)** = lipoprotein(a)
- **MI** = myocardial infarction
- **MNT** = medical nutrition therapy
- **NHW** = non-Hispanic white
- **NLA** = National Lipid Association
- **Non-HDL-C** = non-high-density lipoprotein cholesterol
- **PCOS** = polycystic ovary syndrome
- **RA** = rheumatoid arthritis
- **SA** = South Asian
- **TG** = triglycerides
- **USDA** = United States Department of Agriculture

# Acknowledgments


- The panel wishes to express its gratitude to the following individuals, whose assistance was invaluable in preparation of these recommendations:
  - Ryan J. Essegian, Esq. (NLA)
  - Lindsay Hart (NLA)
  - Chris Seymour (NLA)
  - Anthony Lopez, MD
  - Matthew Topel, MD

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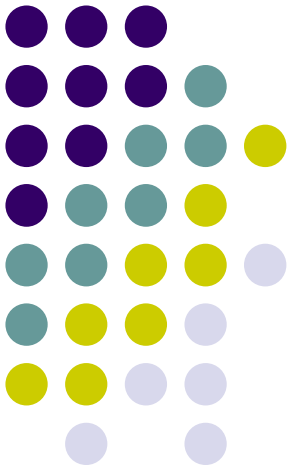
# NLA Recommendations Over the Lifespan: Management of Dyslipidemia in Women

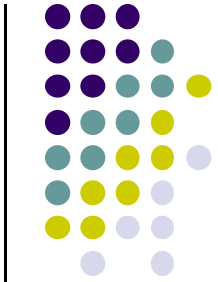
Pamela B. Morris, MD

FACC, FACP, FACPM, FAHA, FIHA, FNLA

NLA, 19 September 2015



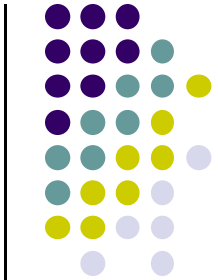
# ASCVD in Women



- Leading cause of death among women
  - >400,000 women die annually (2010)
- In all age groups and ethnicities, women who experience an MI are more likely than men to die within 5 years of the event.
- Women are more likely to develop heart failure within 5 years of MI.
- Higher lifetime risk of stroke
  - 55,000 more women than men experience stroke each year.
- Women account for nearly 60% of stroke deaths.

Circulation. 2014;129:e28-e92

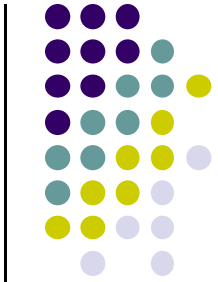
# ASCVD Risk Reduction in Women



- Despite the importance of ASCVD women have been historically under-represented in RCTs of statin therapy.
- Primary prevention statin RCTs not adequately powered to perform subgroup analyses by gender and
  - Meta-analyses have not always included patient-level data to examine potential differences in effect between men and women.
- Secondary ASCVD prevention RCTs not adequately powered to detect a reliable difference in treatment effect between men and women.
  - Point estimates have been very similar, so if there is a difference, it is small.

J Am Coll Cardiol. 2014;25:2889-2934

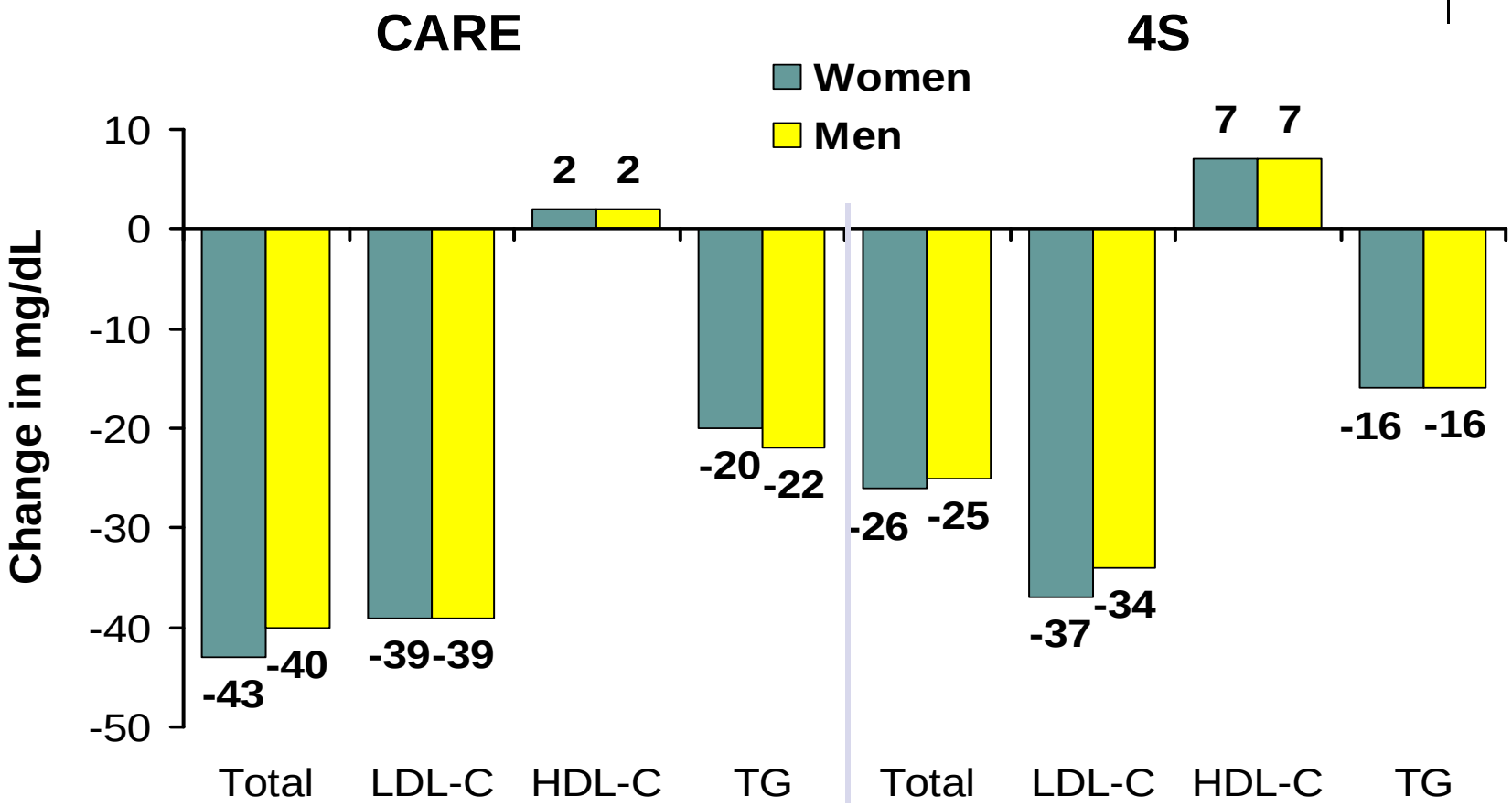
# ASCVD Risk Reduction in Women



- Recent review of statin RCTs that reported participants' numbers by sex/gender
- In the 1990s, RCTs on statins with an average of >500 participants included 18.6% women [95% C.I.: 16.31%, 21.13%].
- By the first decade of the 2000s, women comprised, on average, 31.45% [29.45%, 32.52% (95% C.I.)] of the total cohort of RCTs with more than 500 participants.
- Regression analysis illustrated a significant increase in the recruitment of women for RCTs of statins (p-value < 0.01).

Clin Invest Med. 2014;37(3):E163

# Lipid Response to Statins is Similar in Men and Women

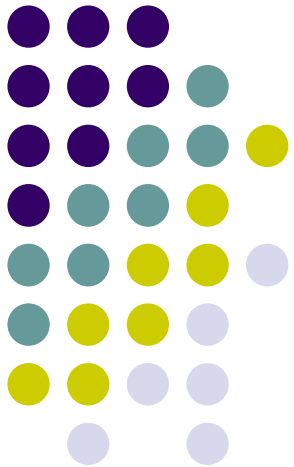




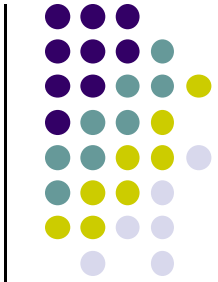
Lewis SJ, et al. JACC 1998;32:140-146

Miettinen TA, et al. Circulation 1997;96:4211-4218

# Recommendations for Management of Dyslipidemia in Women: Primary Prevention



# Primary Prevention of ASCVD in Women



- Although women without previous ASCVD are at lower absolute risk compared to men, the majority of events will occur among them due the numbers of aging women.

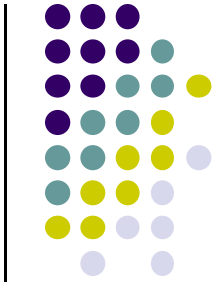
- Approximately 45% of MIs and 20% of strokes are fatal, thus not amenable to primary prevention

- Many incident events cause substantial disability, decline in functional status, and loss of independence.

Lancet. 2012;380:581-590

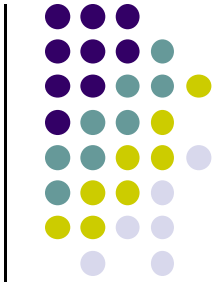
- What is the role of lowering atherogenic lipoproteins in primary prevention of ASCVD events among women?

# Primary ASCVD Prevention in Women



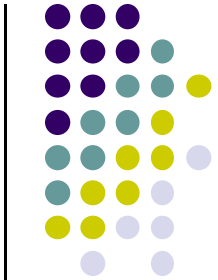
- Lower incidence of ASCVD events than in men requires a large sample size to make valid gender-specific comparisons
- AFCAPS/TEXCAPS, ALLHAT-LLT, ASCOT-LLA, HPS: primary prevention
- Subgroup analyses in women

# Primary ASCVD Prevention in Women



- AFCAPS/TEXCAPS:  45% reduction in CHD events (p=NS), too few events for valid comparison
- ALLHAT-LLT:  no reduction in main analysis or in women
- ASCOT-LLA:  no reduction, too few events for valid comparison
- HPS: 24% reduction CHD events in women overall

# Primary Prevention With Statin in Japanese, Postmenopausal Women: MEGA Trial

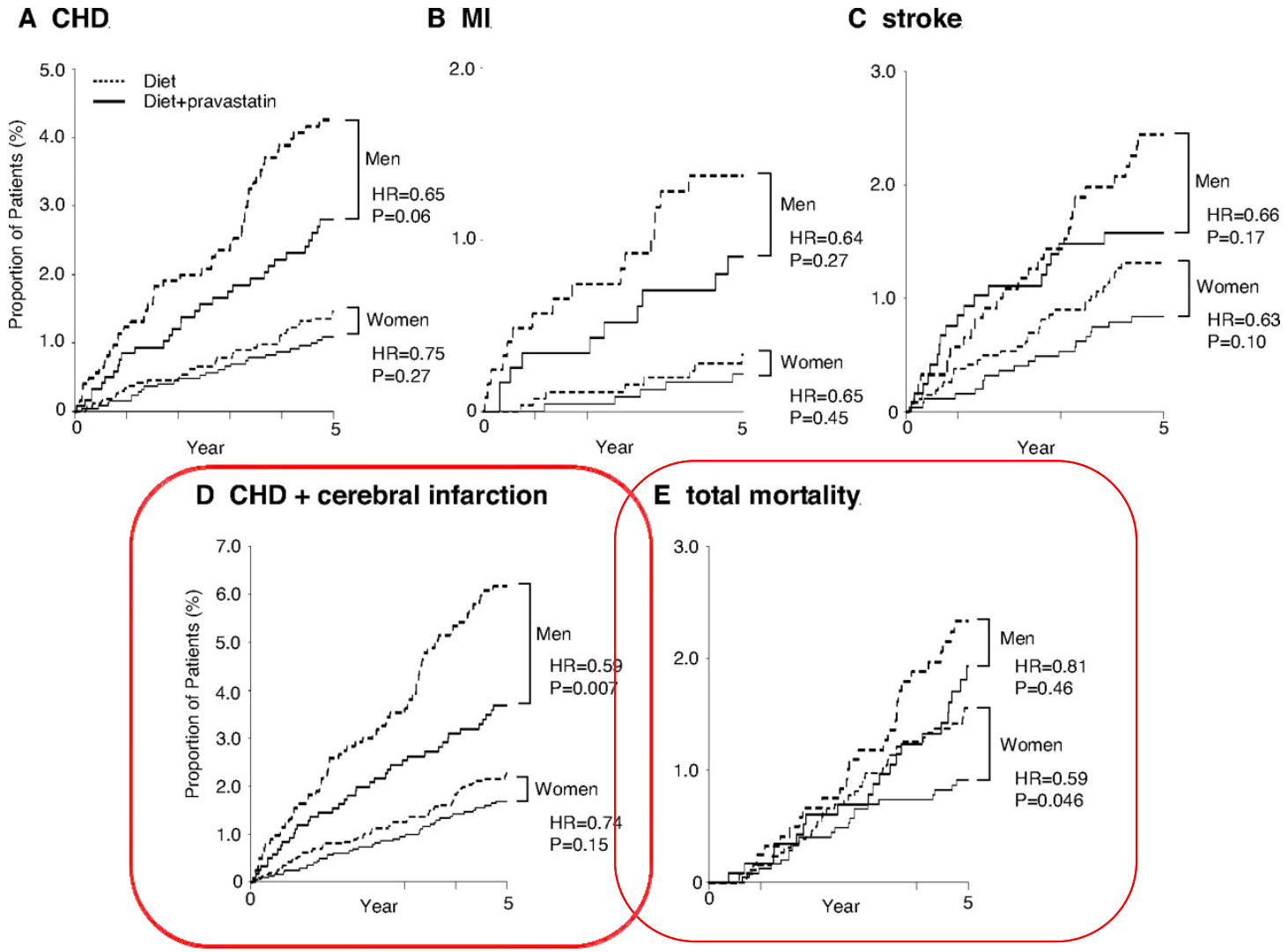


- N=5,356 Japanese women (68%)
  - Total Participants: N=7,832
- Mean age women: 60 years
- No hx of CHD or stroke
- Mean LDL-C 158 mg/dL
- Mean BP 132/78 mmHg
- 43% hypertensive
- 18% diabetic
- 6% smokers

- PROBE design; F/U 5 y
- Prava 10-20 mg/d plus diet vs. diet alone
  - Net 15% ↓ LDL-C Prava
- Women had 2-3 x lower event rates than men
- Well tolerated
- Reduction in events significant only in men
- Significant ↓ in total mortality in women

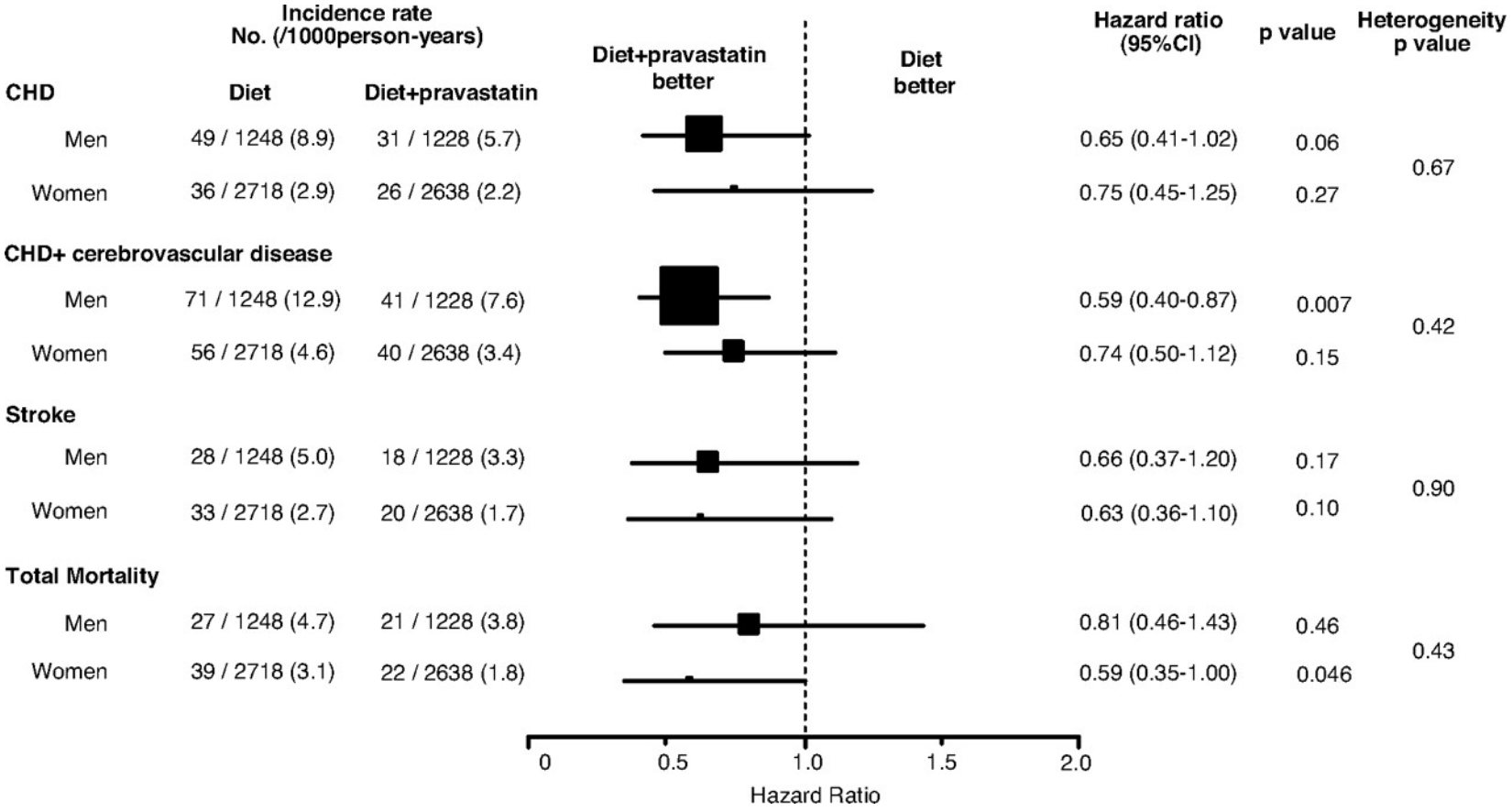
Mizuno et al. MEGA Trial Circulation 2008;117:494-502

# MEGA Trial: Kaplan–Meier curves for major end points in men and women.



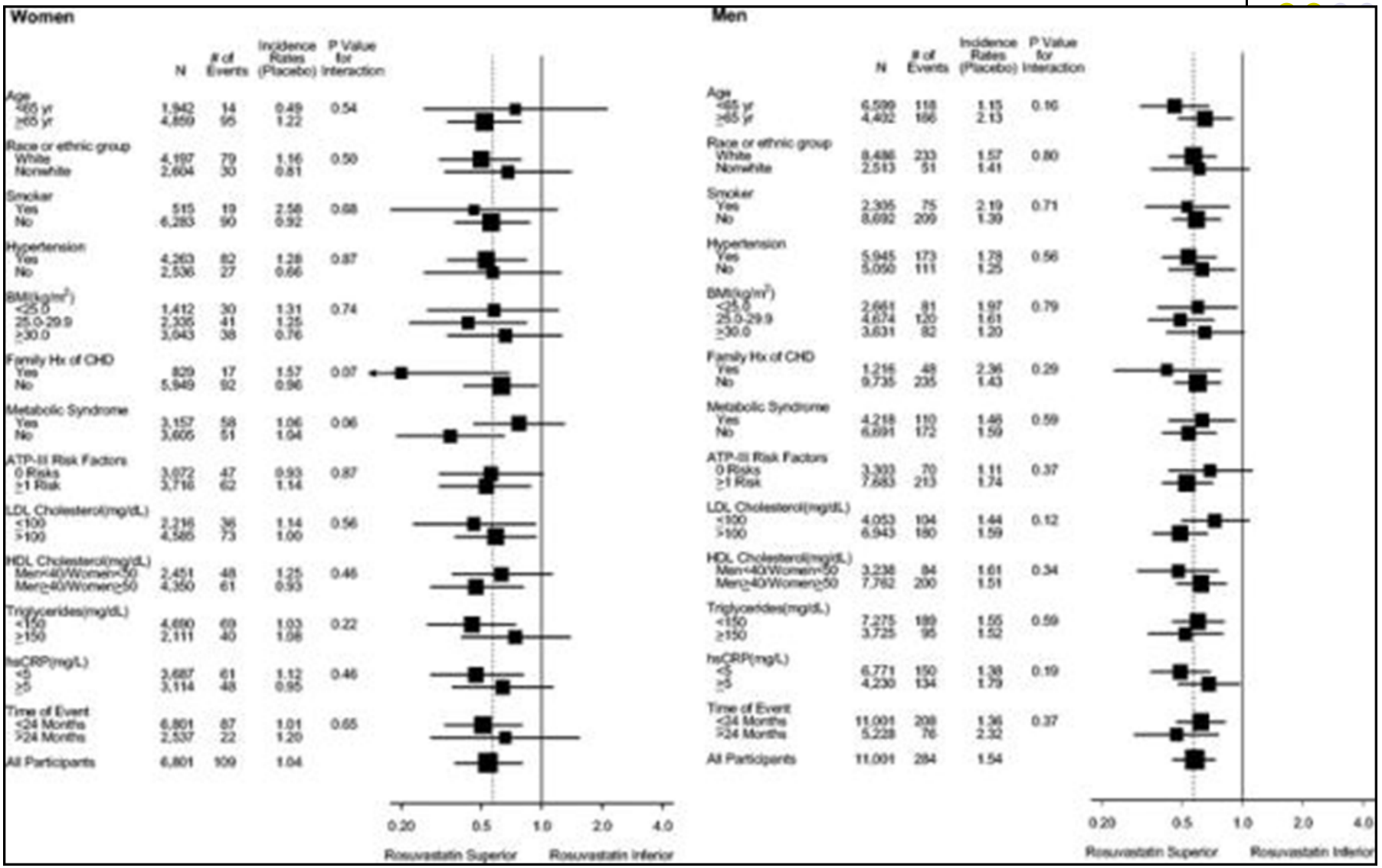

Mizuno K et al. Circulation. 2008;117:494-502

# MEGA Trial: Heterogeneity for major end points between men and women.




Mizuno K et al. Circulation. 2008;117:494-502

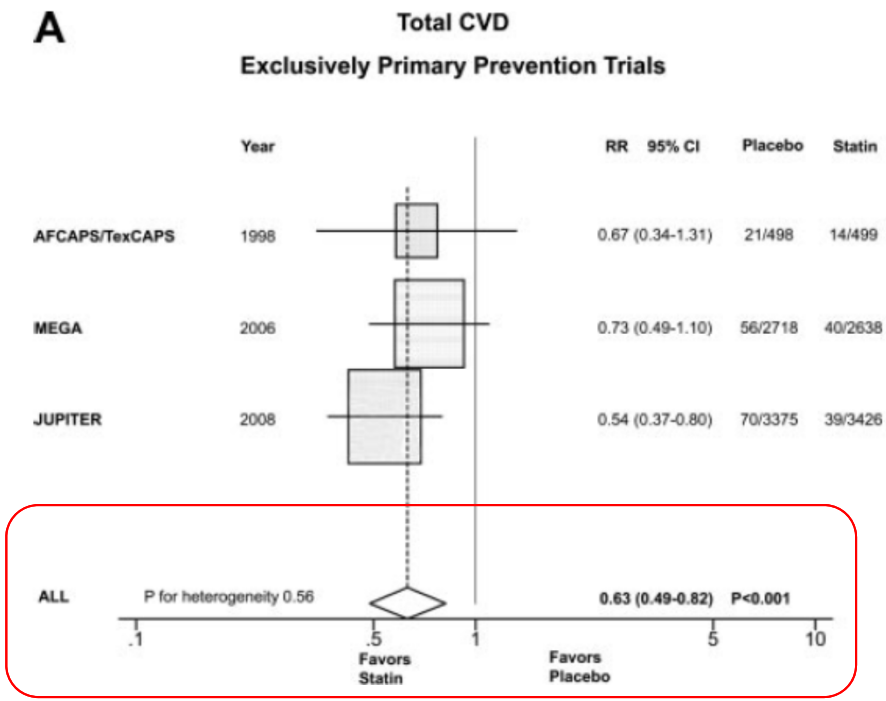
# JUPITER: Results in Women

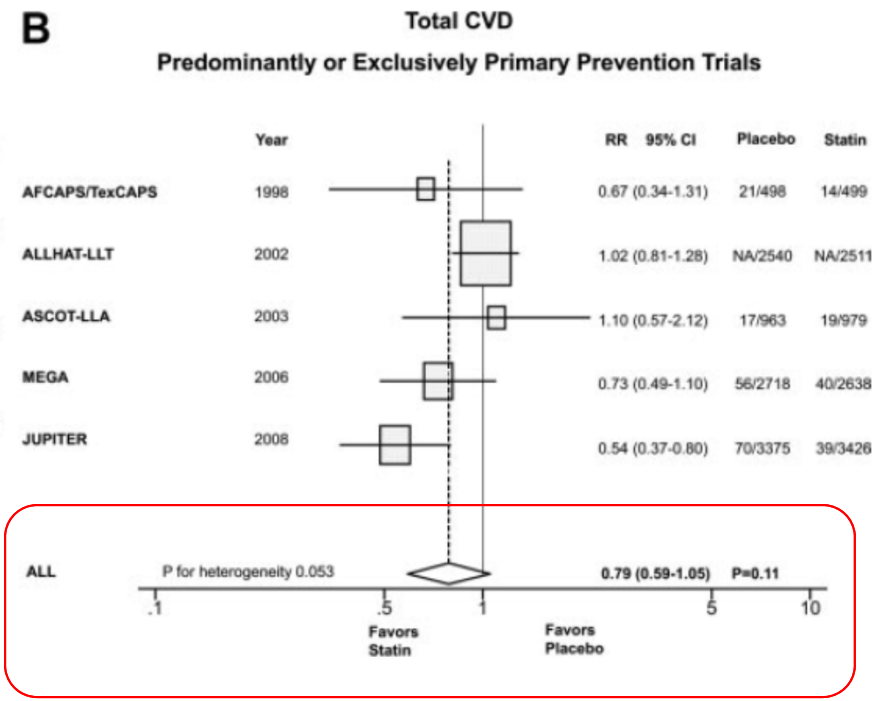



Mora et al. Circ 2010;121;1069-1077

# Updated Meta-Analysis in Women

## Statins for 1º Prevention: Total CVD



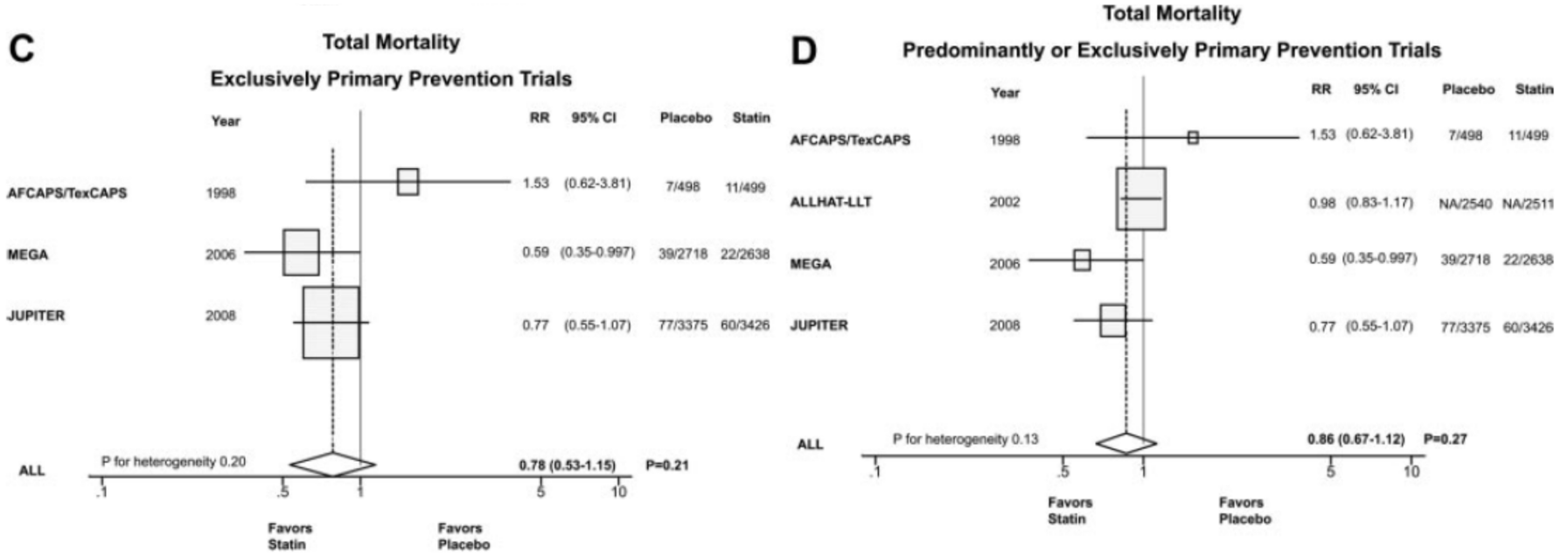

ALL: RR 0.63 (95% CI 0.49-0.82)

ALL: RR 0.79 (95% CI 0.79-1.05)

Mora et al. Circ 2010;121;1069-1077

# Updated Meta-Analysis in Women

## Statins for 1º Prevention: Total Mortality



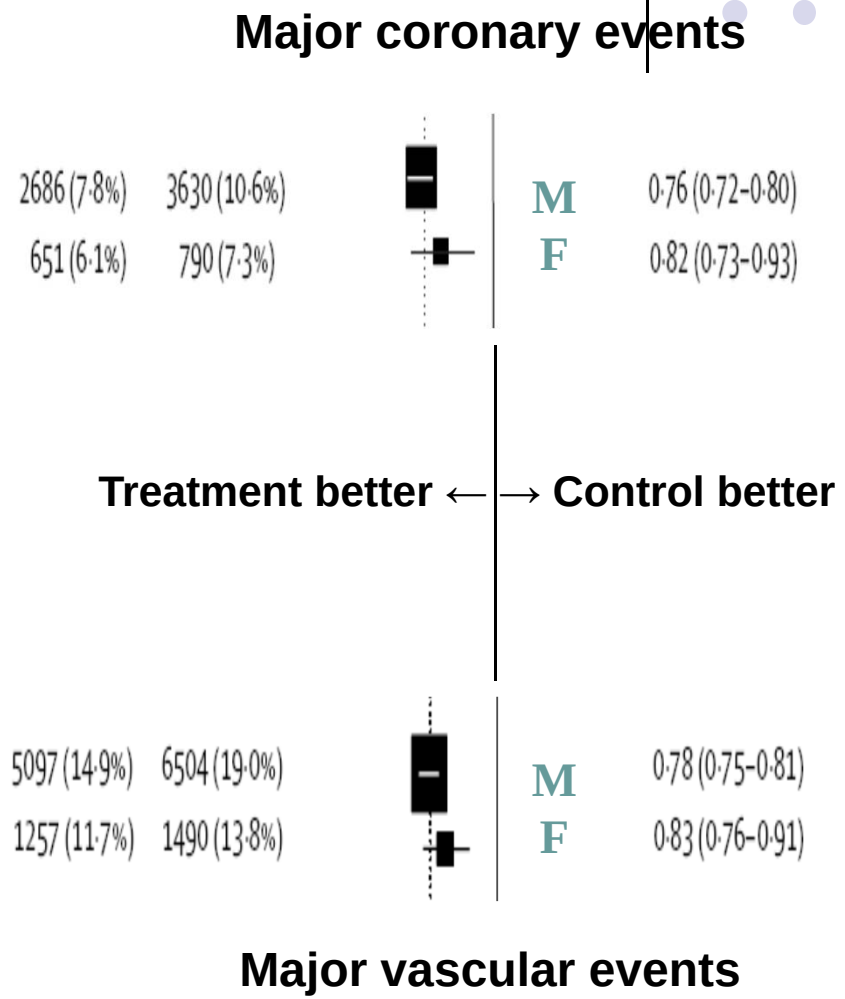

ALL: RR 0.78 (95% CI 0.53-1.15)

ALL: RR 0.86 (95% CI 0.67-1.12)

Mora et al. Circ 2010;121;1069-1077

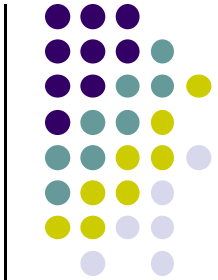
# CTT Meta-Analysis: Gender Subgroups

- 14 trials, N = 90,056
  - Women: 21,575
- Mean F/U 4.7 years
- Mean Δ LDL-C (baseline vs. 1 years): 1.09 mmol/L
- Major coronary events:
  - Men -24%
  - Women -18%
- Major vascular events
  - Men -22%
  - Women -17%
- No interaction by gender




Cholesterol Treatment Trialists. Lancet 2005

# CTT Conclusion



- “The consistency of the proportional benefit in all subgroups studied in the main CTT report suggests clearly that, in women and men with a comparable risk of occlusive vascular disease, the absolute benefits of statin therapy are likely to be similar.

- A decision whether to institute treatment with a statin should be determined mainly by an assessment of risk, and not by a person’s sex.”

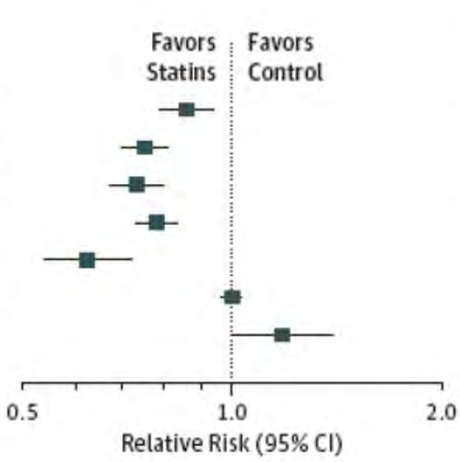
Cholesterol Treatment Trialists’ (CTT) Collaborators
Lancet **2008;371:117–25**

# Statin therapy for primary prevention of cardiovascular disease

- Meta-analysis of 18 trials: 56,934 participants
- Primary Prevention – NNT and NNH (not women specific though, but women were 39.7% of the participants)

Figure. Summary of Relative Risks and Numbers Needed to Treat for 5 Years for Outcomes in Primary Prevention Trials of Statins

| Outcome | Trials, No. | Statin Events, No. | Statin Total No. of Participants | Placebo/Control Events, No. | Placebo/Control Total No. of Participants | Relative Risk (95% CI) | No. Needed to Treat for 5 Years (95% CI) |
|---|---|---|---|---|---|---|---|
| All-cause mortality | 13 | 1077 | 24408 | 1223 | 23652 | 0.86 (0.79-0.94) | 138 (92-321) |
| Total CVD events | 9 | 1103 | 11892 | 1444 | 11913 | 0.75 ( 0.70-0.81) | 49 (40-66) |
| Total CHD events | 14 | 820 | 24217 | 1114 | 23832 | 0.73 (0.67-0.80) | 88 (72-119) |
| Total stroke events | 10 | 345 | 20302 | 442 | 19993 | 0.78 (0.68-0.89) | 155 (106-309) |
| Revascularization | 7 | 286 | 21166 | 461 | 21237 | 0.62 (0.54-0.72) | 96 (78-129) |
| Any adverse event[a] | 12 | 5748 | 20718 | 5090 | 19998 | 1.00 (0.97-1.03) | Not applicable |
| Type 2 diabetes | 2 | 342 | 12205 | 290 | 12202 | 1.18 (1.01-1.39) | 99 (46-1778) |

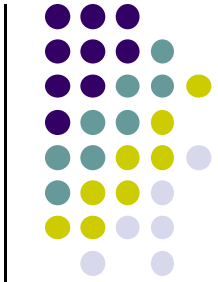



CVD indicates cardiovascular disease; CHD, coronary heart disease.

[a] Adverse events included cancer, myalgia and rhabdomyolysis, arthritis, and increased liver enzyme.

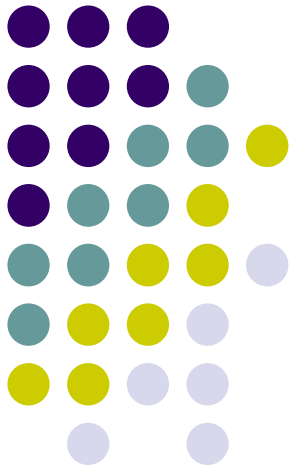
Taylor, JAMA. 2013;310(22):2451-2452. doi:10.1001/jama.2013.281348

# Primary Prevention of ASCVD in Women: Clinical recommendations



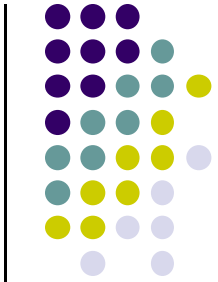
- Women and men have similar reduction in atherogenic lipoproteins in response to statin therapy.
- Women experience a reduction in ASCVD events similar to that in men, when adjusted for age and comorbidities.
- Women without ASCVD should undergo risk assessment and intensity of therapy should be matched to level of risk similar to assessment and treatment of men.

# Recommendations for Management of Dyslipidemia in Women: Secondary Prevention



- What is the benefit of lowering of atherogenic lipoproteins in secondary prevention of ASCVD events among women?

# Secondary ASCVD Risk Reduction in Women



- Cholesterol Treatment Trialists' Collaboration: 2010
- Meta-analysis of 26 RCTs of more- versus less-intensive statin therapy (5 trials) and of statin versus control (21 trials)
- 13 secondary prevention trials only, 1 exclusively primary prevention trial (JUPITER), 12 trials included patients with and without known ASCVD
- Total number of participants: 169,138
  - 45,495 women (27%)
  - 13,012 women in exclusively secondary prevention trials
  - 6801 women in JUPITER (only exclusively primary prevention)
  - 25,682 in trials including patients with and without known ASCVD
  - 7667 women in trials of more- versus less-intensive statin therapy
  - Data not provided for numbers of diabetic *and* women

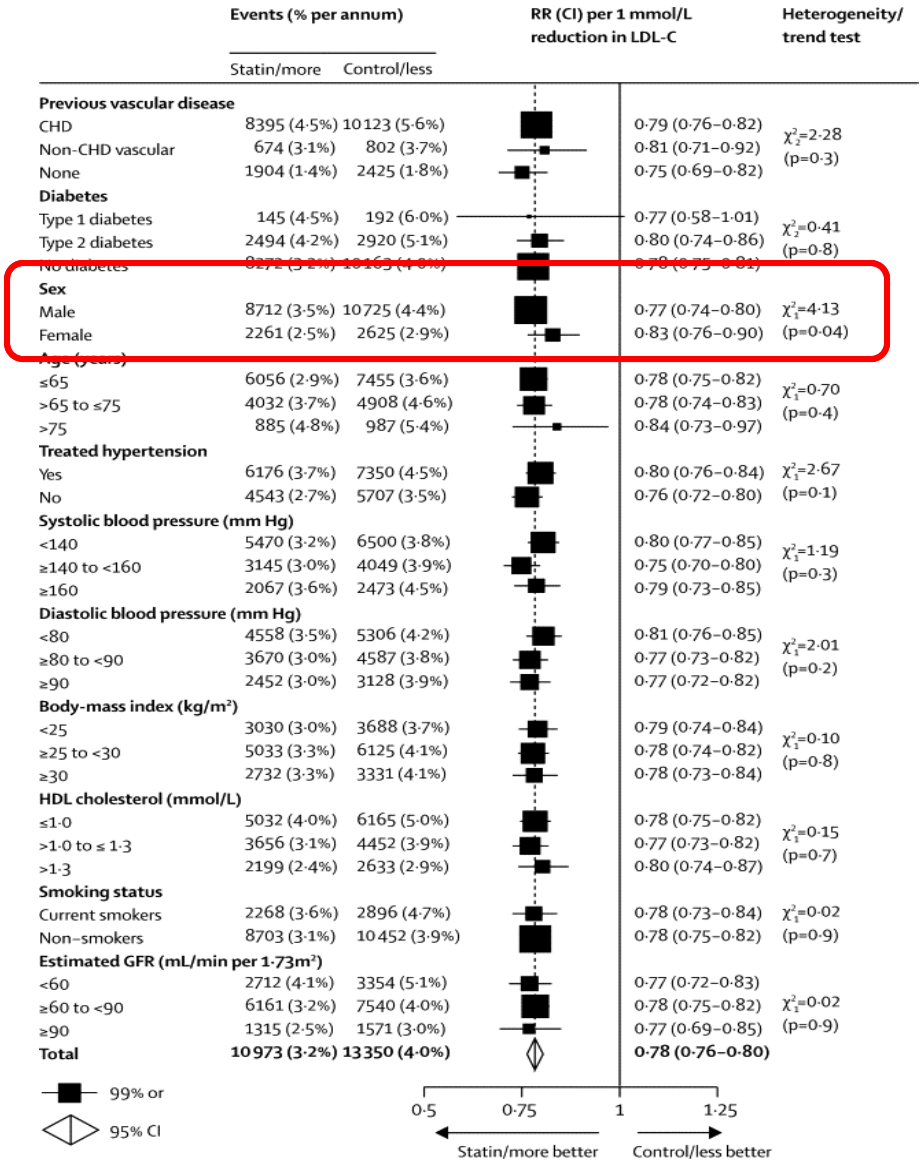
Lancet. 2010;376:1670-1681

# Secondary ASCVD Risk Reduction in Women

| | Number of patients | Treatment comparison (mg per day) | Median follow-up in survivors (years)* | Baseline LDL-C (mmol/L) | LDL-C difference at 1 year (mmol/L) | Women (%) | Diabetes (%) | Prior CHD (%) | Other vascular disease (%)† | No prior vascular disease (%)‡ |
|---|---|---|---|---|---|---|---|---|---|---|
| **More versus less statin** | | | | | | | | | | |
| PROVE-IT | 4162 | A80 vs P40 | 2·1 | 2·62§ | −0·65 | 911 (22%) | 734 (18%) | 4162 (100%) | 328 (8%) | 0 |
| A to Z | 4497 | S40 then S80 vs placebo then S20 | 2·0 | 2·09§ | −0·30 | 1100 (24%) | 1059 (24%) | 4497 (100%) | 479 (11%) | 0 |
| TNT | 10 001 | A80 vs A10 | 5·0 | 2·52 | −0·62 | 1902 (19%) | 1501 (15%) | 10 001 (100%) | 1537 (15%) | 0 |
| IDEAL | 8888 | A40–80 vs S20–40 | 4·8 | 2·64§ | −0·55 | 1702 (19%) | 1069 (12%) | 8888 (100%) | 971 (11%) | 0 |
| SEARCH | 12 064 | S80 vs S20 | 7·0 | 2·50 | −0·39 | 2052 (17%) | 1267 (11%) | 12 064 (100%) | 1062 (9%) | 0 |
| Subtotal (5 trials) | 39 612 | NA | 5·1‖ | 2·53‖ | −0·51‖ | 7667 (19%) | 5630 (14%) | 39 612 (100%) | 4377 (11%) | 0 |
| LIPS | 1677 | F80 vs placebo | 3·9 | 3·42 | −0·92 | 271 (16%) | 202 (12%) | 1677 (100%) | 142 (8%) | 0 |
| HPS | 20 536 | S40 vs placebo | 5·4 | 3·38 | −1·29 | 5082 (25%) | 5963 (29%) | 13 386 (65%) | 8865 (43%) | 3161 (15%) |
| PROSPER | 5804 | P40 vs placebo | 3·3 | 3·79 | −1·04 | 3000 (52%) | 623 (11%) | 1881 (32%) | 1026 (18%) | 3254 (56%) |
| ALLHAT-LLT | 10 355 | P40 vs usual care | 4·9 | 3·76 | −0·54 | 5051 (49%) | 3638 (35%) | 1188 (11%) | 1788 (17%) | 8037 (78%) |
| ASCOT-LLA | 10 305 | A10 vs placebo | 3·3 | 3·44 | −1·07 | 1942 (19%) | 2527 (25%) | 15 (<1%) | 1435 (14%) | 8860 (86%) |
| ALERT | 2102 | F40 vs placebo | 5·5 | 4·14 | −0·84 | 715 (34%) | 396 (19%) | 400 (19%) | 241 (11%) | 1702 (81%) |
| CARDS | 2838 | A10 vs placebo | 4·1 | 3·03 | −1·14 | 909 (32%) | 2838 (100%) | 9 (<1%) | 97 (3%) | 2738 (96%) |
| ALLIANCE** | 2442 | A10–80 vs usual care | 4·7 | 3·80 | −1·16 | 434 (18%) | 540 (22%) | 2442 (100%) | 162 (7%) | 0 |
| 4D** | 1255 | A20 vs placebo | 4·0 | 3·25 | −0·89 | 578 (46%) | 1255 (100%) | 630 (50%) | 666 (53%) | 344 (27%) |
| ASPEN** | 2410 | A10 vs placebo | 4·0 | 2·93 | −0·99 | 811 (34%) | 2410 (100%) | 578 (24%) | 302 (13%) | 1663 (69%) |
| MEGA**†† | 8214 | P10–20 vs usual care | 5·0 | 4·05 | −0·67 | 5547 (68%) | 1686 (21%) | 42 (<1%) | 53 (<1%) | 8119 (99%) |
| JUPITER** | 17 802 | R20 vs placebo | 2·0 | 2·70 | −1·09 | 6801 (38%) | 76 (<1%) | 0 | 0 | 17 802 (100%) |
| GISSI-HF** | 4574 | R10 vs placebo | 4·2 | 3·06 | −0·92 | 1032 (23%) | 1196 (26%) | 1797 (39%) | 4574 (100%) | 0 |
| AURORA** | 2773 | R10 vs placebo | 4·6 | 2·58 | −0·99 | 1050 (38%) | 731 (26%) | 659 (24%) | 743 (27%) | 1663 (60%) |
| Subtotal (21 trials) | 129 526 | NA | 4·8‖ | 3·70‖ | −1·07‖ | 37 828 (29%) | 26 580 (21%) | 48 291 (37%) | 21 543 (17%) | 70 025 (54%) |
| **Total (26 trials)** | 169 138 | NA | 4·9‖ | NA | NA | 45 495 (27%) | 32 210 (19%) | 87 903 (52%) | 25 920 (15%) | 70 025 (41%) |

Lancet. 2010;376:1670-1681

# ASCVD Risk Reduction in Women



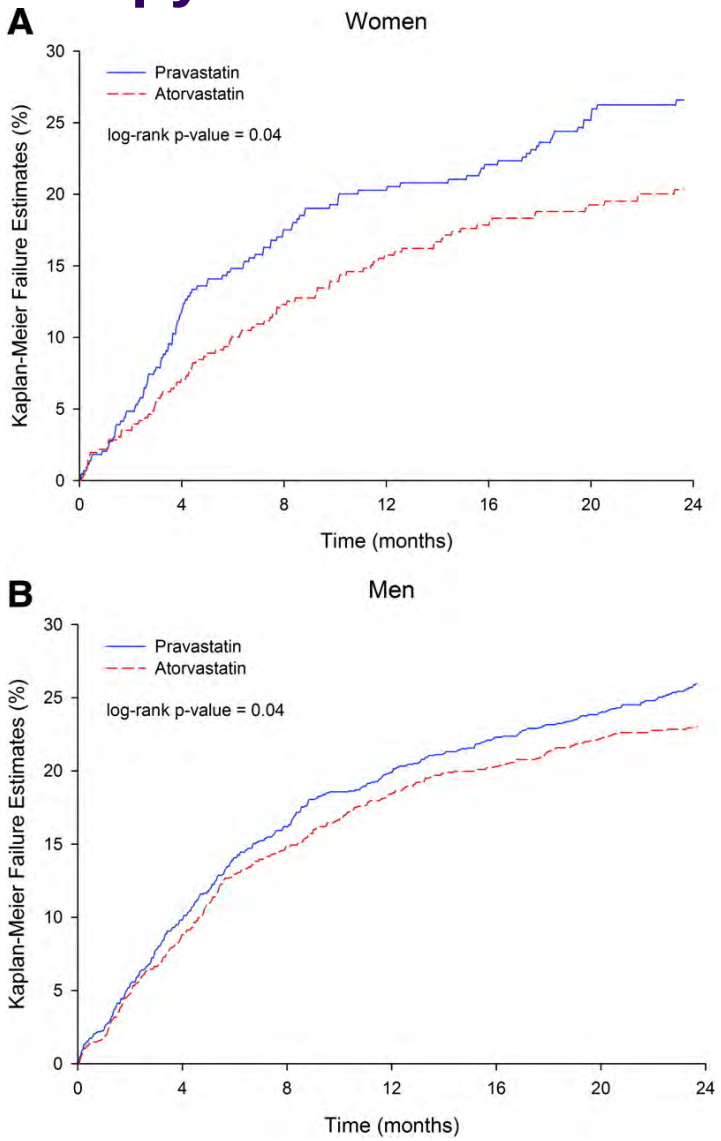

Lancet. 2010;376:1670-1681

# PROVE IT-TIMI 22: High- versus moderate-intensity statin therapy in ACS

- 911 women (21.9%)
- 3251 men (78.1%)

- Women: High-intensity: 25% relative reduction over standard dose
- HR 0.75 (95% CI, 0.57 to 0.99, p=0.04)

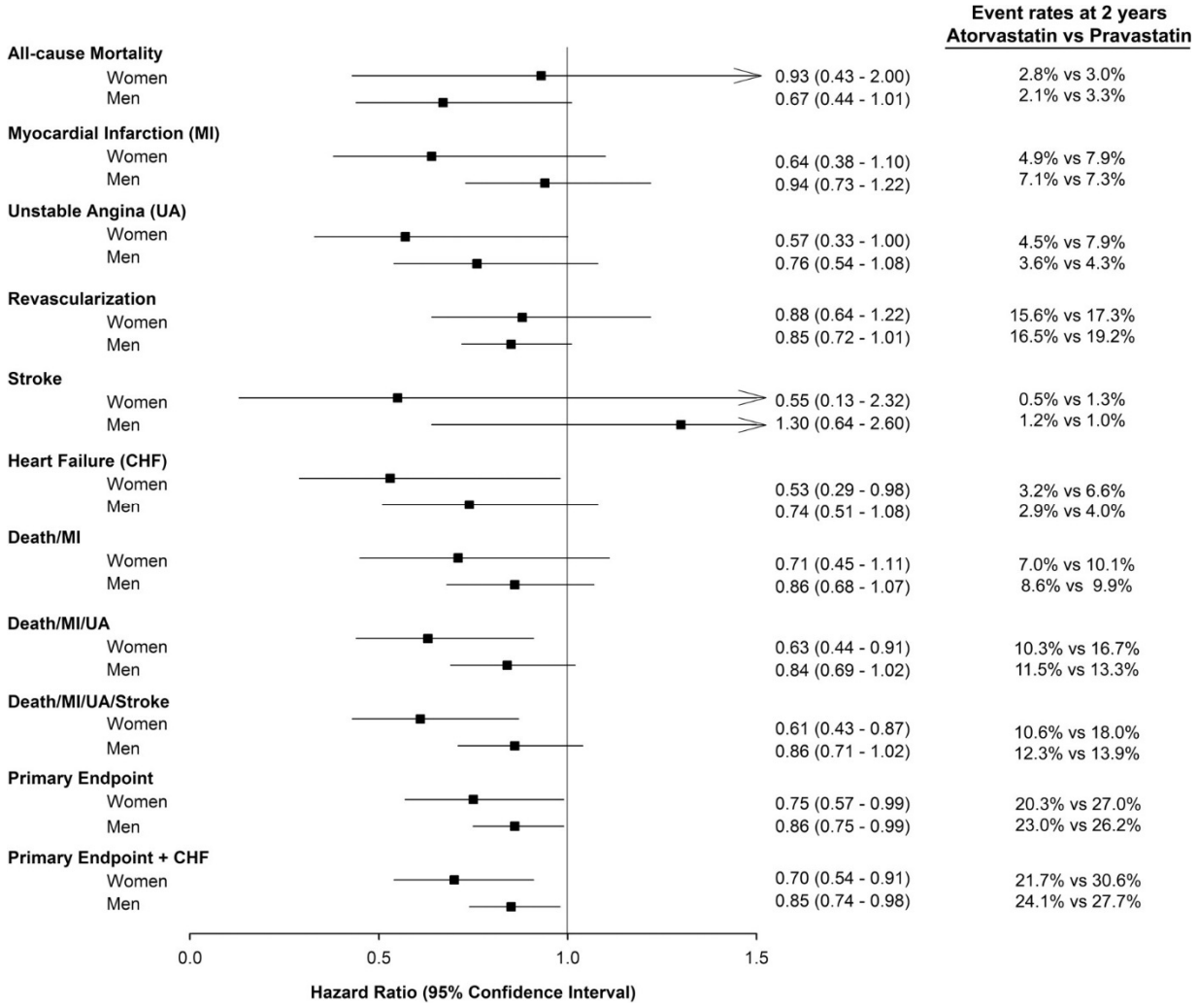
- Men: High-intensity relative reduction 14%
- HR 0.86 (95% CI, 0.75 to 0.99, p=0.04)




Kaplan-Meier curves of primary end point by study termination in women (A) and men (B).

Circ Cardiovasc Qual Outcomes. 2011;4:328-336

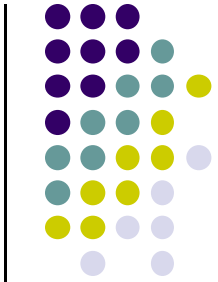
# PROVE IT-TIMI 22: High- versus moderate-intensity statin therapy in ACS




Hazard ratios between intensive-dose atorvastatin and standard-dose pravastatin therapy in women and men.

Circ Cardiovasc Qual Outcomes. 2011;4:328-336

# Secondary ASCVD Risk Reduction in Women

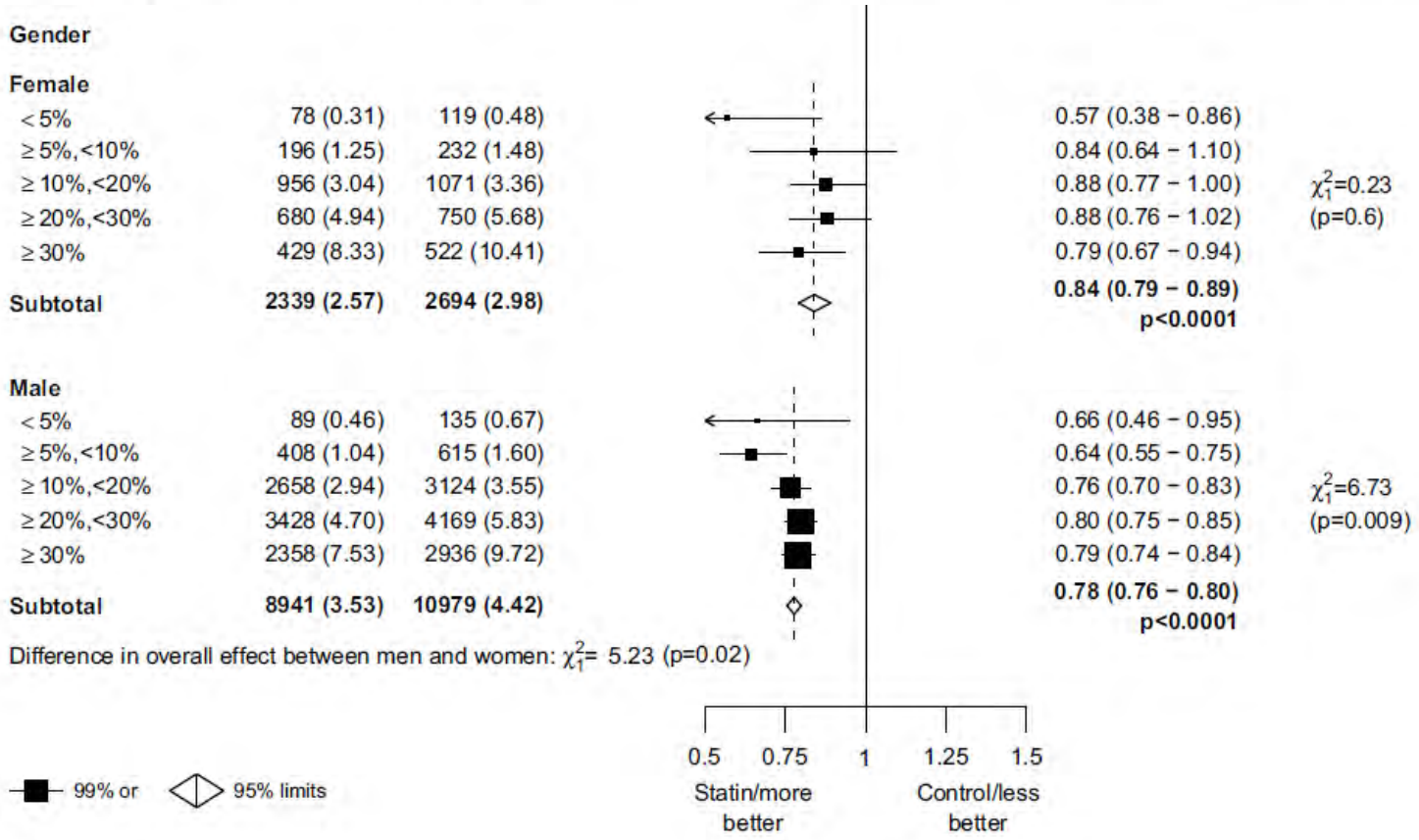


- Cholesterol Treatment Trialists' Collaboration: 2012
  - Effects of statin therapy in "low-risk" individuals compared to those at higher risk
  - Defined "low-risk" as < 10% 5-year major vascular event risk
    - (Mean risk 2.6%)
- 27 RCTs of statin versus control, more- versus less-intensive statin therapy
- Proportional reductions in MVE per 1.0 mmol/L LDL reduction (39 mg/dl) at least as large in "low-risk" individuals as for other participants, even after stratification by age and gender (numbers of women smaller)

Lancet. 2012;380:581-590

# Secondary ASCVD Risk Reduction in Women

**Webfigure 1: Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk, by baseline age and gender**

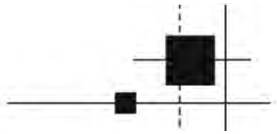



Lancet. 2012;380:581-590

# Outcomes in Search

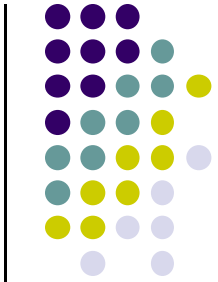
- Trial negative comparing simva 80 vs 20, but women point estimate actually better than men

| | | | |
|---|---|---|---|
| **Sex** | | | |
| Male | 1277/5005 (25·5%) | 1325/5007 (26·5%) | |
| Female | 200/1026 (19·5%) | 228/1026 (22·2%) | |



0·40

# Meta-analysis of statin effects in women versus men



- 18 RCTs with gender-specific outcomes
- N=141,235
  - Women: 40,235
  - 21,468 cardiovascular events
- “Benefit of statin was statistically significant in both sexes, regardless of the type of control, baseline risk, or type of endpoint in both primary and secondary prevention.”
- All-cause mortality was lower with statin therapy without significant interaction by gender.

Kostis, JACC. 2012:59:572-582

# Meta-analysis of statin effects in women versus men

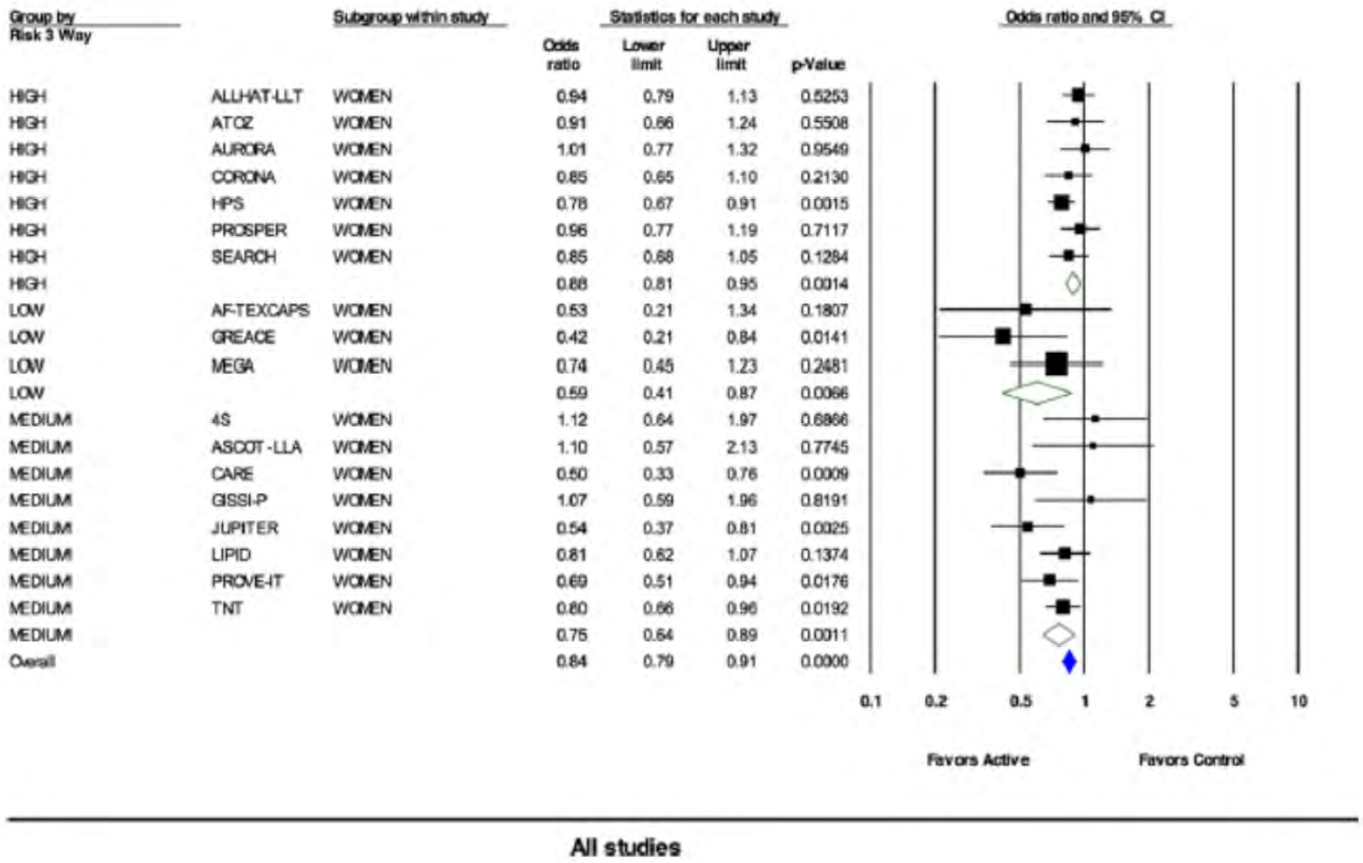
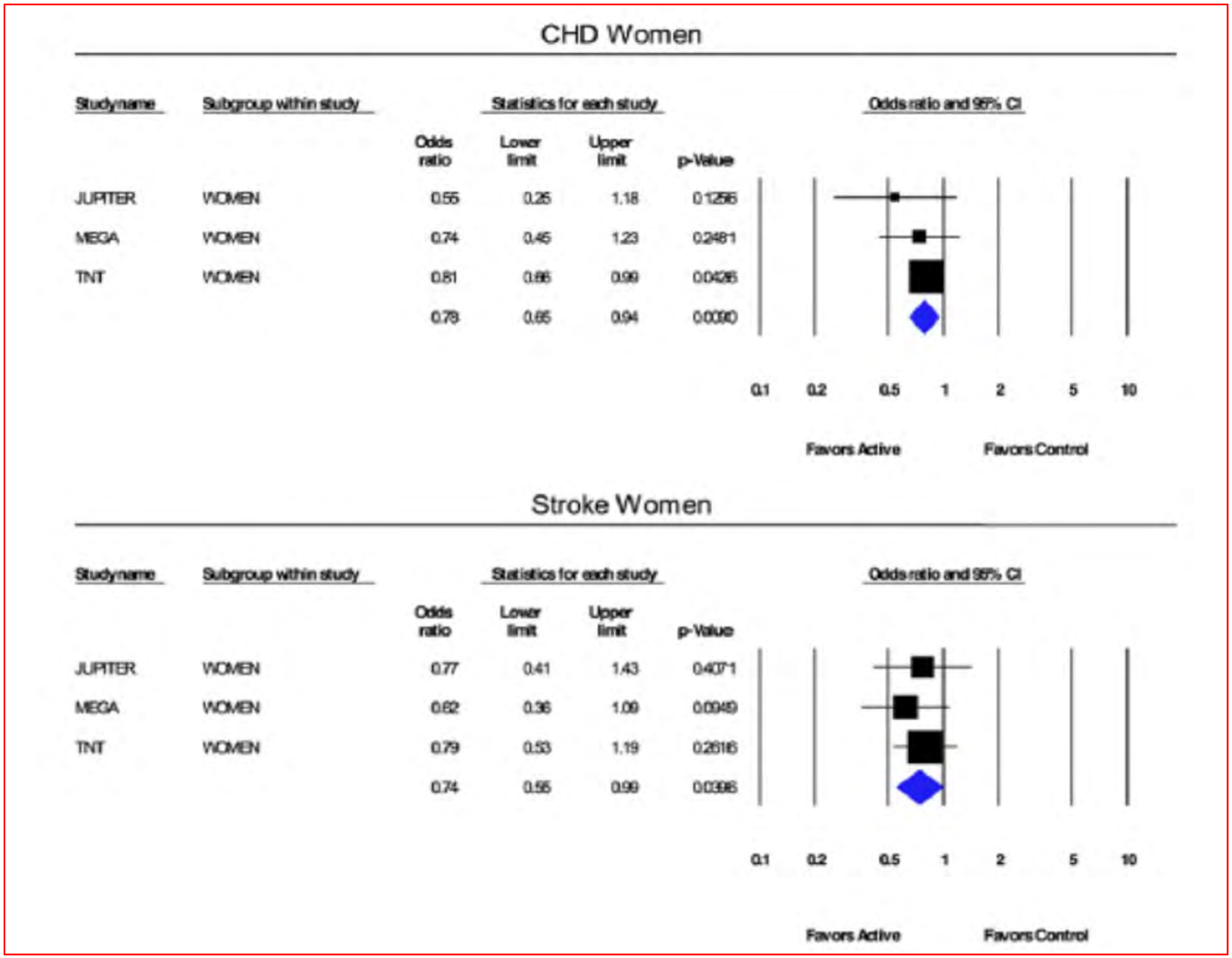



**Figure 2** Forest Plot for the Primary Event by Level of Risk of Participants in Each Study in Women

**Solid squares** represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. **Horizontal lines, diamonds,** and **squares** denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Trial acronyms as in Table 1.

Kostis, JACC.2012:59:572-582

# Meta-analysis of statin effects in women versus men




Kostis, JACC. 2012:59:572-582

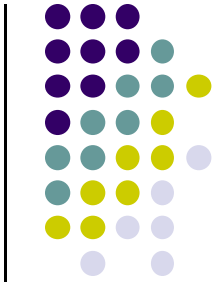
# Secondary ASCVD Risk Reduction in Women

**Table 1** Summary estimates of relative risk of fatal CHD associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies

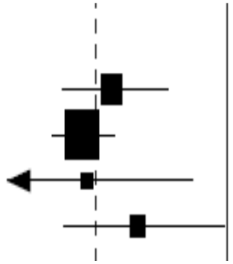
| | RR (95% CI) versus non-diabetic | *p* Value for heterogeneity |
|---|---|---|
| Age adjusted | | |
| Women | 3.69 (2.64–5.15) | 0.007 |
| Men | 2.16 (1.77–2.64) | |
| Multiple adjusted | | |
| Women | 3.12 (2.34–4.17) | 0.008 |
| Men | 1.99 (1.69–2.35) | |

Nutr Metab Cardiovasc Dis. 2010; 20:474-480

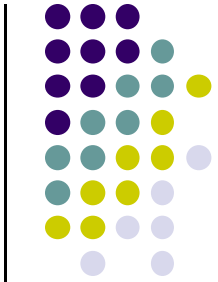
# Outcomes by gender with and without DM in HPS: No gender interaction – women with and without DM benefit



| | | | |
|---|---|---|---|
| **Sex** | | | |
| Male: diabetes | 471/2064 (22·8%) | 580/2083 (27·8%) | |
| no diabetes | 1195/5663 (21·1%) | 1555/5644 (27·6%) | |
| Female: diabetes | 130/914 (14·2%) | 168/902 (18·6%) | |
| no diabetes | 237/1628 (14·6%) | 282/1638 (17·2%) | |



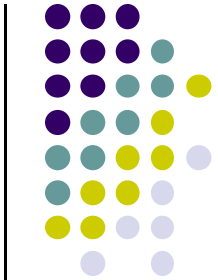
# Secondary ASCVD Risk Reduction in Women



- Trials in diabetic women
  - CARDS: 909 (32%) women: no analysis by gender (atorvastatin 10 mg versus placebo)
  - 4D: 578 (46%) women: diabetic hemodialysis patients (atorvastatin 20 mg versus placebo), no analysis by gender
  - ASPEN: 411 (34%) women: no analysis by gender (atorvastatin 10 mg versus placebo)

Lancet. 2012;380:581-590

# Secondary ASCVD Risk Reduction in Women: Clinical Recommendations

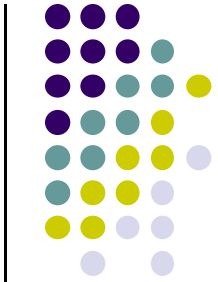


- Women with manifest ASCVD should be treated with high-intensity statin therapy according to current guidelines.

- Women with diabetes and no evidence of ASCVD should be treated with statin therapy according to current guidelines. The intensity of statin therapy should be matched to the level of ASCVD risk.

- Are there gender differences in the risk of adverse events associated with statin therapy?

# Statin Adverse Effects: Gender Effects

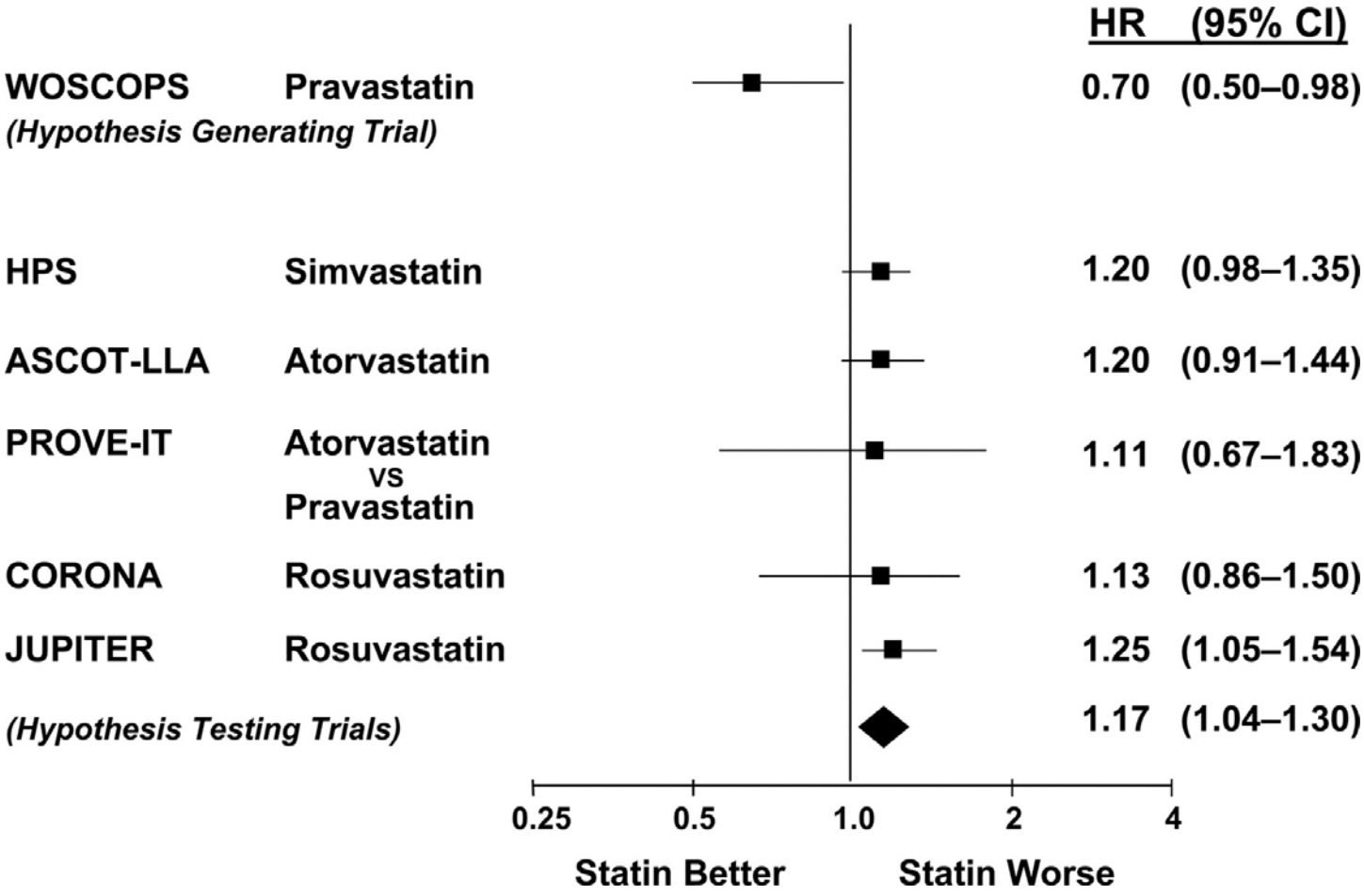


- PROVE IT-TIMI 22
  - No gender differences in adverse effects of high-intensity statin therapy (elevations in LFTs, CK, myalgias/myositis)

- Cholesterol Treatment Trialists' Collaboration: 2010, 2012
  - No safety analysis by gender

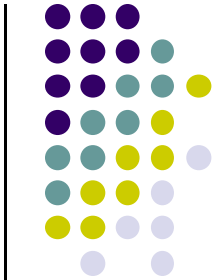
Lancet. 2012;380:581-590
Lancet. 2010;376:1670-1681
Circ Cardiovasc Qual Outcomes. 2011;4:328-336

# Effects of statin therapy on incident diabetes in hypothesis-generating and hypothesis-testing placebo controlled trials.




Ridker P M Circ Cardiovasc Qual Outcomes. 2009;2:279-285

# JUPITER: Gender differences in new physician-diagnosed diabetes



- Increased risk of new physician-diagnosed diabetes in women compared to men
  - Women: HR 1.49 (95% CI, 1.11 to 2.01, p=0.008)
  - Men: HR 1.14 (95% CI, 0.91 to 1.43, p=0.24)

Circulation. 2010;121:1067-1077

# Atorvastatin Meta-analysis (TNT, IDEAL, SPARCL)

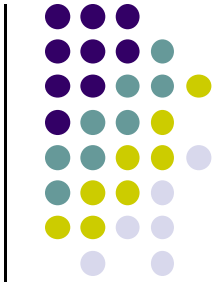
- Predictors of incident DM – male is higher in multivariate analysis, not female suggesting that other characteristics play a role (i.e. baseline glucose). Similar in IDEAL and SPARCL HR>1, but NS)

**Table 4** Univariate and Multivariate Analyses of Predictors of New-Onset T2DM in the TNT Trial

| | Univariate Analysis | | Multivariate Analysis: Full Model | | Multivariate Analysis: Reduced Model | |
|---|---|---|---|---|---|---|
| Baseline Characteristics | HR (95% CI)* | p Value* | HR (95% CI)* | p Value* | HR (95% CI)* | p Value* |
| Age, yrs per 5-yr increase | 0.97 (0.93–1.01) | 0.144 | 0.98 (0.93–1.03) | 0.3804 | — | — |
| Fasting glucose per 10-mg/dl increase | 2.76 (2.56–2.97) | <0.0001 | 2.53 (2.34–2.73) | <0.0001 | 2.53 (2.34–2.73) | <0.0001 |
| BMI per 3-kg/m$^2$ increase | 1.28 (1.25–1.32) | <0.0001 | 1.20 (1.15–1.25) | <0.0001 | 1.21 (1.16–1.26) | <0.0001 |
| Natural log [WBC] per 0.25-log (10$^3$/mm$^3$) increase | 1.27 (1.18–1.38) | <0.0001 | 1.16 (1.06–1.26) | 0.0011 | 1.15 (1.06–1.24) | 0.0012 |
| SBP per 20-mm Hg increase | 1.24 (1.13–1.36) | <0.0001 | 1.072 (0.951–1.210) | 0.254 | — | — |
| DBP per 10-mm Hg increase | 1.21 (1.11–1.31) | <0.0001 | 1.024 (0.92–1.14) | 0.655 | — | — |
| Total cholesterol per 20-mg/dl increase | 1.14 (1.07–1.21) | <0.0001 | — | — | — | — |
| LDL cholesterol per 10-mg/dl increase | 1.032 (0.988–1.078) | 0.162 | — | — | — | — |
| HDL cholesterol per 10-mg/dl increase | 0.76 (0.70–0.82) | <0.0001 | — | — | — | — |
| Total/HDL cholesterol ratio per 1-U increase | 1.51 (1.40–1.63) | <0.0001 | 1.076 (0.96–1.21) | 0.228 | — | — |
| Natural log [triglyceride] per 1.0-log (mg/dl) increase | 2.78 (2.33–3.32) | <0.0001 | 1.67 (1.30–2.16) | 0.0001 | 1.85 (1.53–2.22) | <0.0001 |
| Sex, male | 0.94 (0.77–1.15) | 0.545 | 1.028 (0.82–1.28) | 0.809 | — | — |
| Current smokers | 1.14 (0.92–1.41) | 0.225 | 0.83 (0.623–1.10) | 0.194 | — | — |
| Hypertension | 1.64 (1.40–1.92) | <0.0001 | 1.21 (1.02–1.43) | 0.029 | 1.24 (1.05–1.46) | 0.0098 |
| Use of statins during at screening | 1.065 (0.91–1.25) | 0.436 | 1.013 (0.86–1.19) | 0.874 | — | — |
| Use of beta-blockers (before or at baseline) | 1.28 (1.10–1.50) | 0.0018 | 1.022 (0.87–1.20) | 0.789 | — | — |
| Treatment with atorvastatin 80 mg | 1.15 (0.98–1.34) | 0.082 | 1.10 (0.94–1.29) | 0.221 | 1.10 (0.94–1.29) | 0.226 |

Waters, JACC 2011

# Gender differences in muscle-related toxicity



- US FDA AERS 1997-2011
- 3,472,494 reports
- Rosuvastatin, atorvastatin, simvastatin, pravastatin, cerivastatin
- All 5 associated with muscle-related side effects, (>>cerivastatin)
- No gender differences

Pharmacology & Pharmacy. 2013; 4: 340-346

# SPARCL

- Safety endpoints by sex:

**Table 4. SPARCL Safety by Sex**

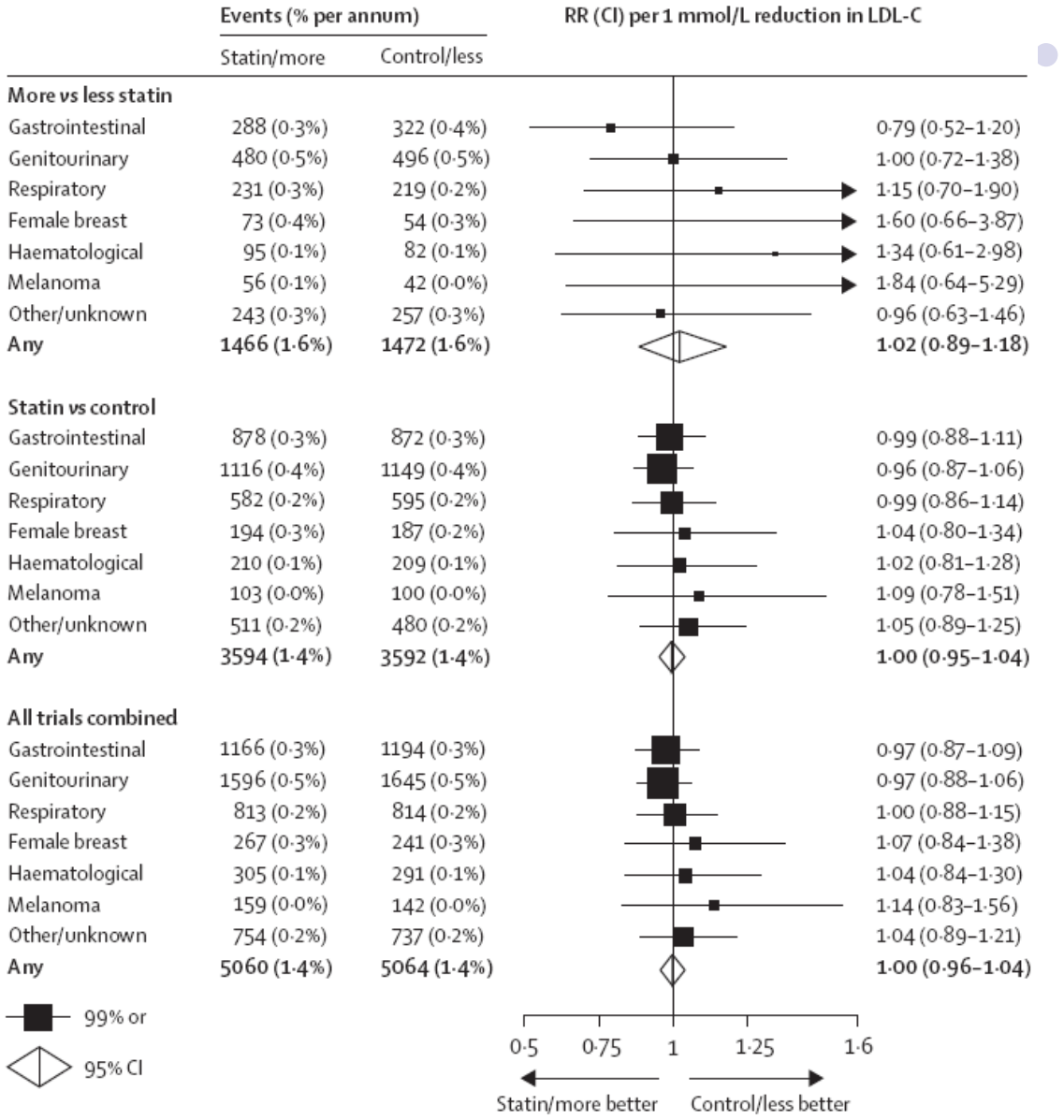
| | Women | | Men | |
|---|---|---|---|---|
| | Atorvastatin (n=938) | Placebo (n=970) | Atorvastatin (n=1427) | Placebo (n=1396) |
| ALT/AST >3×ULN*, n (%) | 13 (1.39%) | 1 (0.10%) | 8 (0.56%) | 2 (0.14%) |
| CPK >10×ULN*, n (%) | 1 (0.11%) | 0 | 1 (0.07%) | 0 |
| Musculoskeletal AEs | | | | |
| Myalgia, n (%) | 63 (6.7%) | 72 (7.4%) | 66 (4.6%) | 69 (4.9%) |
| Myopathy, n (%) | 3 (0.3%) | 2 (0.2%) | 4 (0.3%) | 5 (2.0%) |
| Rhabomyolysis, n (%) | 1 (0.1%) | 2 (0.2%) | 1 (0.1%) | 1 (0.1%) |

*Persistent elevations: 2 consecutive elevations within 4 to 10 days.
ALT indicates Alanine aminotransferase; ULN, upper limits of normal; CPK, creatine phosphokinase.

***Stroke*. 2008;39:2444-2448**

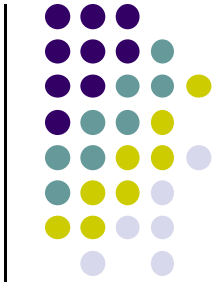
# Cancer Incidence By Site in Statin Trials

No gender specific analysis,
but no increase in breast cancer




CTT Collaboration. ***Lancet* 2010; 376: 1670–81**

# Gender differences in adverse effects of statin therapy: clinical recommendations

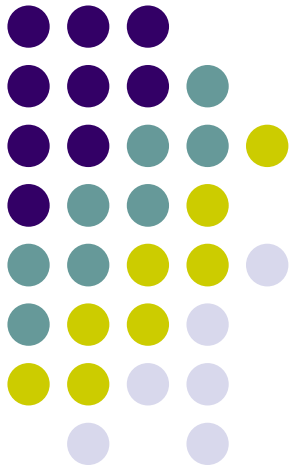


- Women may have an increased risk of muscle-related side effects and new physician-diagnosed diabetes with statin therapy.

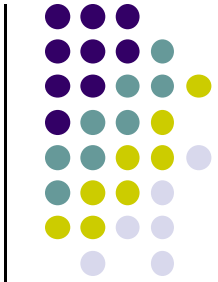
- Differences may be, in part, related to patient characteristics predisposing to adverse effects rather than gender-specific effects (older, insulin resistance, less musculature, etc).

- I need to include USAGE data here…..

# Non-statin therapy in women



# Resins and Ezetimibe



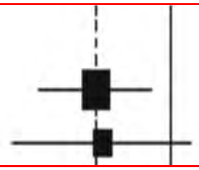
- Resins
  - **1978 Colestipol study**: non-significant ↓ in total mortality, non-significant ↑ in CHD mortality
  - **LRC-CPPT** – all male
- Ezetimibe
  - **ENHANCE** - 350 women with FH; simva plus ezetimibe vs simva alone;  IMT study which failed to meet primary end-point; no gender-specific results
  - **SHARP** - 3492 women with CKD; Ezetimibe plus simvastatin vs placebo. Overall trial 17% reduction in major coronary events

Dorr AE et al. J Chronic Dis 1978;31:5-14; ENHANCE NEJM 2008; SHARP slide presentation (link on theheart.org)

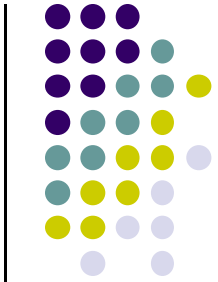
# SHARP

- Main endpoint paper – point estimates identical, CI wider in women due to smaller sample size:

| | | | |
|---|---|---|---|
| Sex ($\chi^2_1$=0·02; p=0·90) | | | |
| Male | 376/2915 (12·9%) | 445/2885 (15·4%) | 0·83 (0·72–0·95) |
| Female | 150/1735 (8·6%) | 174/1735 (10·0%) | 0·85 (0·68–1·05) |



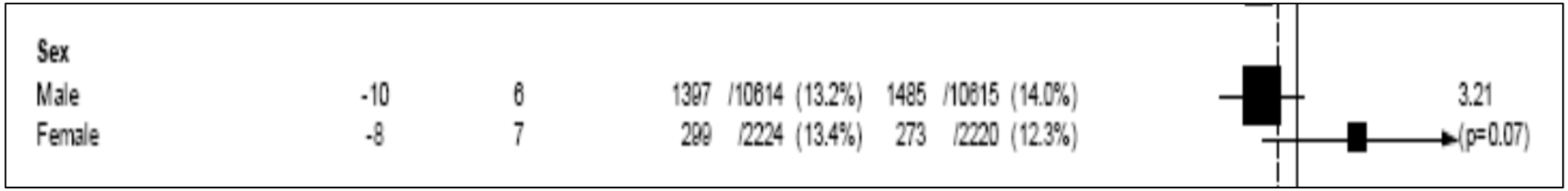
# Niacin Trials



- Coronary Drug Project (JACC 1986)
  - Secondary prevention study
  - All male
- HATS (NEJM 2001)
  - Simva plus niacin without antioxidants had least coronary progression
  - 21 women out of 160 subjects, no gender-specific results
- ARBITER HALTS-6 (final results; JACC 2010)
  - IMT progression less with statin/niacin than with statin/ezetimibe
  - 72 women, no gender specific results
- AIM HIGH
  - 14.8% women
  - No interaction by gender

# Effects of ER niacin laropiprant in high-risk patients: HPS 2Thrive Analysis by Gender

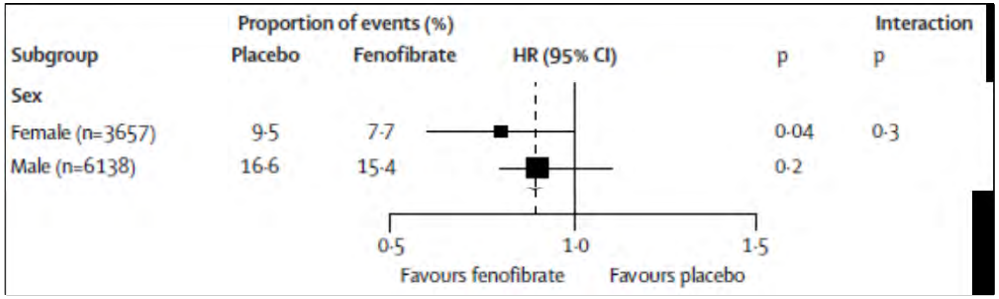
- 25,673 participants (17.3% women)
- From online Summary Appendix 1: note women did worse with NA, almost stat significant
- First major vascular event




N Engl J Med 2014; 371:203-212

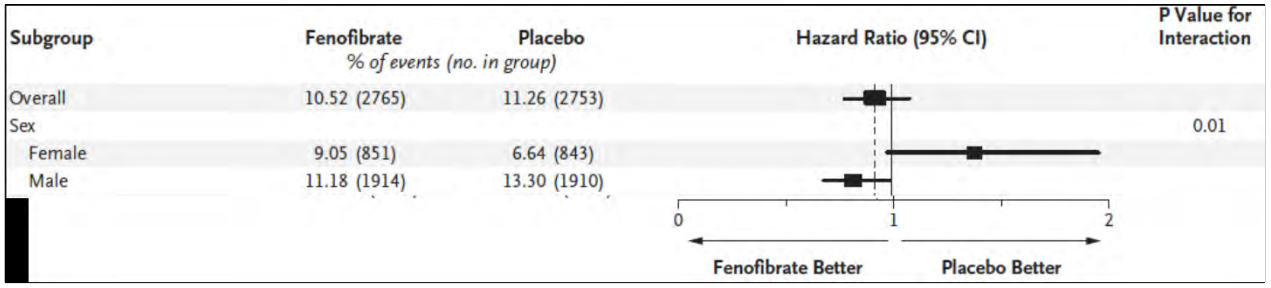
# Fibrate Trials

- Helsinki Heart Study and VA-HIT: all male
- FIELD – Patients with TII DM; 3657 women




- Did not meet primary endpoint
- No gender interaction
- Greater improvement in lipid profile in women
- Similar CV event reduction in dyslipidemia men and women

- ACCORD – Patients with TII DM; 1694 women

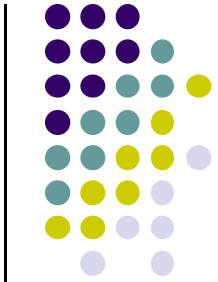



- Did not meet primary endpoint
- Benefit for men, possible harm for women ($p_{interaction}$=0.01)

- However, dyslipidemic women (high TG, low HDL) had same benefit as dyslipidemic men

Field Lancet 2005; Accord NEJM 2010
Diabetologia. 2014
NEJM. 2010;362:1563-1574

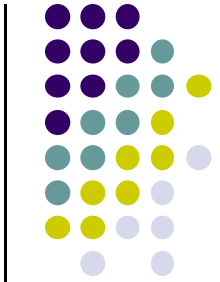
# Fish Oil



- GISSI Prevenzione Trial
  - Secondary prevention; 15% female; no gender-specific data
- JELIS
  - 18,645 Japanese patients (12,786 women); mean F/U 4.6 years
  - Mixed primary and secondary prevention; TC ≥ 6.5 mmol/l (= 250 mg/dL)
  - 1800 mg EPA with statin vs statin only
  - Sudden death, MI, ACS, PCI, CABG combination endpoint
    - Women 2% vs. 1.7% HR 0.87 (0.68 -1.13)
    - Men 6.8% vs. 5.2% HR 0.76 (0.62 - 0.94)
    - P for interaction: 0.43
- Alpha Omega Trial
  - 1054 women (12% of study population) with history of MI; F/U 40.8 months
  - No overall benefit of N-3 FA or alpha-linolenic acid fortified margarine
    - Women HR 0.82, 95% CI 0.58-1.16
    - Men HR 1.06, 95% CI 0.89-1.25

Alpha Omega: NEJM 2010; JELIS: Lancet 2007; GISSI Prevenzione: Lancet 1999

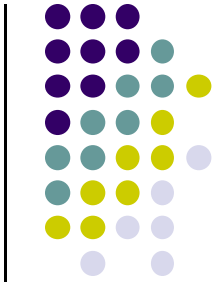
# Non-statin drugs for ASCVD prevention in women: Clinical recommendations



- There is limited gender-specific evidence for the benefit of non-statin drugs in prevention of ASCVD.

.

# ASCVD Risk Assessment for Primary Prevention in Women



- Risk assessment for primary prevention in women should be calculated using a global ASCVD risk prediction algorithm.
- In young women, calculation of lifetime risk may provide important information to guide the decision to initiate statin therapy.
- Other considerations which may inform the decision include: hs-CRP, family history of premature ASCVD among first degree relatives, LDL-C $\geq$160 mg/dl, CAC $\geq$300 Agatston or $\geq$75$^{th}$ percentile, ABI <0.9

# Summary of NLA Recommendations for Management of Dyslipidemia in Women

| Recommendations | Strength | Quality |
|---|---|---|
| In general, women should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015) with the following special considerations. | A | High |
| First-line cholesterol-lowering drug therapy, unless contraindicated, is moderate- to high-intensity statin. The statin dosage may be increased or the patient switched to a more efficacious agent, if goal levels of atherogenic cholesterol are not achieved. Statin therapy should be a consideration for patients at very high risk (i.e., ASCVD or diabetes mellitus with ≥2 major ASCVD risk factors), even if the pre-treatment levels of atherogenic cholesterol are below the treatment goals. | A | High |
| Non-statin drug therapy with cholesterol absorption inhibitor, bile acid sequestrant, fibric acid, nicotinic acid, or long-chain omega-3 fatty acid concentrates (the latter currently indicated only for very high TG) may be considered for women with contraindications for, or intolerance to, statin therapy, or in combination with statin therapy for patients who need additional lowering of atherogenic cholesterol to achieve treatment goals. | A | High |
| Women taking statins may be at increased risk for certain adverse events, particularly myalgia. Variations between men and women observed in clinical studies of statin-related myalgia incidence may have been related to differences in age, comorbidities, body composition, and polypharmacy. | B | Low |

# Management of the Patient with Progressive Atherosclerosis Despite Evidence-based Therapy

Peter H. Jones MD FACP, FNLA
Associate Professor
Methodist DeBakey Heart and Vascular Center
Baylor College of Medicine

# Background

- Evidence-based lipid therapy in secondary prevention is based on the ACC/AHA 2013 Blood Cholesterol guidelines – the use of high-intensity statin, irrespective of baseline LDL-C and non-HDL-C
- The IMPROVE IT study has demonstrated that a nonstatin (ezetimibe) reduction in LDL-C provides incremental benefit over statin therapy alone – lower LDL-C is better!
- IMPROVE IT also showed that the rate of recurrent events in post ACS patients on statin + ezetimibe was still 32% at 7 years!

# Who Are the Patients with Progressive ASCVD Events Despite Evidence-based Therapy?

- Very high risk patients with less than expected lipid response to moderate or high-intensity statins, and those with intolerance to optimal statin dosing
- Very high risk patients with recurrent events on high-intensity statins
- FH patients with established CVD not at target LDL-C and non-HDL-C on maximally tolerated lipid drug therapy

# What are the Potential "Lipid" Factors Responsible for Progressive ASCVD Events?

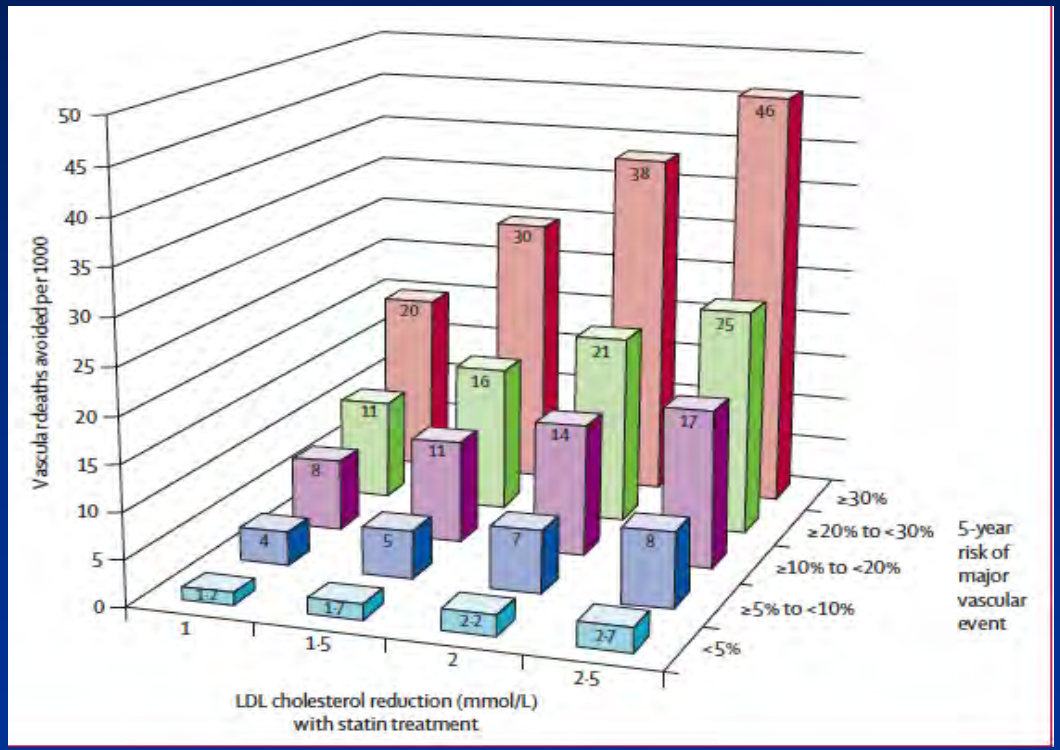
- Discordance in atherogenic particle number:
  - LDL cholesterol at goal but elevated non-HDL-C, apo B and/or LDL-P
  - Most frequently associated with insulin resistance (MeS, NAFLD), high TGRL and T2DM
- High Lp(a): > 50 mg/dL (> 75 nmol/L)
- Low HDL cholesterol and/or poor efflux function

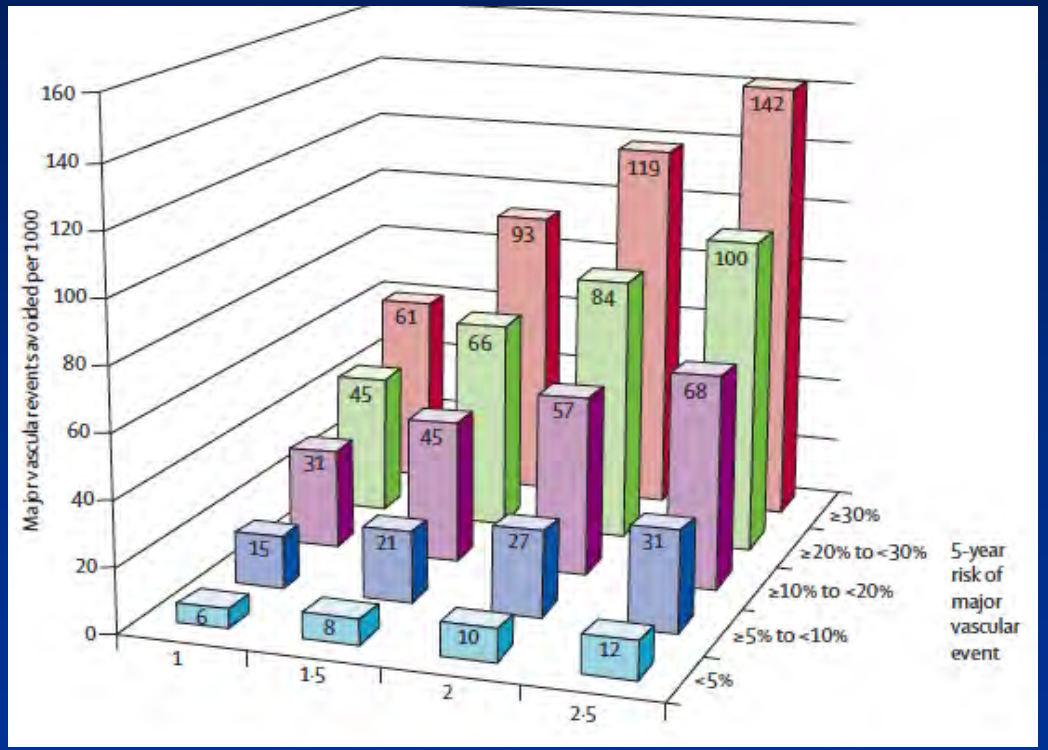
# Other Factors Responsible for Recurrent ASCVD Events

- Compliance to therapy
- Manageable risk factors:
  Smoking, BP, glucose control, fitness/exercise, dietary pattern, possibly inflammation (RA, SLE, psoriasis)
- Thrombosis control
- Psychologic:
  Stress, depression, poor sleep (OSA)
- “Black box” of genetics, aging

# Effects of Lowering LDL-C with Statins in People at Risk for Vascular Disease

## CTT Meta-analysis of individual data from 27 randomized trials




Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet 2012;380:581–90.

REVIEW

CLINICIAN'S CORNER

# Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins

## A Meta-analysis

**Conclusion** Among statin-treated patients, on-treatment levels of LDL-C, non–HDL-C, and apoB were each associated with risk of future major cardiovascular events, but the strength of this association was greater for non–HDL-C than for LDL-C and apoB.

Boekholdt et al. JAMA. 2012;307:1302-09.

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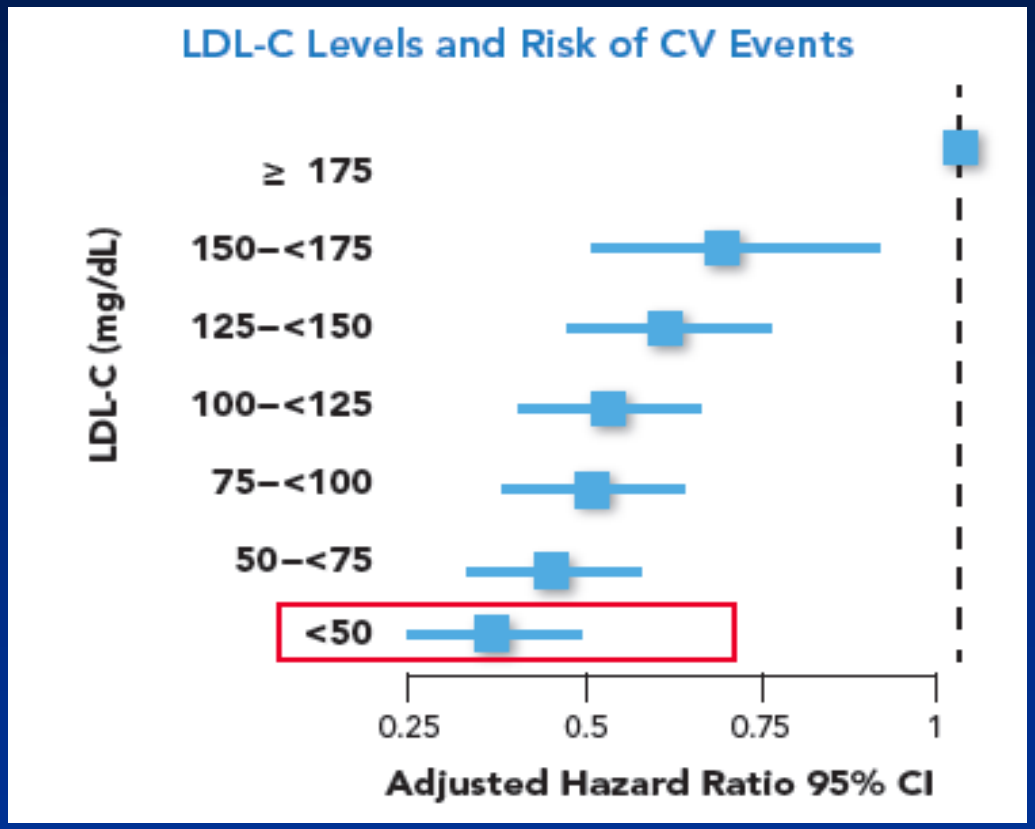
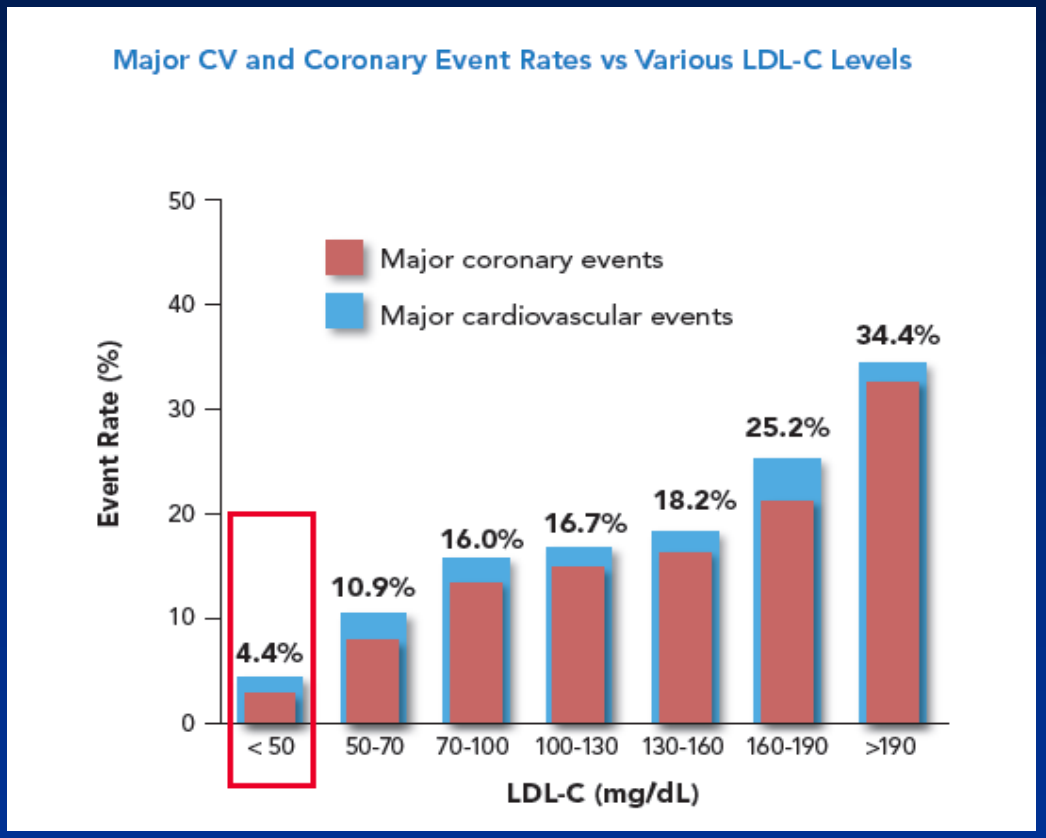
http://dx.doi.org/10.1016/j.jacc.2014.02.615

# Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events

## A Meta-Analysis of Statin Trials

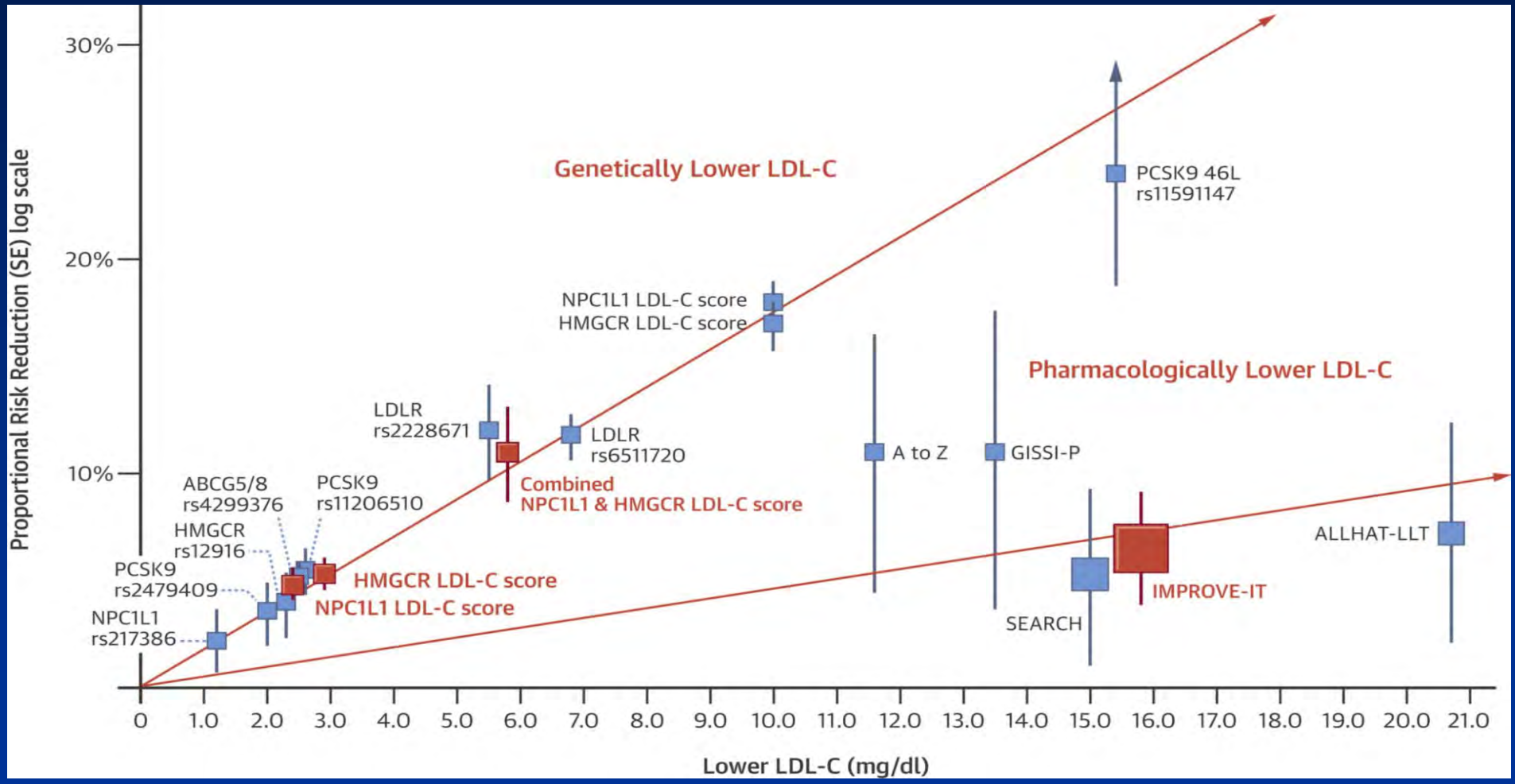
S. Matthijs Boekholdt, MD, PhD,* G. Kees Hovingh, MD, PhD,† Samia Mora, MD, MHS,‡ Benoit J. Arsenault, PhD,† Pierre Amarenco, MD,§ Terje R. Pedersen, MD, PhD,‖ John C. LaRosa, MD,¶ David D. Waters, MD,# David A. DeMicco, DPharm,** R. John Simes, MD,†† Antony C. Keech, MBBS, MSc,†† David Colquhoun, MD,‡‡ Graham A. Hitman, MD,§§ D. John Betteridge, MD,‖‖ Michael B. Clearfield, DO,¶¶ John R. Downs, MD,##*** Helen M. Colhoun, MD,††† Antonio M. Gotto, Jr, MD, DPhil,‡‡‡ Paul M. Ridker, MD, MPH,‡ Scott M. Grundy, MD, PhD,§§§ John J.P. Kastelein, MD, PhD†




Boekholdt et al. J Am Coll Cardiol 2014;64:485–94.

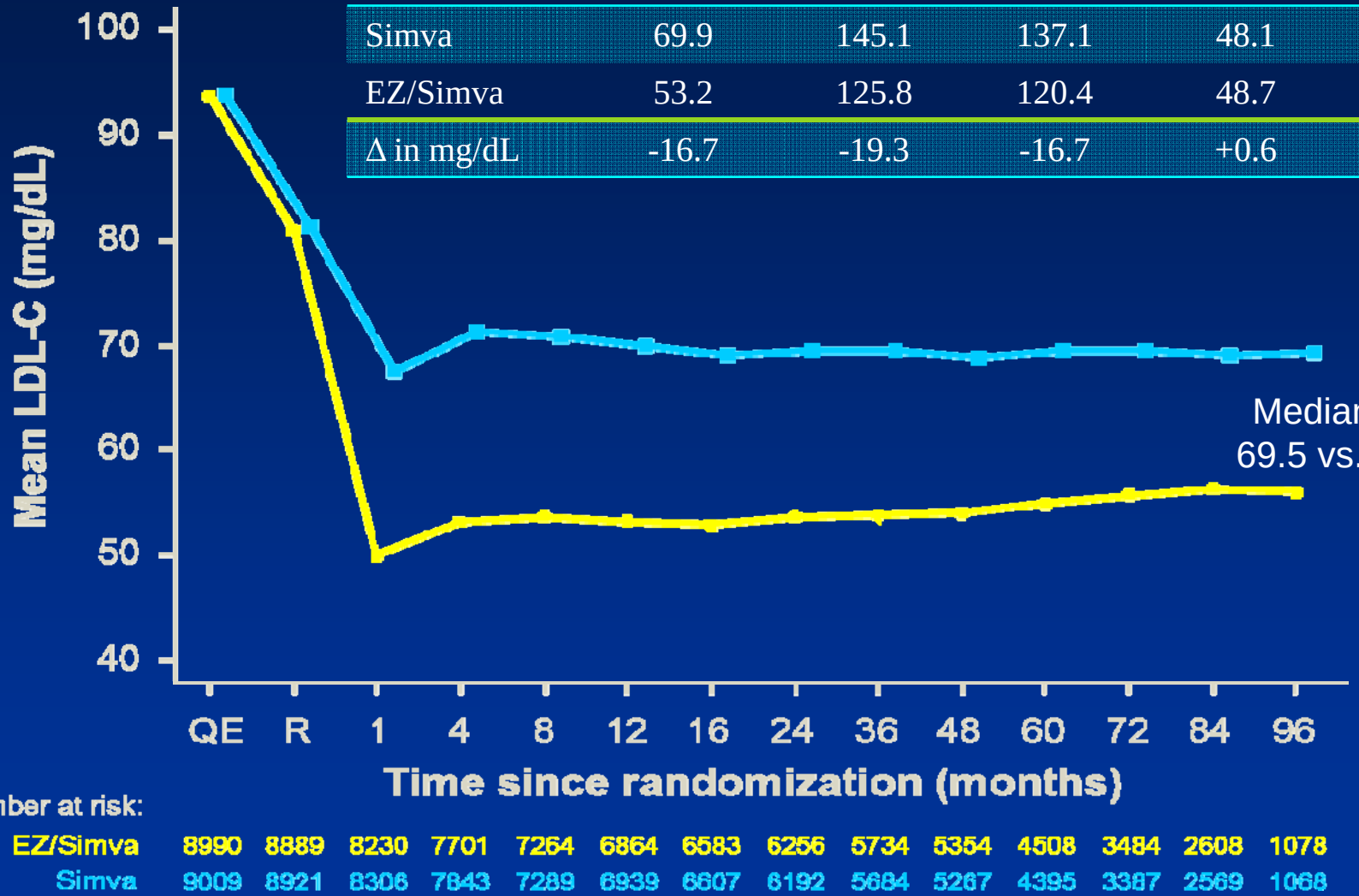
# Effect of Naturally Random Allocation to Lower LDL-C on Risk of CHD Mediated by Polymorphisms in NPC1L1, HMGCR, or Both: A 2 × 2 Factorial Mendelian Randomization Study




**Ference BA et al.** ***J Am Coll Cardiol.*** **2015;65:1552-1561.**

# IMPROVE IT: LDL-C and Lipid Changes

| 1 Yr Mean | LDL-C | TC | TG | HDL | hsCRP |
|---|---|---|---|---|---|
| Simva | 69.9 | 145.1 | 137.1 | 48.1 | 3.8 |
| EZ/Simva | 53.2 | 125.8 | 120.4 | 48.7 | 3.3 |
| Δ in mg/dL | -16.7 | -19.3 | -16.7 | +0.6 | -0.5 |

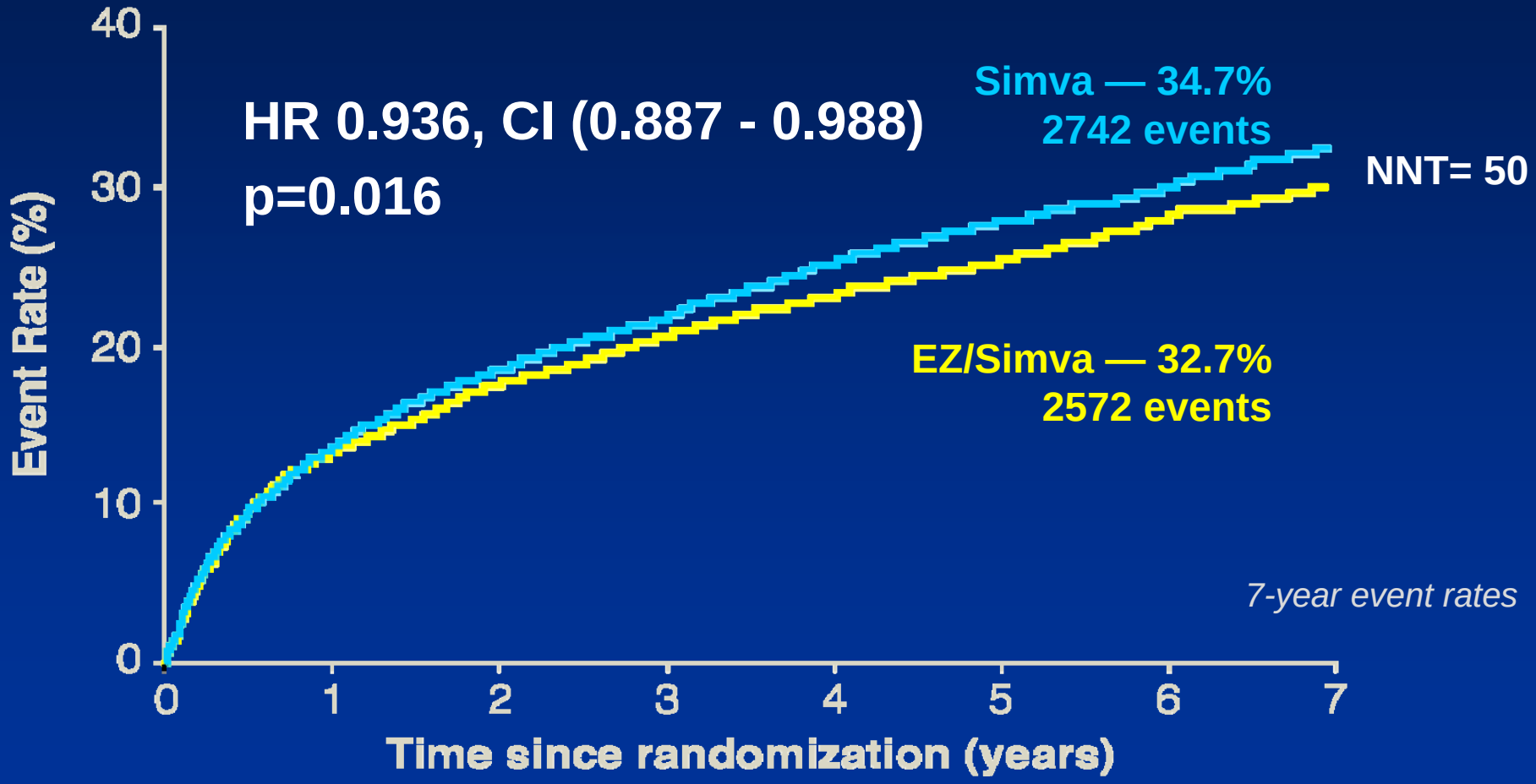



Median Time avg.
69.5 vs. 53.7 mg/dL

NEJM 2015

# IMPROVE IT: Primary Endpoint — ITT

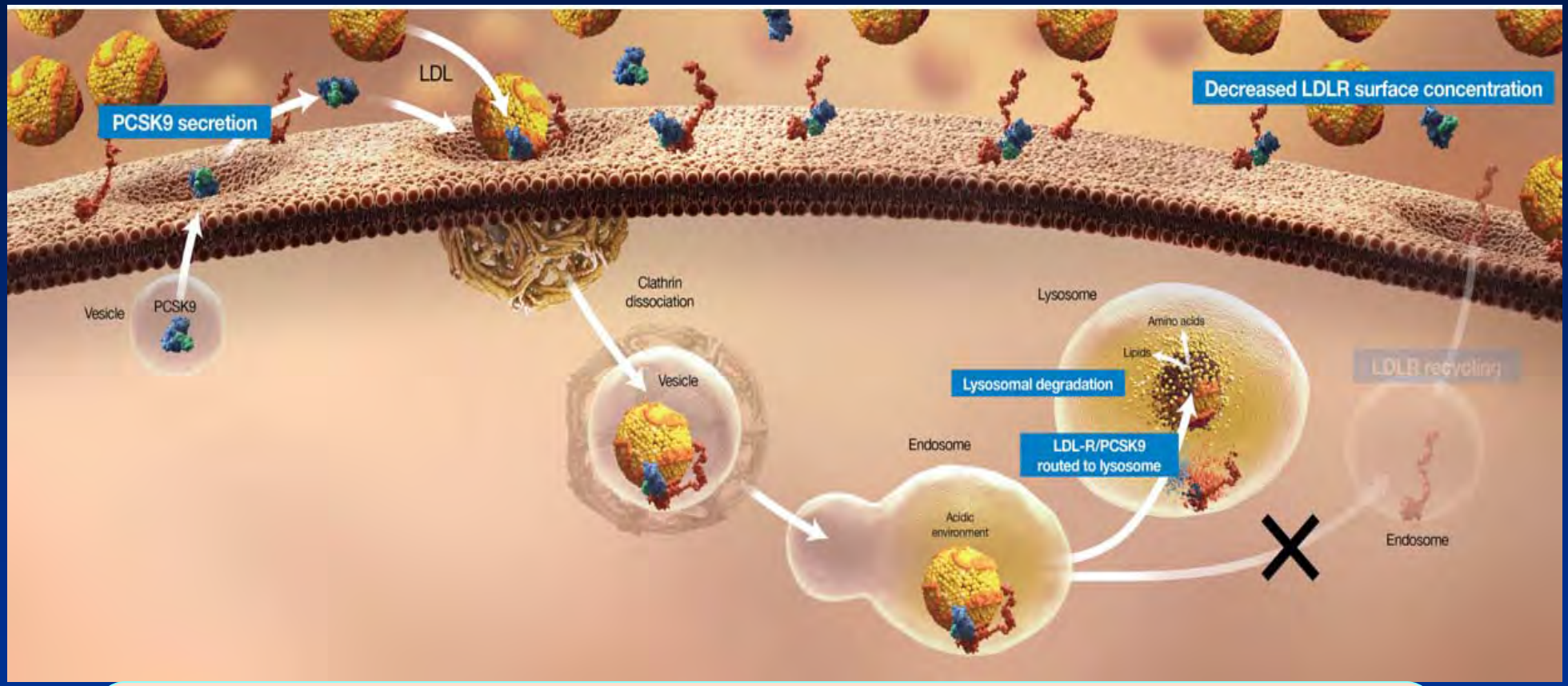
*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke*




NEJM 2015

# Is Residual Risk All About Lower Atherogenic Particle Number?

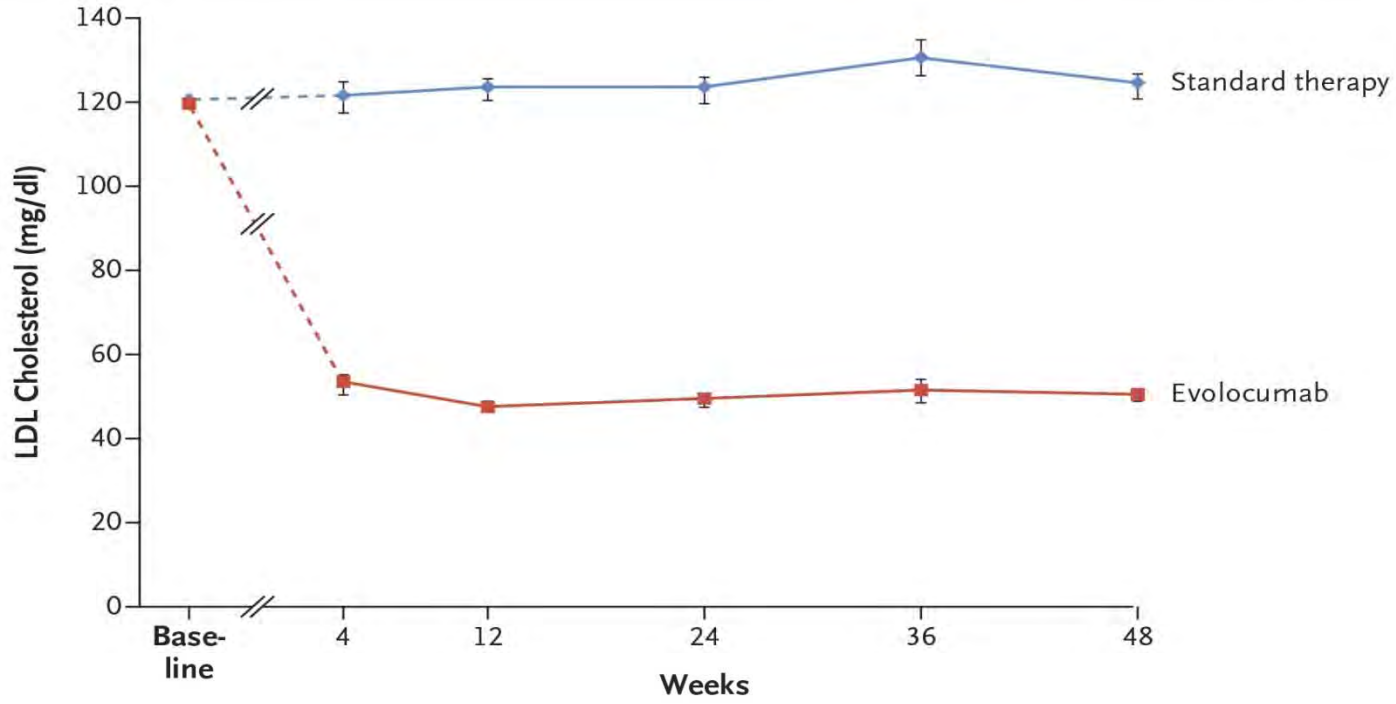
# Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Is a Regulator of LDL-R Recycling




- **PCSK9 mediates degradation of the LDL-R by interacting with the extracellular domain and targeting the receptor for degradation**

Horton et al. J Lipid Res. 2009;50:S172-S177. Qian et al. J Lipid Res. 2007;48:1488-1498. Zhang et al. J Biol Chem. 2007;282:18602-12. **4.** Lopez. Biochim Biophys Acta. 2008;1781:184-91.

# LDL-C Change: Evolocumab vs Standard Therapy



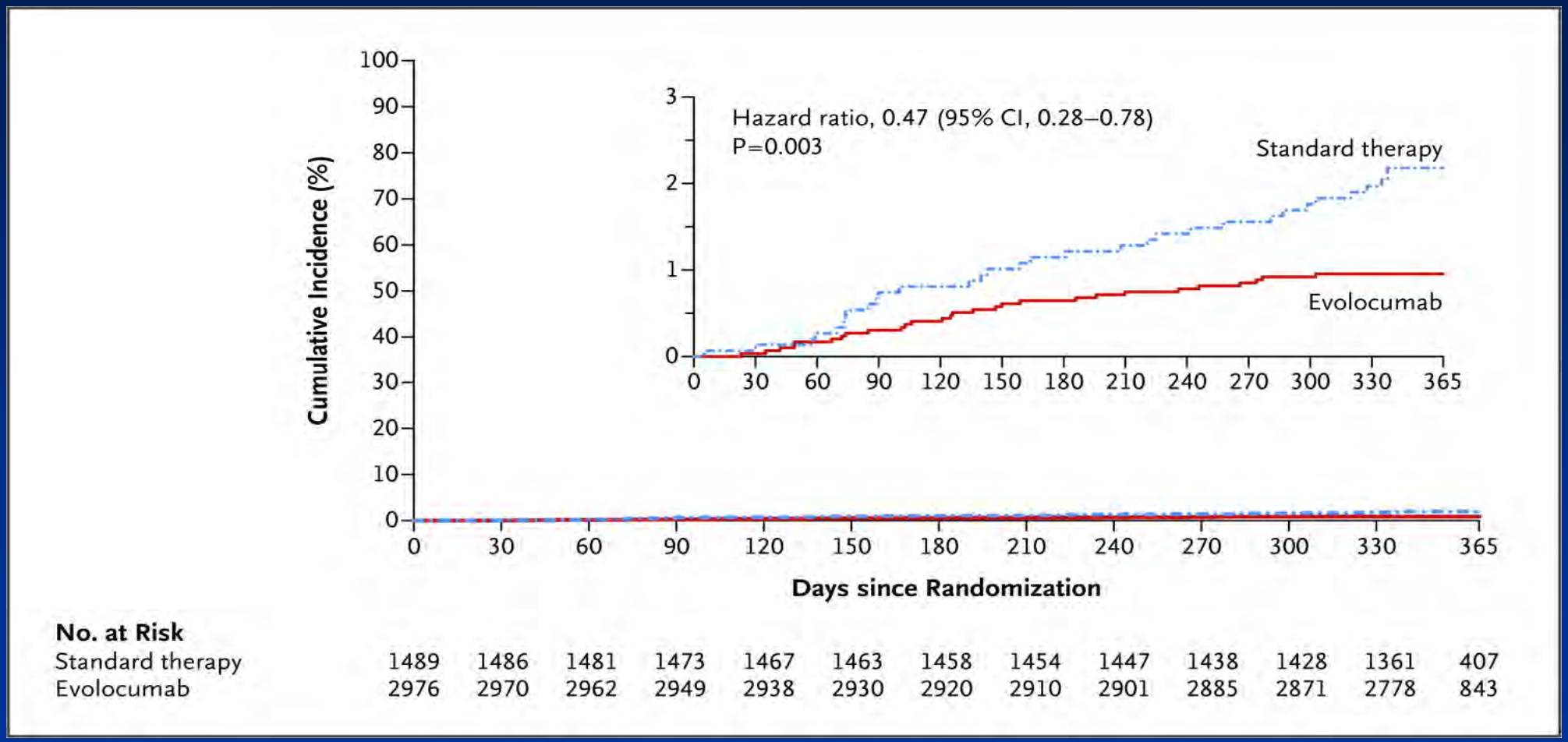

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Standard therapy | 1489 | 394 | 1388 | 1376 | 402 | 1219 |
| Evolocumab | 2976 | 864 | 2871 | 2828 | 841 | 2508 |
| Absolute reduction (mg/dl) | | 60.4 | 73.4 | 70.4 | 72.7 | 70.5 |
| Percentage reduction | | 45.3 | 60.9 | 58.8 | 54.0 | 58.4 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

**Sabatine MS et al. *N Engl J Med.* 2015;372:1500-1509.**

The NEW ENGLAND JOURNAL of MEDICINE

# Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

## Cumulative Incidence of Cardiovascular Events.



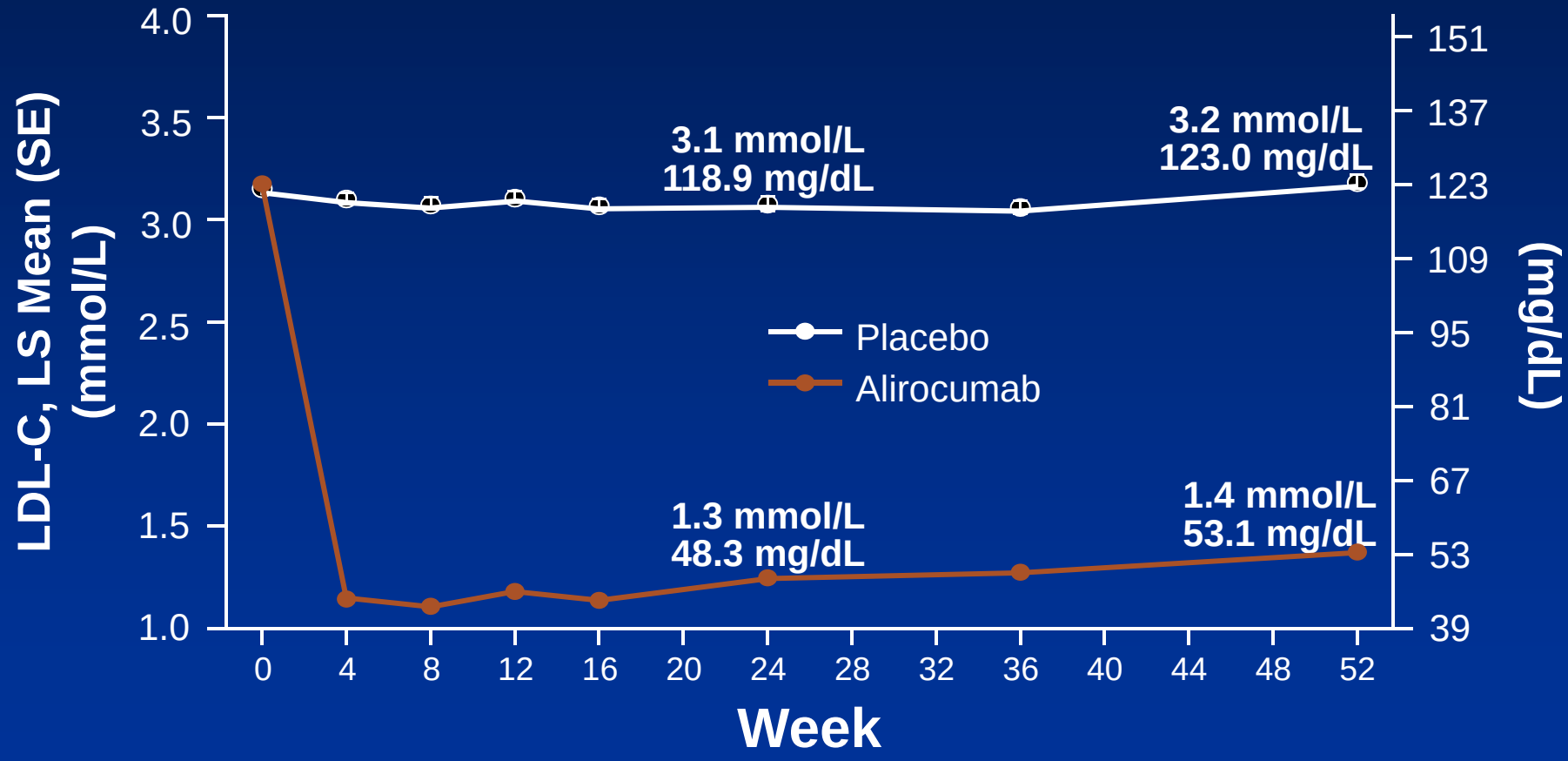

| No. at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Standard therapy | 1489 | 1486 | 1481 | 1473 | 1467 | 1463 | 1458 | 1454 | 1447 | 1438 | 1428 | 1361 | 407 |
| Evolocumab | 2976 | 2970 | 2962 | 2949 | 2938 | 2930 | 2920 | 2910 | 2901 | 2885 | 2871 | 2778 | 843 |

Sabatine MS et al. N Engl J Med 2015;372:1500-1509

# ODDYSSY LONG TERM Study: LDL-C Reduction Maintained Over 52 Weeks

## Achieved LDL-C over Time

All patients on background of maximally-tolerated statin ± other lipid-lowering therapy

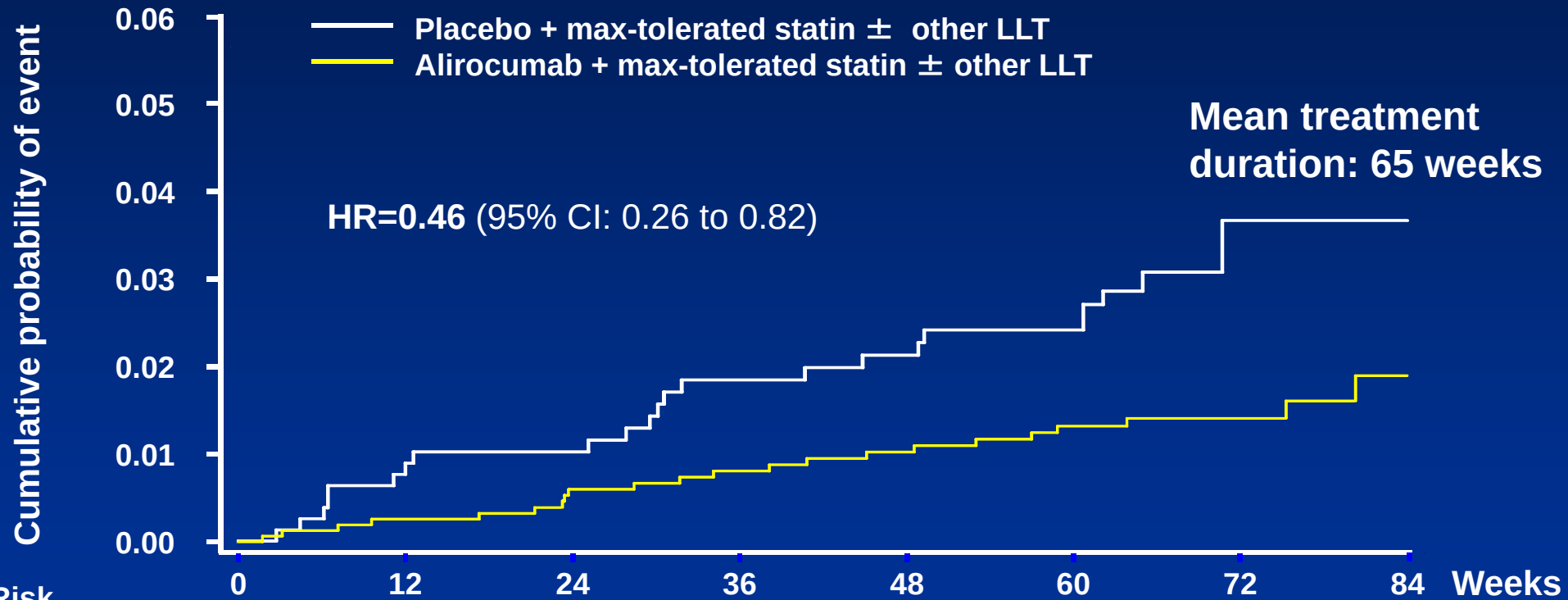



**Intent-to-treat (ITT) analysis.**

NEJM 2015;372: 1489

# ODYSSEY Long term: Post-hoc Adjudicated Cardiovascular Events†

## Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 788 | 776 | 731 | 703 | 682 | 667 | 321 | 127 |
| Alirocumab | 1550 | 1534 | 1446 | 1393 | 1352 | 1335 | 642 | 252 |

†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization. LLT, lipid-lowering therapy.

NEJM 2015;372:1489

# PCSK9 Inhibitor Cardiovascular Outcomes Trials

| | Evolocumab | Alirocumab | Bococizumab | |
|---|---|---|---|---|
| Sponsor | Amgen | Sanofi / Regeneron | Pfizer | |
| Trial | **FOURIER** | **ODYSSEY Outcomes** | **SPIRE I** | **SPIRE II** |
| Sample size | 22,500 | 18,000 | 18,000 | 8,300 |
| Patients | MI, stroke or PAD | 4-52 wks post-ACS | High risk of CV event | |
| Statin | Atorva ≥20 mg or equiv | Evid-based med Rx | Lipid-lowering Rx | |
| LDL-C mg/dL(mmol/L) | ≥70 (≥1.8) | ≥70 (≥1.8) | 70-99 (1.8-2.6) | ≥100 (≥2.6) |
| PCSK9i Dosing | Q2W or Q4W | Q2W | Q2W | |
| Endpoint | 1°: CV death, MI, stroke, revasc or hosp for UA,<br>Key 2°: CV death, MI, or stroke | CHD death, MI, ischemic stroke, or hosp for UA | CV death, MI, stroke, or urgent revasc | |
| Completion | 12/2017 | 1/2018 | 8/2017 | |

www.clinicaltrials.gov

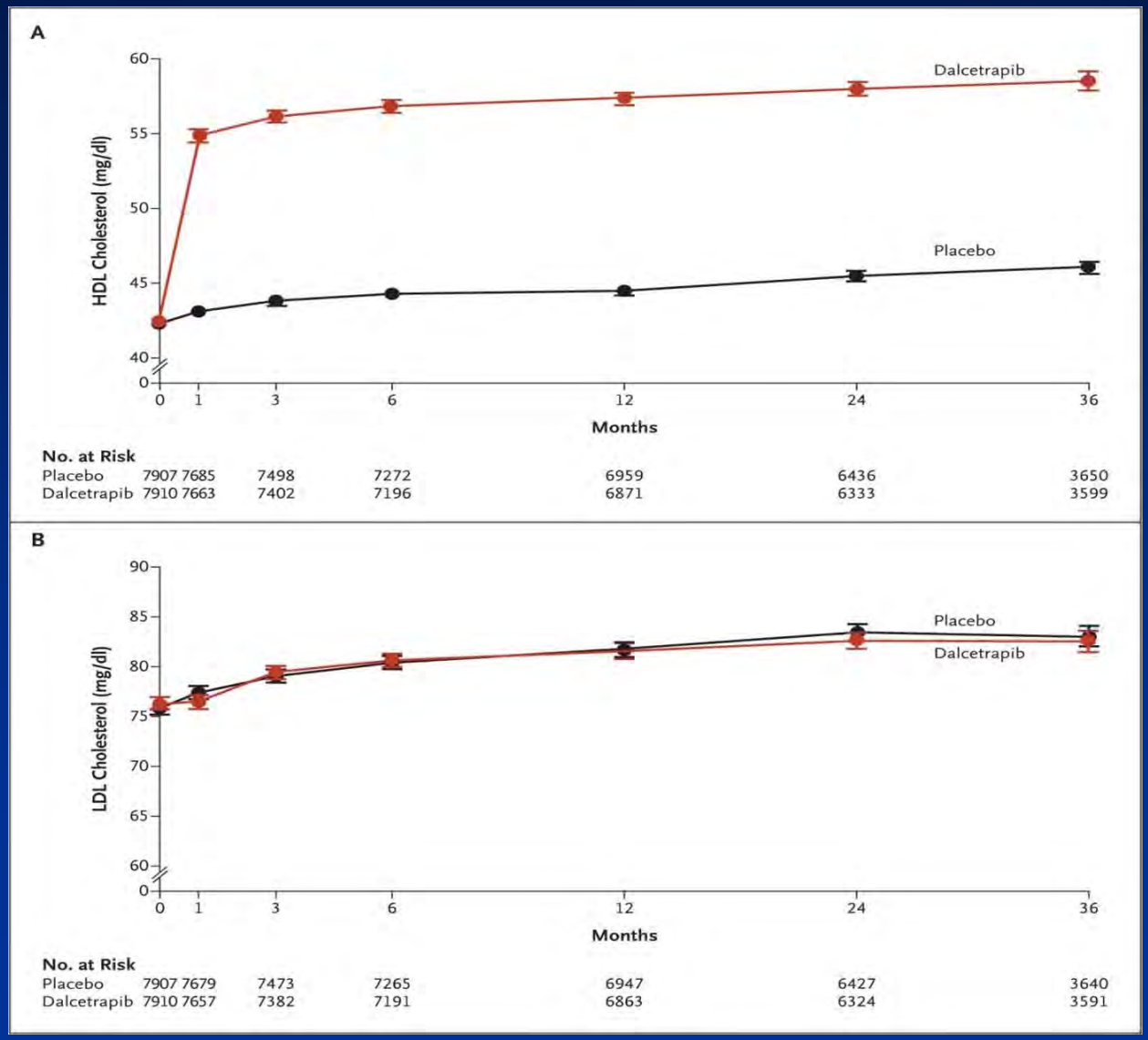
# DEFINE: Changes in Lipid/apoproteins in the Anacetrapib-Treated Patients

| Variable | Baseline | Week 24 | Week 76 | |
|---|---|---|---|---|
| LDL cholesterol (mg/dL) | 81.2 | 44.7 | 48.9 | -40% |
| HDL cholesterol (mg/dL) | 40.5 | 101.2 | 102.3 | 150% |
| Non-HDL cholesterol (mg/dL) | 109.7 | 69.7 | 73.0 | |
| Apolipoprotein B (mg/dL) | 88.4 | 70.1 | 69.6 | -20% |
| Apolipoprotein A1 (mg/dL) | 142.5 | 208.0 | 203.0 | 42% |
| Total cholesterol (mg/dL) | 150.3 | 170.8 | 175.2 | |
| Lipoprotein(a) (mmol/L) | 26.8 | 14.8 | 16.4 | -40% |

•DEFINE = Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib.

N Engl J Med. 2010;363(25):2406-15

# Effect of Dalcetrapib on HDL-C and LDL-C* in dalOUTCOMES

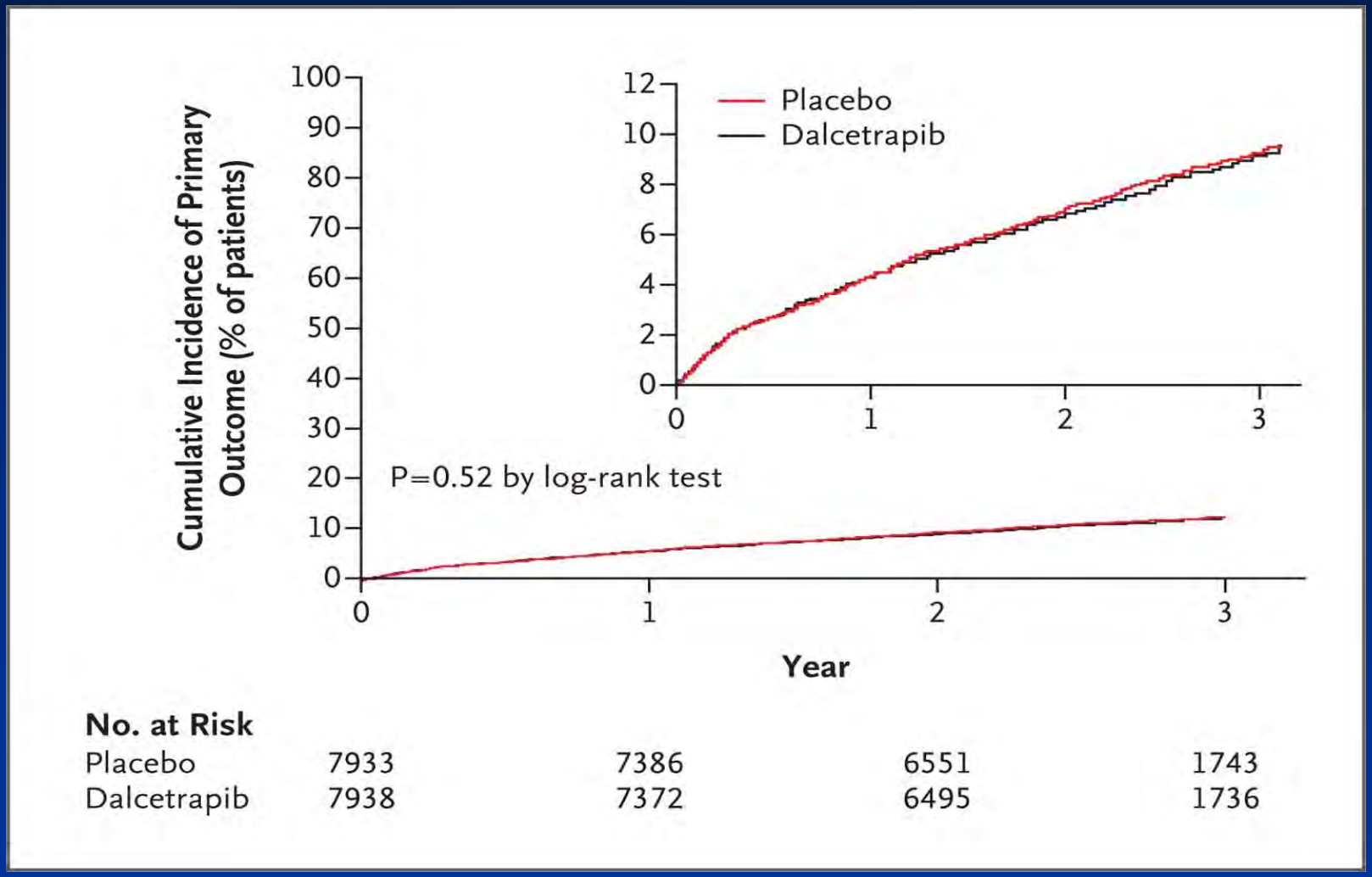



*Mean levels.

*N Engl J Med.* 2012;367:2089-2099.

The NEW ENGLAND JOURNAL of MEDICINE

# dalOUTCOMES: Incidence of Primary Efficacy Endpoint




*N Engl J Med.* 2012;367:2089-2099.

The NEW ENGLAND JOURNAL of MEDICINE

# Lipoprotein (a)

- LPA gene is causally related to CVD risk. Lp(a) is predictive of outcomes post PCI (AJC 2015;115:157) and post CABG (Atherosclerosis 2014;235:477)
- LPA gene is associated with greater prevalence of aortic stenosis (NEJM 2013; 368:503, JAMA 2014; online 10/2014))
- **AIM HIGH** study showed that baseline and on-treatment Lp(a) predicted CV events in both treatment arms (JACC 2013;62:1575). The **LIPID** trial also found similar baseline and on-treatment relationship of highest quartile Lp(a) to events (ATVB 2013;33:2902). Finally, **JUPITER** showed that highest Lp(a) tertile predicted CVD in primary prevention subjects at baseline and on-treatment (Circulation 2014;129:635)

# What to do with high risk Lp(a)?

- If Lp(a) > 75 nmol/L (or > 50 mg/dL):

  High intensity statin +/- other LLT
  - Niacin
  - Alirocumab, evolocumab [reduce LDL and Lp(a)]

Eur Heart J 2010; 31:2844

# Is Residual Risk Reduction All About Reducing TGRLs?

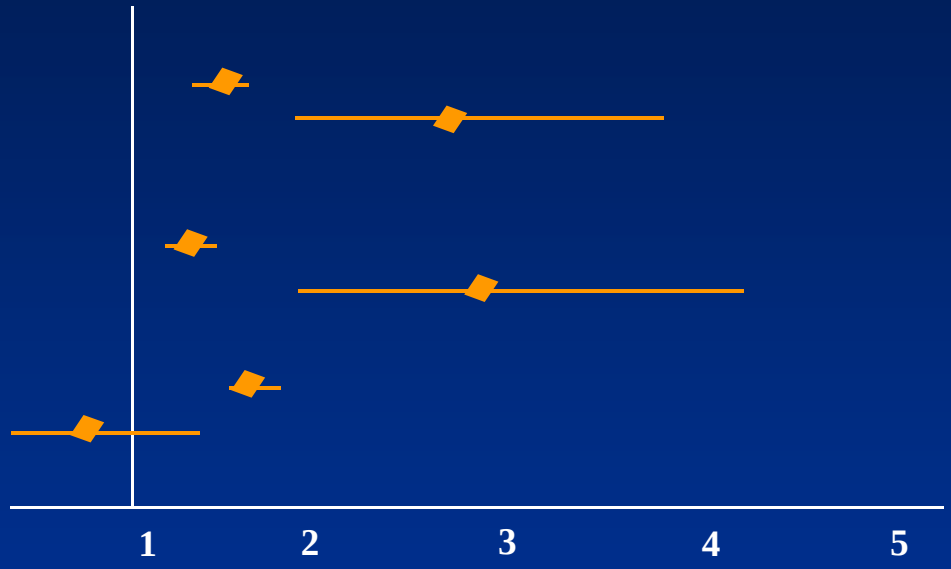
- Disturbed TGRL metabolism (e.g. in IR and T2DM) results in discordance between the cholesterol content of LDL and particle number.
- As a result, intensification of medical therapies that correct the lipid disturbance, and the discordance, could further reduce the risk.

# MendelianRandomization*: Causal Association Between Remnant Cholesterol in TRL and ASCVD

**Remnant cholesterol**
Observational: Elevated plasma levels
Causal: Genetically elevated levels

**Remnant cholesterol/HDL-C ratio**
Observational: Elevated plasma levels
Causal: Genetically elevated levels

**HDL-C**
Observational: Reduced plasma levels
Causal: Genetically reduced levels




**Lifelong exposure to genetically elevated remnant cholesterol in TGRL can increase ASCVD**

*Mendelian randomization design was used to overcome confounding between remnant cholesterol and other risk factors, including reduced HDL-C.
TGRL= TG-rich lipoproteins

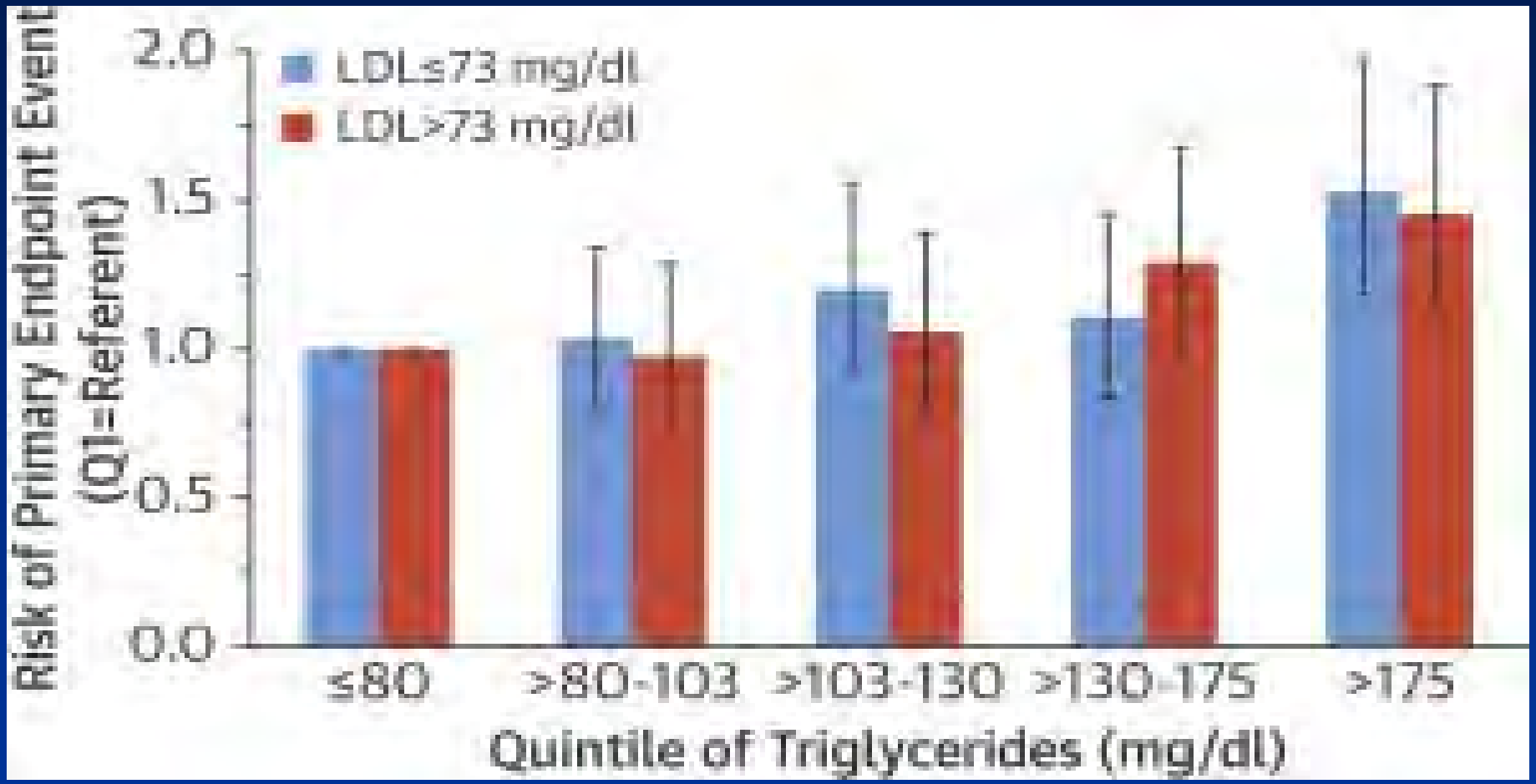
J Am Coll Cardiol. 2013;61:427–436.

# Mendelian Randomization Studies of Triglycerides and CHD Risk: Loss-of-function Mutations in Apo C3

- 2 studies - Exome Sequencing Project, and 2 populations (Copenhagen City Heart Study and Copenhagen General Population Study) – evaluated LOF mutations in Apo C3 and triglycerides on CHD risk
- Frequency of LOF in Apo C3 between 1:150 and 1:250
- These LOF mutations associated with 40% lower fasting and nonfasting TGs, as well as lower apo B and LDL-C (-16%) and higher HDL-C (+20%).
- Both studies found a 40% lower CHD risk than unaffected cohort

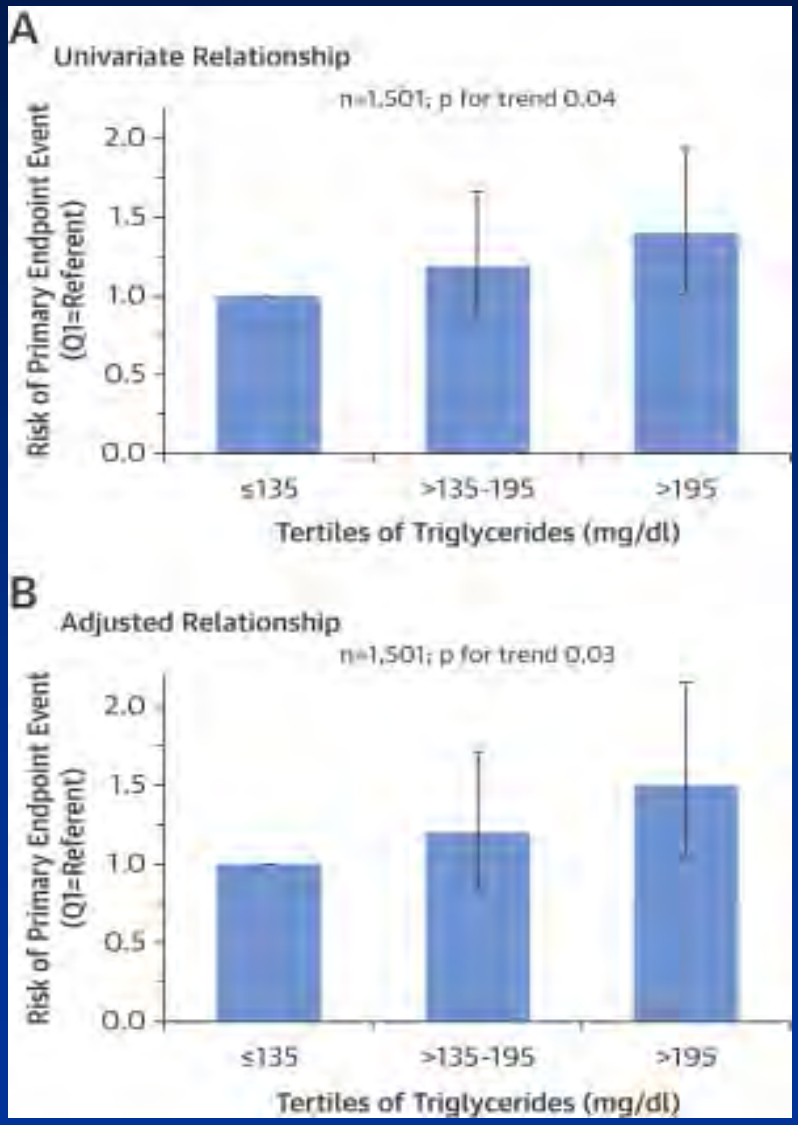
NEJM 2014; 371: 22 and 32

# Fasting Triglycerides Predict Recurrent Ischemic Events in Patients with low LDL-C on Statins: dal-OUTCOMES




Journal of the American College of Cardiology, 2015; 65: 2267 - 2275

# Fasting Triglycerides Predict Recurrent Ischemic Events in Patients With ACS Treated With Atorvastatin 80 for 16 weeks: MIRACL




Journal of the American College of Cardiology 2015; 65: 2267 - 2275

# Mixed Dyslipidemia: Discordance Between LDL-C and ApoB / non–HDL-C

| | |
|---|---|
| TC | 198 mg/dL |
| LDL -C | 130 mg/dL |
| TG | 90 mg/dL |
| HDL -C | 50 mg/dL |
| Non –HDL- C | 148 mg/ dL |
| ApoB | 95 mg/ dL |

● Cholesterol

● ApoB

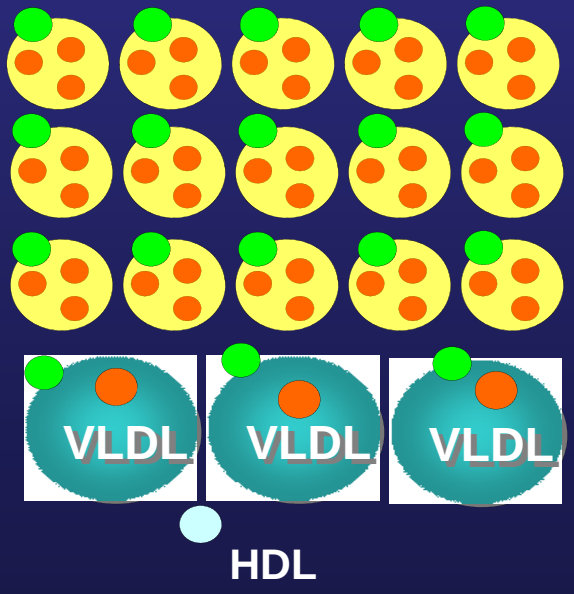
| | |
|---|---|
| TC | 210 mg/dL |
| LDL -C | 130 mg/dL |
| TG | 250 mg/dL |
| HDL -C | 30 mg/dL |
| Non –HDL- C | 180 mg/ dL |
| ApoB | 118 mg/dL |

**Large LDL** ***(pattern A)***


Same LDL-C

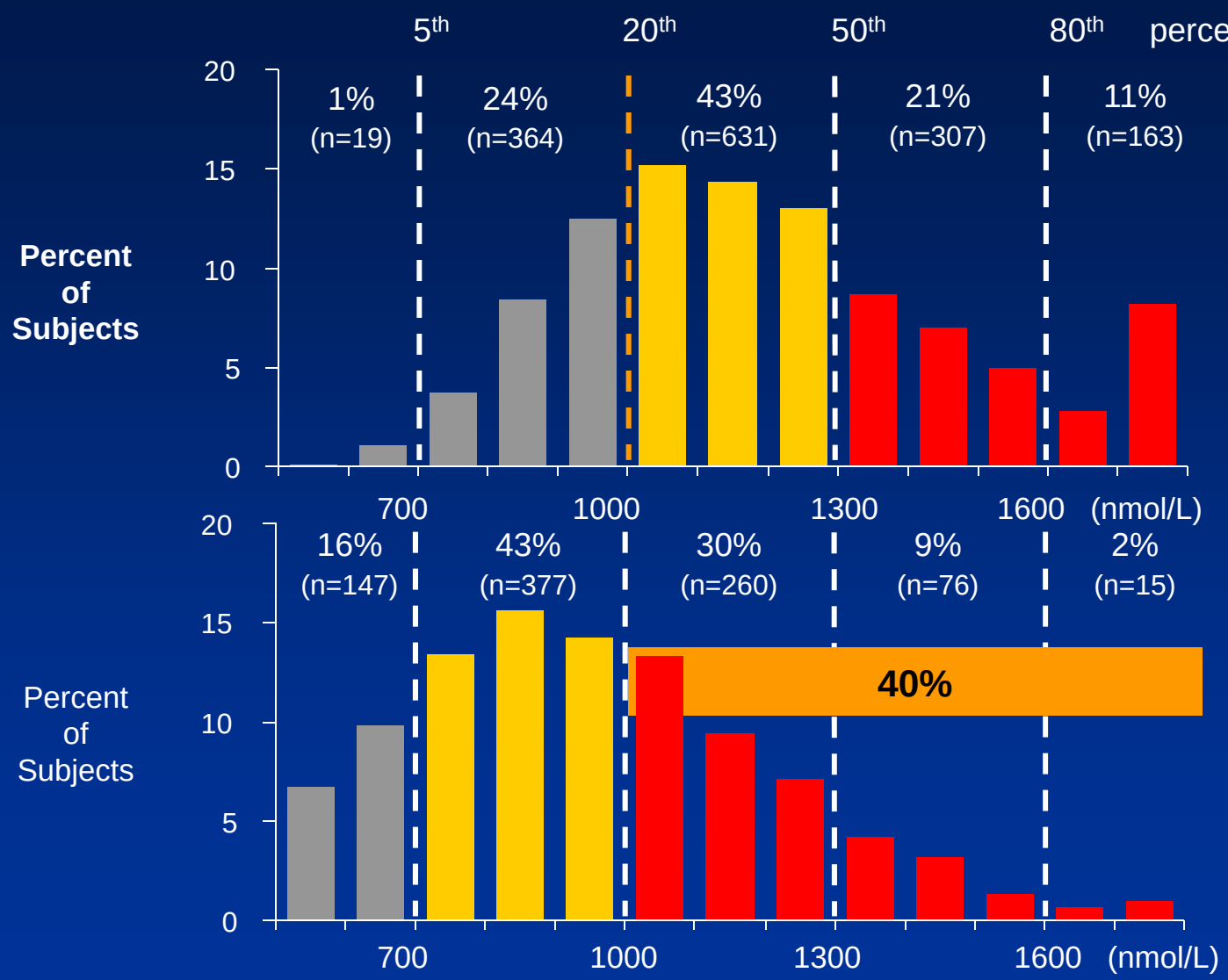
Different non –HDL -C, ApoB

***Small, dense LDL (pattern B)***




Size doesn't matter – particle number is more important!

# LDL Particle Number Distribution in T2DM Subjects in MESA



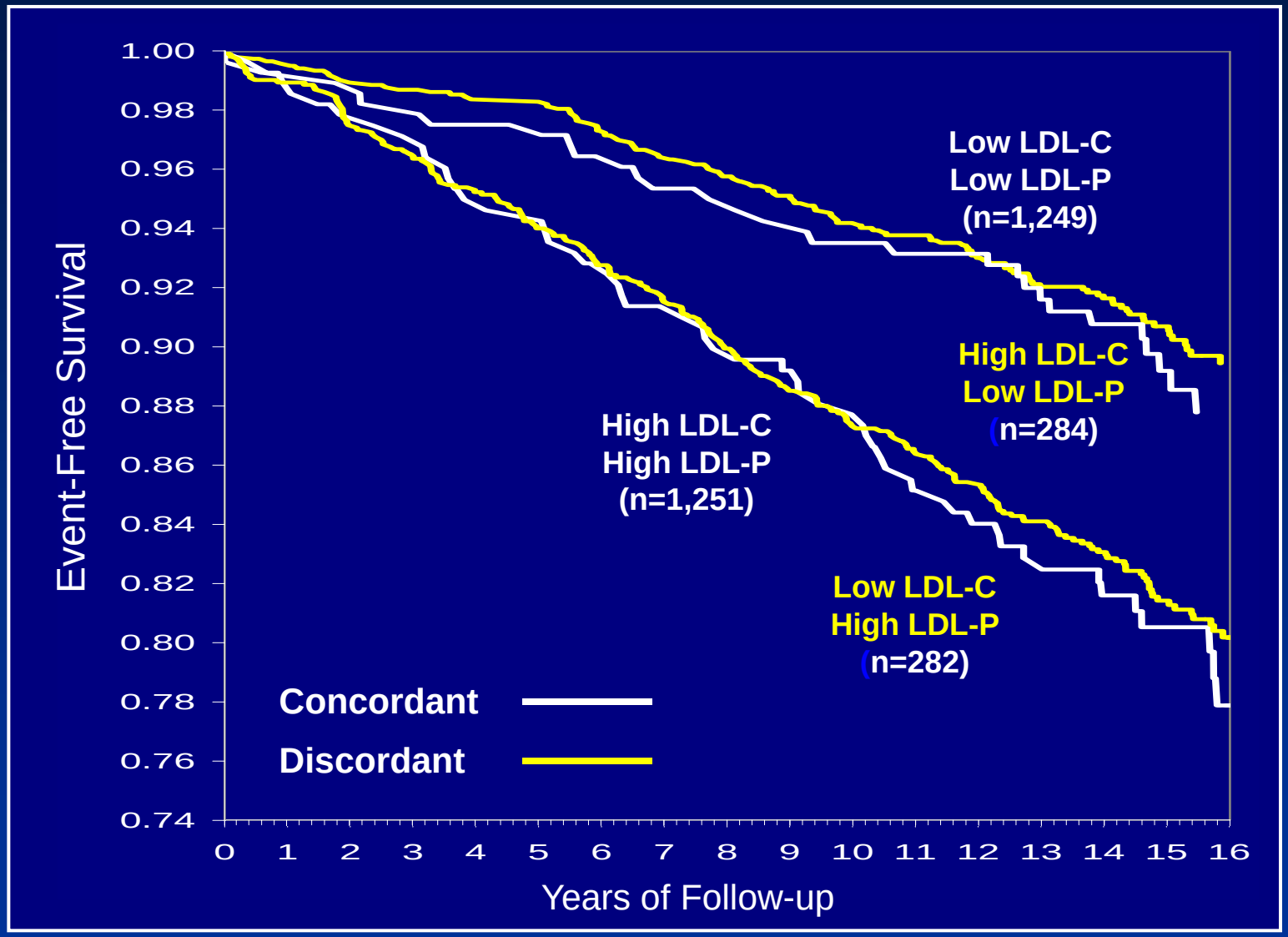

LDL-C
70-99 mg/dL
(n=1484)

LDL-C
<70 mg/dL
(n=871)

Cromwell WC, Otvos JD. *Am J Cardiol.* 2006;98(12):1599-1602.

# CHD Event Associations of LDL-P versus LDL-C

Framingham Offspring Study (n=3,066)




*J Clin Lipidology* 2007;1(6):583-592.

- Therefore, when LDL-C and nonHDL-C are **discordant**, risk tracks with particle number (which can be determined by non-HDL-C preferably, or apo B or LDL-P).

  Post hoc subgroup analysis from AIM HIGH, HPS 2 THRIVE and ACCORD Lipid suggest that additional lipid drug therapy to reduce non-HDL (or LDL-P or apo B) could provide incremental risk reduction under this clinical situation.

  Prescription OM3 are addressing this in outcomes trials – REDUCE IT and STRENGTH

# Is Residual Risk All About HDL-C?

- Well, the trials have not given us an answer:
  - AIM HIGH
  - HPS 2 THRIVE
  - dalOUTCOMES
- We may not get the answer from REVEAL or ACCELERATE, even if they prove beneficial, because of their LDL-C lowering efficacy
- HDL function may be a plausible mechanism of benefit but this is difficult to measure and even more challenging to modulate.

# Is Residual Risk Reduction All About Inflammation?

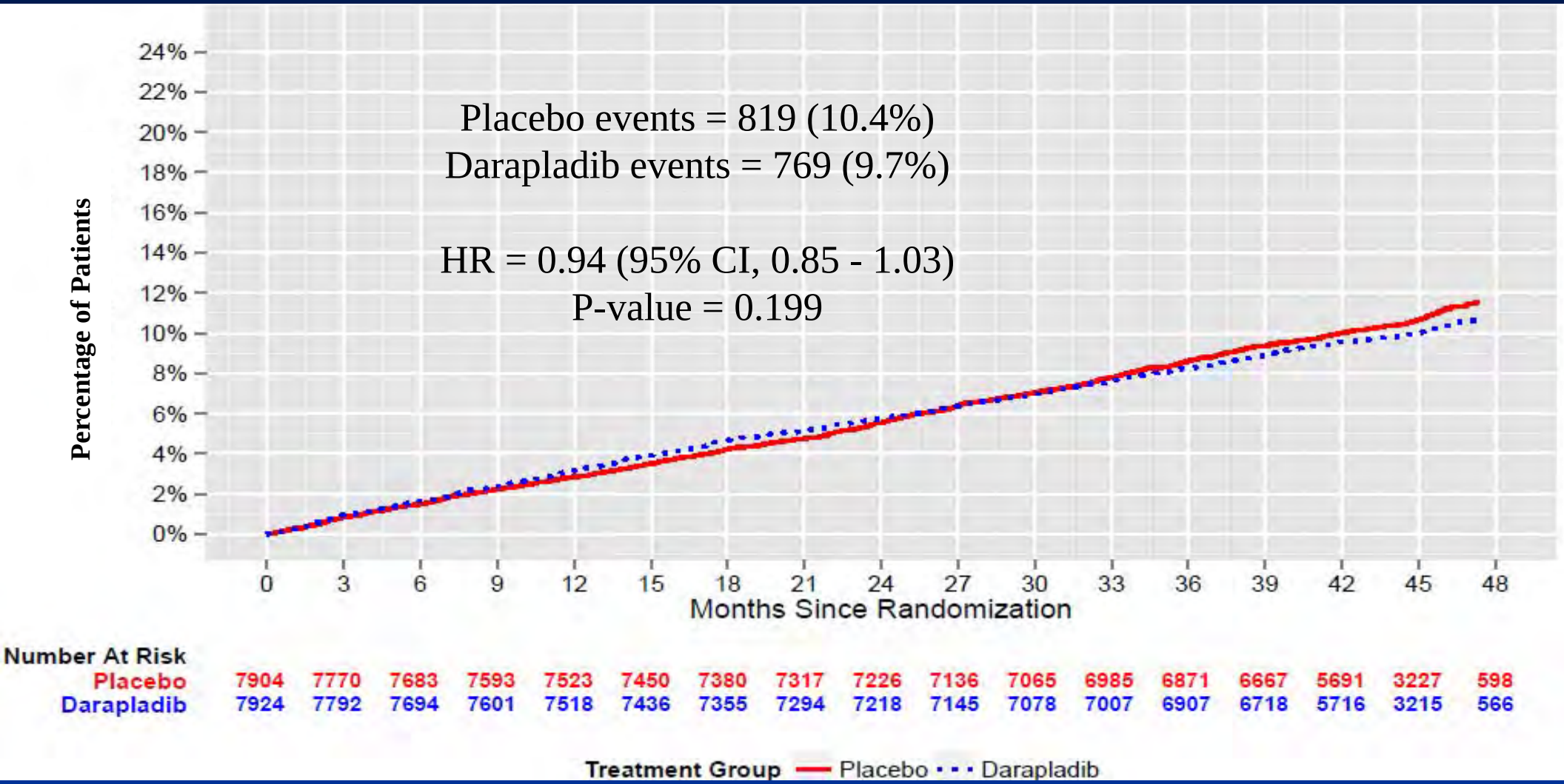
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease

The authors are as follows: Harvey D. White, D.Sc., Claes Held, M.D., Ph.D., Ralph Stewart, M.D., Elizabeth Tarka, M.D., Rebekkah Brown, Dr.PH., Richard Y. Davies, M.S., Andrzej Budaj, M.D., Ph.D., Robert A. Harrington, M.D., Ph. Gabriel Steg, M.D., Diego Ardissino, M.D., Paul W. Armstrong, M.D., Alvaro Avezum, M.D., Ph.D., Philip E. Aylward, B.M., B.Ch., Ph.D., Alfonso Bryce, M.D., Hong Chen, M.D., Ming-Fong Chen, M.D., Ph.D., Ramon Corbalan, M.D., Anthony J. Dalby, M.B., Ch.B., Nicolas Danchin, M.D., Ph.D., Robbert J. De Winter, M.D., Ph.D., Stefan Denchev, M.D., Ph.D., Rafael Diaz, M.D., Moses Elisaf, M.D., Ph.D., Marcus D. Flather, M.B., B.S., Assen R. Goudev, M.D., Christopher B. Granger, M.D., Liliana Grinfeld, M.D., Ph.D., Judith S. Hochman, M.D., Steen Husted, M.D., D.Sc., Hyo-Soo Kim, M.D., Ph.D., Wolfgang Koenig, M.D., Ales Linhart, M.D., Ph.D., Eva Lonn, M.D., M.Sc., José López-Sendón, M.D., Ph.D., Athanasios J. Manolis, M.D., Emile R. Mohler III, M.D., José C. Nicolau, M.D., Ph.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Ph.D., Terje R. Pedersen, M.D., Ph.D., Daniel Pella, M.D., Ph.D., Marco A. Ramos-Corrales, M.D., Mikhail Ruda, M.D., Mátyás Sereg, M.D., Saulat Siddique, M.D., Peter Sinnaeve, M.D., Ph.D., Peter Smith, Pharm.D., Piyamitr Sritara, M.D., Henk P. Swart, M.D., Rody G. Sy, M.D., Tamio Teramoto, M.D., Ph.D., Hung-Fat Tse, M.D., Ph.D., David Watson, M.Sc., W. Douglas Weaver, M.D., Robert Weiss, M.D., Margus Viigimaa, M.D., Ph.D., Dragos Vinereanu, M.D., Ph.D., Junren Zhu, M.D., Christopher P. Cannon, M.D., and Lars Wallentin, M.D., Ph.D., for the STABILITY Investigators

# STABILITY Primary Endpoint:
# Time to First Occurrence of CV Death, MI, Stroke



Original Investigation

# Varespladib and Cardiovascular Events in Patients With an Acute Coronary Syndrome

## The VISTA-16 Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; John J. P. Kastelein, MD, PhD; Gregory G. Schwartz, MD, PhD; Dianna Bash, RN; Robert S. Rosenson, MD; Matthew A. Cavender, MD, MPH; Danielle M. Brennan, MS; Wolfgang Koenig, MD; J. Wouter Jukema, MD, PhD; Vijay Nambi, MD, PhD; R. Scott Wright, MD; Venu Menon, MD; A. Michael Lincoff, MD; Steven E. Nissen, MD; for the VISTA-16 Investigators

**IMPORTANCE** Secretory phospholipase $A_2$ ($sPLA_2$) generates bioactive phospholipid products implicated in atherosclerosis. The $sPLA_2$ inhibitor varespladib has favorable effects on lipid and inflammatory markers; however, its effect on cardiovascular outcomes is unknown.

**OBJECTIVE** To determine the effects of $sPLA_2$ inhibition with varespladib on cardiovascular outcomes.

**DESIGN, SETTING, AND PARTICIPANTS** A double-blind, randomized, multicenter trial at 362 academic and community hospitals in Europe, Australia, New Zealand, India, and North America of 5145 patients randomized within 96 hours of presentation of an acute coronary syndrome (ACS) to either varespladib (n = 2572) or placebo (n = 2573) with enrollment between June 1, 2010, and March 7, 2012 (study termination on March 9, 2012).

**INTERVENTIONS** Participants were randomized to receive varespladib (500 mg) or placebo daily for 16 weeks, in addition to atorvastatin and other established therapies.

**MAIN OUTCOMES AND MEASURES** The primary efficacy measure was a composite of cardiovascular mortality, nonfatal myocardial infarction (MI), nonfatal stroke, or unstable angina with evidence of ischemia requiring hospitalization at 16 weeks. Six-month survival status was also evaluated.

**RESULTS** At a prespecified interim analysis, including 212 primary end point events, the independent data and safety monitoring board recommended termination of the trial for futility and possible harm. The primary end point occurred in 136 patients (6.1%) treated with varespladib compared with 109 patients (5.1%) treated with placebo (hazard ratio [HR], 1.25; 95% CI, 0.97-1.61; log-rank $P = .08$). Varespladib was associated with a greater risk of MI (78 [3.4%] vs 47 [2.2%]; HR, 1.66; 95% CI, 1.16-2.39; log-rank $P = .005$). The composite secondary end point of cardiovascular mortality, MI, and stroke was observed in 107 patients (4.6%) in the varespladib group and 79 patients (3.8%) in the placebo group (HR, 1.36; 95% CI, 1.02-1.82; $P = .04$).

**CONCLUSIONS AND RELEVANCE** In patients with recent ACS, varespladib did not reduce the risk of recurrent cardiovascular events and significantly increased the risk of MI. The $sPLA_2$ inhibition with varespladib may be harmful and is not a useful strategy to reduce adverse cardiovascular outcomes after ACS.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT01130246

*JAMA*. doi:10.1001/jama.2013.282836
Published online November 18, 2013.

Supplemental content at jama.com

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** The VISTA-16 Investigators are listed at the end of this article.

**Corresponding Author:** Stephen J. Nicholls, MBBS, PhD, South Australian Health and Medical Research Institute, PO Box 11060, Adelaide, SA 5001, Australia (stephen.nicholls@sahmri.com).

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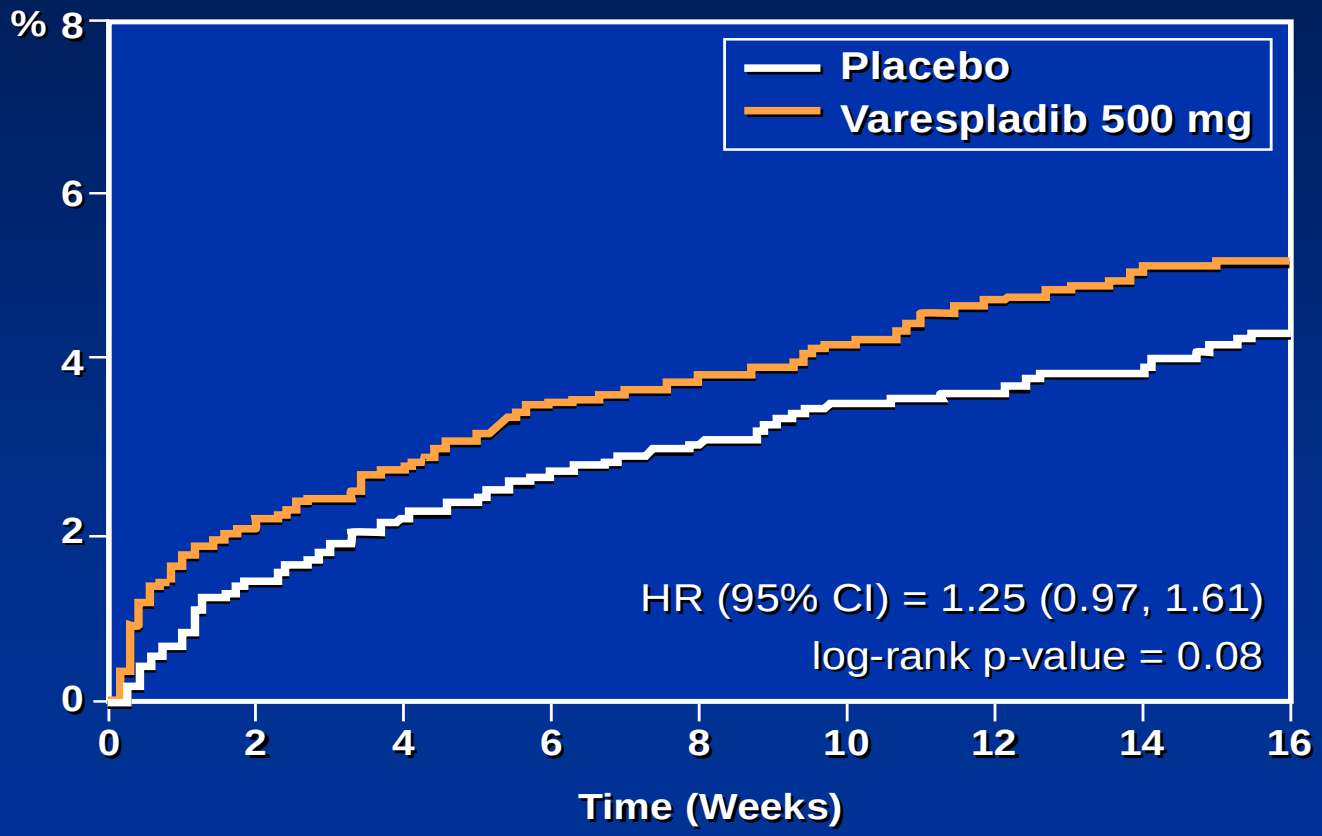
# VISTA Primary Efficacy Endpoint

## Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina




**No. at Risk:**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2573 | 2474 | 2361 | 2255 | 2166 | 2062 | 2000 | 1927 | 1646 |
| Varespladib | 2572 | 2467 | 2360 | 2241 | 2160 | 2038 | 1967 | 1883 | 1641 |

# CVD Outcomes Trials Targeting Inflammation

- Il-1B monoclonal antibody (canakinumab) – CANTOS
  Post ACS, injection every 12 weeks.
- Cardiovascular Inflammation Reduction Trial (CIRT)
  NIH-sponsored; Patients with T2DM or MeS and CVD; methotrexate vs PBO in 7000 subjects
- Il-6 receptor monoclonal antibody (tocilizumab) vs TNF-alpha monoclonal antibody (etanercept) in RA patients to prevent CVD events.
- Colchicine to be studied post PCI and ACS on short-term outcomes

# Take Home Messages

- Maximize statin dosing, plus other LLTs, to achieve non-HDL-C and LDL-C goals in:
  - All CVD patients with/without FH
  - All CVD patients with recurrent events

  This includes the use of ezetimibe and BAS, and potentially evolocumab/alirocumab. Fenofibrate, prescription OM3 or niacin can be considered in selected patients with non-HDL-C discordance.
- Targeting low HDL-C/HDL-P with drug therapy is not supported by the data yet
- Targeting high Lp(a) with drug therapy is reasonable, but therapy should be primarily directed to achieving non-HDL-C/LDL-C goals

# Statin Intolerance as a Barrier to Atherosclerotic Disease Risk Reduction

**Paul D. Thompson, MD**

**Director of Cardiology**

**Henry Low Heart Center**
**Hartford Hospital**

**Hartford, CT**

# Collaborators

- Brown University – Peter Herbert, Eileen Cullinane, Stan Sady
- University of Pittsburgh – Joe Zmuda, Rich Zimet, Susan Yurgalevitch
- Duke University – John Guyton
- Hartford Hospital - Beth (Parker) Taylor, Jeff Capizzi, Amanda Zaleski, William Roman, Lindsay Lorson, Brenda Foxen, Mary Beth Moran, Cherie Biblie, Rick Seip, Gualberto Ruano, Greg Panza
- Umass - Priscilla Clarkson, Maria Urso, Amy Kearns
- Tufts University – Richard Karas
- Washington Children's Medical Center - Eric Hoffman

# Statin Intolerance as a Barrier to Risk Reduction

- Why Care About Statin Associated Symptoms (SAS) ?
- What Are SAS ?
- How Do We Diagnose SAS ?
- How Frequent Are SAS ?
- How Should We Manage SAS ?

# Why Care About Statin Associated Symptoms (SAS) ?

Patient Outcomes

Medical Cost From -

Poorer Outcomes

Medications

European Heart Journal (2013) **34**, 2940–2948
doi:10.1093/eurheartj/eht295

CLINICAL RESEARCH
*Prevention and epidemiology*

## Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences

Rajiv Chowdhury[1†], Hassan Khan[1†*], Emma Heydon[1†], Amir Shroufi[1], Saman Fahimi[1], Carmel Moore[1], Bruno Stricker[2], Shanthi Mendis[3], Albert Hofman[2], Jonathan Mant[1], and Oscar H. Franco[2*]

**Performed a Systematic Review / Meta Analysis**

**Of 44 Prospective Studies - 1, 978,919 Participants**

**Good Adherence ≥ 80%**

**RR Good vs Less Good = 0.55 (0.46-0.67)**

**9+ CVD Cases / 100,000 Per Year**

European Heart Journal (2013) **34**, 2940–2948
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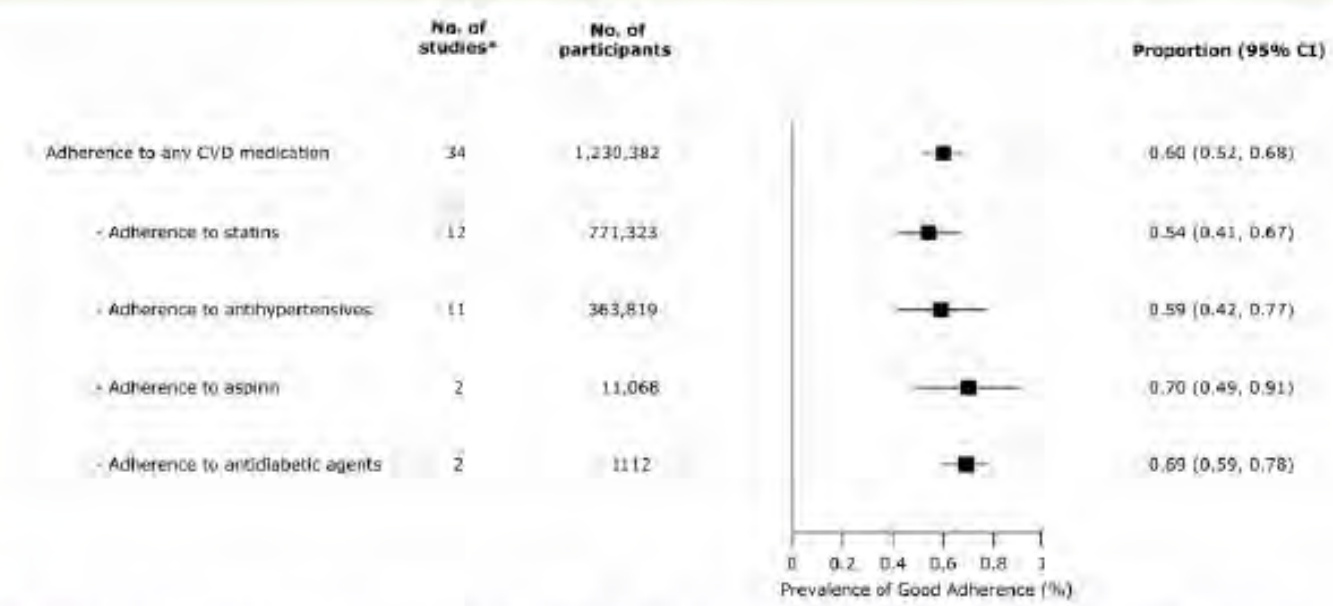
**CLINICAL RESEARCH**
*Prevention and epidemiology*

# Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences




*Based on subset of the included studies with available prevalence information. Studies, which did not provide proportion of participants with good adherence, were not included in this figure.

**Figure 2** Prevalence (95% CI) of good adherence to cardiovascular medications among participants in prospective studies with available information.

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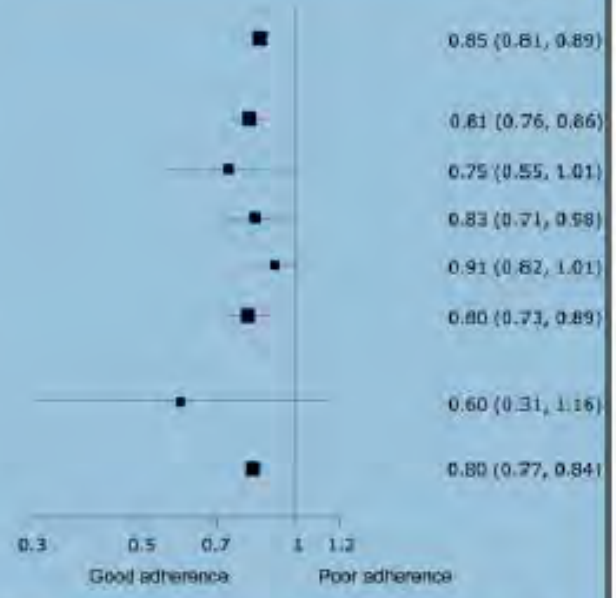
**CLINICAL RESEARCH**
*Prevention and epidemiology*

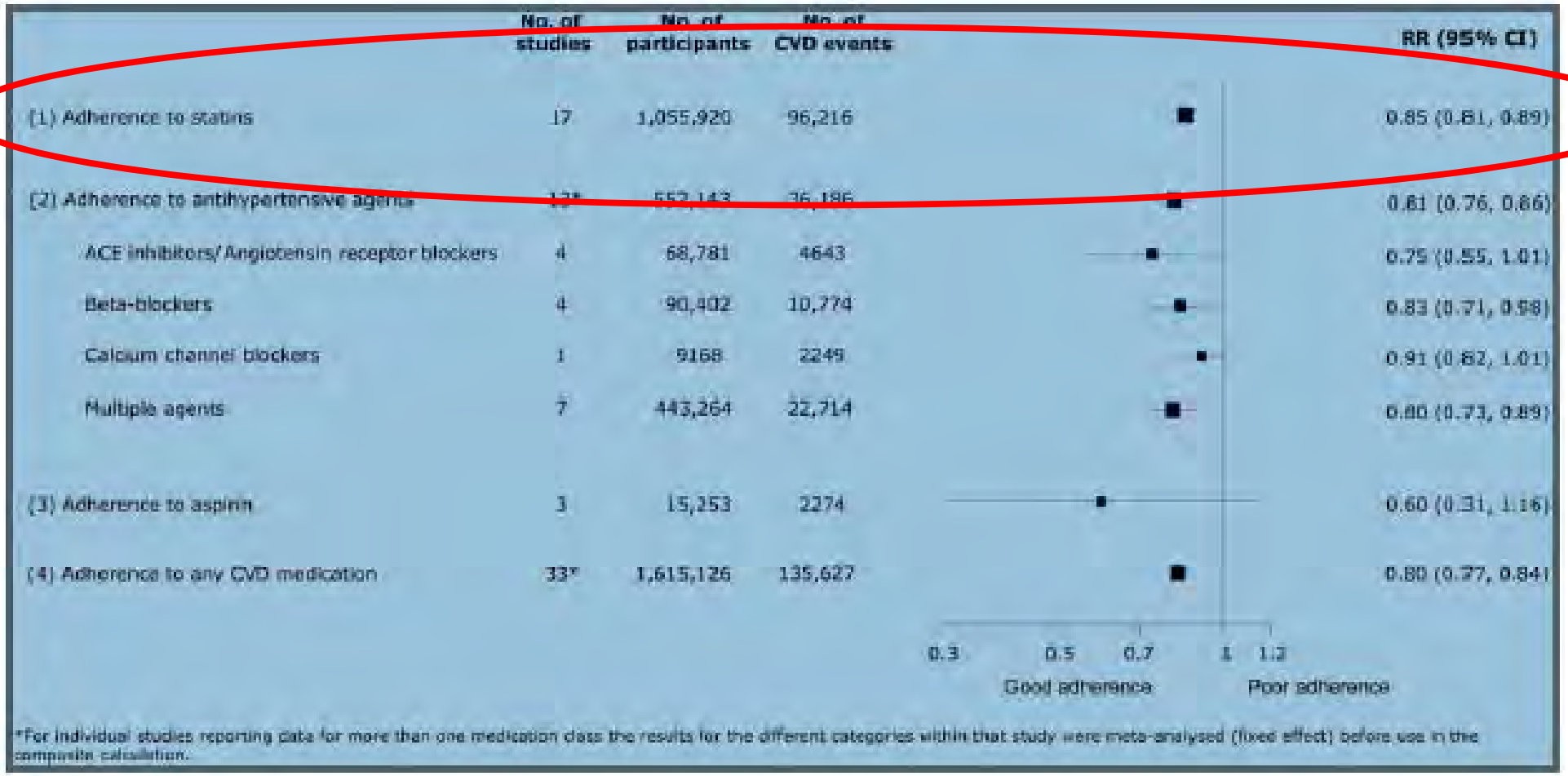
# Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences

| | No. of studies | No. of participants | No. of CVD events | RR (95% CI) |
|---|---|---|---|---|
| (1) Adherence to statins | 17 | 1,055,920 | 96,216 | 0.85 (0.81, 0.89) |
| (2) Adherence to antihypertensive agents | 13* | 552,143 | 36,186 | 0.81 (0.76, 0.86) |
| ACE inhibitors/Angiotensin receptor blockers | 4 | 68,781 | 4643 | 0.75 (0.55, 1.01) |
| Beta-blockers | 4 | 90,402 | 10,774 | 0.83 (0.71, 0.98) |
| Calcium channel blockers | 1 | 9168 | 2249 | 0.91 (0.82, 1.01) |
| Multiple agents | 7 | 443,264 | 22,714 | 0.80 (0.73, 0.89) |
| (3) Adherence to aspirin | 3 | 15,253 | 2274 | 0.60 (0.31, 1.16) |
| (4) Adherence to any CVD medication | 33* | 1,615,126 | 135,627 | 0.80 (0.77, 0.84) |




*For individual studies reporting data for more than one medication class the results for the different categories within that study were meta-analysed (fixed effect) before use in the composite calculation.

**Figure 3** Relative risks for any cardiovascular disease in good vs. poor adherence to major cardiovascular disease medications.

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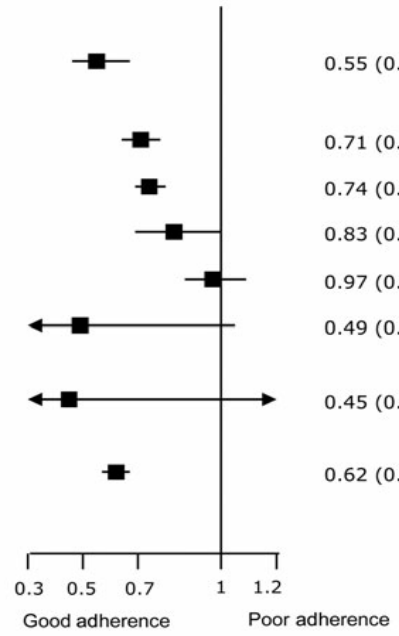
CLINICAL RESEARCH
*Prevention and epidemiology*

# Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences

| | No. of studies | No. of participants | No. of deaths | Proportion (95% CI) |
|---|---|---|---|---|
| (1) Adherence to statins | 11 | 291,864 | 29,605** | 0.55 (0.46, 0.67) |
| (2) Adherence to antihypertensive agents | 11* | 205,598 | 12,288** | 0.71 (0.64, 0.78) |
| ACE inhibitors/Angiotensin receptor blockers | 4 | 62,196 | 886** | 0.74 (0.69, 0.80) |
| Beta-blockers | 7 | 67,991 | 5,441** | 0.83 (0.69, 1.00) |
| Calcium channel blockers | 1 | 9168 | 2696 | 0.97 (0.87, 1.09) |
| Multiple agents | 3 | 81,342 | 2978 | 0.49 (0.23, 1.05) |
| (3) Adherence to aspirin | 3 | 12,980 | 1573 | 0.45 (0.16, 1.29) |
| (4) Adherence to any CVD medication | 23* | 533,381 | 94,126** | 0.62 (0.57, 0.67) |




*For individual studies reporting data for more than one medication class the results for the different categories within that study were meta-analysed (fixed effect) before use in the composite calculation; **Groups in which not all studies reported the number of deaths.

Relative risks for all-cause mortality in good vs. poor adherence

# Relative risks for all-cause mortality in good vs. poor adherence

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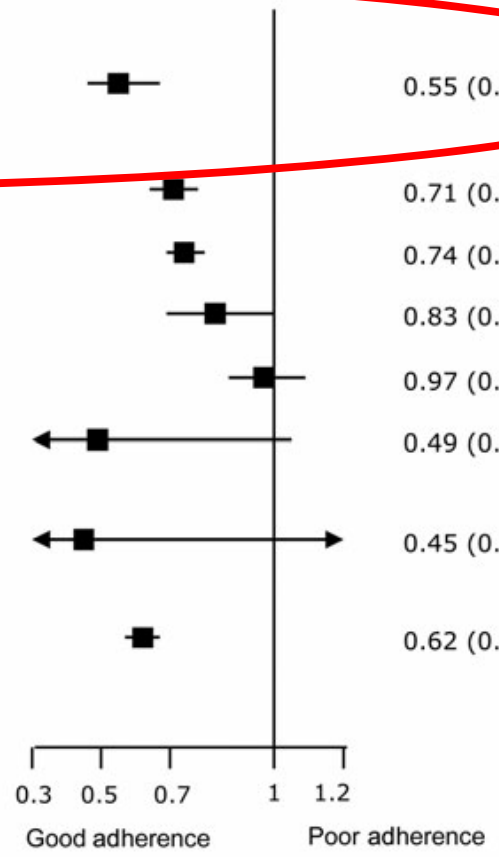


*For individual studies reporting data for more than one medication class the results for the different categories within that study were meta-analysed (fixed effect) before use in the composite calculation; **Groups in which not all studies reported the number of deaths.

# Why Care About Statin Associated Symptoms (SAS) ?

Patient Outcomes

Medical Cost From -

Poorer Outcomes

Medications

FiercePharma

# Payers fret about the next drug doomsday: Pricey PCSK9 cholesterol meds

May 7, 2014 | By Tracy Staton

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Quick! Which group of hotly anticipated, next-generation therapies for a widespread health problem is expected to cost payers beaucoup bucks when they hit the market? If you said the new crop of hepatitis C treatments, you'd be half right. Pharmacy benefits managers say they're just as worried--perhaps even more so--by a coming class of cholesterol drugs known as PCSK9 inhibitors.

As the *Pink Sheet* reports, executives from CVS Caremark ($CVS) and Express Scripts ($ESRX), the two biggest U.S. PBMs, say these drugs are groundbreaking treatments that are proving safe and effective at controlling cholesterol in people who've had little success at that in the past. But at an estimated $10,000 per year, drugs like Sanofi ($SNY) and Regeneron's ($REGN) alirocumab, Pfizer's ($PFE) bococizumab, and Amgen's ($AMGN) evolocumab won't fit the healthcare budget.

FiercePharma

NEWS TOPICS ANALYSIS FEA

Topics: Financials | Sales and Marketing

# Say what? CVS Health execs figure PCSK9 meds to cost up to $150B

February 17, 2015 | By Tracy Staton

# Statin Intolerance as a Barrier to Risk Reduction

Why Care About Statin Associated Symptoms (SAS) ?

What Are SAS ?

How Do We Diagnose SAS ?

How Frequent Are SAS ?

How Should We Manage SAS ?

# What Is / Are SAS ?

Statin Associated Muscle Symptoms (SAMS)

Myalgia, Cramps, Weakness,

Central Nervous System Effects

Memory Problems, Amnesia

Elevated LFTs

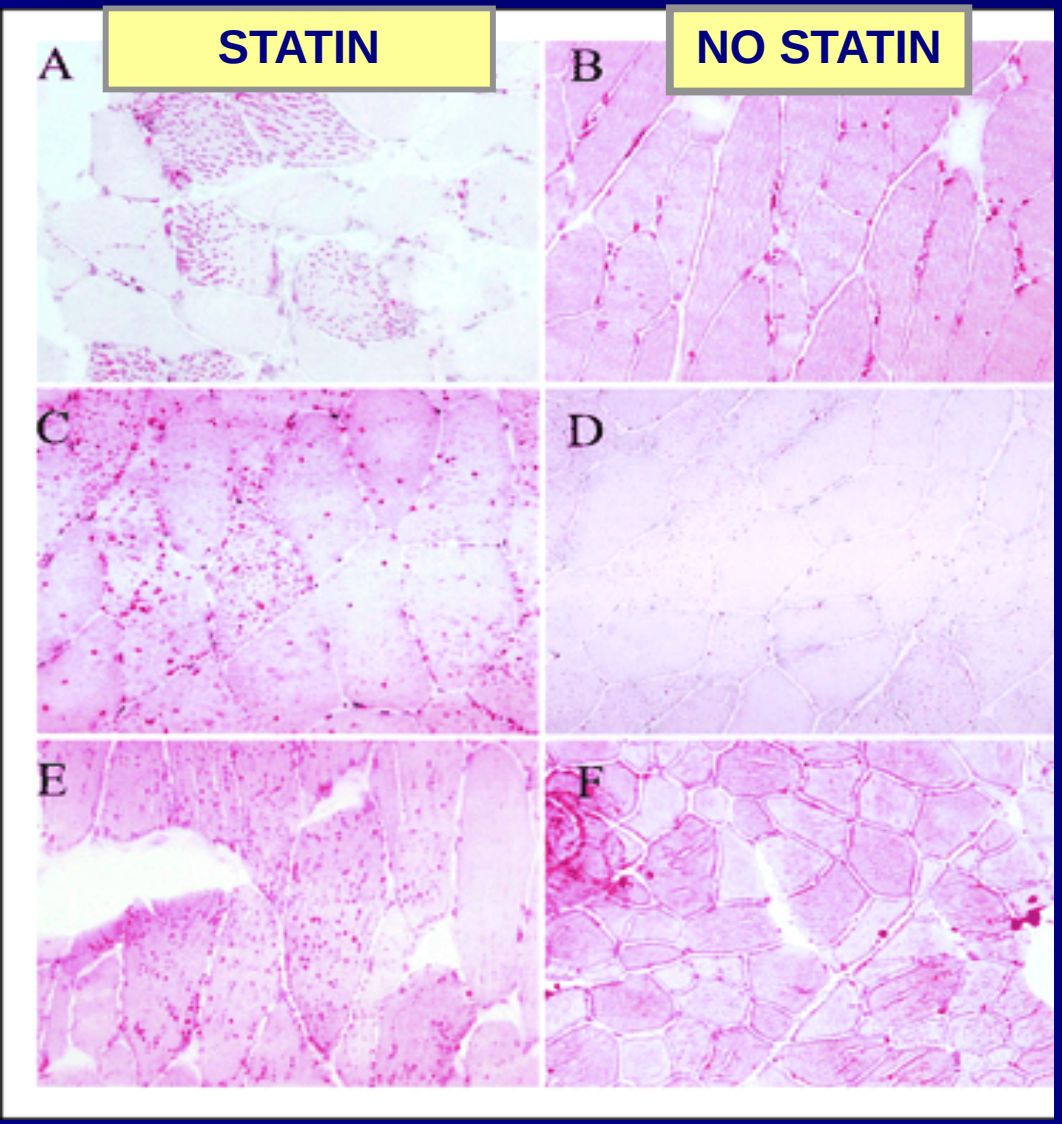
Worsening Glucose Tolerance

Tendinopathy

# Definitions of Statin Myopathy J Clin Lipidology June 2014

- Myalgia – Aching, Stiffness, Cramps
- Myopathy - Weakness
- Myositis - Inflammation
- Myonecrosis - ↑ CK
  - Mild: >3 Fold
  - Moderate: >10 Fold
  - Severe: >50 Fold
  - Clinical Rhabdomyolysis: Creatinine ↑ 0.5mg/dl

# Damage to Type 1 Fibers




**Patients who experienced muscle symptoms with normal CK levels**

**Statins withdrawn for 3 mo**

**When placebo was used, Symptoms disappeared**

**Stained For Lipid**

Phillips et al., 2003

**Weakness is Not An Uncommon Complaint…Complaints of Decreased Exercise Tolerance Are Uncommon**

Very Few Statin Studies Have Examined Exercise Performance or Muscle Strength

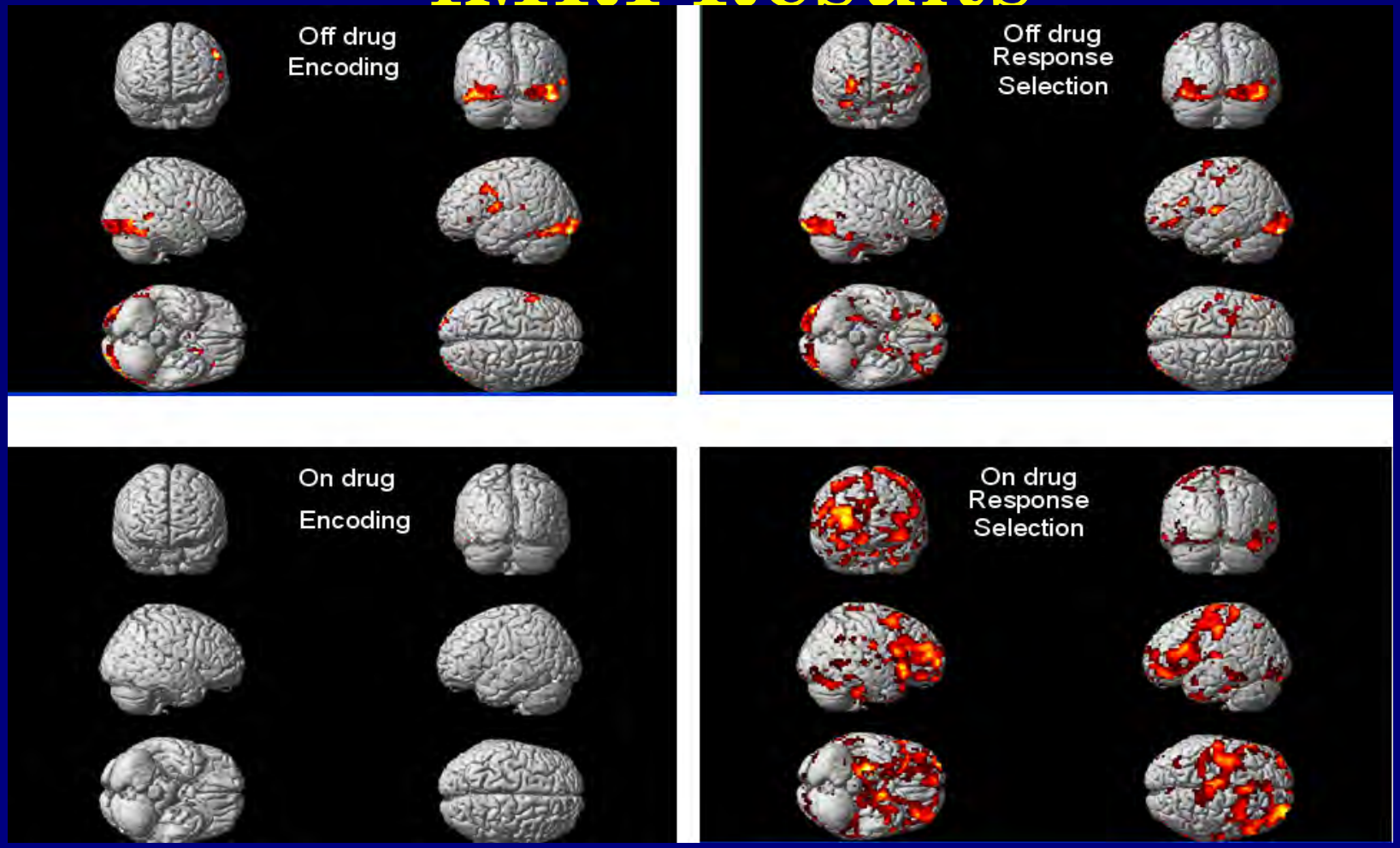
# Do Statins Affect Cognition ?

# Case Study #1

- 65-year-old Caucasian
- On atorvastatin 10 mg/day
  - Mood alteration, memory difficulties
- Cognitive evaluation and fMRI of the brain
- On and off (2 months) statin therapy
- Significant improvement in cognitive function off statins

Parker…Thompson. Pharmacotherapy. 2010

# fMRI Results

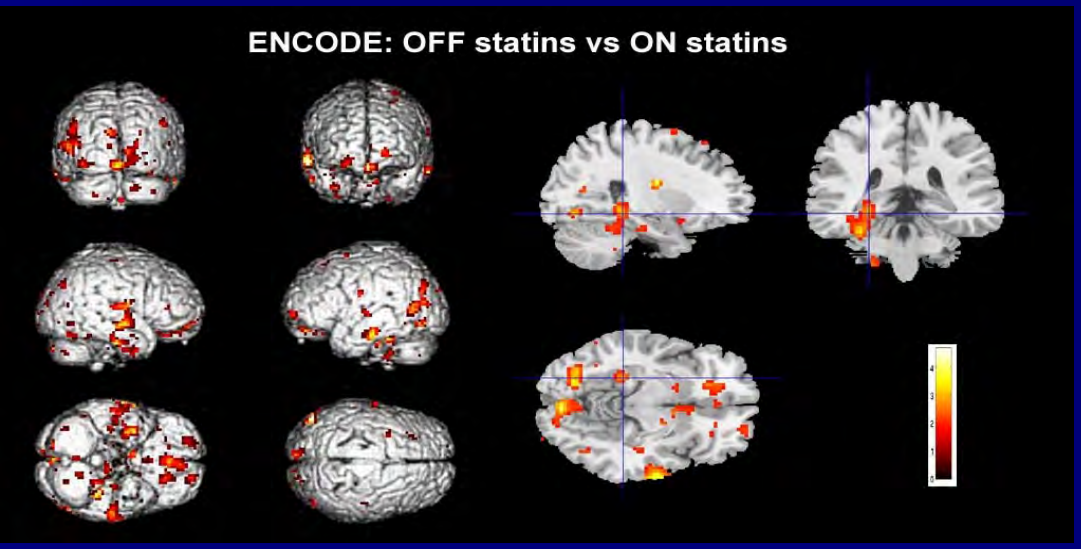



Neuronal activation during the difficult version of the Sternberg Task, depicted by colored regions on the 3D-rendered brains, during encoding (left) and response selection (right) while the subject was on 10 mg atorvastatin (bottom) and 2 months following atorvastatin cessation (top).

# Pilot Study

- fMRI during two tasks
  - Sternberg Task
  - Figural Memory Test
- 19 adults from 6 month statin study
  - 14 on atorvastatin and 5 on placebo
- Pre-post scans

# FMRI Results: FIG MEM



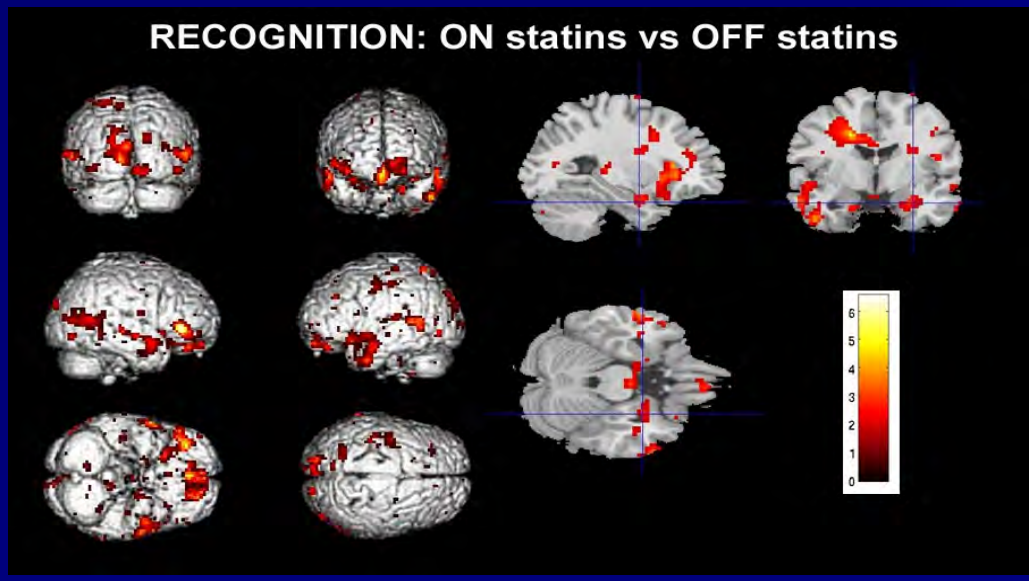




Figure 2. FMRI activation on 3D-rendered brain showing changes in activation with statin use displayed at p=0.005 uncorrected level during the encoding (left) and recognition (right) phase of the Figural Memory Test.

Notice of Award

*RESEARCH*

**Issue Date:** 08/09/2010

Department of Health and Human Services
National Institutes of Health
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

**Grant Number:** 1R01HL098085-01A1

**Principal Investigator(s):**
Beth Parker (contact), PHD
Donna Polk

**Project Title:** The Effect of High-Dose Atorvastatin on Neuronal Activity and Cognitive Function

# Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial

*Paul M Ridker, Aruna Pradhan, Jean G MacFadyen, Peter Libby, Robert J Glynn*

- **Jupiter Trial - 20 of Rosuva v. Placebo**
- **CRP > 2….in 17,603 Subjects**
- **Among Those with Diabetes Risk Factors (Metabolic S, Fasting Glucose > 100, BMI > 30, A1c > 6)…Risk Increased 25% (5-49%)**
- **New Diabetics: 270 v 216….54 More New Diabetics**
- **But…39% < CV Events, 36% < VTE, 18% < Deaths !!!!**
- **134 < CV Events vs 54 New Diabetics in 17,603 Subjects**
- **If No DM Risk Factors, No New Diabetes**

Lancet 380: 565, 2012

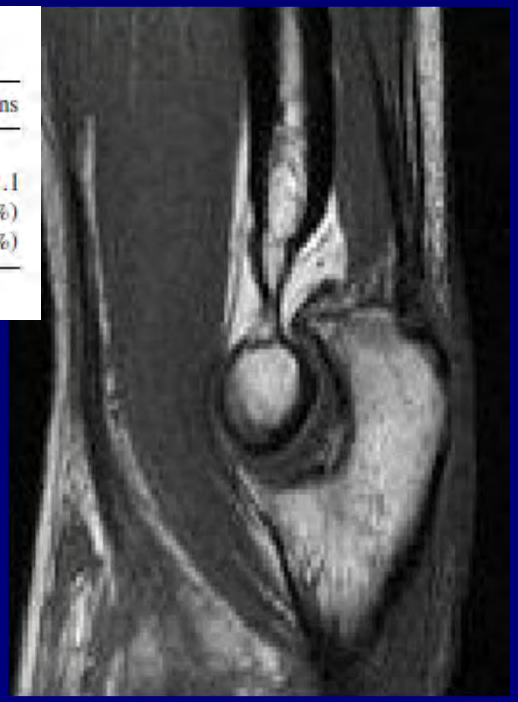
## Tendon Rupture Associated With *Simvastatin/Ezetimibe* Therapy

Raja C. Pullatt, MD[a], Mamatha Reddy Gadarla, MD[b], Richard H. Karas, MD, PhD[c], Alawi A. Alsheikh-Ali, MD[c], and Paul D. Thompson, MD[b,*]

Table 1
Food and Drug Administration database of tendon rupture associated with statin use as of March 31, 2006

| | Lovastatin | Simvastatin | Pravastatin | Atorvastatin | Fluvastatin | Rosuvastatin | Cerivastatin | All Statins |
|---|---|---|---|---|---|---|---|---|
| No. of reports | 5 | 37 | 32 | 124 | 19 | 10 | 20 | 247 |
| Age (yrs) | 70 ± 6 | 60 ± 12 | 55 ± 13 | 57 ± 10 | 57 ± 9 | 59 ± 8 | 55 ± 11 | 57.4 ± 11.1 |
| Men | 3(60%) | 31 (84%) | 28 (88%) | 101 (81%) | 15 | 10 (100%) | 16 (80%) | 204 (82%) |
| Hospitalization | 1 (20%) | 26 (70%) | 20 (62%) | 66 (53%) | 10 (53%) | 5 (50%) | 10 (50%) | 138 (56%) |

Values expressed as number (percent) or mean ± SD unless noted otherwise.



Tenocytes Degrade Type I Collagen to Repair Tendons

Using Matrix Metalproteinases (MMP) 2 & 9

Statins Reduce MMP – 9 mRNA

**Am J Cardiol 2007;100:152–153**

# Statin Intolerance as a Barrier to Risk Reduction

- Why Care About Statin Associated Symptoms (SAS) ?
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- How Do We Diagnose SAS ?
- How Frequent Are SAS ?
- How Should We Manage SAS ?

# How To Diagnose SAS ?

- There Are No Validated Diagnostic Strategies
- CK May or May Not Be Elevated
- Classic Symptoms & Temporal Relationship Help
- Challenge / Rechallenge is ? Best Diagnostic Approach But Subjective, Etc, Etc

Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey

G Kees Hovingh[1], Shravanthi R Gandra[2], Jan McKendrick[3], Ricardo Dent[2], Heather Wieffer[3], Alberico L Catapano[4], Paul Oh[5], Robert S Rosenson[6], Erik S Stroes[1]

Screened 2,653 Clinicians

In 13 Countries

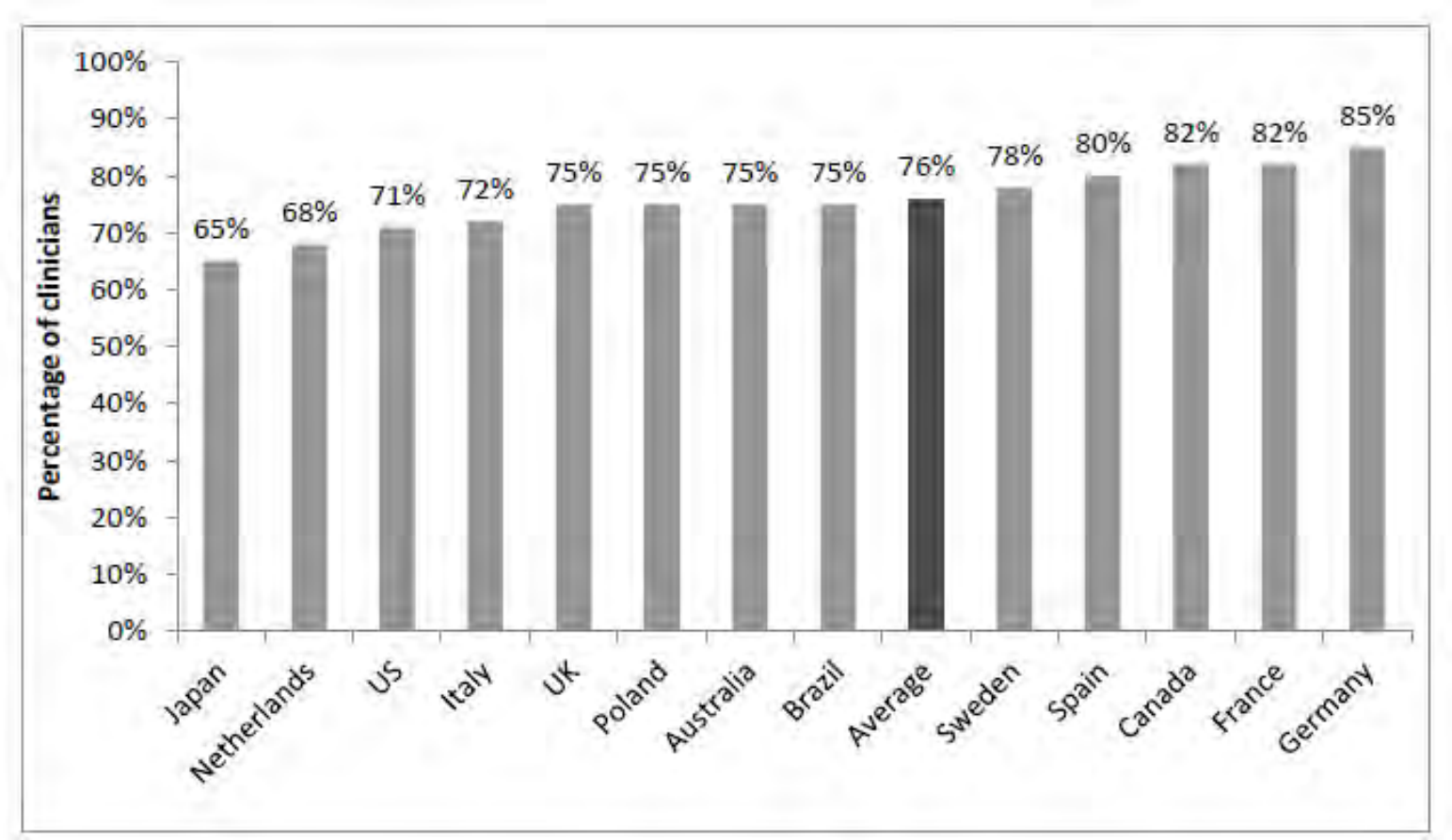
1,525 (57.5%) Met Criteria

810 (53.1%) completed survey

77% cardiologists

**Atherosclerosis In Press**

# % Clinicians Trying ≥ Statin Before Diagnosing SAMS




**Hovingh et. al. Atherosclerosis In Press**

Journal of Clinical Lipidology (2014) 8, 558–571

Journal of Clinical Lipidology

Original Contribution

# An assessment by the Statin Muscle Safety Task Force: 2014 update

Robert S. Rosenson, MD, FNLA*, Steven K. Baker, MSc, MD, FRCP(C), Terry A. Jacobson, MD, FNLA, Stephen L. Kopecky, MD, Beth A. Parker, PhD

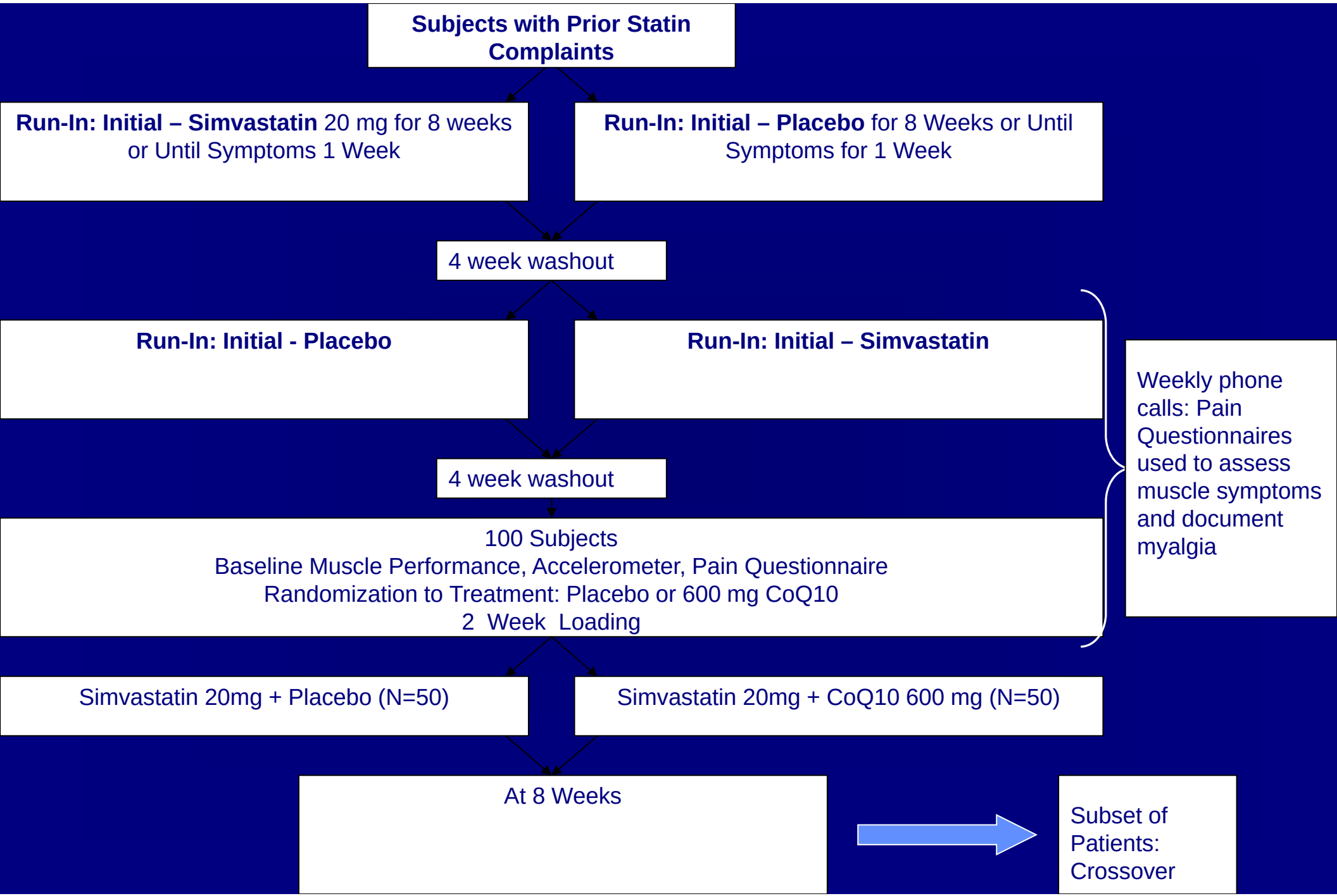
**Table 2** Proposed statin myalgia clinical index score

| | |
|---|---|
| Clinical symptoms (new or increased unexplained muscle symptoms) | |
| Regional distribution/pattern | |
| Symmetric hip flexors/thigh aches | 3 |
| Symmetric calf aches | 2 |
| Symmetric upper proximal aches | 2 |
| Non-specific asymmetric, intermittent | 1 |
| Temporal pattern | |
| Symptoms onset <4 weeks | 3 |
| Symptoms onset <4 weeks | 3 |
| Symptoms onset 4–12 weeks | 2 |
| Symptoms onset >12 weeks | 1 |
| Dechallenge | |
| Improves upon withdrawal (<2 weeks) | 2 |
| Improves upon withdrawal (2–4 weeks) | 1 |
| Does not improve upon withdrawal (>4 weeks) | 0 |
| Challenge | |
| Same symptoms reoccur upon rechallenge <4 weeks | 3 |
| Same symptoms reoccur upon rechallenge 4–12 weeks | 1 |
| Statin myalgia clinical index score | |
| Probable | 9–11 |
| Possible | 7–8 |
| Unlikely | <7 |

# But The Diagnosis is Tough

# Coenzyme Q10 in Statin Myopathy


1 RC1 AT005836-01
NIH/NCCAM


Subjects with Prior Statin Complaints
Run-In: Initial – Simvastatin 20 mg for 8 weeks or Until Symptoms 1 Week
Run-In: Initial – Placebo for 8 Weeks or Until Symptoms for 1 Week
4 week washout
Run-In: Initial - Placebo
Run-In: Initial – Simvastatin
4 week washout
100 Subjects
Baseline Muscle Performance, Accelerometer, Pain Questionnaire
Randomization to Treatment: Placebo or 600 mg CoQ10
2 Week Loading
Weekly phone calls: Pain Questionnaires used to assess muscle symptoms and document myalgia
Simvastatin 20mg + Placebo (N=50)
Simvastatin 20mg + CoQ10 600 mg (N=50)
At 8 Weeks
Subset of Patients: Crossover

Atherosclerosis 238 (2015) 329–335

Contents lists available at ScienceDirect

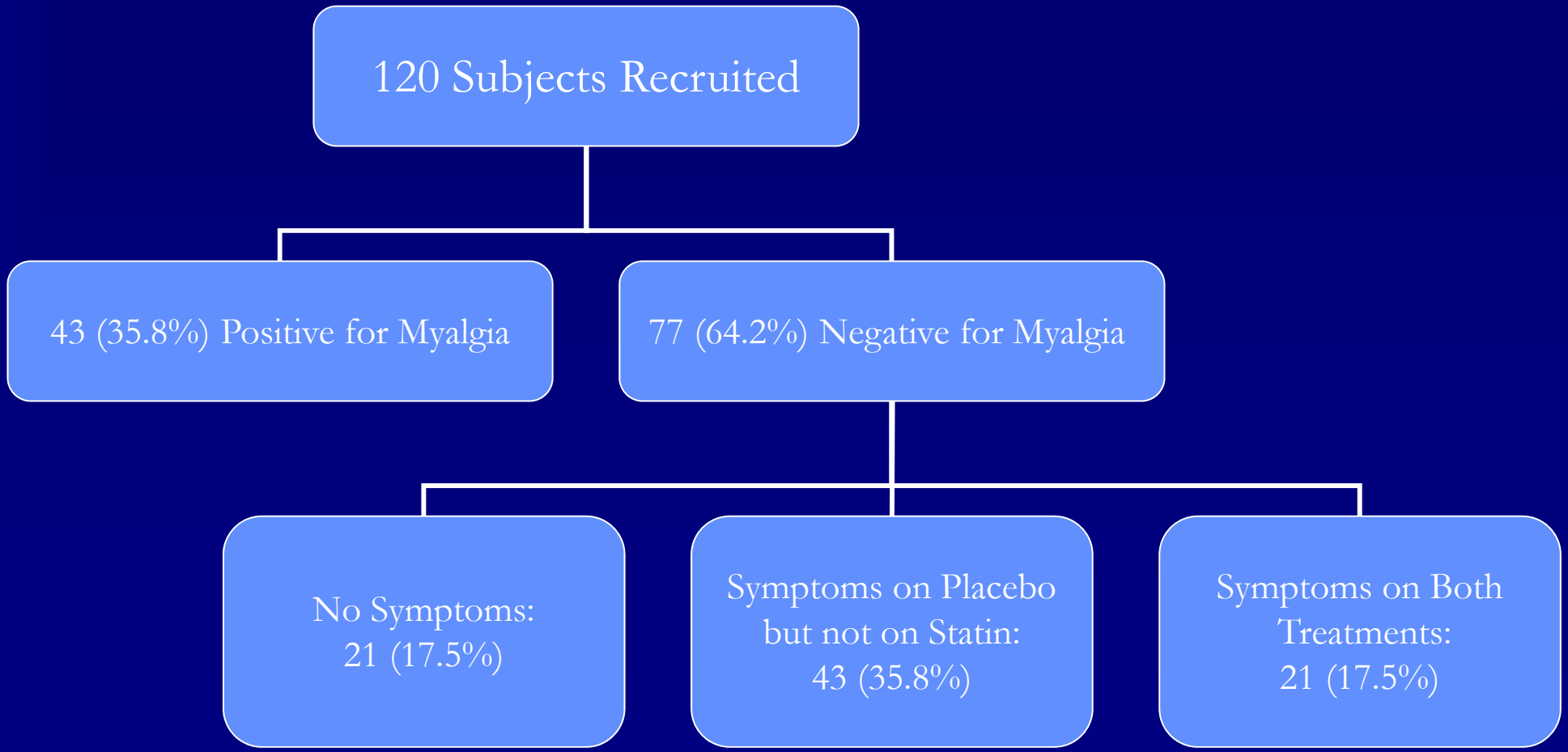
Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

# A randomized trial of coenzyme Q10 in patients with confirmed Statin Myopathy

Beth A. Taylor [a, b, c, *], Lindsay Lorson [a], C. Michael White [a, c], Paul D. Thompson [a, c]

# Few Met the Definition of Myalgia



# Statin Intolerance as a Barrier to Risk Reduction

Why Care About Statin Associated Symptoms (SAS) ?

What Are SAS ?

How Do We Diagnose SAS ?

How Frequent Are SAS ?

How Should We Manage SAS ?

# Do SAS Even Exist ?

**From:** Jane Armitage [mailto:jane.armitage@ctsu.ox.ac.uk]
**Sent:** Thursday, July 16, 2015 1:30 PM
**To:** Thompson, Paul

…. I'm afraid we will just have to agree to differ on these points! But I'm sorry that you find it so difficult to believe the mass of randomized data showing no significant adverse muscle effects and your own data which support this lack of effect. I certainly agree that lots of people attribute their muscle symptoms to statins (often having been warned that statins might cause such symptoms) but this is exactly the problem with using non-blinded observational evidence to draw conclusions about causality.

# A Systematic Review of Statin-Induced Muscle Problems in Clinical Trials

Identified 1012 Reports on Statin Trials - 42 Qualified for Analysis

4 Reported Average CK

26 Reported Muscle Problems

Only 1 Queried For Muscle Problems

All Studies: Muscle Problems on Statin (12.7%) vs Placebo (12.4%) (p=0.06).

Ganga, Slim, Thompson. Am H J (in press)

# Don’t Ask….Don’t Tell

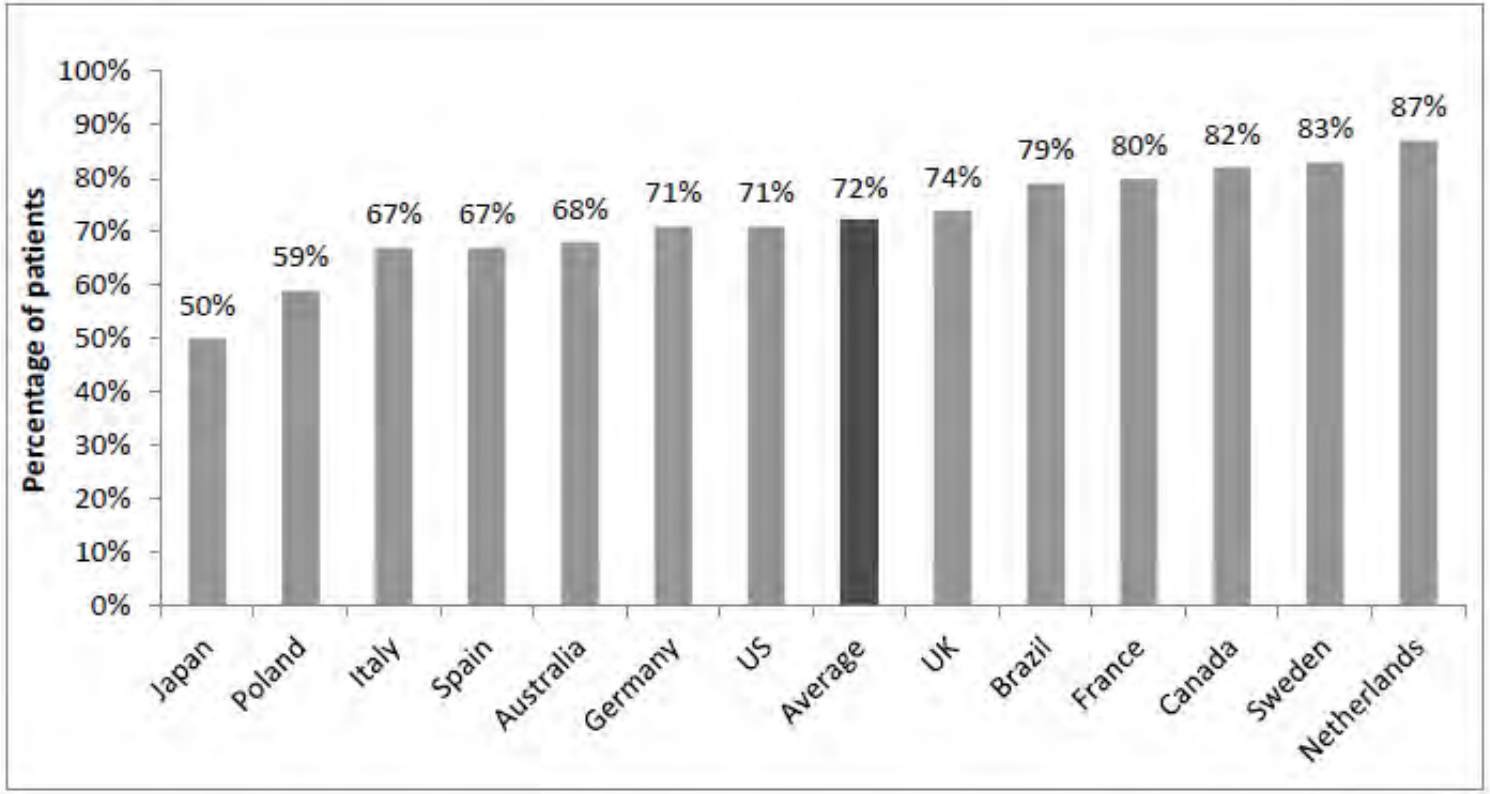
# PRedIction of Muscular Risk in Observational Conditions or PRIMO Study

- 7,924 French Patients on Fluva 80, Atorva 40-80, Prava 40, Simva 40-80, for 3 mos
- 10.5% Reported Muscular Symptoms

Bruckert CV Drugs & Therapy 2005

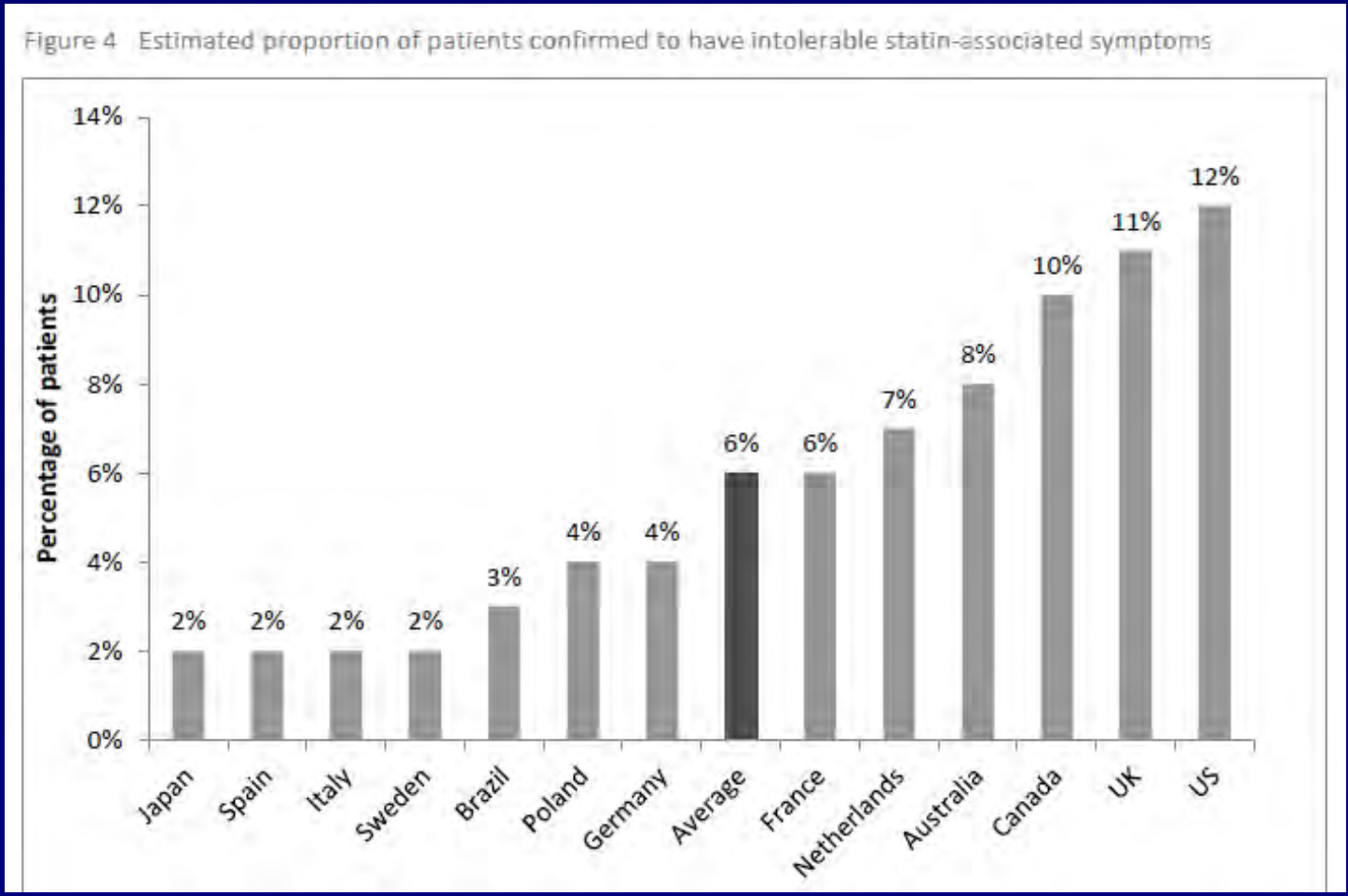
# % New Statin Patients with Possible SAMS

Figure 2 Proportion of patients newly prescribed statins reported to present with potential statin-associated muscle symptoms




**Hovingh et. al. Atherosclerosis In Press**

# % Patients Confirmed to Have Intolerable SAS




Hovingh et. al. Atherosclerosis In Press

# The STOMP Study

## The Effect of STatins On Skeletal Muscle Performance

## NHLBI (NIH): R01HL081893

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

**Effect of Statins on Skeletal Muscle Function**

Beth A. Parker, Jeffrey A. Capizzi, Adam S. Grimaldi, Priscilla M. Clarkson, Stephanie M. Cole, Justin Keadle, Stuart Chipkin, Linda S. Pescatello, Kathleen Simpson, C. Michael White and Paul D. Thompson

*Circulation*. 2013;127:96-103; originally published online November 26, 2012;

# Experimental Design

- Subjects (n=440)
  - Men and women
  - >20 yr
  - No prior statin use

- Design
  - Randomized, double blind
    - 80 mg dose of Atorva or placebo for six months
- Muscle function
  - Handgrip strength
  - Elbow flexor/extensor
  - Knee flexor/extensor
- Aerobic performance ($VO_2Max$)
- Physical activity (accelerometer)
- Muscle symptoms

# Study Definition of Statin-Related Myopathy

1. They report new or increased myalgia, cramps, or muscle aching,
2. These symptoms have persisted for at least 2 weeks,
3. The symptoms resolve within 2 weeks of stopping the study drug, and
4. The symptoms reoccur within 4 weeks of restarting the medication

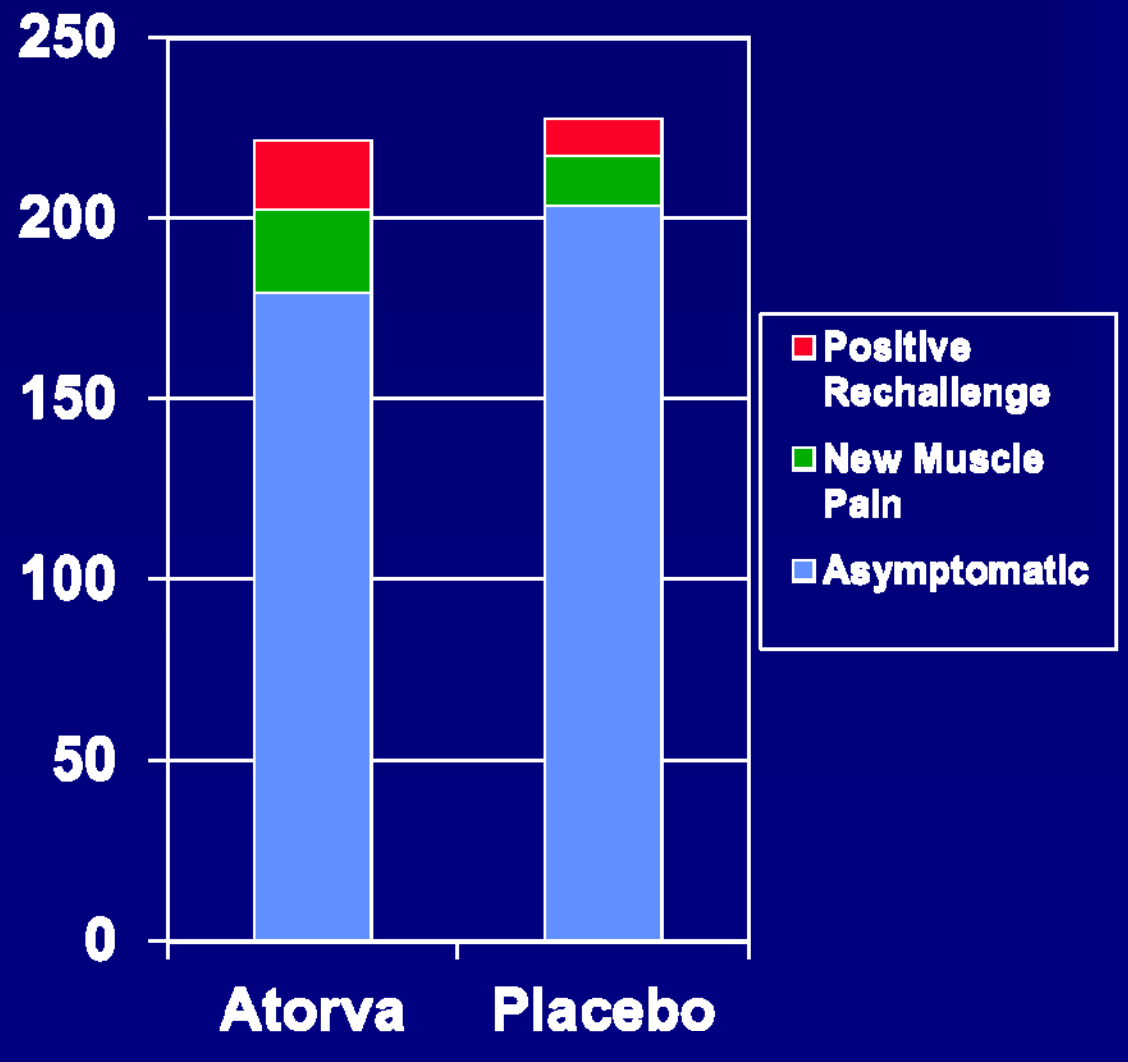
# STOMP Myalgia Results

23 Atorva & 14 Placebo Developed Pain

$X^2$=3.16; p = 0.08

19 Atorva & 10 Placebo Met Myalgia Definition

$X^2$=3.74; p = 0.05



# There Were No Differences in Maximal Exercise Capacity or Handgrip, Arm or Leg Strength Between the Atorva & Placebo Groups With 6 Mos of Therapy

**Table 3. Absolute (Post Minus Baseline) Aerobic and Strength Data by Drug Assignment**

| | ATOR (n=202*) | PL (n=217) |
|---|---|---|
| Resting RER | 0.0 (–0.01 to 0.01) | 0.0 (–0.03 to 0.03) |
| $\dot{V}o_2$max, mL·kg$^{-1}$·min$^{-1}$ | –0.8 (–1.3 to –0.3) | –0.8 (–1.4 to –0.2) |
| VT, mL·kg$^{-1}$·min$^{-1}$ | –0.9 (–1.6 to –0.2) | –0.6 (–1.6 to 0.4) |
| Hand grip, kg | 0.1 (–0.5 to 0.7) | –0.6 (–1.3 to 0.1) |
| Arm strength (APT), N-m | | |
| Isom Ext | 0.8 (–0.2 to 1.8) | 0.3 (–0.6 to 1.2) |
| Isom Flex | –0.5 (–2.1 to 1.1) | –0.2 (–1.1 to 0.7) |
| Isok Ext at 60°/s | 0.5 (–0.2 to 1.2) | –0.2 (–0.9 to 0.5) |
| Isok Flex at 60°/s | 0.0 (–0.6 to 0.6) | 0.0 (–0.6 to 0.6) |
| Isok Ext at 180°/s | 0.5 (–0.2 to 1.2) | 0.6 (0.2 to 1.2) |
| Isok Flex at 180°/s | 0.2 (–0.6 to 1.0) | 0.1 (–0.5 to 0.7) |
| Leg strength (APT), N-m | | |
| Isom Ext | –2.1 (–5.1 to 0.9) | –0.4 (–3.4 to 2.6) |
| Isom Flex | –1.8 (–3.2 to –0.4) | –1.3 (–2.6 to 0.0) |
| Isok Ext at 60°/s | 1.2 (–0.8 to 3.2) | 0.9 (–1.1 to 2.9) |
| Isok Flex at 60°/s | 0.9 (–0.5 to 2.3) | –0.5 (–2.7 to 1.7) |
| Isok Ext at 180°/s | 3.9 (2.0 to 5.8) | 3.8 (2.3 to 5.3) |
| Isok Flex at 180°/s | 2.7 (1.5 to 3.9) | 2.1 (1.0 to 3.2) |
| Knee endurance fatigue index | –0.1 (–1.6 to 1.4) | 0.2 (–0.8 to 1.2) |

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

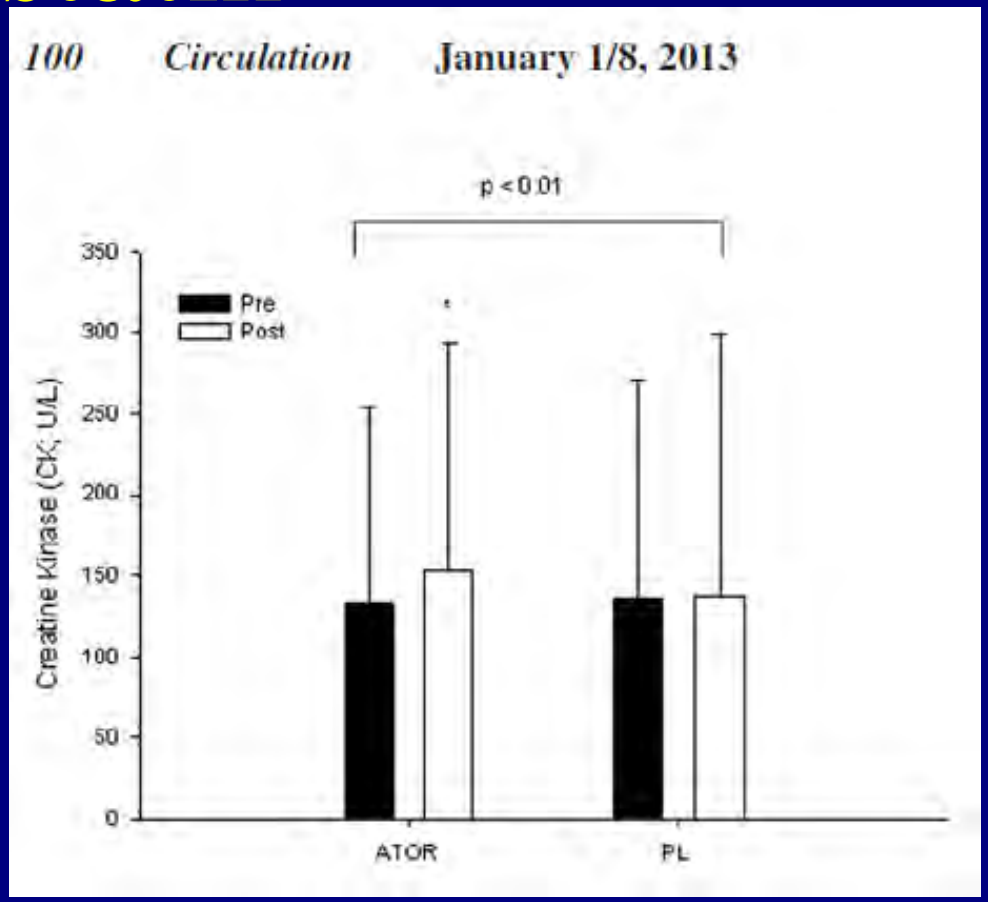
American Heart Association.

**Effect of Statins on Skeletal Muscle Function**

Beth A. Parker, Jeffrey A. Capizzi, Adam S. Grimaldi, Priscilla M. Clarkson, Stephanie M. Cole, Justin Keadle, Stuart Chipkin, Linda S. Pescatello, Kathleen Simpson, C. Michael White and Paul D. Thompson

**No Subject Had Any CK Value Persistently Greater Than 10 Times Normal...But**

# Average CK Increased 20.8±141.1 U/L ($P$<0.0001) with Atorvastatin

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# Managing Patients With SAS / SAMS ?

- Are Symptoms Tolerable? Measure CK
- Stop Drug Until No SX
- Try Another Statin
- Try Lower Doses Plus Minus Ezetimibe
- Try Another Class of Drug
- Try Chinese Red Rice Yeast 2 Tabs HS
- Try Atorva / Rosuva / Pitava QOD or BIW
- Do "Pulse Therapy"
- Use Q10 Supplements ????
- Measure / Replete Vitamin D
- Use PCSK 9 Inhibitors

# Statin Intolerance as a Barrier to Atherosclerotic Disease Risk Reduction

**Paul D. Thompson, MD**

**Director of Cardiology**

**Henry Low Heart Center**
**Hartford Hospital**

**Hartford, CT**

# How Effective is Dietary Therapy for Marked Hypertriglyceridemia?

Kathy Rhodes, PhD, RDN
Cardiovascular Medicine
Frankel Cardiovascular Center
University of Michigan
Ann Arbor, MI
September 19, 2015

# “If you have HTG, triglycerides are a barometer of your diet.”

Carl Orringer, MD


“Perhaps no lipid parameter responds better to nutritional intervention (and increased physical activity) than TG levels.”

Bays et al, *JCL.* 2013;*7:304-383*

# Distribution of triglyceride levels in adults ≥20 years old NHANES 2001 to 2006

| Triglyceride Level (mg/dl) | Definition NLA Part 1 | Sample Size (n = 5,680) | Population Estimate (n = 197,088,927) | Percentage of Population |
|---|---|---|---|---|
| <150 | Normal | 3,812 | 133,660,634 | 67.80 |
| 150–200 | Borderline high | 839 | 27,933,114 | 14.20 |
| 200–<500 | High | 939 | 32,056,089 | 16.30 |
| 500–2,000 | Very High | 87 | 3,357,214 | 1.70 |
| >2,000 | Very High (SHTG) | 3 | 81,877 | 0.00 |
| Total | — | 5,680 | 197,088,927 | 100.00 |

Christian et al, *Am J Cardiol*. 2011;107:891–897

# NLA Recommendations for Patient-Centered Management of Dyslipidemia

- Reducing elevated triglycerides contributes to reduction in non HDL-C.
- Triglycerides are **not** targets of therapy per se **except** when very high. When the triglyceride concentration is ≥500 mg /dL and especially if ≥1000 mg/dL, reducing the concentration to ≤500 mg/dL to prevent pancreatitis becomes the primary goal of therapy.

# Introduction

- Hypertriglyceridemia (HTG) is multifactorial.
- HTG results from the interaction of genetic and environmental factors.
- Identify and treat non-dietary secondary causes of HTG, such as medications and disease conditions.
- First line therapy is lifestyle. Lifestyle is a predictor of failure to achieve goals independent of drug therapy.*
- Individualization of nutrition recommendations is important.
- Good diet history is necessary to guide patient.

*Pinto X, et al. *Curr Med Res Opin.2014*;30:19-26

# Objectives

- Review the NLA Lifestyle Recommendations: Dietary considerations for management of hypertriglyceridemia
- Assess the impact of diet & weight reduction on management of HTG in patients with TG>150 mg/dL and <500 mg/dL
- Compare the treatment for TG<500 mg/dL versus $\geq$ 500 mg/dL
- Describe the outcomes of a nutrition trial for patients presenting with TG $\geq$ 500 mg/dL to a Lipid Management Program

# Dietary Factors and Triglyceride Reduction TG 150-500 mg/dL

| Dietary Factor | % Change in TG |
|---|---|
| Weight loss of 5-10% | - 20% |
| (per gram) | |
| Eliminate trans fatty acids (per 1% replacement with MUFA/PUFA) | - 1% |
| Alcohol (per 1oz./day) | + 5-10% |
| Glycemic load | Inconclusive |
| Normalization of glycemic control | |

Overall, optimization of nutrition-related practices can result in a marked triglyceride-lowering effect that ranges between 20% and 50%.

Adapted from Miller et al. *Circulation.*2011;123:2292-333

# Weight Loss

- Reduction in TG is related to magnitude of weight loss
  - 3-5% reduction in body weight can lower TG
  - 3 kg weight loss expected to result in a TG reduction of at least 15 mg/dL
  - 5-10% weight loss expected to lower TG by approximately 20%
- Strong association noted between TG and weight, elevated BMI, and visceral fat.
- Lower carbohydrate diets during weight loss and maintenance may lower TG more than higher carbohydrate diets

Jensen et al. *JACC* 2014;63:2986-3023; Miller et al. *Circulation* 2011;123:2292-333;
Bays et al, *JCL.* 2013;*7:304-383*

# OmniHeart

- Randomized, 3 period, crossover, controlled feeding study
- 164 participants with pre HTN or HTN
- 3 options of heart healthy diets
  - DASH 58% CHO 15% pro 27% fat
  - Higher protein 48% CHO 25% pro 27% fat
  - Mediterranean 48% CHO 15% pro 37% fat

Appel et al. *JAMA* 2005;294:2455-2464

# OmniHeart: Conclusions

- BP, LDL-C and estimated CHD risk were lowered in all 3 diets compared to baseline.
- Higher protein diet further decreased BP, LDL-C and TG.
- Mediterranean diet further decreased BP and TG; increased HDL-C.
- Estimated 10 year risk was lower and similar on protein and Mediterranean style diets.
- A range of  macronutrient compositions may have beneficial effects.

Appel et al. *JAMA* 2005;294:2455-2464

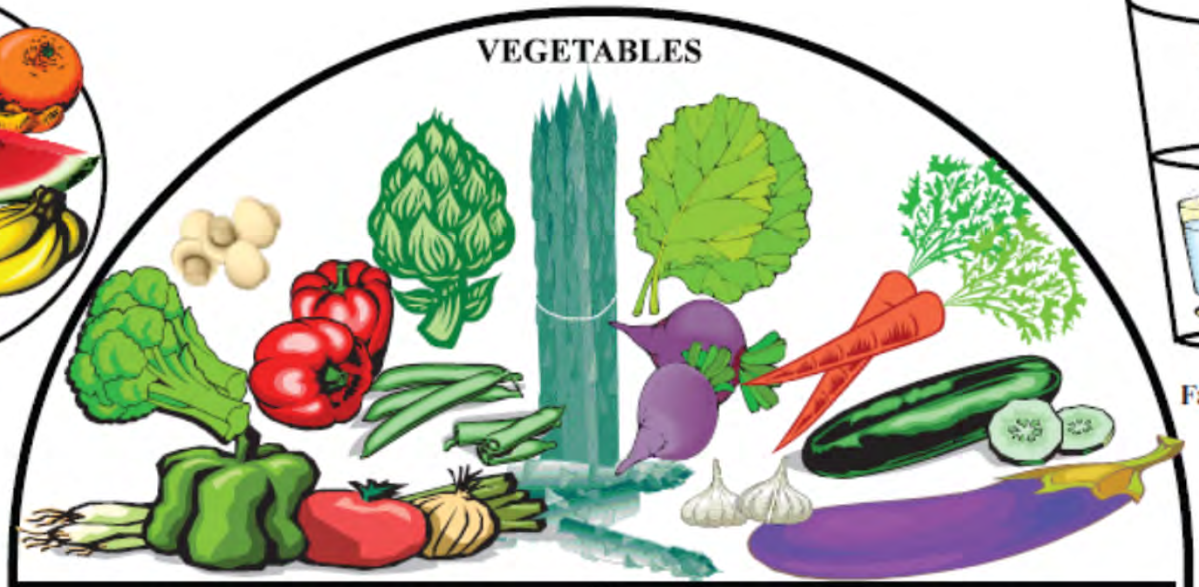
# Mediterranean Style Eating Plan

- Emphasis on plant-based foods
  - Fruits, vegetables, whole grains, nuts and legumes
- Olive oil instead of butter; low fat milk and cheeses
- Eat fish and poultry; limit red meat
- Generally interpreted as 32-45% fat
- Red wine in moderation
- A whole foods approach
- Physical activity, enjoying mealtimes with family & friends



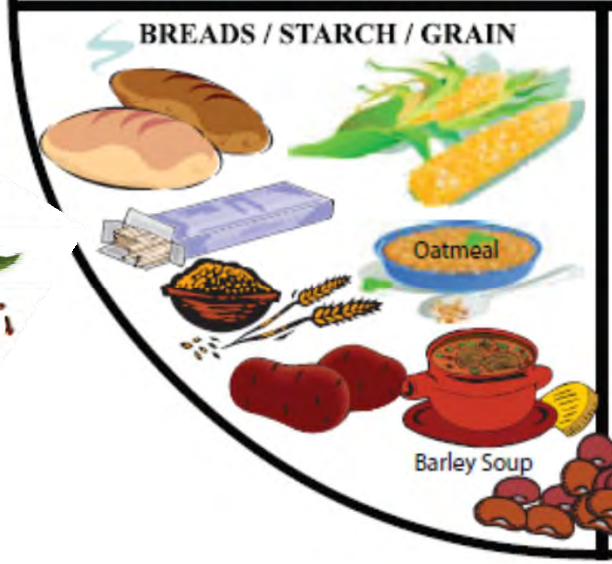
# The Plate for a Healthy Heart

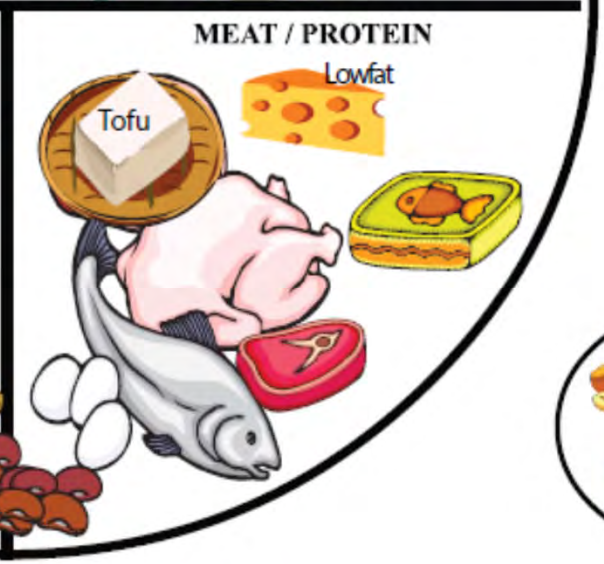
FRUITS





Fat free, ½%, 1% milk
or
dairy alternative





ACCENTS

HEALTH SYSTEM
UNIVERSITY OF MICHIGAN

## Triglycerides with Healthful Eating and Physical Activity*

**IN SUGAR:**

comes
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fruit-flavored
ks, some sports
), and fruit juice
gh in sugar.

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**R CONSUME
OUNTS:**

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ra calories that

# How Much Sugar Are You Eating And Drinking?

| | |
|---|---|
| Coffee Frappuccino, **13 oz** | **12 teaspoons** |
| Sugar sweetened cola, **12 oz** | **10-11 teaspoons** |
| Orange juice, **12 oz** | **9-10 teaspoons** |
| Fruit smoothie, **12 oz** | **9-10 teaspoons** |
| Cranberry juice or lemonade, **12 oz** | **8 teaspoons** |
| Fruit flavored sports drink, **12 oz** | **6 teaspoons** |
| Ice cream, **½ cup** | **7 teaspoons** |
| Pudding, **½ cup** | **5 teaspoons** |

The American Heart Association recommends no more than **100 calories/day** (6 ½ teaspoons) from added sugar for women and **150 calories/day** (10 teaspoons) for men. When reading nutrition facts labels, check total carbohydrate content, not just the sugar content. The total carbohydrate number includes both sugar and starches and gives the best information about how much the food could raise your triglyceride level.

***mg/dL, special nutrition recommendations may be important. Please consult with your healthcare provider.***
***diet changes, your clinician may recommend additional forms of medical treatment or therapy to lower your***

# Case Study: 55 y.o. male with severe hypertriglyceridemia

- PMH: Familial HTG, DM, HTN, CAD with stent placement 2001, S/P pancreatitis due to HTG (12/2013)
- FH: HTG in his brother and mother
- Meds: include pravastatin, fenofibrate, omega-3 acid ethyl esters, metformin
- TG =10,000 mg/dL 6 weeks ago
- He went on low carbohydrate nutrient dense plan high in healthy fats; eliminated red meat; ate chicken, fish, vegetables, large amounts of olive oil and nuts;
  + exercise

# Case Study: 55 y.o. male with severe hypertriglyceridemia

- Reports losing 16 lb, normalizing blood glucose and blood pressure
- Off Lantus
- January 5, 2015: fasting triglycerides remained 3458 mg/dL
- Diet intervention: chylomicron clearing protocol <15% fat

# Nutrition Therapy for Severe HTG: Chylomicron Clearing Protocol

Limit total fat to 10-15% calories (20-40 g)

Avoid alcohol

No added simple or refined carbohydrate; partially replace with high fiber foods

Limit fruit; no fruit juice or sugary beverages

Spread calories and carbohydrates evenly through the day

Limit calories, if weight loss indicated

If extra calories needed, add MCT oil and increase gradually

Exercise 30-60 min most days

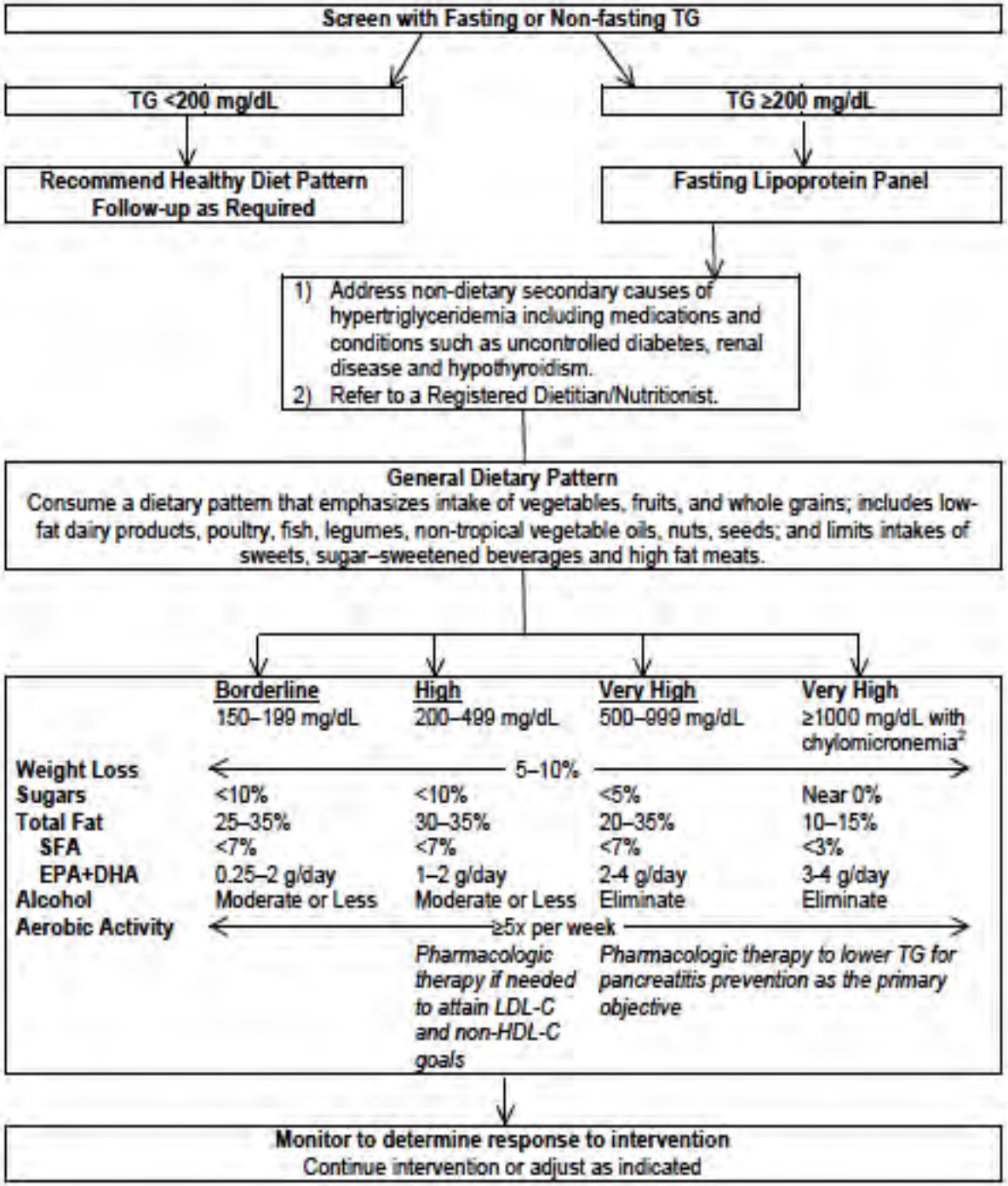
Adjust diabetes medications as appropriate to maintain glycemic control

Once chylomicrons cleared and triglycerides <500 mg/dL, gradually advance to tolerance

NLA Part 2

# Case Study: 55 y.o. male with severe hypertriglyceridemia

- Called patient 2 weeks later to review labs:
  - Triglycerides =705 mg/dL down from 3458 mg/dL
  - HgA1c = 5.7%


Screen with Fasting or Non-fasting TG
TG <200 mg/dL
TG ≥200 mg/dL
Recommend Healthy Diet Pattern
Follow-up as Required
Fasting Lipoprotein Panel
1) Address non-dietary secondary causes of hypertriglyceridemia including medications and conditions such as uncontrolled diabetes, renal disease and hypothyroidism.
2) Refer to a Registered Dietitian/Nutritionist.
General Dietary Pattern
Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, nuts, seeds; and limits intakes of sweets, sugar–sweetened beverages and high fat meats.
Borderline
150–199 mg/dL
High
200–499 mg/dL
Very High
500–999 mg/dL
Very High
≥1000 mg/dL with chylomicronemia[2]
Weight Loss
5–10%
Sugars
<10%
<10%
<5%
Near 0%
Total Fat
25–35%
30–35%
20–35%
10–15%
SFA
<7%
<7%
<7%
<3%
EPA+DHA
0.25–2 g/day
1–2 g/day
2-4 g/day
3-4 g/day
Alcohol
Moderate or Less
Moderate or Less
Eliminate
Eliminate
Aerobic Activity
≥5x per week
Pharmacologic therapy if needed to attain LDL-C and non-HDL-C goals
Pharmacologic therapy to lower TG for pancreatitis prevention as the primary objective
Monitor to determine response to intervention
Continue intervention or adjust as indicated


Silk
QUAKER OAT BRAN
University of Michigan
Department of Internal Medicine
Cardiovascular Medicine

# How Effective is Dietary Therapy for TG ≥ 500 mg/dL?

- To document the effect of an initial lifestyle therapy by RDN for patients with TG ≥ 500 mg/dL
  - With and without pharmacological therapy
  - With and without prior nutrition counseling

Rhodes et al *J Clin Lipidol.2015;* 9:559-569

# Clinic Protocol

| T1<br>Initial visit | T2<br>1 month after T1 | T3<br>Last consult within one year of T1 |
|---|---|---|
| • Comprehensive traditional and novel risk factor assessment<br>• 75 minute MNT consult including assessment and initiation of an individualized diet and exercise intervention | • Lipid profile, ALT, ± glucose<br>• 30 minute RDN follow-up visit<br>• Initial consult with lipid specialist providing comprehensive assessment and care plan | • Lipid profile, ALT, ± glucose<br>• Any follow-up combination of consults with RDN, MD or NP<br>• Patients may have also seen a stress management counselor or EP |

Rhodes et al *J Clin Lipidol.2015;* 9:559-569

# Characteristics of Patients with TG ≥ 500 mg/dL at Time 1 (n = 168)

| Descriptives | n | % |
|---|---|---|
| Age (range) | 49.03 ± 11.22 (23.60-77.47) | |
| BMI (range) | 32.61 ± 5.85 (19.14 – 54.31) | |
| Gender (Male participants) | 117 | 69.6 |
| Ethnicity (Caucasian) | 135 | 80.4 |
| Married or living with someone (n = 167) | 130 | 77.8 |
| Employed (n = 153) | 88 | 57.5 |
| Prior RD visit | 94 | 56.0 |
| **Risk Factors** | | |
| Family history of premature CHD | 79 | 47 |
| Smoking | 52 | 31.0 |
| CHD/ PVOD | 36 | 21.4 |
| Hypertension | 91 | 54.2 |
| Diabetes Mellitus | 69 | 41.1 |
| History of pancreatitis | 33 | 19.6 |

Rhodes et al *J Clin Lipidol.2015;* 9:559-569

# Characteristics of Patients at Time 1

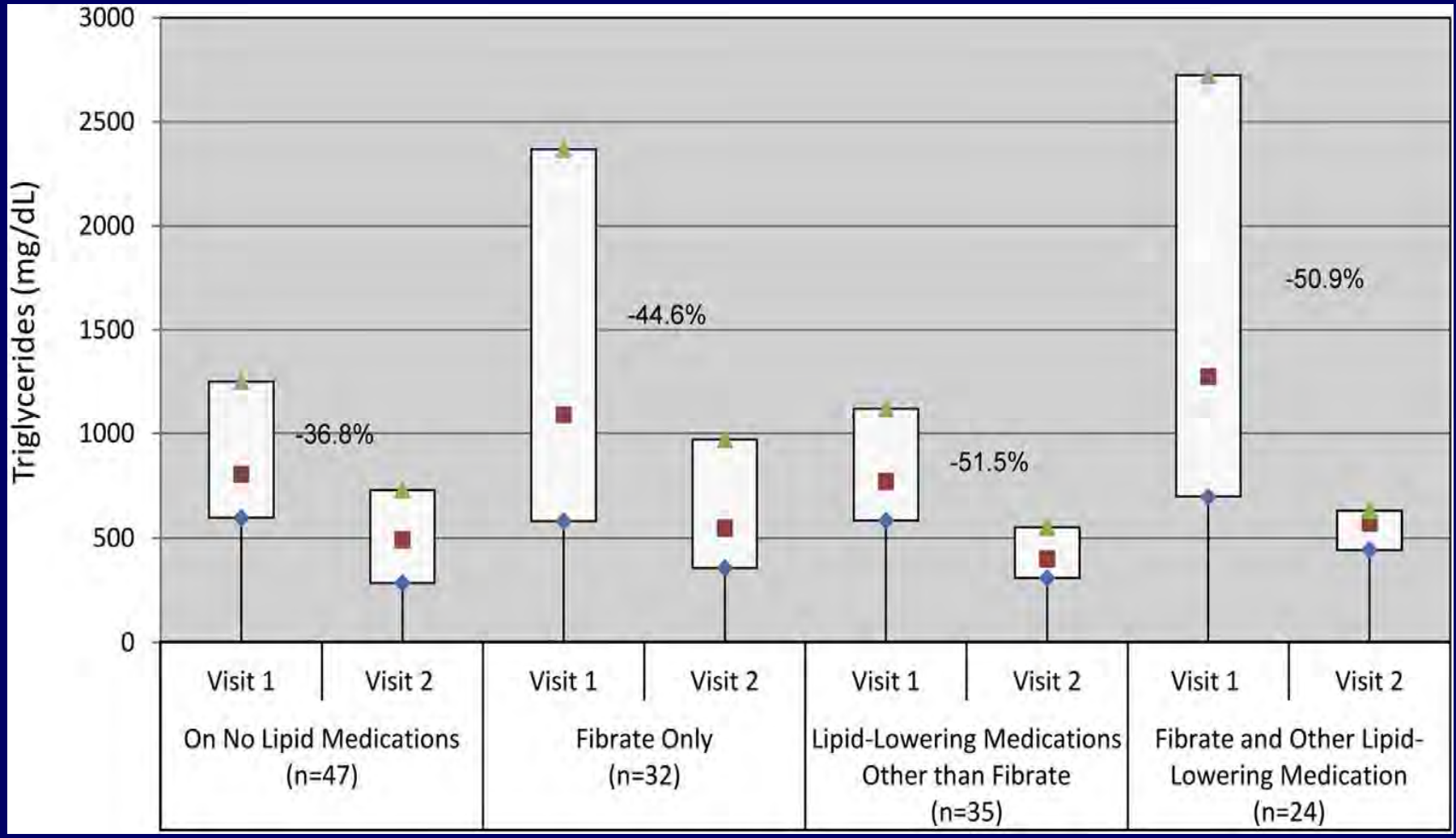
| Medications | n | % |
|---|---|---|
| Intolerance to lipid-lowering medication | 76 | 45.2 |
| On lipid-lowering medication | 110 | 65.5 |
| Statin | 53 | 31.5 |
| Fibric acid derivatives | 68 | 40.5 |
| Bile-acid sequestrant | 3 | 1.8 |
| Cholesterol absorption inhibitor | 15 | 8.9 |
| Niacin derivative | 26 | 15.5 |
| Combination of lipid-lowering medications | 45 | 26.8 |
| Fish oil [b] | 29 | 17.3 |
| On hypertension medication | 99 | 58.9 |
| On diabetes medication | 60 | 35.7 |
| On lipid and hypertension medication | 75 | 44.6 |
| On lipid and diabetes medication | 49 | 29.2 |
| On lipid, hypertension, and diabetes medication | 35 | 20.8 |
| **Behavioral Assessment** | **Mean ± SD** | **Range** |
| Exercise frequency in days/week (n = 157) | 1.2 ± 2.1 | (0– 7) |
| Total energy intake (food plus alcohol) in kcal [c] (n = 153) | 2106 ± 864 | (532– 5192) |
| Total intake from alcohol in kcal (n = 153) | 39 ± 303 | (0 – 3600) |
| Carbohydrate intake in percent total food calories (n = 151) | 47.2 ± 1.1 | (5.0 – 80.0) |
| Protein intake in percent of total food calories (n = 151) | 18.2 ± 0.6 | (5.0 – 49.0) |
| Fat intake in % of total food calories (n = 151) | 34.7 ± 1.0 | (12.0 – 64.0) |

# Lipids, glucose and exercise pre- and post-initial MNT prior to intervention by lipid specialist (n = 158)

| Variable | Prior to Referral | T1 Median (IQR) | T2 Median (IQR) | % Change T1 to T2 Median (IQR) | Wilcoxon p value Prior to T1 | Wilcoxon p value T1 to T2 |
|---|---|---|---|---|---|---|
| Total Cholesterol (mg/dL) | 308.0 (235.0 – 460.0) | 308.0 (239.0 – 404.3) | 223.0 (182.8 – 306.0) | -20.9 (-38.5 to -8.1) | 0.454 | < 0.0001 |
| Triglycerides (mg/dL) | 1161.5 (647.3 – 2377.3) | 961.5 (611.5 - 1785.3) | 493.0 (337.0 – 736.3) | -48.8 (-73.3 to -23.2) | 0.085 | < 0.0001 |
| HDL-C (mg/dL) (n = 153) | 34.0 (27.0 – 45.0) | 40.0 (31.0 - 52.0) | 34.5 (27.0 - 45.0) | -8.6 (-26.5 to 5.1) | 0.008 | < 0.0001 |
| LDL-C (mg/dL) (n = 146) | 82 (62.5 – 142.0) | 85.0 (54.0 – 122.5) | 92.0 (74.0 - 142.0) | 16.3 (-6.7 to 63.2) | 0.700 | <0.0001 |
| TC/HDL-C Ratio (n = 153) | 8.3 (6.1 – 14.3) | 7.6 (6.1 - 9.7) | 6.5 (5.4 - 8.2) | -12.2 (-29.3 to 2.2) | 0.003 | < 0.0001 |
| Non-HDL-C (n = 153)[e] | 264.0 (200.0 – 405.0) | 262.0 (207.0 – 355.0) | 192.0 (151.0- 258.8) | -21.9 (-42.2 to -8.4) | 0.525 | < 0.0001 |
| Glucose (mg/dL) (n = 77) | --- | 108.0 (97.0 - 133.0) | 105.0 (95.0 – 126.3) | -7.6 (-21.5 to 4.9) | --- | <0.0001 |
| Weight (lbs) (n = 157) | --- | 208.7 (182.7 – 241.4) | 203. 0 (175.9 – 235.4) | -2. 5 (-4.6 to -0.8) | --- | < 0.0001 |
| Exercise (days per week) (n = 141) | --- | 0.0 (0.0 - 2.0) | 2.5 (0.0 - 4.0) | not applicable | --- | < 0.0001 |

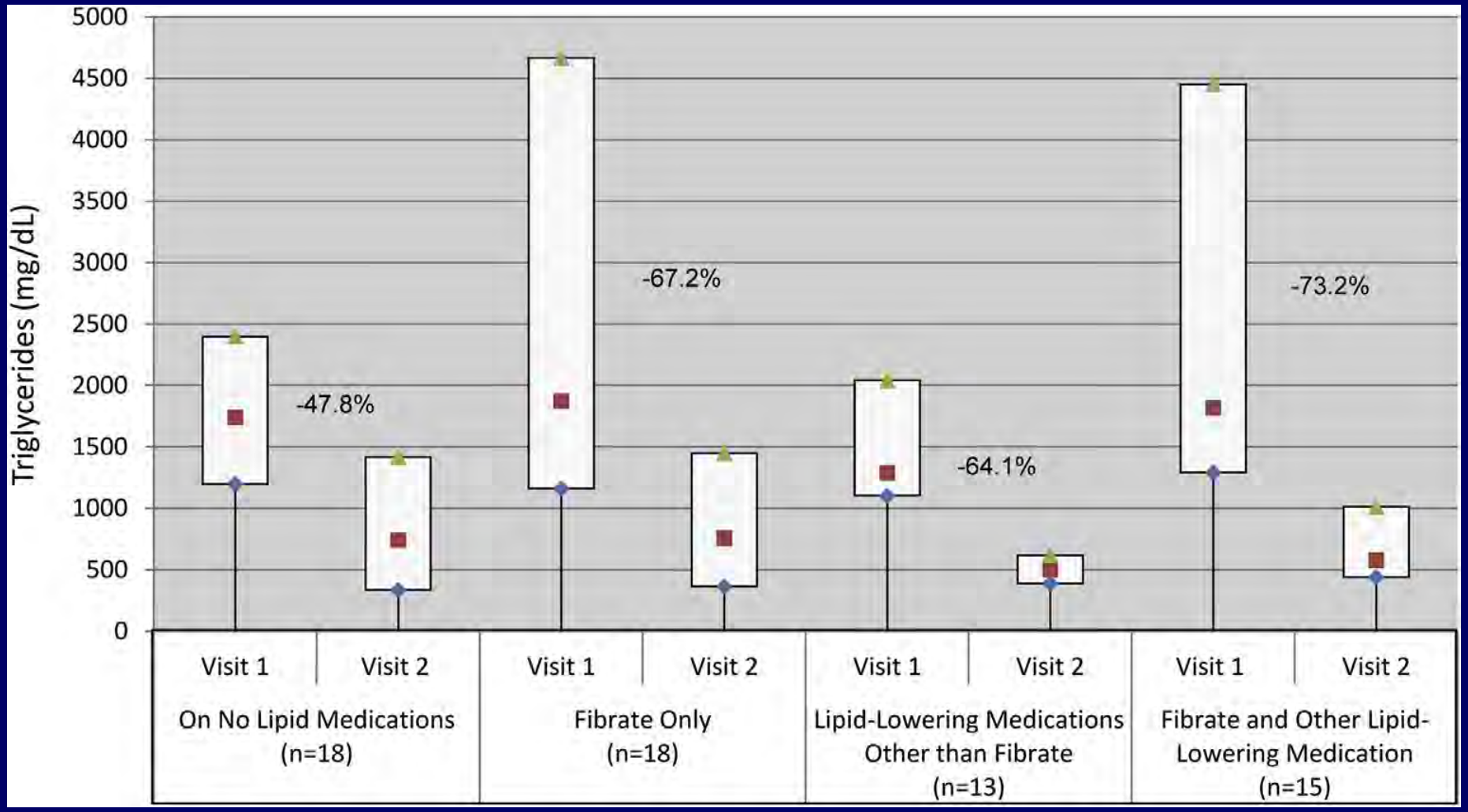
Rhodes et al *J Clin Lipidol.2015;* 9:559-567

Median (IQR) changes in triglycerides before and after initial nutrition intervention with and without lipid-lowering medication (n = 138)



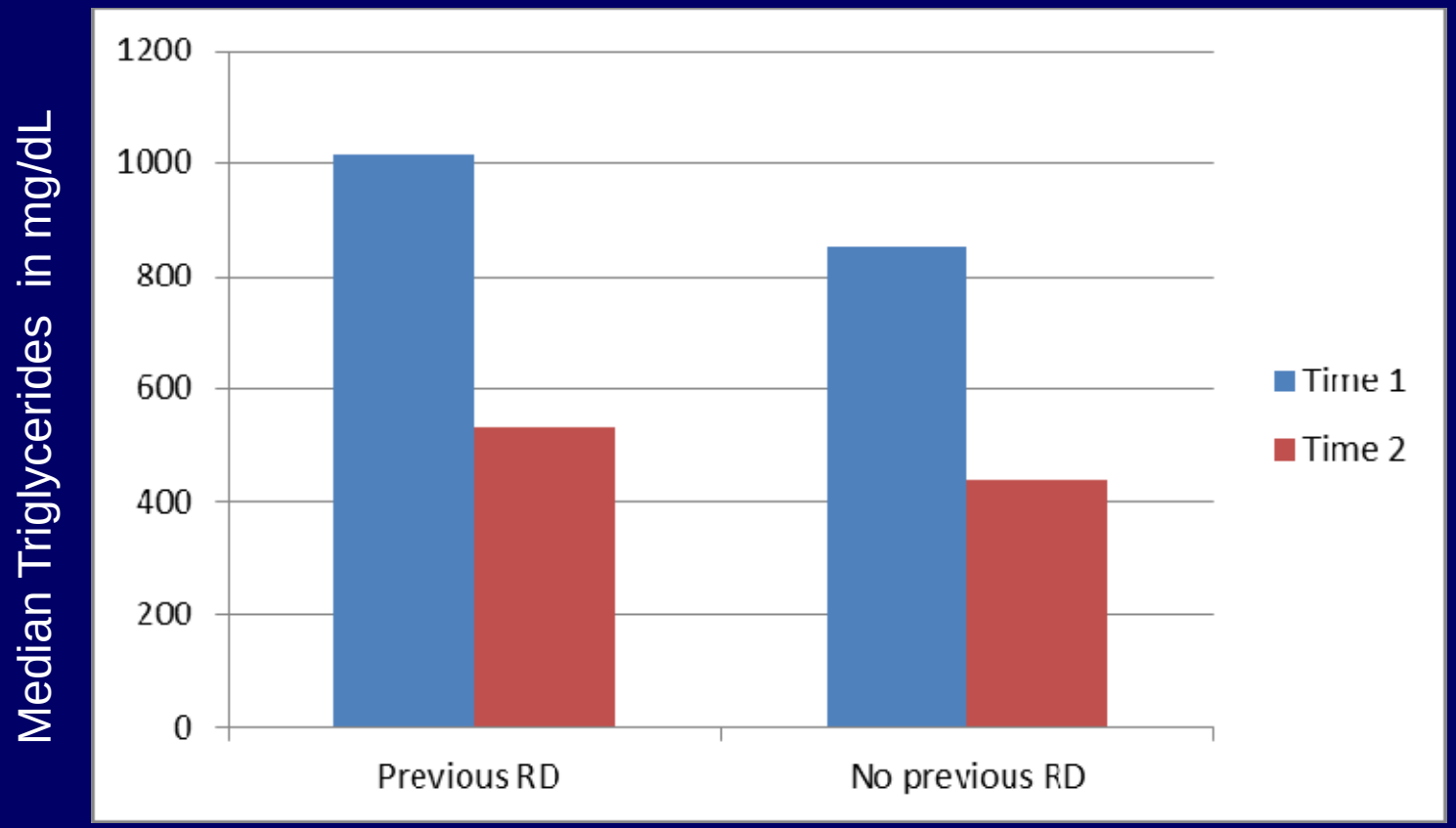

Rhodes et al. *J Clin Lipidol.2015;*9:559-567

Median (IQR) changes in triglycerides before and after initial nutrition intervention with and without lipid-lowering medication in patients with initial triglycerides >1000 mg/dL

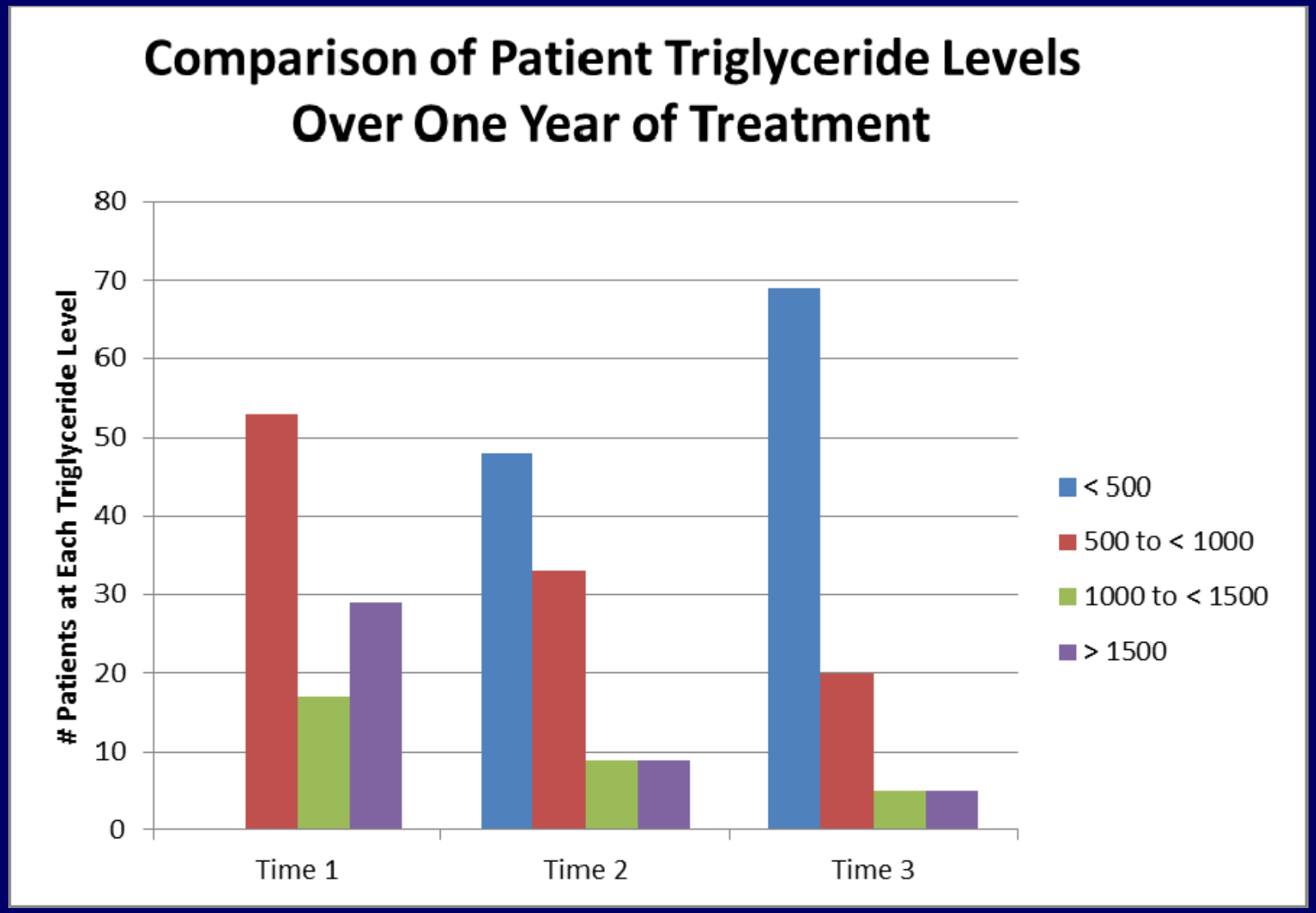



Rhodes et al. *J Clin Lipidol.2015;*9:559-567

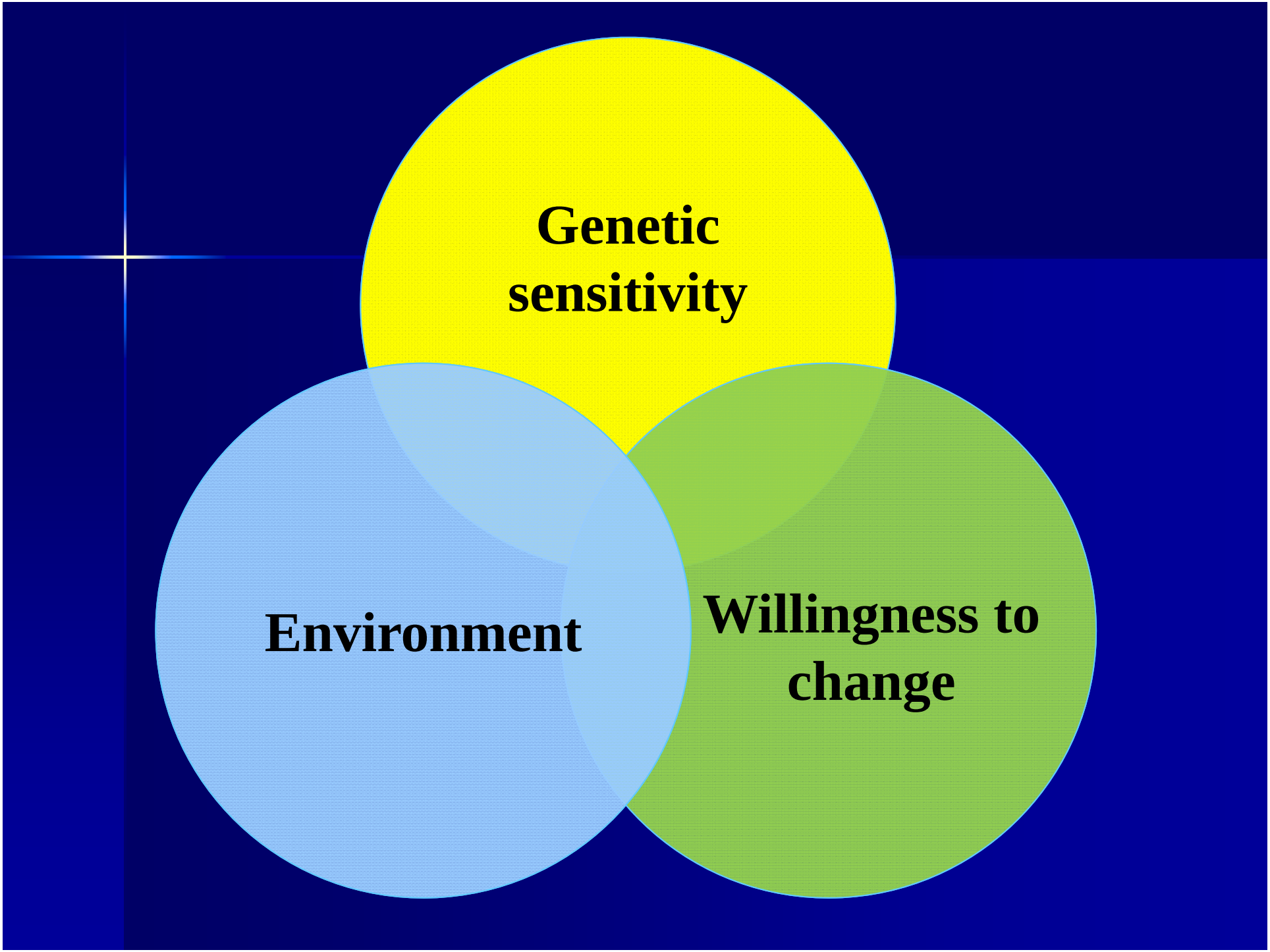
# Triglyceride reduction for patients who had previously met with RDN and those who had not




Rhodes et al. *J Clin Lipidol. 2015;*9: 559-569

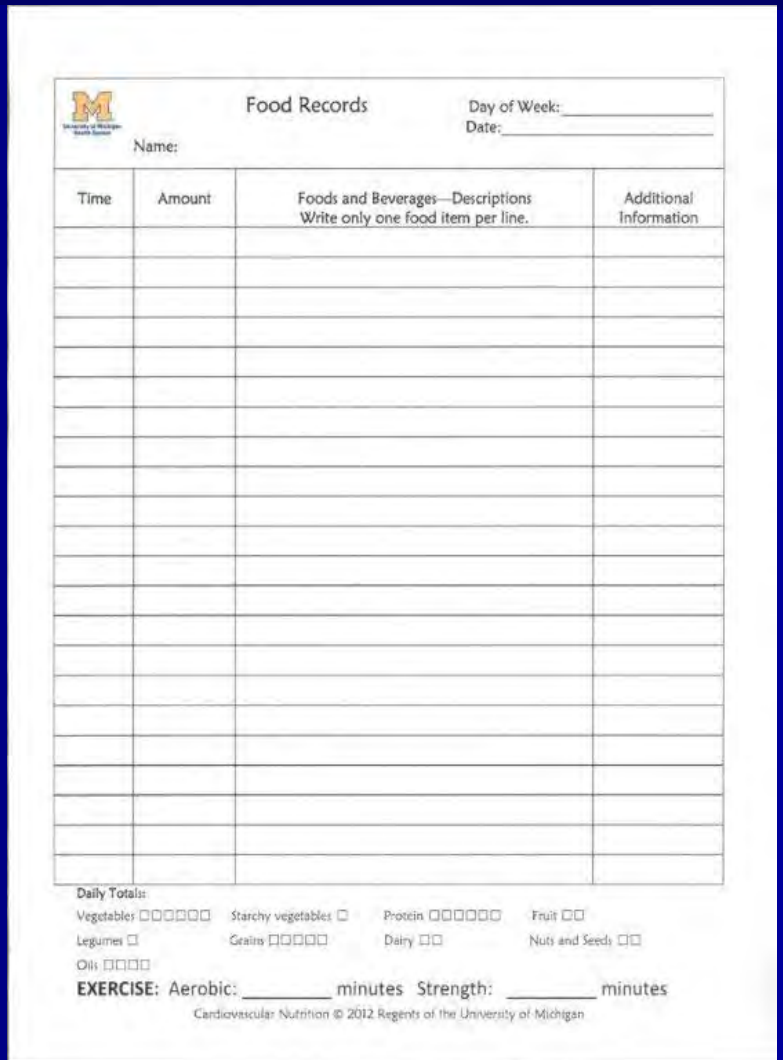



Rhodes, *unpublished*


Genetic sensitivity
Environment
Willingness to change

# Clinical Pearl: Keep food records 1 week before every lipid draw

- Enhances patient awareness
- Allows learning diet sensitivity
- Reveals patterns
- Basis for problem solving



Food Records

Day of Week: _____
Date: _____

Name:

| Time | Amount | Foods and Beverages—Descriptions<br>Write only one food item per line. | Additional Information |
|---|---|---|---|
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Daily Totals:
Vegetables □□□□□□ Starchy vegetables □ Protein □□□□□□ Fruit □□
Legumes □ Grains □□□□□ Dairy □□ Nuts and Seeds □□
Oils □□□□

**EXERCISE:** Aerobic: _____ minutes Strength: _____ minutes

# Summary: Nutrition recommendations vary with triglyceride level

- Dietary management of HTG differs between borderline/ high and very high TG.
- Always: R/O non dietary secondary causes, weight loss, low simple/refined carbohydrate, reduced trans fat, low alcohol, + exercise, glycemic control
- Triglycerides:
  - <150-500 mg/dL--weight loss, low sugar, moderate fat
  - 500-1000 mg/dL--assess history
  - >1000-2000+ mg/dL--chylomicron clearing; <15% fat; gradually liberalize

Monitor and learn patient's tolerance

Jacobs et al *J Nutr 2004;*134:1400-1405

# Take Home Messages


- Nutrition recommendations need to be individualized based on patient genetics, metabolic needs, and preferences.
- TG are a barometer of diet.
- Nutrition therapy differs with initial TG level.
- Effect of diet is independent  of medications.
- The nutrition message may need repeating.
- As clinicians, it is our role to help patients be aware of how what they eat affects their health.

# The Evolving Role of Lp(a) in Clinical Lipidology

*Alan T. Remaley, MD, PhD*

**Section Chief**
**Lipoprotein Metabolism Section**
**Cardiopulmonary Branch, NHLBI**
**National Institutes of Health**

# Lp(a) Questions

- Does it cause CHD? Yes!
- Should we measure it? Yes!
- Should we treat it? Yes!

# Overview

- Lp(a) Biology
- Lp(a) Measurement
- Lp(a) Therapy

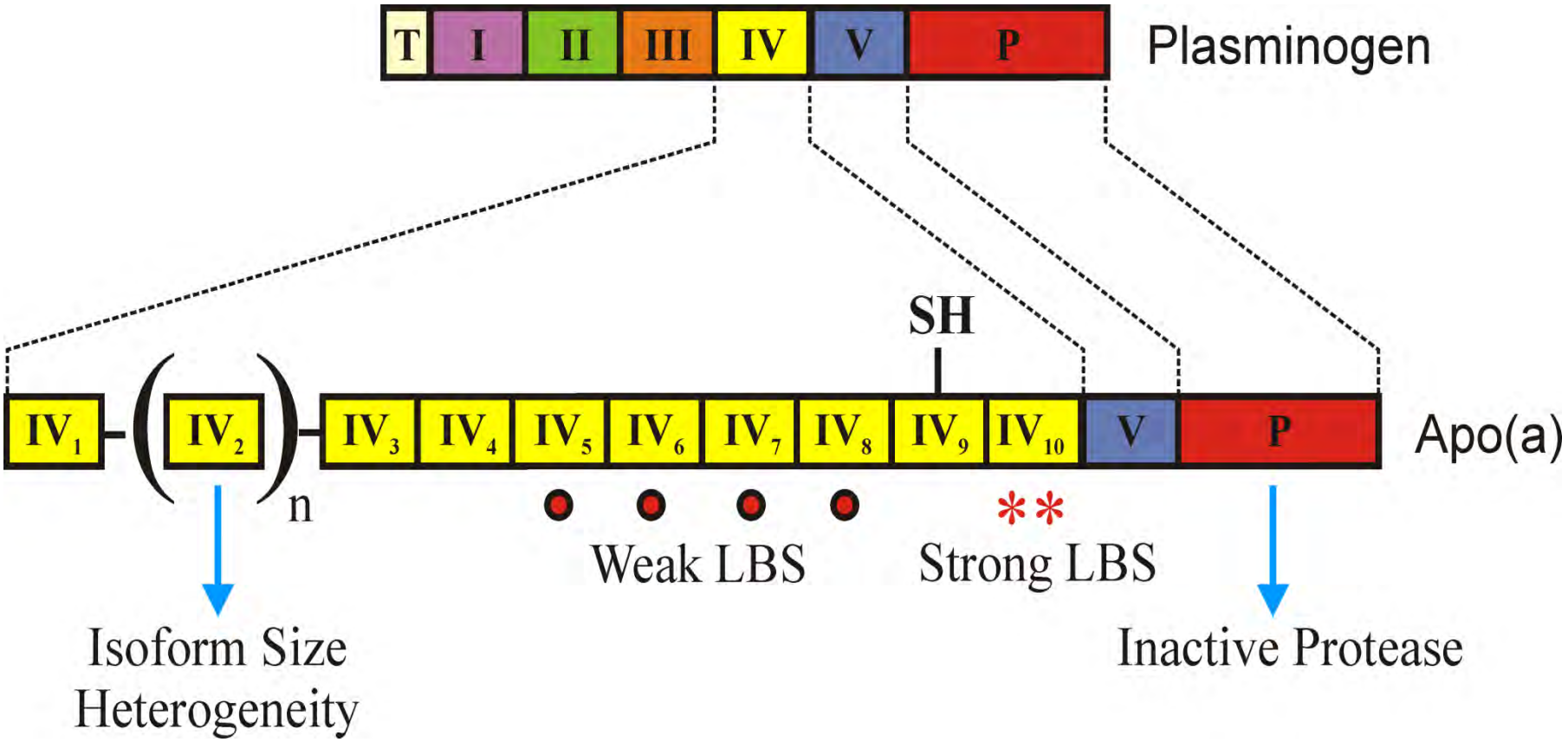
# Lp(a) History

- Discovered by Kare Berg: 1963
- Particle structure containing a single copy of apolipoprotein B covalently linked to a protein of variable mass not found in other lipoproteins
- Early studies noted its association with vascular disease (coronary, cerebral and peripheral) and then later discounted in 1990s
- Resurrected in 2009 from epidemiologic/genetic studies

# Elevated Lp(a) levels are a risk factor for a variety of vascular diseases

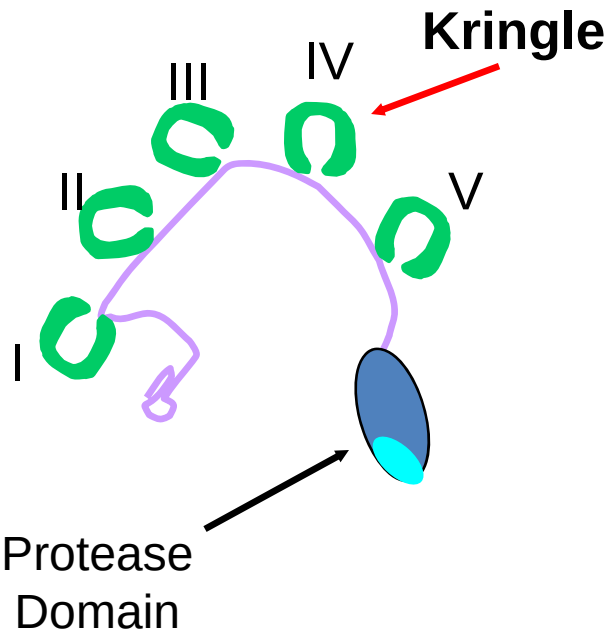
- Peripheral arterial disease
- Abdominal aortic aneurysm
- Transplant arteriopathy
- Stroke
- Aortic valve stenosis
- Coronary heart disease

# Comparison of apo(a) and plasminogen



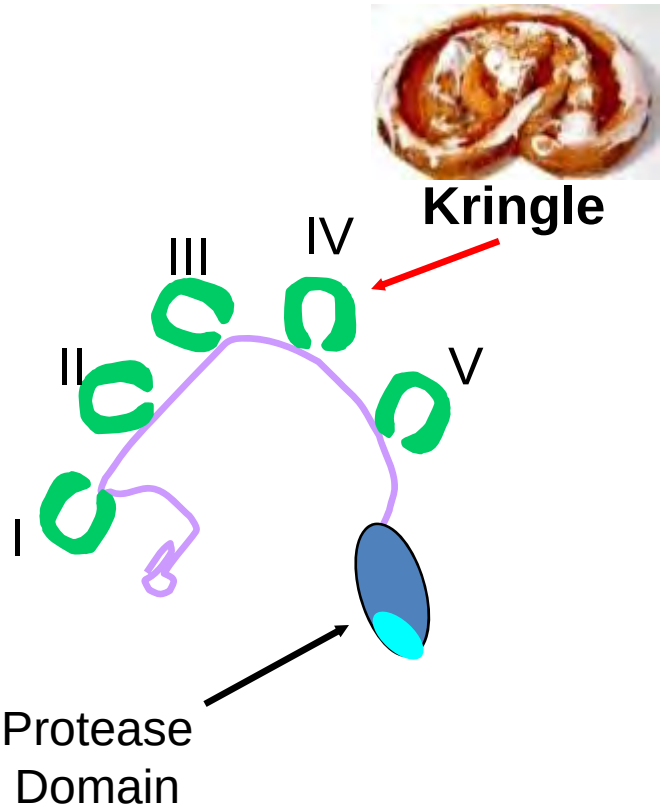

Boffa MB, in *Therapeutic Lipidology* (2008)

# Lp(a) Structure




**Unlike plasminogen, Lp(a) is only present in Humans, Apes, Old World Monkeys and the E. Hedgehog, but differences in Lp(a) structure exist among all species**

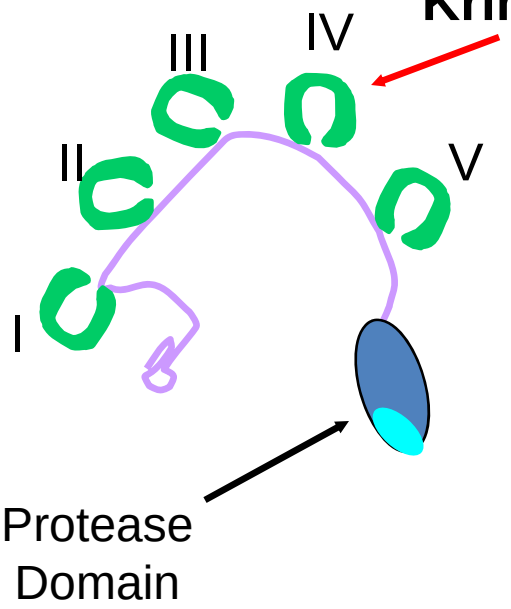
# Lp(a) Structure




**Unlike plasminogen, Lp(a) is only present in Humans, Apes, Old World Monkeys and the E. Hedgehog, but differences in Lp(a) structure exist among all species**

# Lp(a) Structure

Kringle

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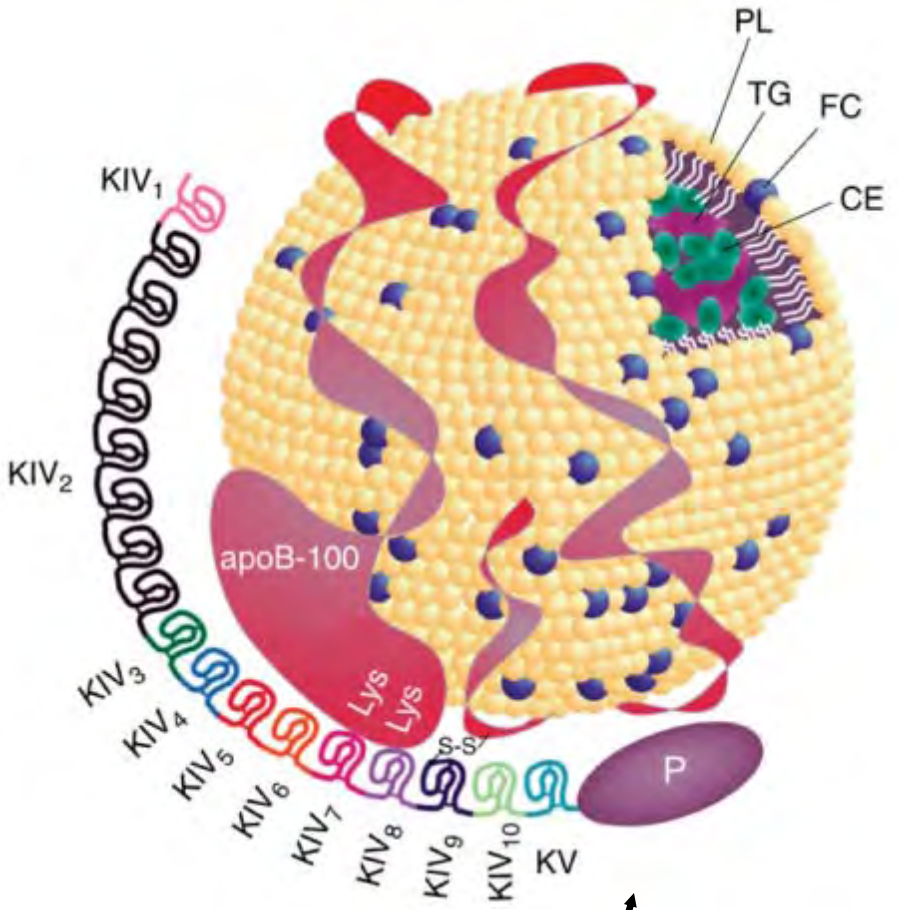
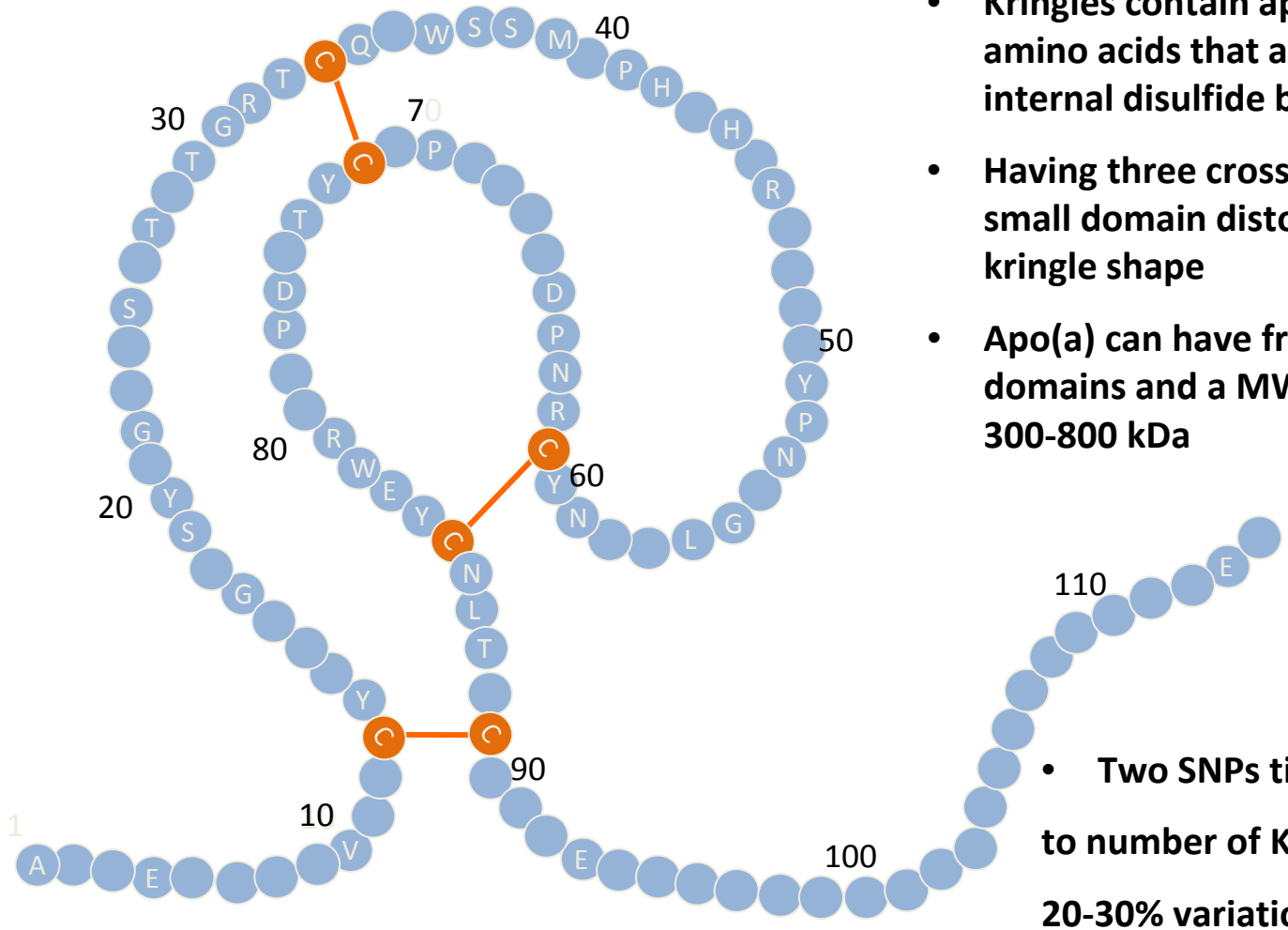



Inactive Protease

# Typical Kringle Structure

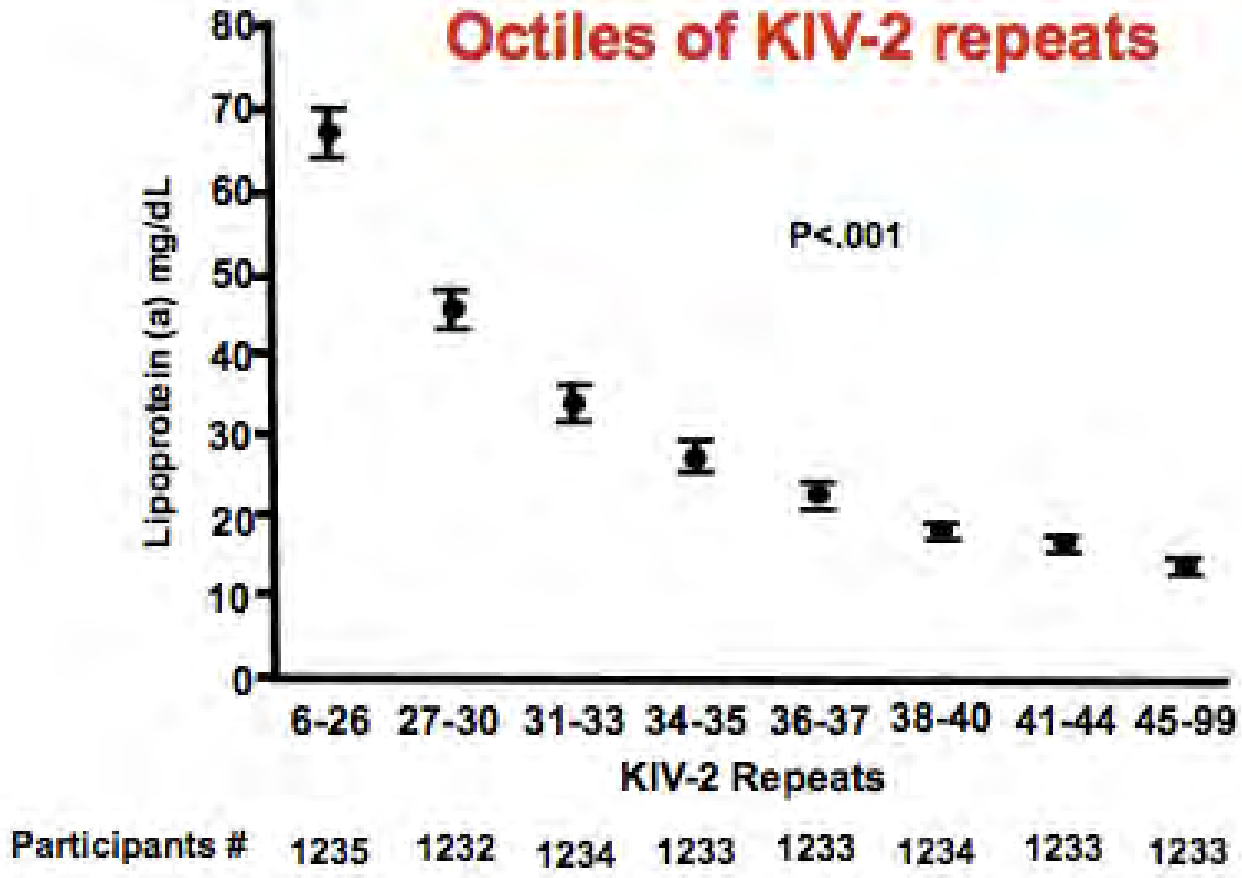



- **Kringles contain approximately 80 amino acids that are cross-linked by 3 internal disulfide bonds**
- **Having three cross links within such a small domain distorts it, creating the kringle shape**
- **Apo(a) can have from 4-30 KIV-2 domains and a MW ranging from 300-800 kDa**
- **Two SNPs tightly linked to number of KIV-2 repeats and 20-30% variation in levels**

Letters represent various amino acids

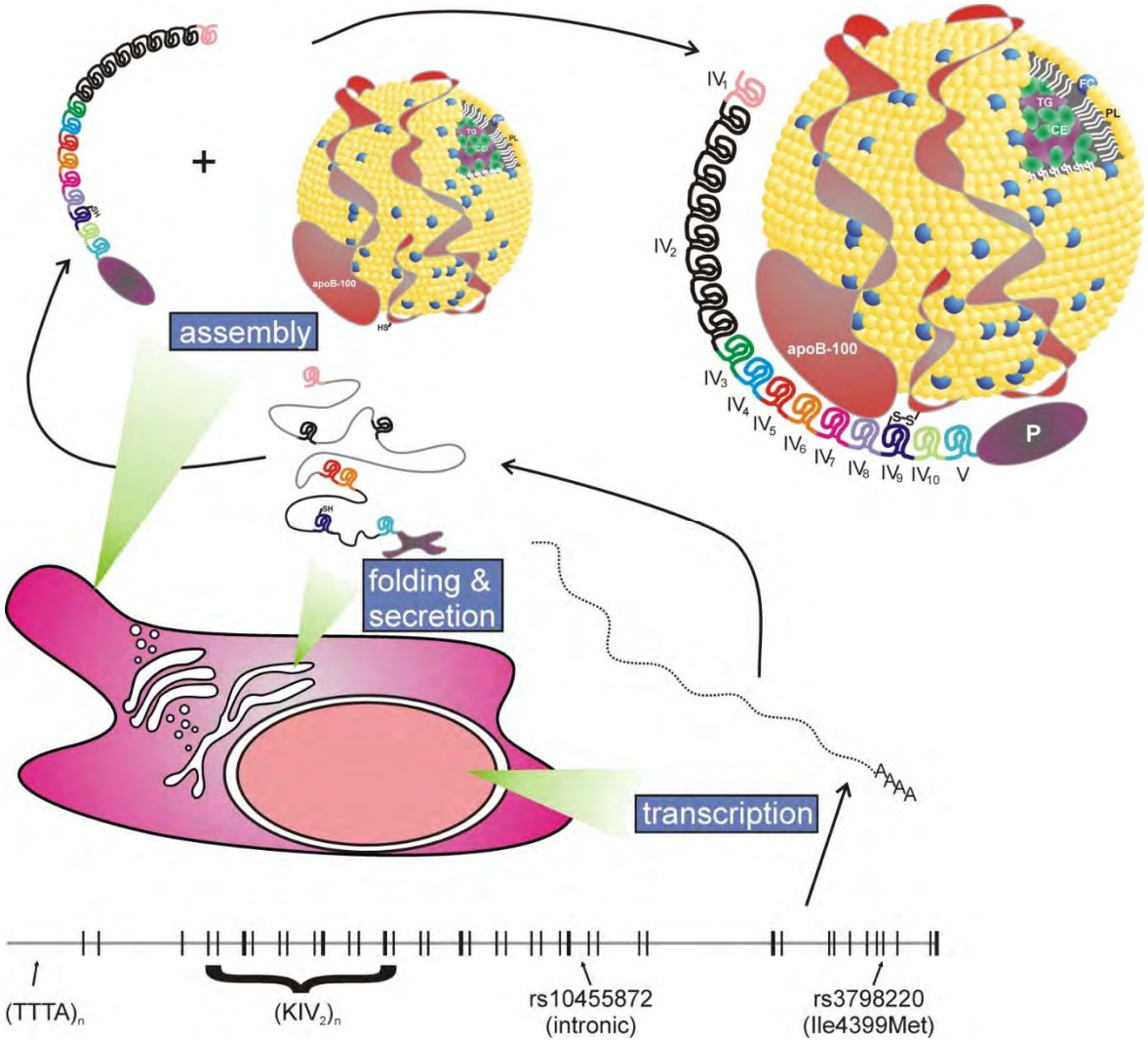
Gotto & Pownall Manual of Lipid Disorders Lippincott 1999

# Plasma Lp(a) mass versus number of kringles




Kamstrup PR et al. JAMA. 2009;3

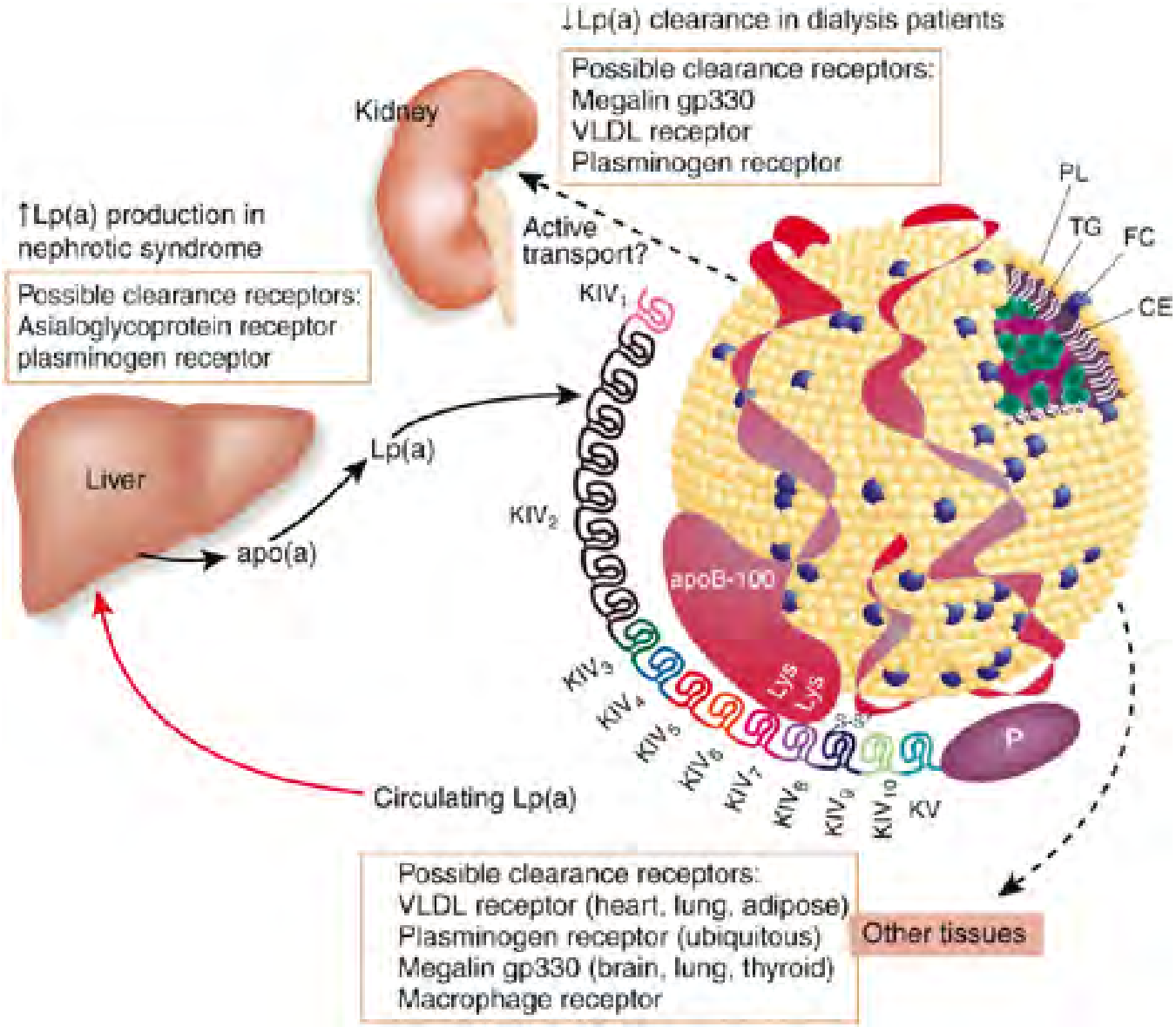
# Lp(a) Assembly and Secretion




**First step**: non-covalent association with lysine residues in apoB-100 with apo(a) KIV type 6-8; can be inhibited by the lysine analogue e-ACA.

**Second step**: disulfide bond formation between free SH in apo(a) KIV type 9 and apoB-100 (Cys4326) to form covalent Lp(a) particles

# Lp(a) Clearance



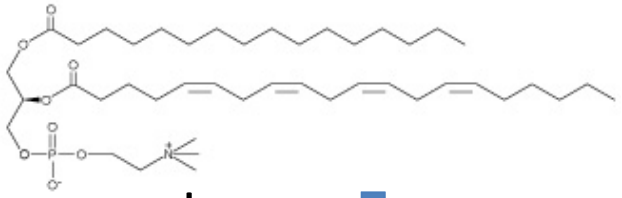

Albers JJ, *Kidney Int.* 2007;71;961

# Why is Lp(a) Atherogenic?
# Triple Whammy!

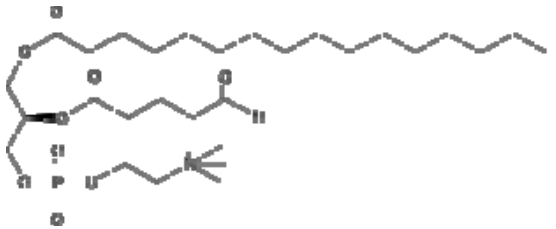
- Has all the proatherogenic properties of LDL.
- Has structural homology with plasminogen and inhibits fibrinolysis.
- Lp(a) serves as a sink for oxidized phospholipids.

# Oxidized phospholipids and Lp(a)

- Phospholipid molecule where the FA chain(s) have reactive terminal aldehyde groups

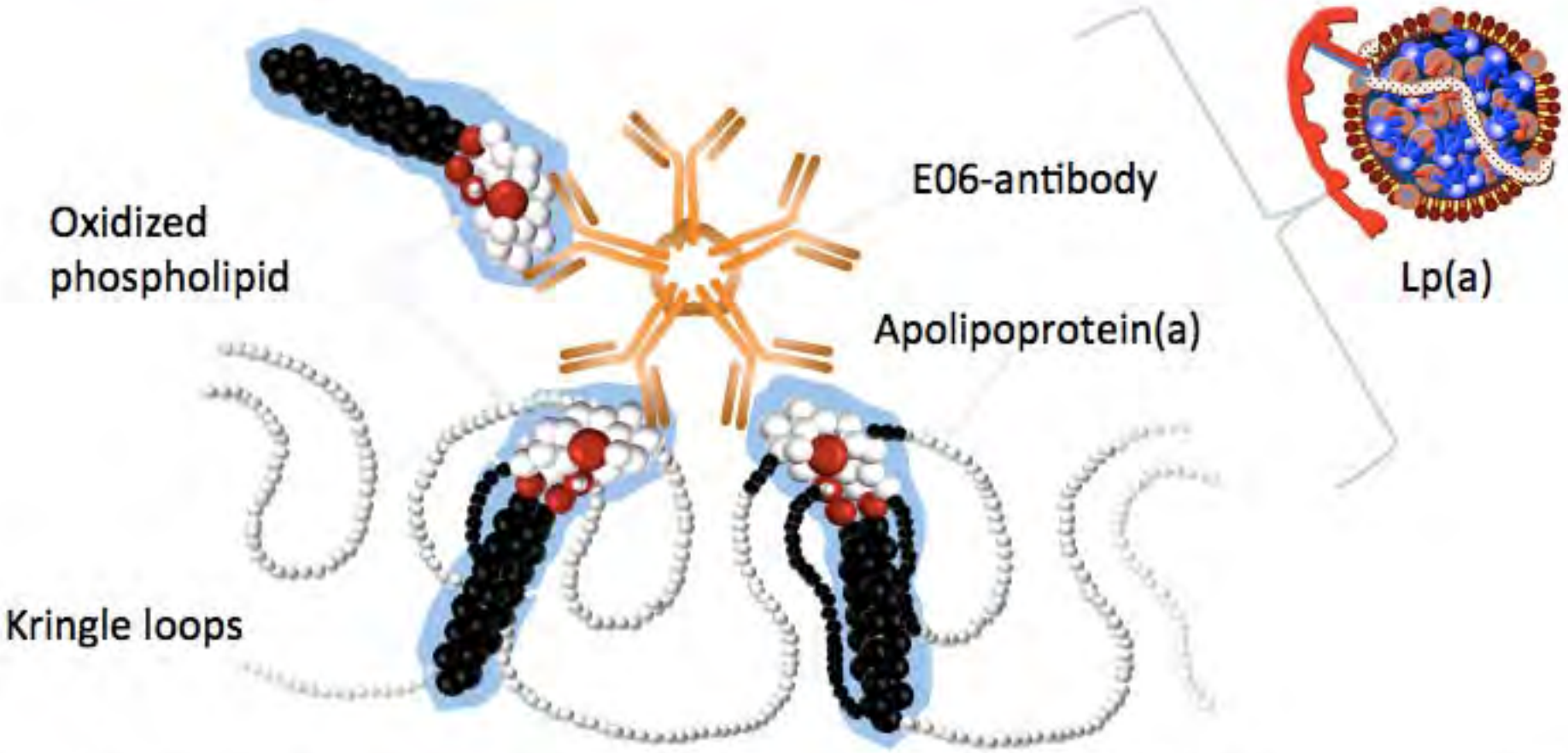


- Oxidized PL have been implicated in the onset and progression of atherosclerosis
  - induce apoptosis in ER-stressed macrophages
  - Increase foam cell formation
  - Increase monocyte adhesion
  - Play a role in the inflammatory response



- OxPLs have been detected on Lp(a) and apo(a) and plasminogen

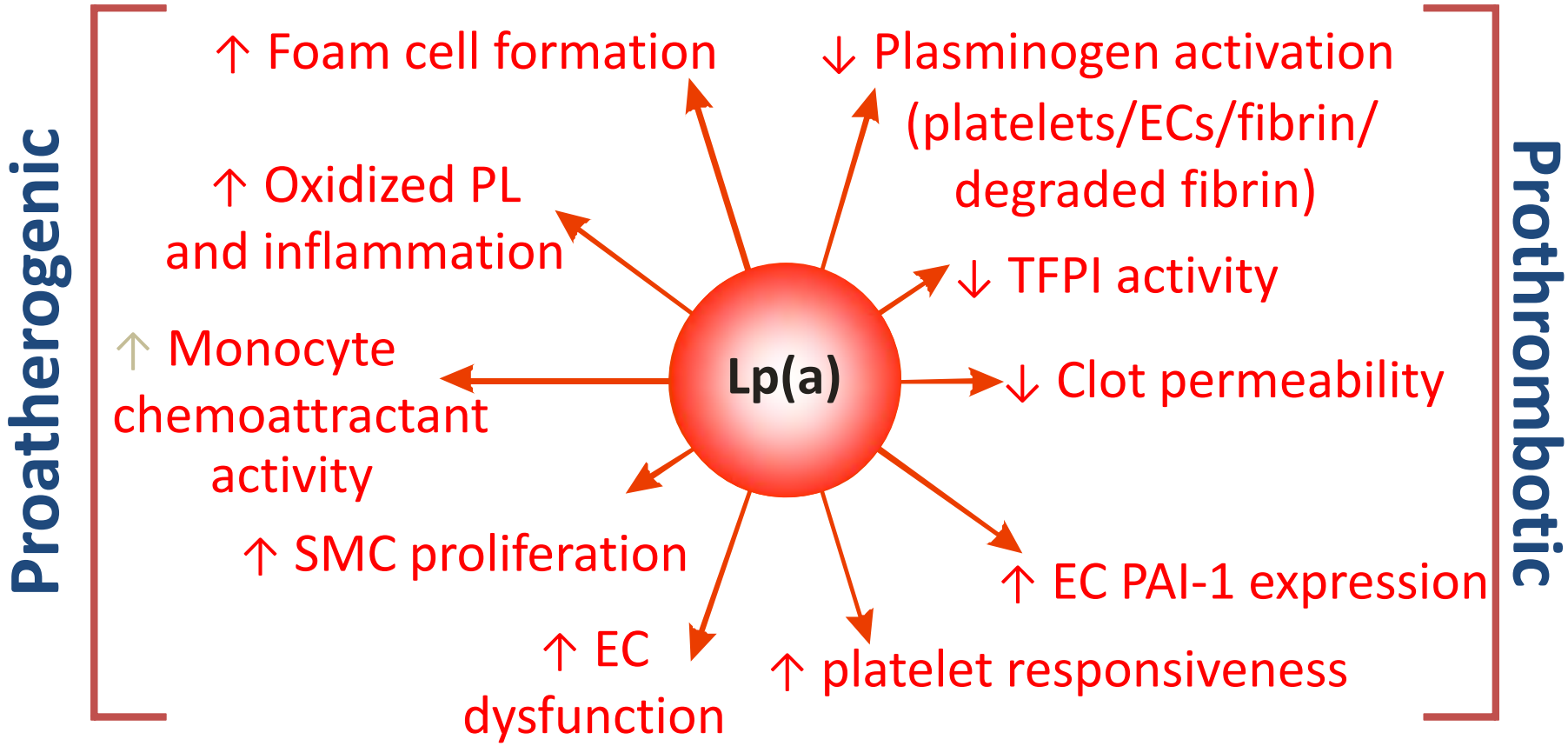
# Oxidized phospholipids binds to kringles




Modified Lp(a) lipoprotein, which accumulates in atherosclerotic lesions, can be detected at higher levels in the blood with the use of E06, an antibody that recognizes oxidized phospholipids

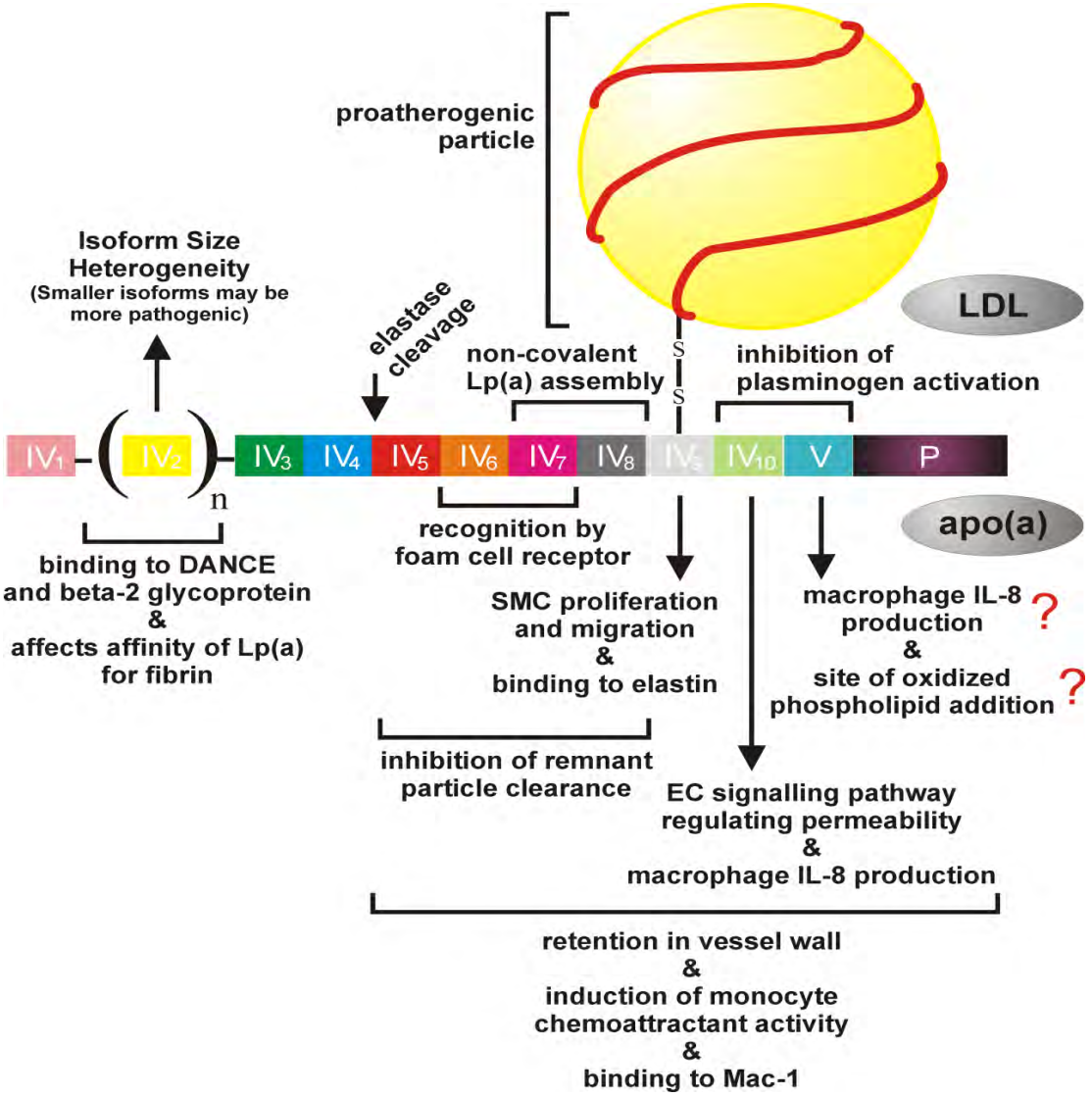
Berliner JA et al. NEJM 2005;351:9-11

# Multiple pathogenic mechanisms for Lp(a)



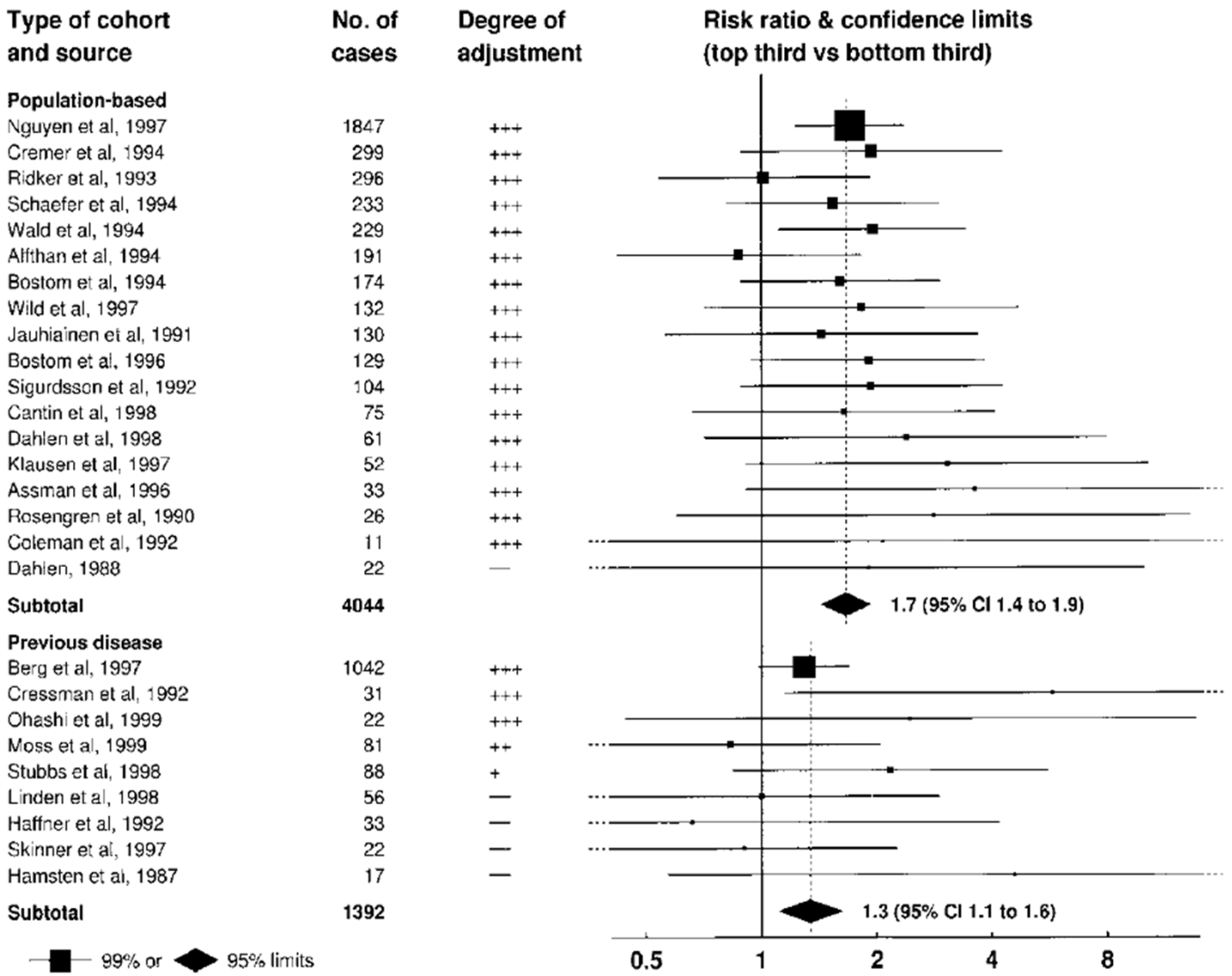

Modified from Koschinsky & Marcovina *Curr. Opin. Lipidol.* 2004;15:167

# Lp(a) Proatherogenic Structural Motifs



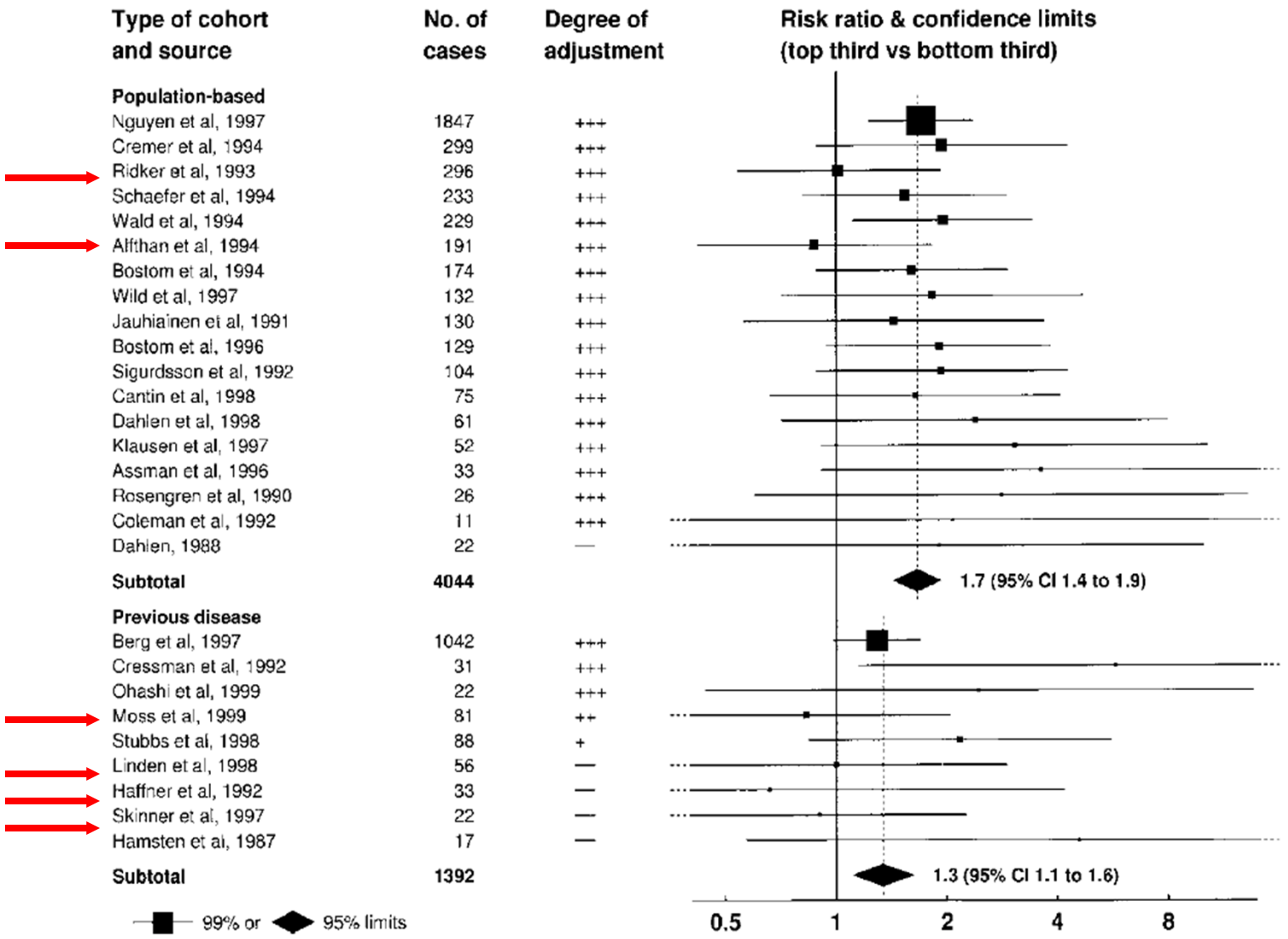

*Koschinsky M.L. and Marcovina S.M., in Therapeutic Lipidology: A Companion to Braunwald's Heart Disease. (2009).*

# Lp(a) Meta Analysis



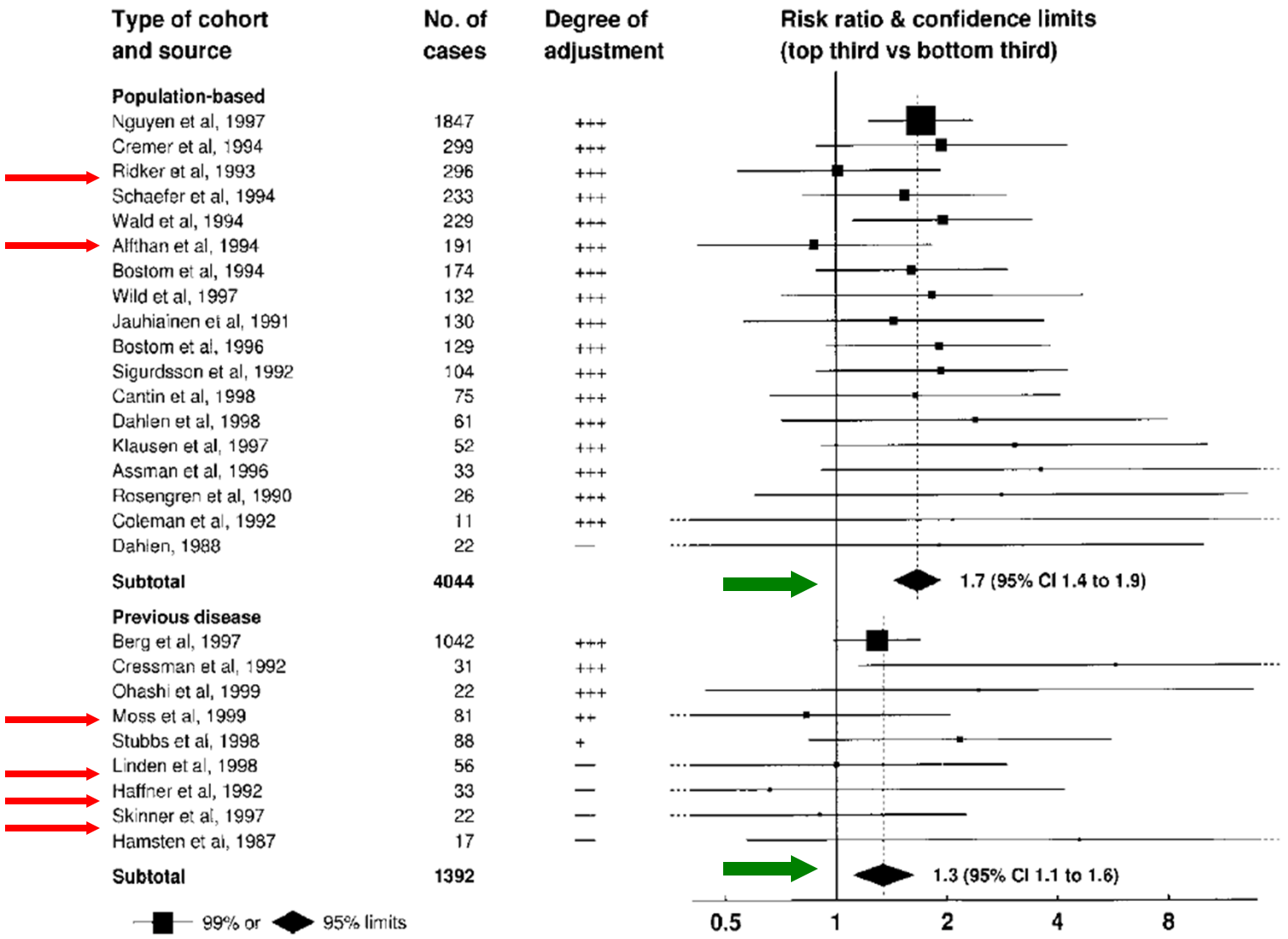

Danesh J, et al.,Circulation. 2000;102(10):1082-5

# Lp(a) Meta Analysis




Danesh J, et al.,Circulation. 2000;102(10):1082-5

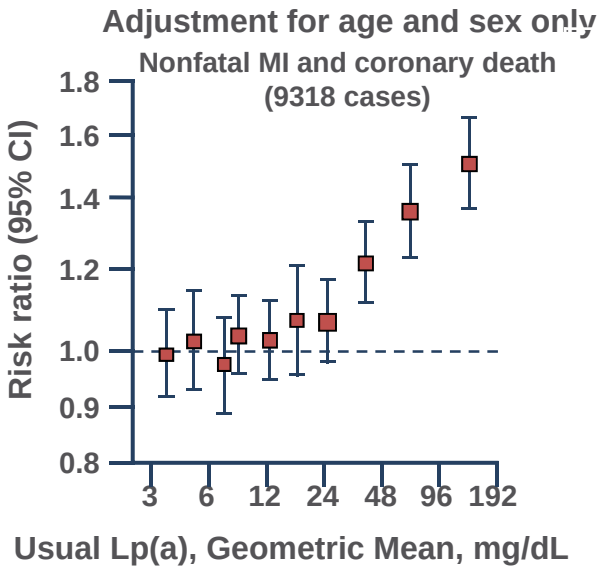
# Lp(a) Meta Analysis




Danesh J, et al.,Circulation. 2000;102(10):1082-5

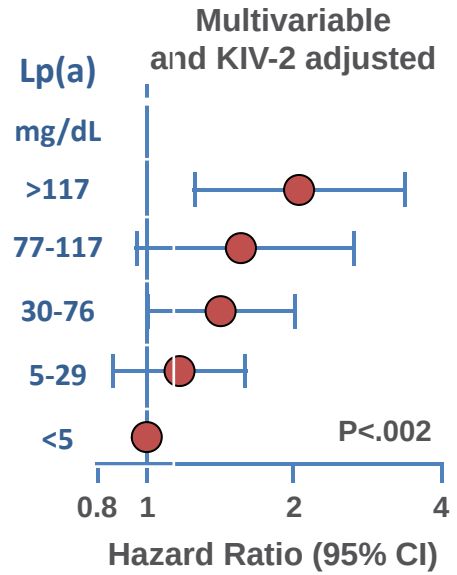
# Evidence Base for Lp(a) as an Independent, Causal, Genetic Risk Factor for CVD

## Epi/Meta-analyses ERFC



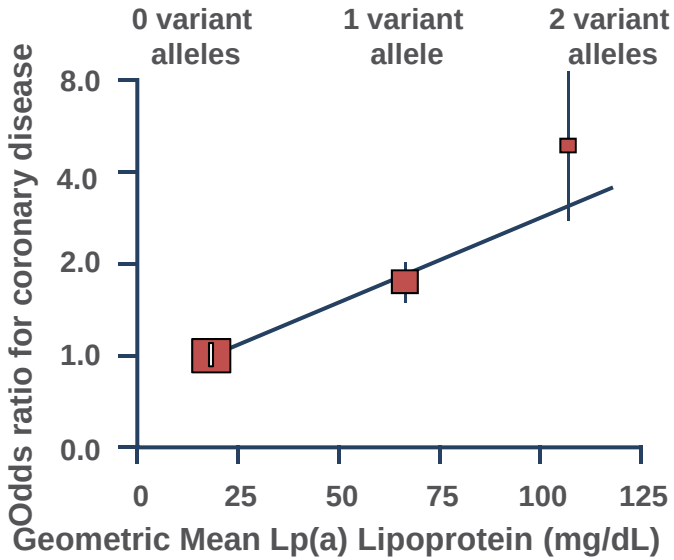

## Mendelian Randomization

45,098 patients, 2824 MI events over 4-16 years




## Genome-wide Association

3352 controls, 3145 cases



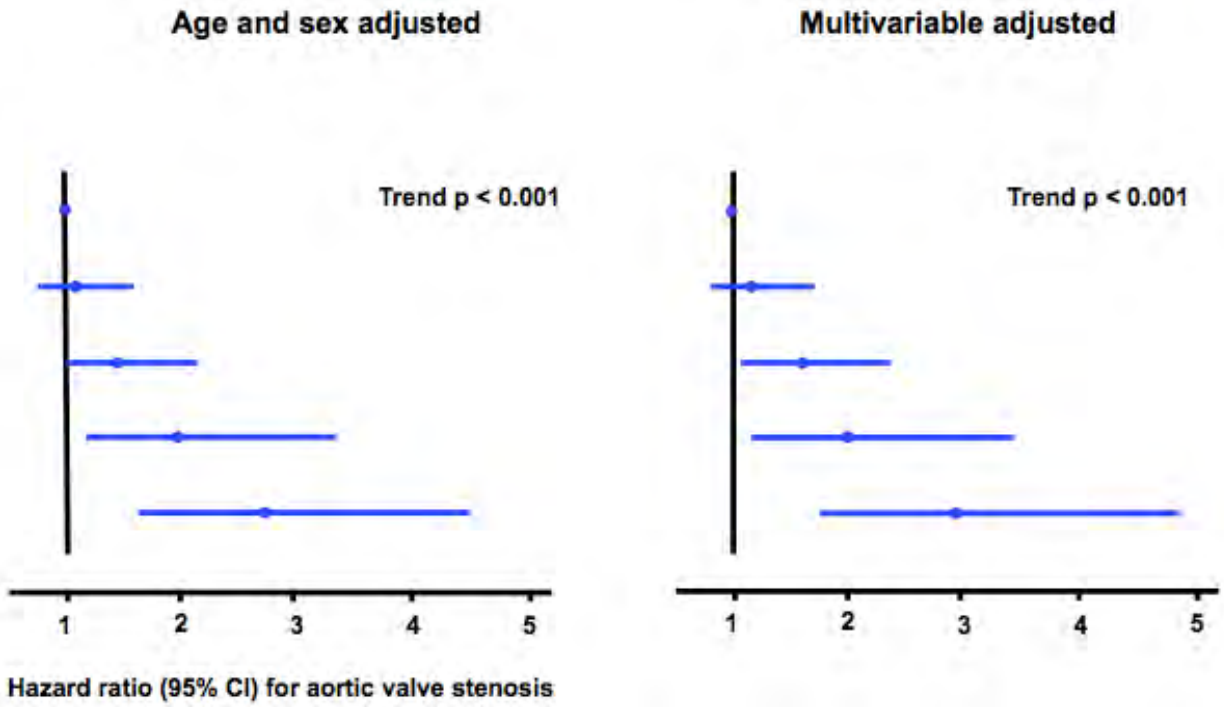

Erqou et al JAMA 2009:302:412-23

Kamstrup et al JAMA 2009:301;2331-9

Clarke et al NEJM 2009:361:2518-28

# Risk of Aortic Valve Stenosis as Function of Elevated Lp(a) Levels

| Lp(a) percentile | mg/dL | Participants | Events |
|---|---|---|---|
| < 22 | 3(2-4) | 6123 | 53 |
| 22-66 | 11(7-17) | 13053 | 127 |
| 67-89 | 40(30-51) | 6677 | 87 |
| 90-95 | 80(63-95) | 1728 | 27 |
| >95 | 124(104-148) | 1435 | 30 |




Analyses were adjusted for (left) age and sex or (right) multivariable adjusted additionally for total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking, and diabetes mellitus. Lp(a) in mg/dl is shown as median (interquartile range). CI = confidence interval

Kamstrup PR et al. J Am Coll Cardiol 2014;63:470–7

European Heart Journal
doi:10.1093/eurheartj/ehq386

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[†]**

[1]Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, DK-2730 Herlev, Denmark; [2]European Atherosclerosis Society, INSERM UMR-S939, Pitié-Salpetrière University Hospital, Paris 75651, France; [3]St George's University of London, London, UK; [4]University of Gothenburg, Sweden; [5]Catholic University Medical School, Rome, Italy; [6]University of Western Australia, Perth, Australia; [7]Columbia University, New York, USA; [8]Bichat University Hospital, Paris, France; [9]University of Milan, Italy; [10]Hopital de Jolimont, Haine Saint-Paul, Belgium; [11]New York University, New York, USA; [12]Wihuri Research Institute, Helsinki, Finland; [13]University of Amsterdam, The Netherlands; [14]Universitat Rovira & Virgili, Reus, Spain; [15]University Hospital Center Zagreb, Croatia; [16]Biomedicum, Helsinki, Finland; [17]Hacettepe University, Ankara, Turkey; and [18]Rigshospitalet, University of Copenhagen, Denmark

*Received 11 June 2010; revised 17 August 2010; accepted 24 September 2010*

Eur Heart J. 2010 Dec;31(23):2844-53

# Lp(a) Genetic Inheritance

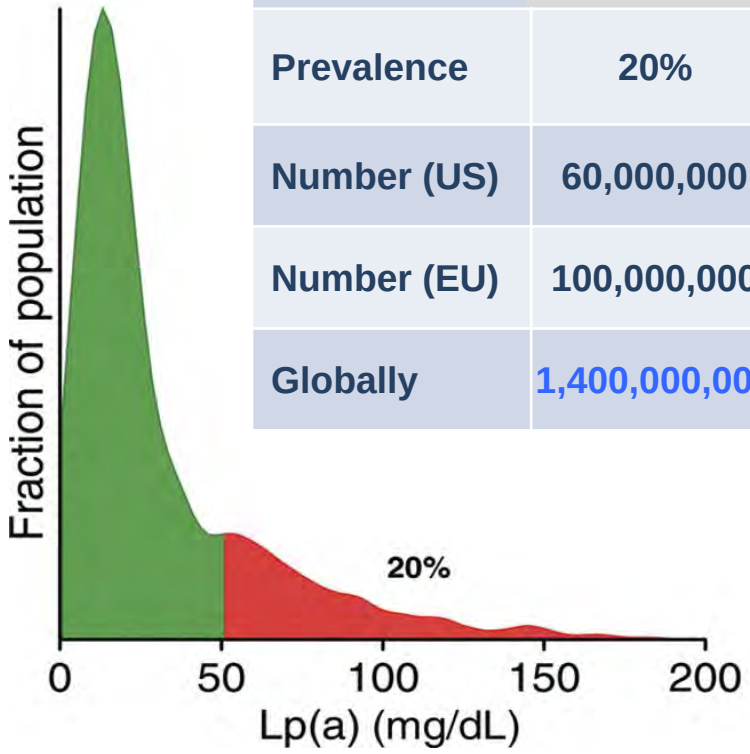
- Heritability is approximately 90%
- Not influenced significantly by environmental factors
- Autosomal co-dominant inheritance pattern
- Chromosome 6q26-27
- Very common genetic abnormality
  - Elevated values in 30-35% of the general population
    - Lp(a) mass value > 30 mg/dL

# Apo (a) Isoform Size Effect

- Large isoforms:
  - Likely not as atherogenic as small isoforms
  - Secreted poorly.
  - Produce increased signals on immunoassay
  - False positive
- Small isoforms
  - Likely the more atherogenic form
  - Associates with LDL more rapidly
  - Produce decreased signals on immunoassay
  - False negative

# Population Distribution of Lp(a) Levels

| Lp(a) distribution in general population extrapolated from the graph | | | | | |
|---|---|---|---|---|---|
| **Lp(a) Level** | **≥50 mg/dL** | **≥100 mg/dL** | **≥150 mg/dL** | **≥200 mg/dL** | **≥250 mg/dL** |
| **Prevalence** | **20%** | **5%** | **1%** | **0.2%** | **0.02%** |
| **Number (US)** | **60,000,000** | **15,000,000** | **3,000,000** | **600,000** | **60,000** |
| **Number (EU)** | **100,000,000** | **25,000,000** | **5,000,000** | **1,000,000** | **100,000** |
| **Globally** | **1,400,000,000** | **350,000,000** | **70,000,000** | **14,000,000** | **1,400,000** |




Lp(a)>30 mg/dL may be optimal for Africans

MESA-Guan W, et al. ATVB 2015;35:996-1001

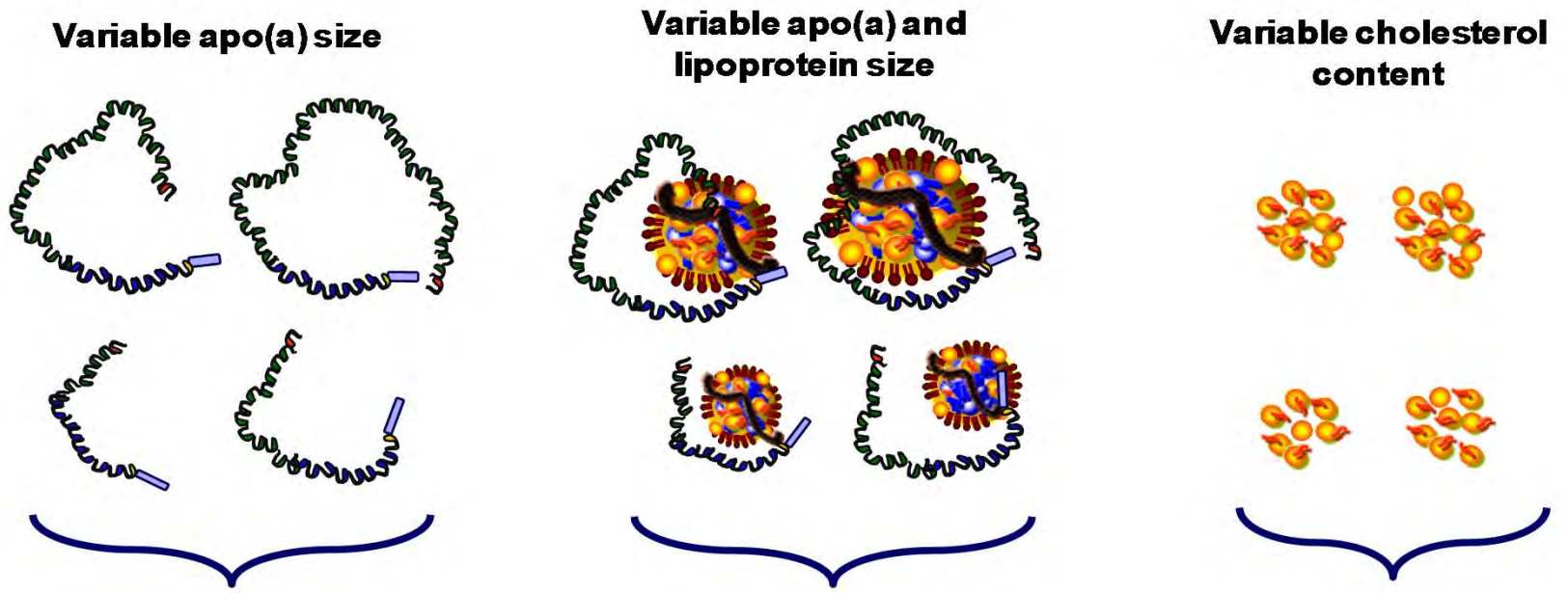
**Nordestgaard et al. European Heart Journal 2010:31;2844–2853**

# Overview

- Lp(a) Biology
- Lp(a) Measurement
- Lp(a) Therapy

# Lp(a) Measurements

**Apo(a) mass is the amount of apoprotein (a) in a dL of plasma**
**Lp(a)-P is the # of LDL particles carrying apo(a) that exist in a dL of plasma**
**Lp(a)-C is the cholesterol trafficked within all of the Lp(a) particles per dL**

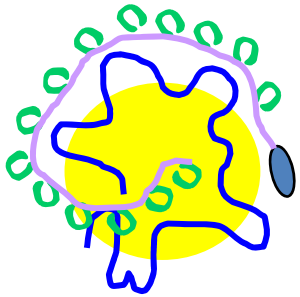



**Apo(a)mass or size** **Lp(a)-Particle** **Lp(a)-Cholesterol**

Modified from Dr. Thomas Dayspring

# Effect of Kringle Number on Lp(a) Analysis

*Clinical Chemistry* 46:12
1956–1967 (2000)



Lipids, Lipoproteins, and Cardiovascular Risk Factors

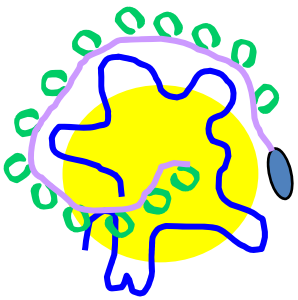
## Use of a Reference Material Proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to Evaluate Analytical Methods for the Determination of Plasma Lipoprotein(a)

Santica M. Marcovina,[1*] John J. Albers,[1] Angelo M. Scanu,[2] Hal Kennedy,[1] Federico Giaculli,[1] Kåre Berg,[3] Rémy Couderc,[4] Francesco Dati,[5] Nader Rifai,[6] Ikunosuke Sakurabayashi,[7] Jillian R. Tate,[8] and Armin Steinmetz[9]

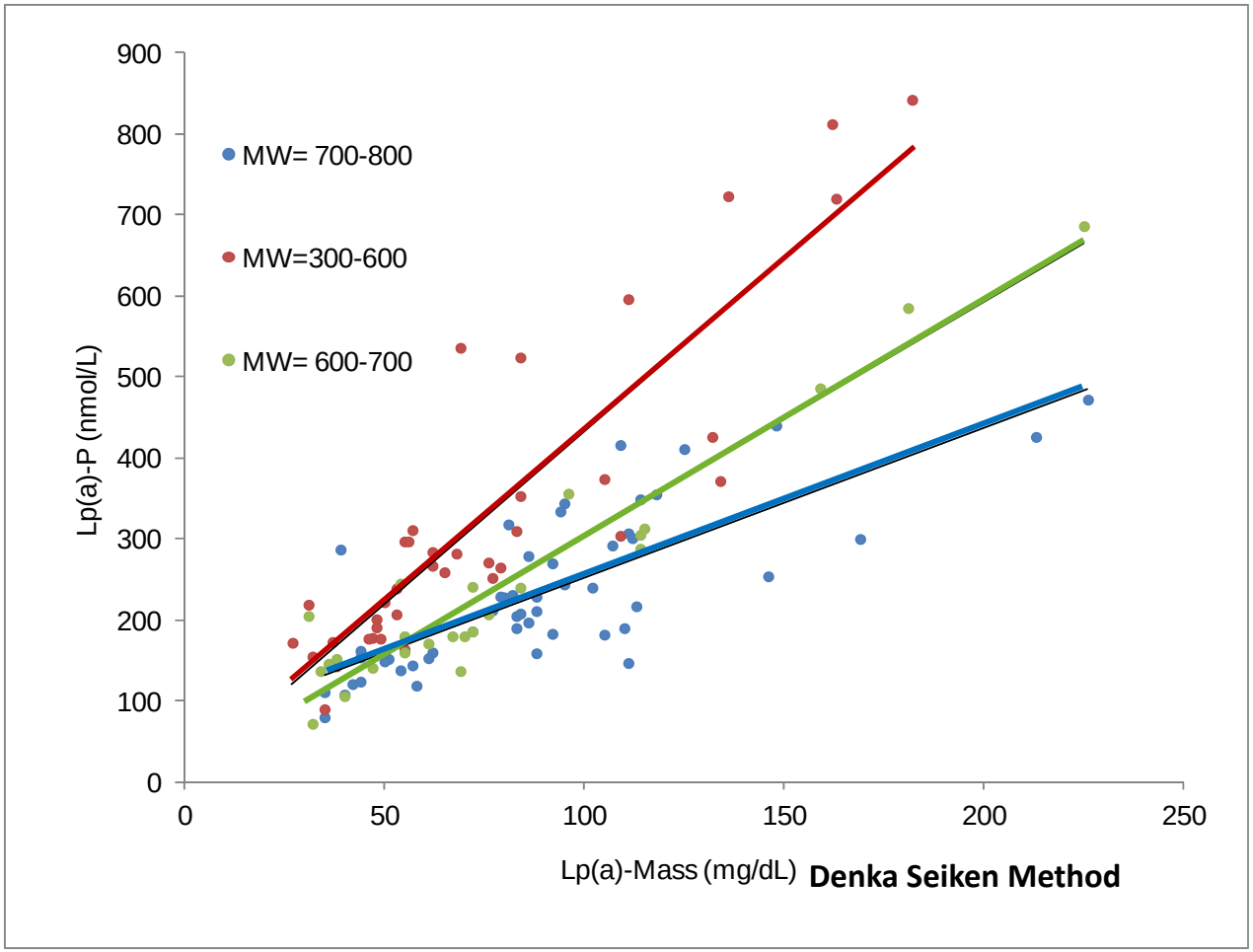
# Marcovina SM et al, Clinical Chemistry: 2000

- "To various degrees, apo(a) size heterogeneity affects the outcome of the immunochemical methods used to measure Lp(a)."

- "The major problem in the lack of accuracy is the over- or underestimation of Lp(a) values as a result of apo(a) size heterogeniety."



# Lp(a) mass overestimated values when apo(a) mass was high and underestimated when mass was low




Guadagno PA et al Clin Chim Acta 2015;439:215-224

# Apo(a) Isoform size and Coronary Artery Disease

## Apolipoprotein(a) Size and Lipoprotein(a) Concentration and Future Risk of Angina Pectoris with Evidence of Severe Coronary Atherosclerosis in Men: The Physicians' Health Study

Nader Rifai,[1*] Jing Ma,[2] Frank M. Sacks,[3] Paul M. Ridker,[5] Wendy Jade L. Hernandez,[3] Meir J. Stampfer,[2,3,4] and Santica M. Marcovina[6]

***Conclusions:*** High Lp(a) predicts risk of angina, and the risk is substantially increased with high concomitant LDL-cholesterol. Small apo(a) size predicts angina with greater strength and independence than Lp(a) concentration.



**Only about one third of patients have two apo(a) size isoforms by immunoblot either because of null allelles, poor secretion of large isoforms, and or low sensitivity.** Arterioscler Thromb Vasc Biol. 2014;34:2095-2099

# Lipoprotein (a) Measurement Controversies

- Ideally, Lp(a) mass should be reported in molar units (nmol/L) not mg/dL because assay measures apo(a) protein.

- The conversion factor from mg/dL to nmol/L varies from 2.85 for a small Lp(a) size to 1.85 for a large one and thus a factor of 3.5 is too high, and we suggest a mean conversion factor of 2.4, even though the conversion can be more or less imprecise depending on the apo(a) size.

Brown, WV et al. J Clin Lipidol 2010;240-247

# Lipoprotein (a) Measurement Controversies

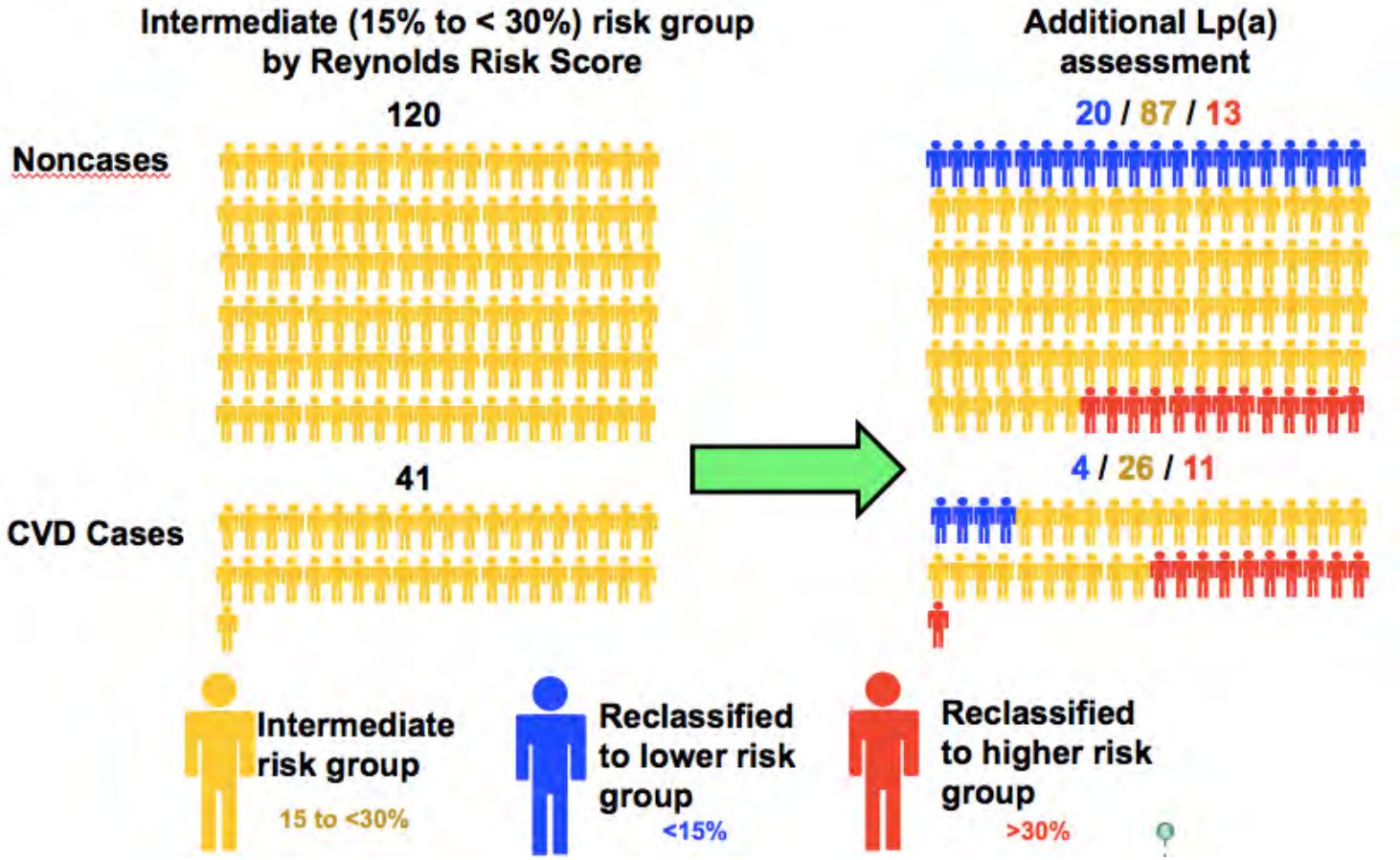
- However, the major problem of Lp(a) values is not the units used to report the results but is related to the inaccuracy of the methods that are affected by apo(a) size heterogeneity
- These methods overestimate the levels of Lp(a) in individuals with large Lp(a) molecules and consequently underestimate the levels in individuals with small Lp(a) molecules
- Values near cutpoint should be repeated by a reference lab with a validated and accurate method.

Brown, WV et al. J Clin Lipidol 2010;240-247

# Discrimination and Net Reclassification of Cardiovascular Risk With Lipoprotein(a)

## Prospective 15-Year Outcomes in the Bruneck Study

Peter Willeit, MD, PhD,*† Stefan Kiechl, MD,* Florian Kronenberg, MD,‡ Joseph L. Witztum, MD, PhD,§ Peter Santer, MD,|| Manuel Mayr, MD, PhD,¶ Qingbo Xu, MD, PhD,¶ Agnes Mayr, MD,|| Johann Willeit, MD,* Sotirios Tsimikas, MD§



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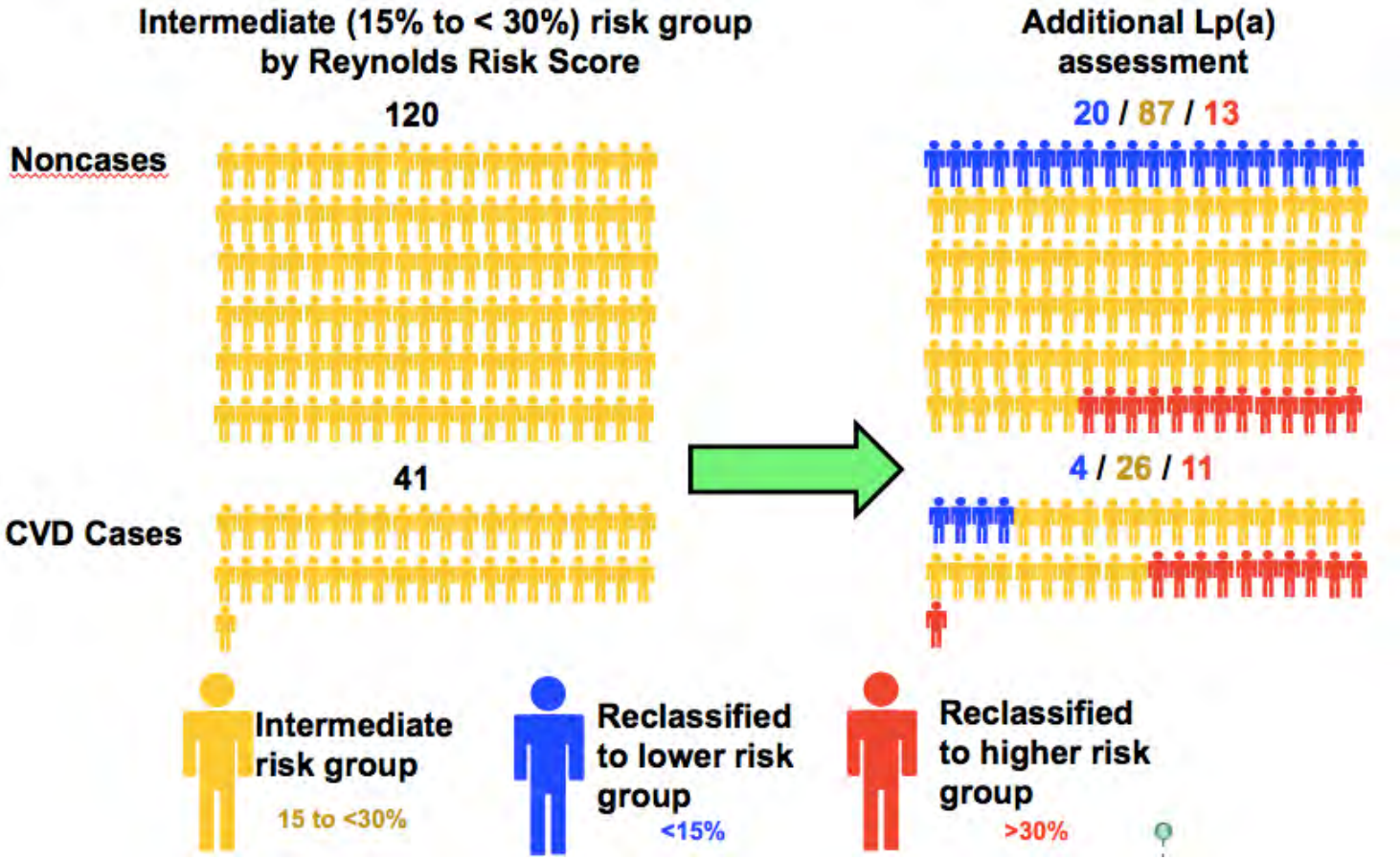
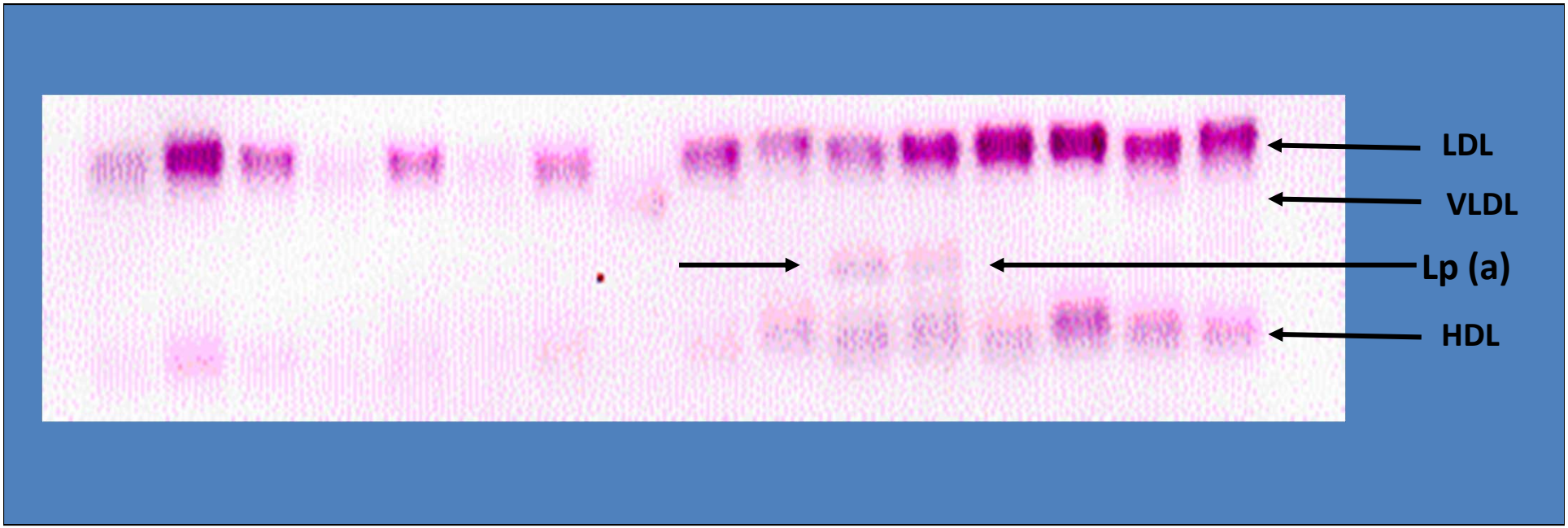



Lp(a) Mass
NRI=6.5%

Apo(a) size
Isoform
not independently predictive of CVD

# Lp (a) Cholesterol Measurement

Electrophoresis and enzymatic cholesterol staining

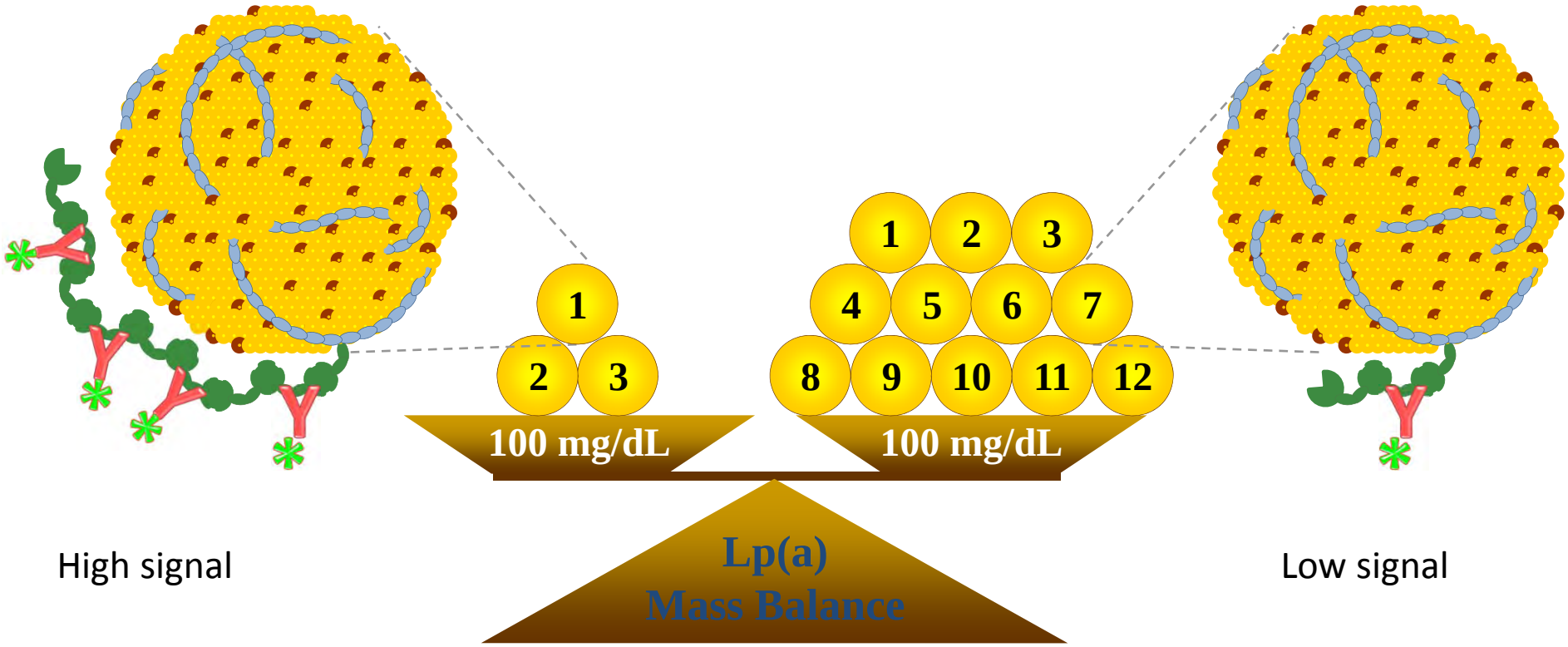



Lp (a) cholesterol measurement is not influenced by apo (a) size

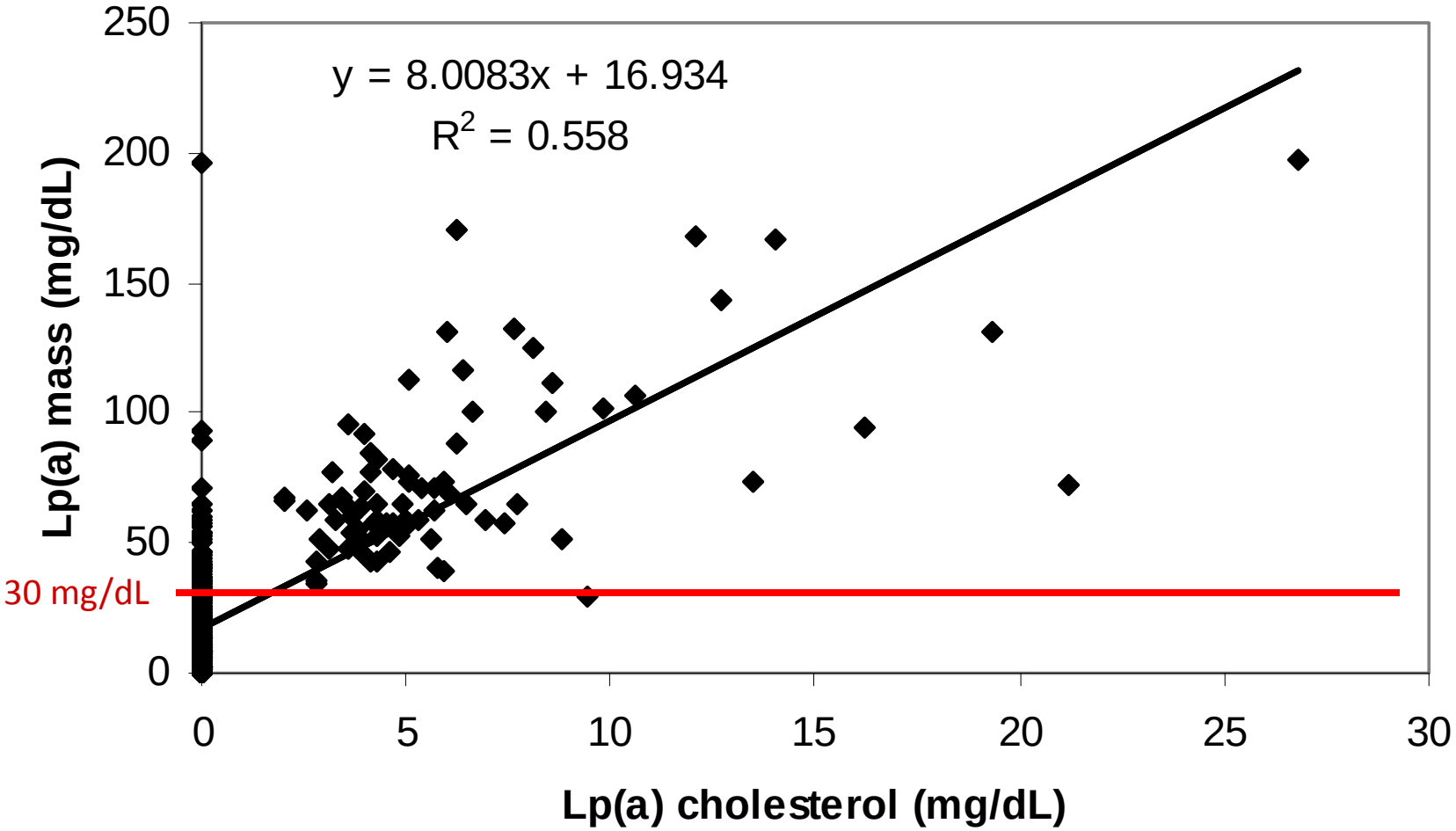
Baudhuin LM, Mcconnell JP, et al. Clin Biochem, 2004. Mayo Clinic

# Discordance Between Lp(a)-C and Lp(a) Mass When Kringles Vary

**Lp(a)-C = 3 mg/dL** **Lp(a)-C = 12 mg/dL**



# Why is Lp(a) cholesterol more predictive than Lp(a) mass?



# HR For CVD Events in 425 non-AMI Multivariate

| Variable | HR | 95% CI |
|---|---|---|
| Age | 1.3 | 0.96 - 1.88 |
| Male Gender | 1.2 | 0.62 - 2.49 |
| Hypertension | 1.3 | 0.74 - 2.30 |
| Smoking | 1.2 | 0.68 - 2.23 |
| LDL cholesterol | 1.0 | 0.69 - 1.45 |
| HDL cholesterol | 0.83 | 0.61 - 1.13 |
| Log triglyceride | 0.97 | 0.70 - 1.34 |
| Log CRP | 1.1 | 0.73 - 1.55 |
| Fibrinogen | 1.6 | 1.16 - 2.29 |
| Lp-PLA2 | 1.3 | 1.05 - 1.57 |
| Lp(a) mass: > 30 mg/dL | 0.60 | 0.27 - 1.33 |
| Lp(a) cholesterol: >3 mg/dL | 3.2 | 1.45 - 7.09 |

McConnell et al, Circulation 2007 Oct; 116(16 Suppl S):818.

# 2010 European Atherosclerosis Society Consensus Panel on Lp(a)

- Lp(a) should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with
  - Premature CVD
  - Familial hypercholesterolemia
  - A family history of premature CVD and/or elevated Lp(a)
  - Recurrent CVD despite statin treatment
  - ≥3% 10-year risk of fatal CVD according to the European guidelines and
  - ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines

- Repeat measurement is only necessary if treatment for high Lp(a) levels is initiated in order to evaluate therapeutic response.

Nordesgaard BG et al. Eur Heart J. 2010 Dec;31(23):2844-53

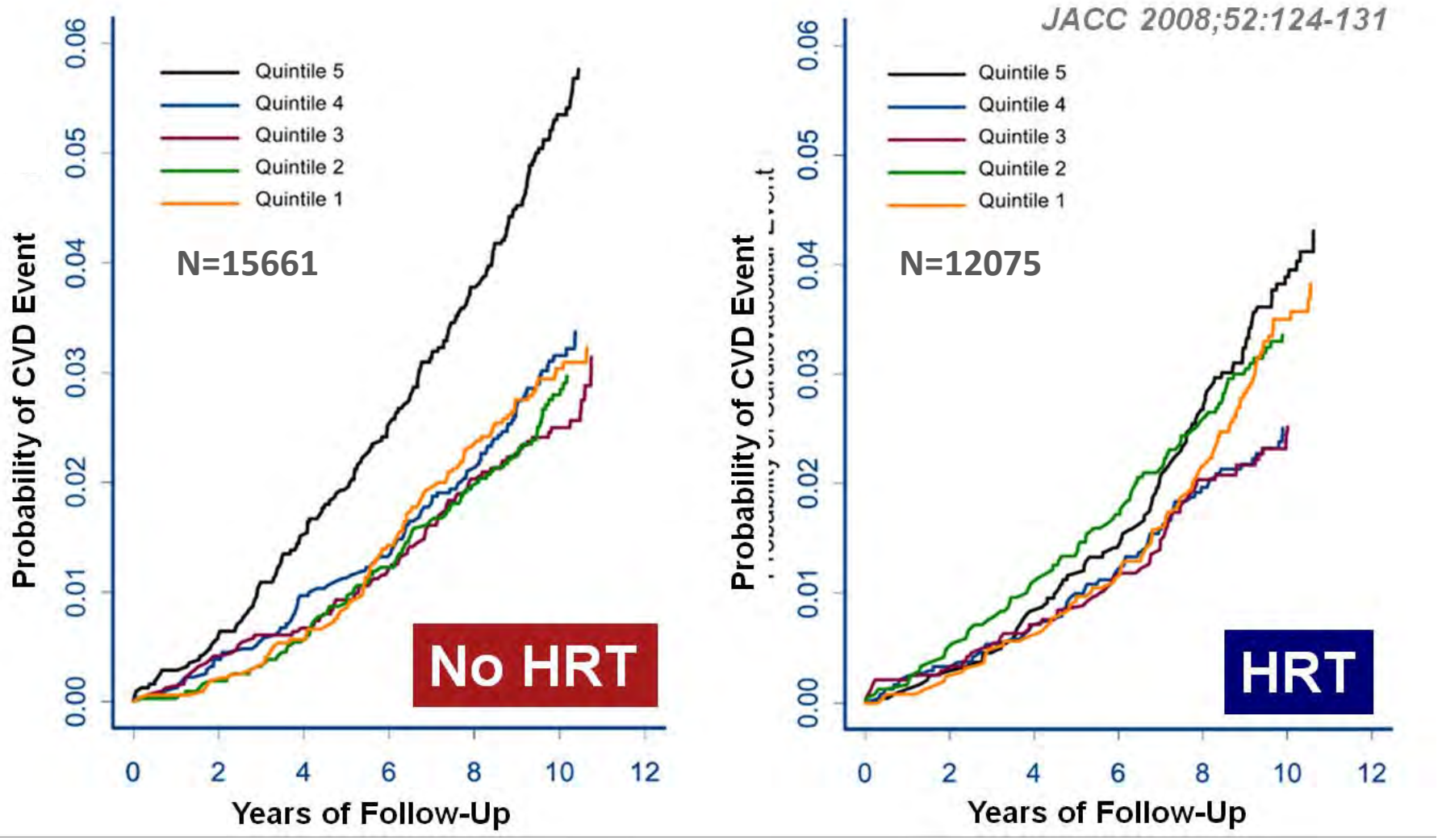
# Overview

- Lp(a) Biology
- Lp(a) Measurement
- Lp(a) Therapy

# Treating Lp(a): How?

- No good way to reduce Lp(a) specifically
  - General recommendation-Statins
    - Treat other risk factors (LDL-C) aggressively
    - Early statin data suggests decreasing LDL-C reduces Lp(a) related risk
- Niacin-recommended by EAS
    - Treat to 50 mg/dL or lower with Niacin (20-40% reduction)
    - Controversial-lack of evidence, large number, AIM-HIGH
- HRT in women with high Lp(a)

# Probability of CVD by Increasing Concentration of Lp(a) in WHS



# Lp(a): How Should We Treat?

| Effect Lp(a) Level | |
|---|---|
| • Niacin | 20-40% |
| • Aspirin | 10-20% |
| • L-Carnitine | 20% |
| • HRT | 15–25% |
| • LDL aphereis | ≈ 80% |
| • Mipomersen | 30-40% |
| • PCSK9 MoAb | 20-30% |
| •ASOs-apo(a) | 80% |

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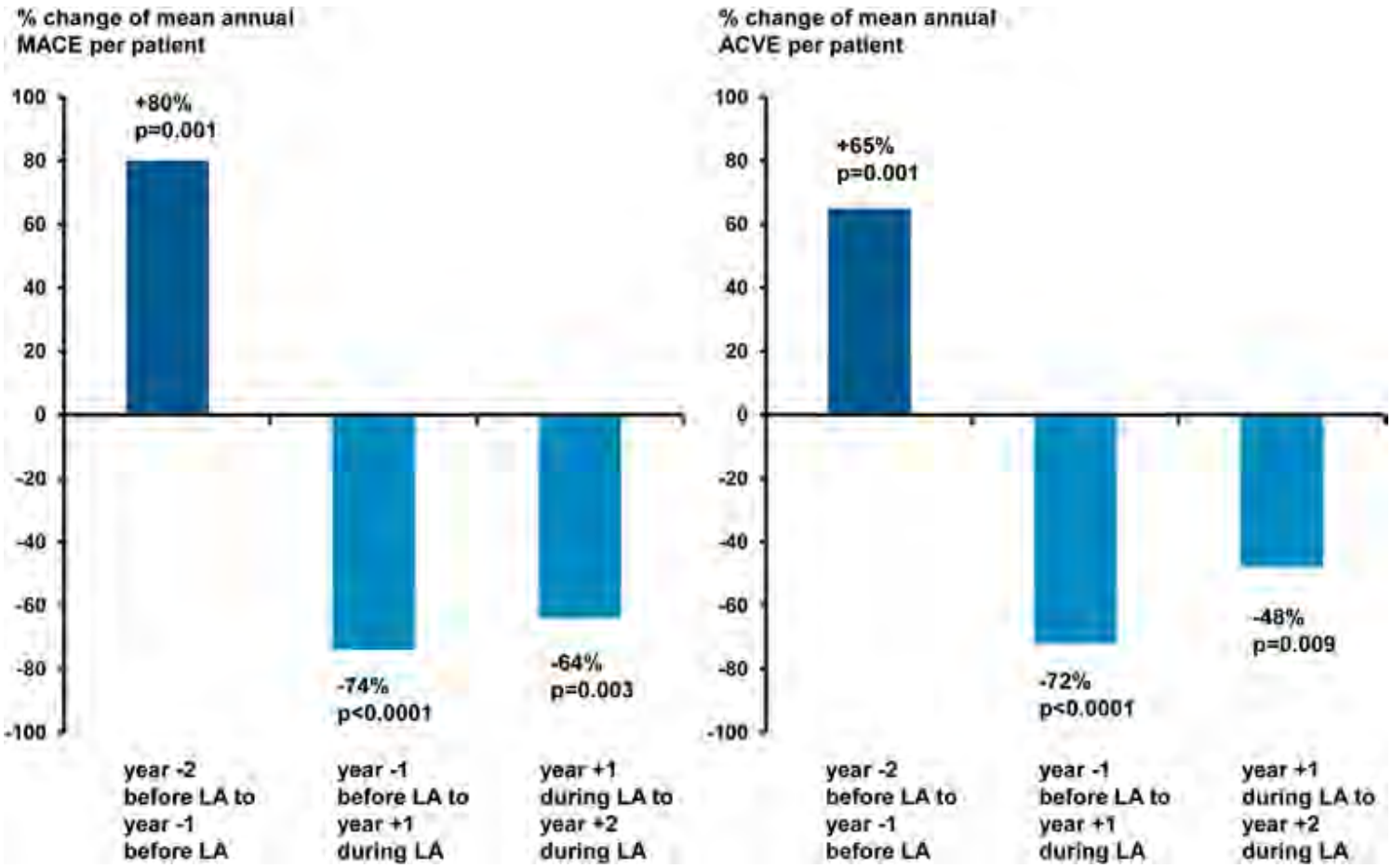
| • Mipomersen | 30-40% |
| • PCSK9 MoAb | 20-30% |
| •ASOs-apo(a) | 80% |

**No effect on Lp(a)**

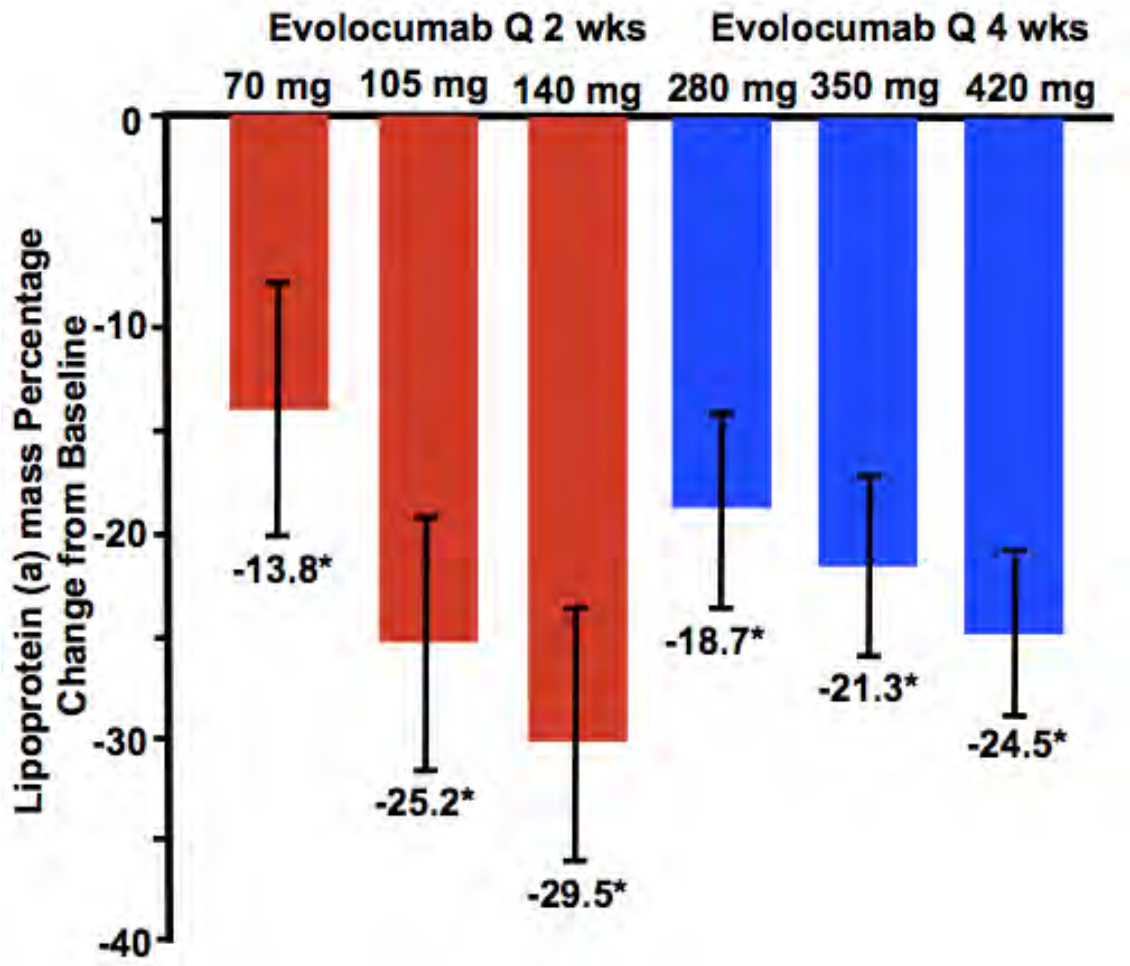
- Statins
- Fibrates
- Ezetamibe
- Lifestyle changes
  - Diet and exercise
- Raloxifene

# Apheresis for Isolated elevated Lp(a) >60 mg/dL reduces MACE



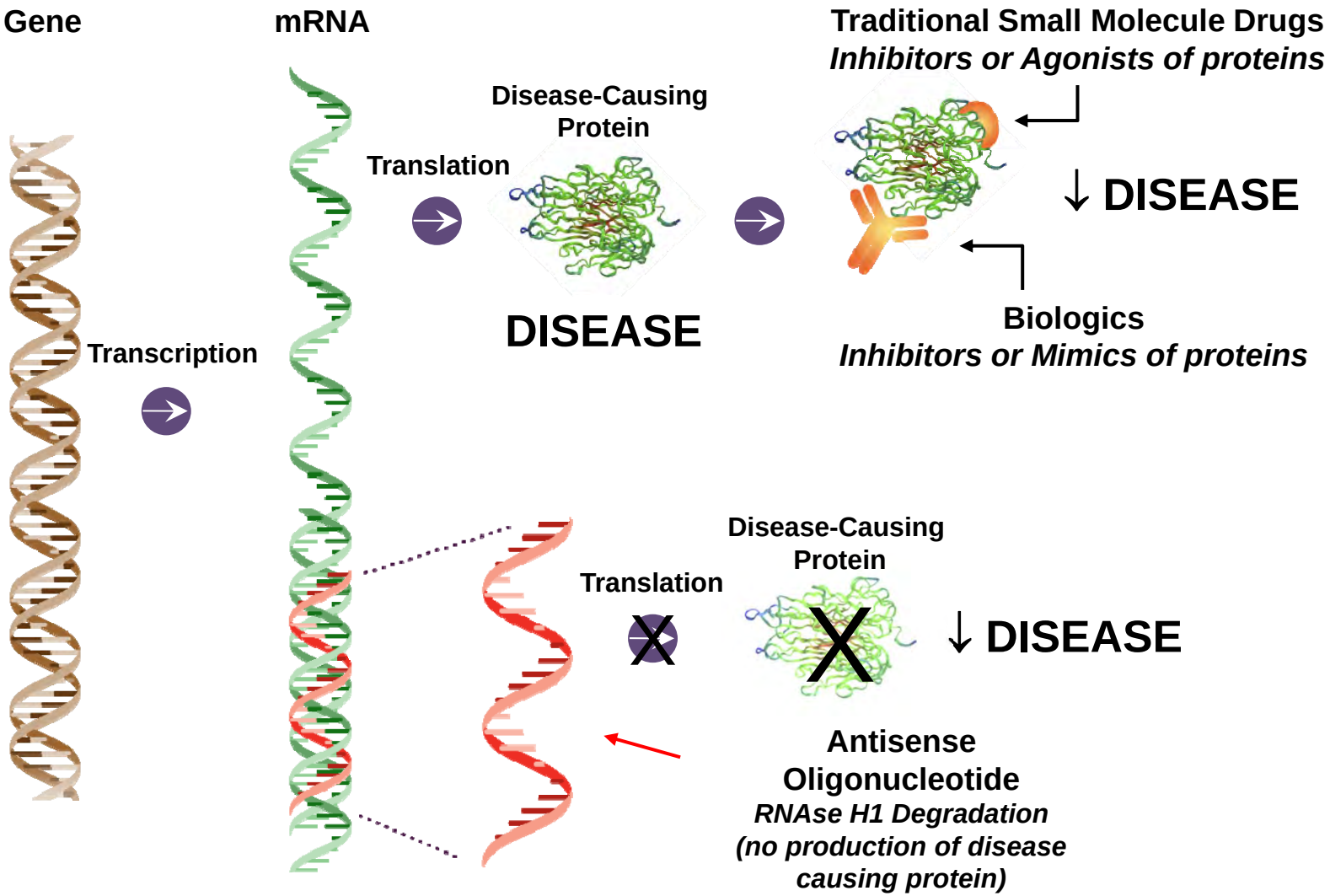

Leebman et al. *Circulation 2013;128:2567–2576*

# Evolocumab-induced Lp(a) Percentage Change from Baseline to 12 weeks




Raal FJ et al. JACC 2014;63:1278-88

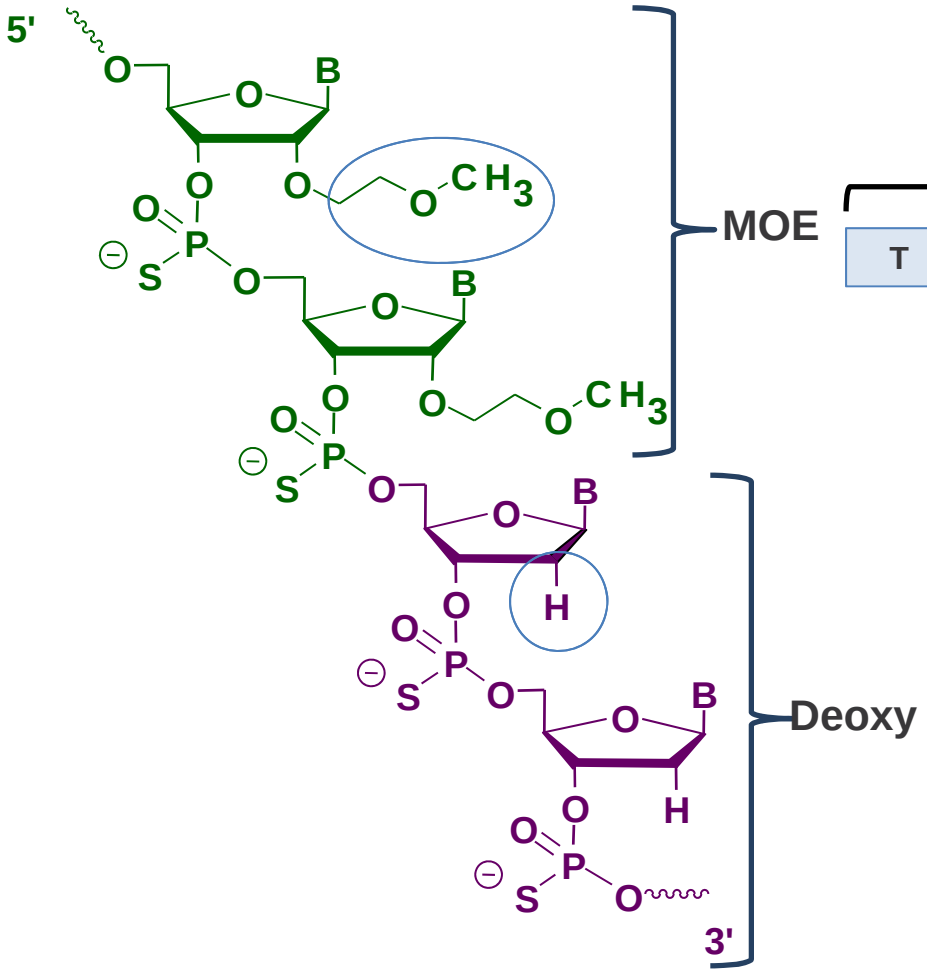
# Antisense Technology Reduces Disease Causing Protein Levels by Targeting mRNA

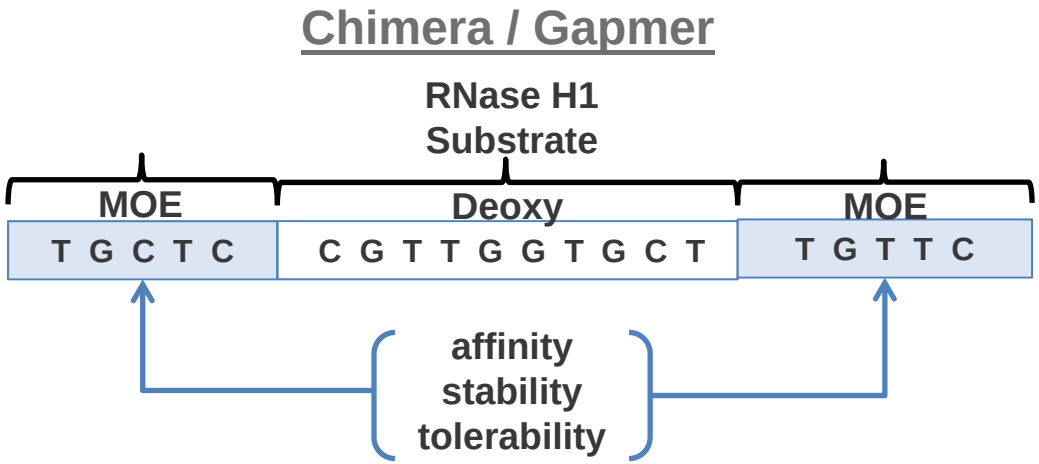


# ISIS-APO(a)$_{Rx}$ is Designed to Lower Lp(a)

*Second Generation Antisense Drug*

**2‘ Methoxyethyl Phosphorothioate Oligonucleotide (2’ MOE Gapmer)**



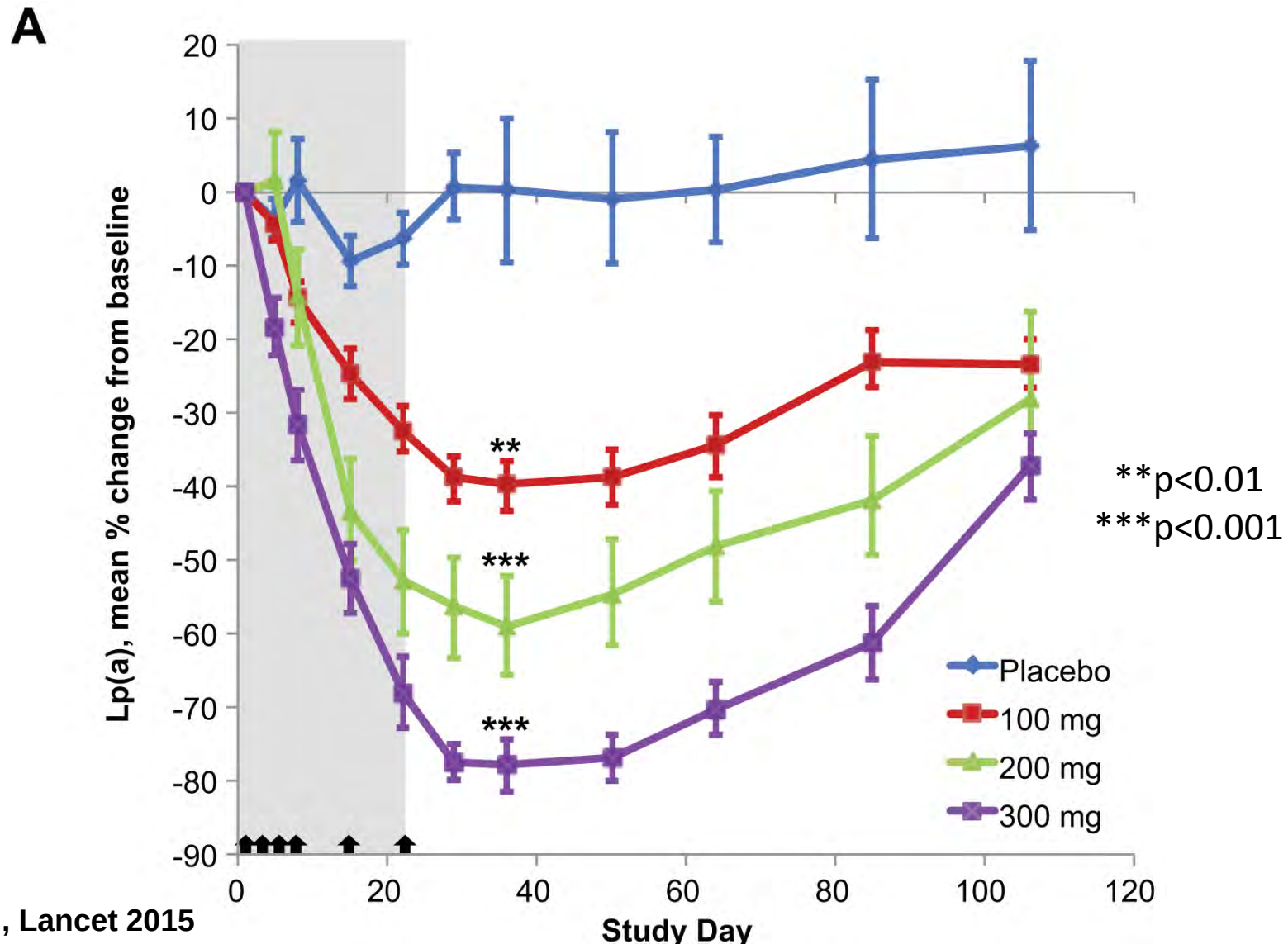




**ISIS-APO(a)$_{Rx}$ targets the splice site of exon 24/25 of apo(a) mRNA, corresponding to a Kringle-IV$_2$ repeat**

**It does not bind to or reduce hepatic expression of plasminogen mRNA**

# ISIS-APO(a)$_{Rx}$ Phase I Trial

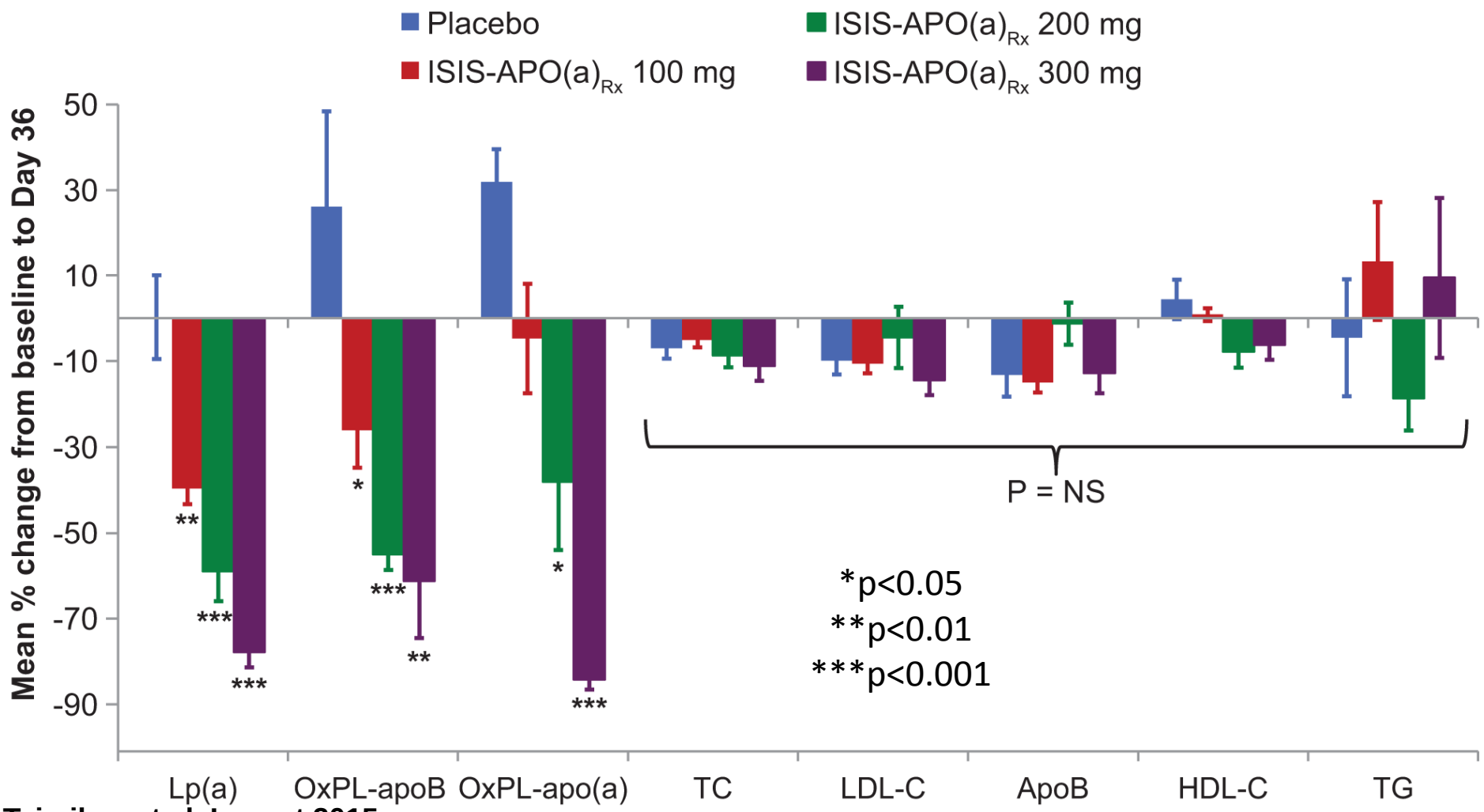
*Mean percent change in Lp(a) by treatment group in the multiple-dose cohort*




Tsimikas et al, Lancet 2015

# ISIS-APO(a)$_{Rx}$ Phase I Trial

*Mean percent change in Lp(a), OxPL-apoB, OxPL-apo(a), total cholesterol, LDL-C, apoB, HDL-C, and triglycerides*




**Tsimikas et al, Lancet 2015**

# Lp(a) Questions

- Does it cause CHD?

Yes, and maybe other diseases.

- Should we measure it?

Yes, but need better assays.

- Should we treat it?

Yes, for now with statins. Need to determine in future RCTs if specific drugs lower CHD events.

# Contributors

- Dr. Sam Tsimikas-Univ. of California SanDiego
- Dr. Joseph McConnel-Health Diagnostic Labs
- Dr. Marlys Koschinsky-Univ. of British Columbia
- Dr. Tom Dayspring-Foundation for Health Improvement and Technology

# Contact Information

**Alan T. Remaley MD, PhD**
**National Institutes of Health**
**Building 10, Room 2C-433**
**Bethesda, MD 20892**
**Tel: 301-219-9233**
**email:**
**aremaley1@nhlbi.nih.gov**

# What is the Effect of Changes in Body Fat on Dyslipidemia

Eric C. Westman, M.D. M.H.S.

Duke University Medical Center

Durham, North Carolina

ewestman@duke.edu

Associate Professor of Medicine

President, Obesity Medicine Association (formerly ASBP)

Director, Duke Lifestyle Medicine Clinic

Course Director, Medical Management of Obesity

Fellow, The Obesity Society

Author of The New Atkins for a New You

# Initial Body Weight Indices and Change in Body Weight Indices for Effects of Weight Reduction on Blood Lipids and Lipoproteins

| Variable | Mean ± SD |
|---|---|
| Initial weight (kg) | 98.5 ± 17.6 |
| Initial body mass index | 34.8 ± 6.2 |
| Weight loss (kg) | 16.6 ± 12.6 |
| Final % ideal body weight | 125.8 ± 10.1 |
| Final body mass index | 27.8 ± 3.2 |

Dattilo, Kris-Etherton. Effects of Weight Reduction on Blood Lipids and Lipoproteins: a Meta-analysis. Am J Clin Nutr 1992;56:320-8.

# Effects of Weight Reduction on Blood Lipids and Lipoproteins

| | | | | |
|---|---|---|---|---|
| | Before | After | Change | Percent Change |
| Total Chol (mmol/l) | 5.93 | 5.14 | -0.79 | -13.3% |
| LDL-C (mmol/l) | 3.44 | 3.05 | -0.39 | -11.3% |
| HDL-C (mmol/l) | 1.17 | 1.08 | -0.09 | -0.8% |
| TAG (mmol/l) | 2.05 | 1.39 | -0.66 | -32.2% |

**Dattilo, Kris-Etherton. Effects of Weight Reduction on Blood Lipids and Lipoproteins: a Meta-analysis. Am J Clin Nutr 1992;56:320-8.**

# Outpatient LCKD Randomized Controlled Trials: Design

| Reference | Design | Setting | Patients | Duration | Visits |
|---|---|---|---|---|---|
| Sondike 2003 | RCT | Clinic | Healthy teens | 3m | q2Wk |
| Brehm 2003 | RCT | Clinic | Healthy adults | 6m | q2Wk x 6, then @ 6mo |
| Samaha 2003<br>Stern 2004 | RCT | Clinic | Outpt adults | 6m 12m | qWk x 4, then monthly |
| Foster 2003 | RCT | Clinic | Healthy adults | 12m | q2Wk x 2, q4Wk x 4, then Wk 26, 34, 42, 52 |
| Yancy 2004 | RCT | Clinic | Healthy adults | 6m | q2Wks x 6, then monthly |
| Brinkworth 2009 | RCT | Clinic | Healthy adults | 12 m | q2Wks x 4, then monthly |

**Nordmann et al. Arch Intern Med 2006;166:285-293.**

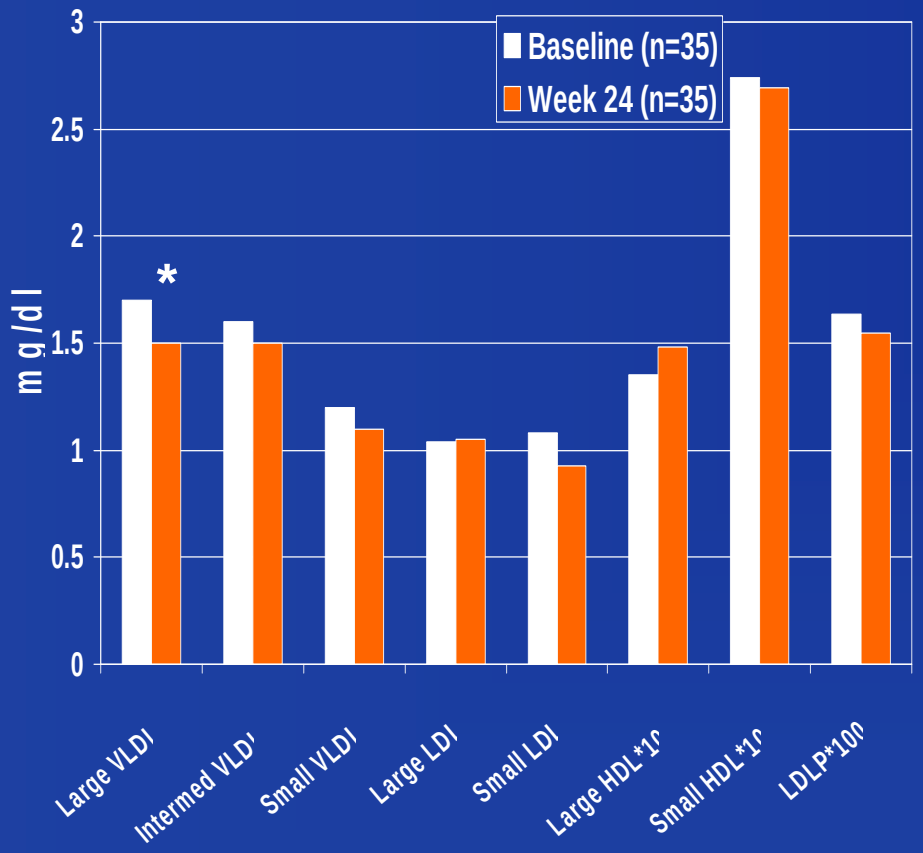
# Outpatient LCKD RCTs: Weight Loss and Serum Lipids

| | | Low Fat | | | | Low Carbohydrate | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ref** | **Duration** | **Weight** | **LDL** | **Trig** | **HDL** | **Weight** | **LDL** | **Trig** | **HDL** |
| Sondike n=30 | 3 mo | -4.1kg | -17%* | -6% | +2% | -9.9kg* | +4% | -48%* | +4% |
| Brehm n=42 | 6 mo | -3.9kg† | -5% | +2% | +8% | -8.5kg*† | 0% | -23%* | +13% |
| Samaha/ Stern n=132 | 6 mo | -1.9kg† | +3% | -4% | -2% | -5.8kg*† | +4% | -20%* | 0% |
| | 12 mo | -3.1kg | -3% | +2% | -12% | -5.1kg | +6% | -29% | -2% |
| Foster | 6 mo | -5.3kg† | -3% | -13% | +4% | -9.7kg*† | +4% | -21% | +20%* |
| n=63 | 12 mo | -4.5kg† | -6% | +1% | +3% | -7.3kg† | +1% | -28%* | +18%* |
| Yancy n=119 | 6 mo | -6.5kg | -3% | -15% | -1% | -12.0kg* | +2% | -42%* | +13%* |
| Brinkworth N=40 | 12 mos | -11.5kg | +3% | -12% | 0% | -14.5kg | +3% | -35% | +21% |

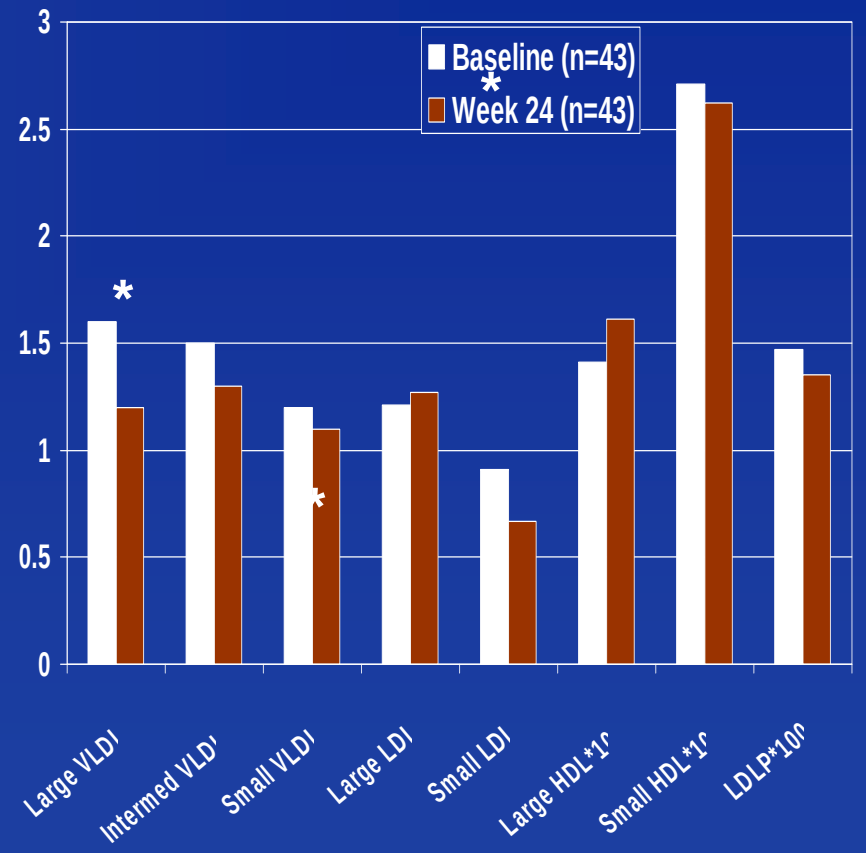
* p<0.05 for between-groups comparison

# Effect on Fasting Lipid Subfractions

## LOW FAT DIET GROUP



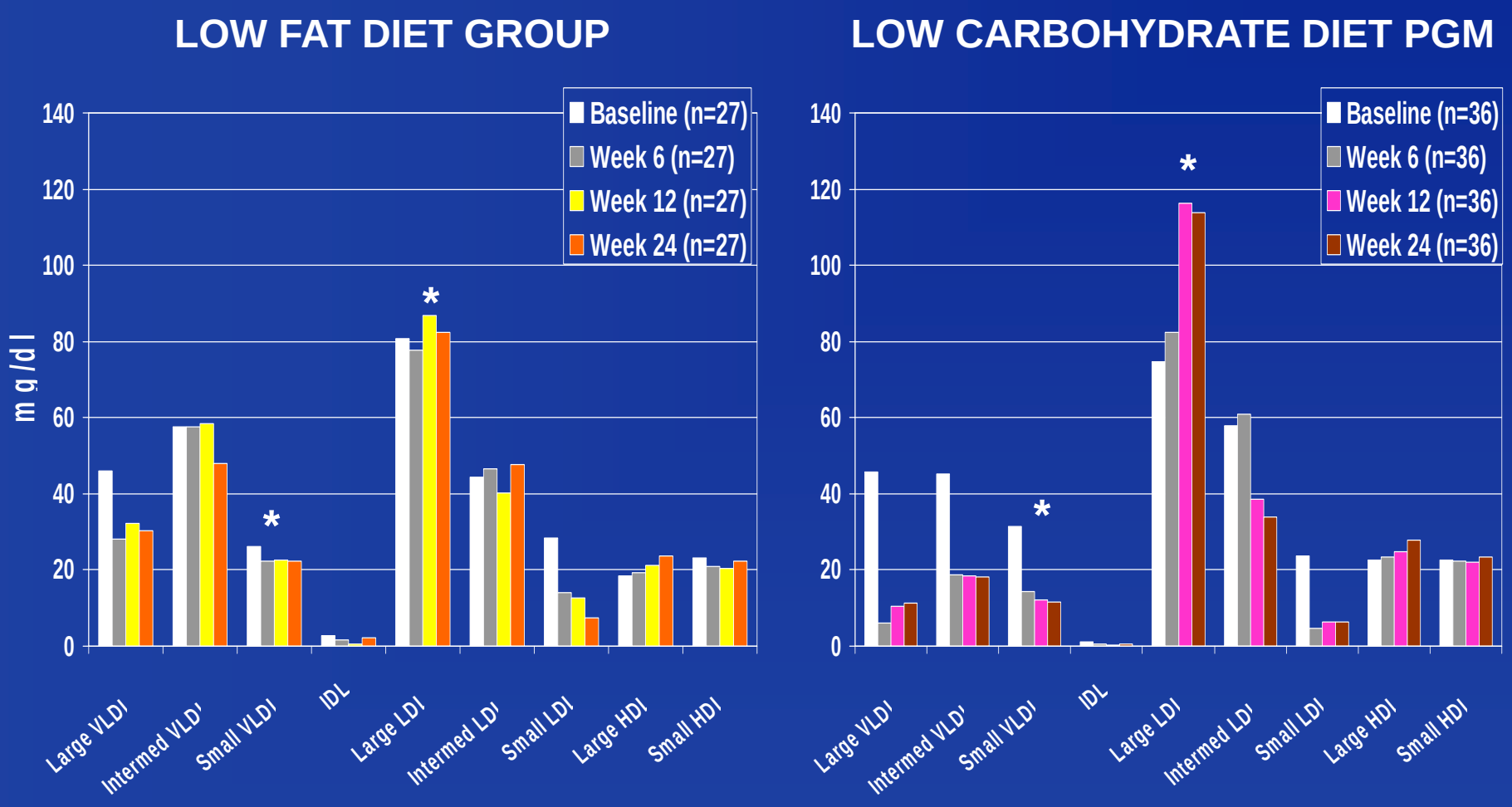

## LOW CARBOHYDRATE DIET PGM




*** p < 0.05 for comparison between groups**

**Seshadri et al. Am J Med 2004;117:398-405 (subanalysis of Samaha/Stern)**

# Effect on Fasting Lipid Subfractions




*** p < 0.05 for comparison between groups**

**Westman et al. Int J Cardiol 2006;110:212-216. (subanalysis of Yancy)**

# Popular Diet Effects on Weight Loss and Cardiac Risk Factors

"To approximate the realistic long-term sustainability of each diet, we asked participants to follow their dietary assignment to the best of their ability to their 2 month assessment, after which time we encouraged them to follow their assigned diet according to their own self-determined interest level."

**2 months ("efficacy")**

| Group | n | kcal/d | CHO | PRO | FAT | Weight | LDL | Trig | HDL | L/H |
|---|---|---|---|---|---|---|---|---|---|---|
| Atkins | 40 | 1736 | 137g | 93.5 | 89.5 | -3.6 kg | +1.3 | -32.3 | +3.2 | -0.18 |
| Zone | 40 | 1434 | 157 | 90.4 | 54.5 | -3.8 kg | -9.7 | -54.1 | +1.8 | -0.33 |
| WWatchers | 40 | 1615 | 191 | 80.5 | 54.5 | -3.5 kg | -12.1 | -9.2 | -0.2 | -0.42 |
| Ornish | 40 | 1393 | 230 | 70.0 | 27.5 | -3.6 kg | -16.5 | -0.4 | -3.6 | -0.21 |

**12 months ("effectiveness")**

| Group | n | kcal/d | CHO | PRO | FAT | Weight | LDL | Trig | HDL | L/H |
|---|---|---|---|---|---|---|---|---|---|---|
| Atkins | 40 | 1886 | 190g | 86.0 | 80.5 | -2.1 kg | -7.1 | -1.2 | +3.4 | -0.39 |
| Zone | 40 | 1757 | 173 | 90.4 | 71.5 | -3.2 kg | -11.8 | -2.5 | +3.3 | -0.52 |
| WWatchers | 40 | 1832 | 208 | 82.5 | 64.0 | -3.0 kg | -9.3 | -12.7 | -3.4 | -0.55 |
| Ornish | 40 | 1819 | 218 | 76.5 | 64.0 | -3.3 kg | -12.6 | +5.6 | -0.5 | -0.31 |

**Dansinger ML et al. JAMA 2005;293:43-53.**

# Popular Diet Effects on Weight Cardiac Risk Among Women

"Each diet group attended 1-hour classes led by a registered dietician once per week for 8 weeks and covered approximately one eighth of their respective books per class...Efforts to maximize retention included email and telephone reminders…and incentive payments."

**2 months ("efficacy")**

| Group | n | kcal/d | CHO | PRO | FAT | Weight | LDL | Trig | HDL | DBP |
|---|---|---|---|---|---|---|---|---|---|---|
| Atkins | 77 | 1381 | ~62g | 97 | 84 | -4.3 kg | +2.3 | -52.3 | -0.4 | -2.9 |
| Zone | 79 | 1455 | 152 | 87 | 57 | -2.0 kg | -5.3 | -24.8 | -0.5 | -2.1 |
| LEARN | 79 | 1476 | 180 | 73 | 49 | -2.8 kg | -7.3 | -17.2 | -3.8 | -1.4 |
| Ornish | 76 | 1408 | 220 | 60 | 33 | -2.8 kg | -10.1 | -10.9 | -5.3 | -0.4 |

**12 months ("effectiveness")**

| Group | n | kcal/d | CHO | PRO | FAT | Weight | LDL | Trig | HDL | DBP |
|---|---|---|---|---|---|---|---|---|---|---|
| Atkins | 77 | 1599 | ~140g | 84 | 78 | -4.5 kg | +0.8 | -29.3 | +4.9 | -4.4 |
| Zone | 79 | 1594 | 179 | 80 | 62 | -1.5 kg | 0 | -4.2 | +2.2 | -2.1 |
| LEARN | 79 | 1654 | 194 | 79 | 61 | -2.5 kg | +0.6 | -14.6 | -2.8 | -2.2 |
| Ornish | 76 | 1505 | 195 | 68 | 50 | -2.4 kg | -3.8 | -14.9 | 0 | -0.7 |

**Gardner CD et al. JAMA 2007;297:969-977.**

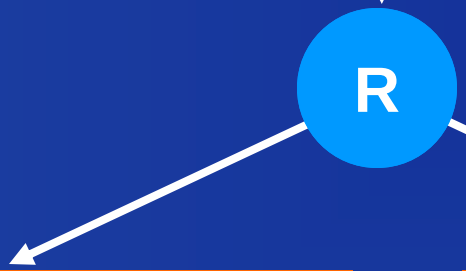
# Effect of Diet Programs on Metabolic Syndrome Parameters From Baseline to 12 Months

| | Atkins *(n=77)* | Zone *(n=79)* | LEARN *(n=79)* | Ornish *(n=76)* | P *value* |
|---|---|---|---|---|---|
| BMI, $kg/m^2$ | -1.65 | -0.53 | -0.92 | -0.77 | .01 |
| Waist-hip ratio | -0.019 | -0.013 | -0.009 | -0.012 | .10 |
| HDL-C, mg/dL | +4.9 | +2.2 | +2.8 | 0.0 | 0.002 |
| Triglycerides, mg/dL | -29.3 | -4.2 | -14.6 | -14.9 | 0.01 |
| Non-HDL-C, mg/dL | -5.1 | -0.5 | -4.0 | -6.8 | 0.36 |
| Insulin, μU/mL | -1.8 | -1.5 | -1.8 | -0.2 | 0.17 |
| Glucose, mg/dL | -1.8 | -1.6 | +0.5 | -0.8 | 0.54 |
| Diastolic b.p., mmHg | -4.4 | -2.1 | -2.2 | -0.7 | 0.009 |
| Systolic b.p., mmHg | -7.6 | -3.3 | -3.1 | -1.9 | <0.001 |

Gardner CD et al. JAMA 2007;297:969-977.

# Low Carb vs. Low Fat Diet + Orlistat Study Design

**146 overweight VA outpatient volunteers**




**Low Fat Diet + Orlistat**

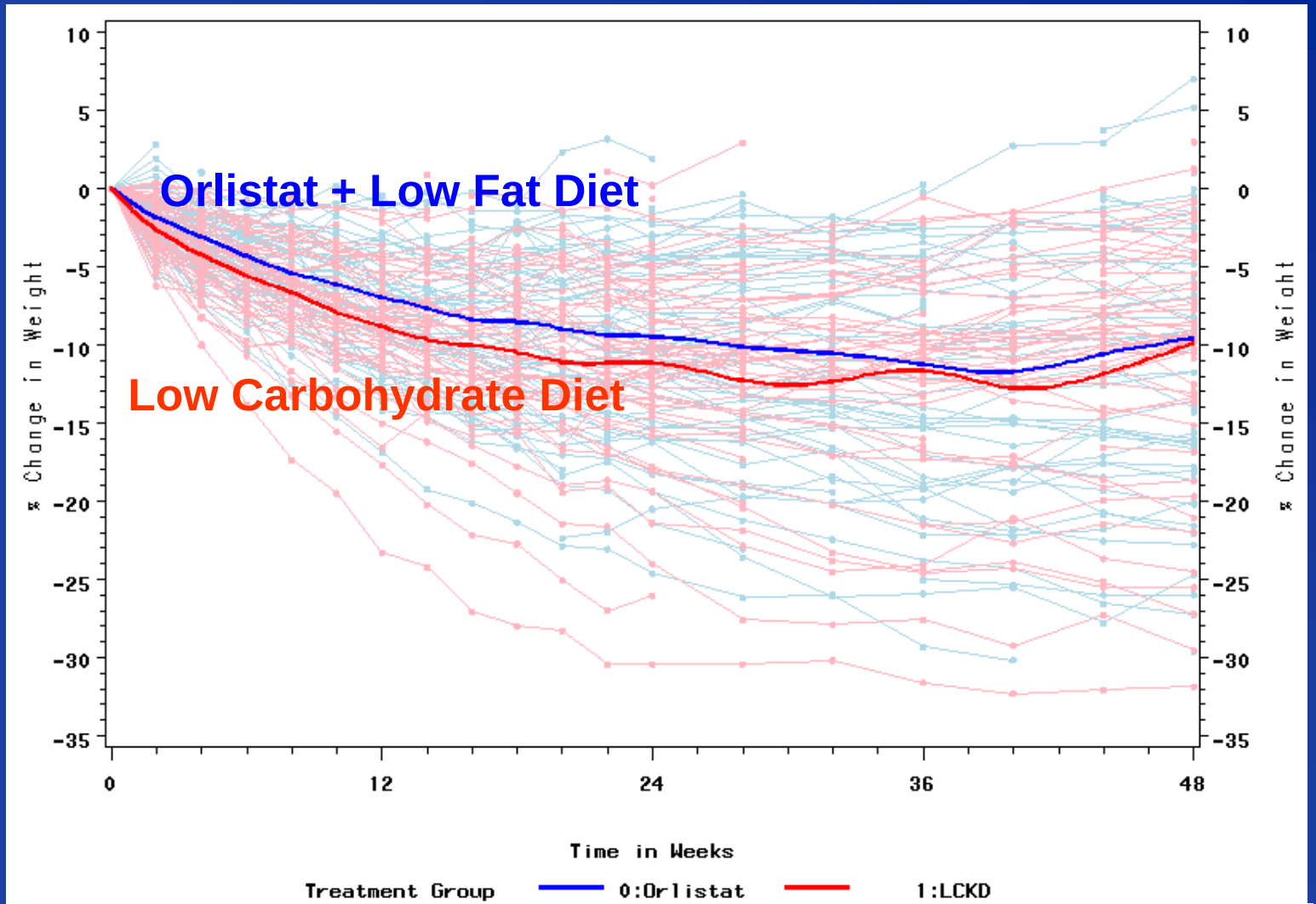
- **group meetings for 48 wks**
- **exercise recommendation**
- **multivitamin daily**
- **Orlistat (Xenical™) 120 mg three times a day**

**Low Carb Ketogenic Diet**

- **group meetings for 48 wks**
- **exercise recommendation**
- **multivitamin daily**

Yancy et al. A randomized trial of a low-carbohydrate diet vs orlistat plus a low-fat diet for weight loss. Arch Intern Med 2010;170:136-145.

# Mean % Weight Change Over Time*




| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n= 65 | 74 | 71 | 66 | 65 | 60 | 61 | 69 | 61 | 52 | 53 | 46 | 54 |
| n= 57 | 72 | 64 | 58 | 58 | 51 | 50 | 57 | 48 | 43 | 54 | 41 | 40 |

# LCKD vs. Orlistat + LFD: Serum Lipids at 24 Weeks

| | Low Carb Ketogenic Diet | | | Orlistat + Low Fat Diet | | | |
|---|---|---|---|---|---|---|---|
| | Wk 0 | Wk 24 | Change | Wk 0 | Wk 24 | Change | |
| Total Chol (mg/dl l) | | 181.5 | 183.4 | +1.6% | 185.0 | 167.8 | -9.3% |
| LDL-C (mg/dl) | 115.6 | 123.7 | +7.0% | 118.1 | 104.2 | -11.8% | |
| HDL-C (mg/dl) | 37.6 | 41.0 | +10.6% | 39.1 | 39.4 | +0.7% | |
| TAG (mg/dl) | 142.2 | 100.0 | -29.7% | 139.1 | 118.0 | -15.2% | |
| CRP (mg/l) | 0.60 | 0.53 | -11.7% | 0.8 | 0.75 | -6.3% | |
| LDL/HDL | 3.07 | 3.01 | -2.0% | 3.02 | 2.64 | -12.6% | |
| TAG/HDL | 3.78 | 2.43 | -35.7% | 3.56 | 2.99 | -16% | |

Yancy et al. A randomized trial of a low-carbohydrate diet vs orlistat plus a low-fat diet for weight loss. Arch Intern Med 2010;170:136-145.

# Cardiovascular Risk Markers After 24 weeks on a Very Low Carb Diet or an Energy Matched HC diet

| | VLCHF Week 24 | Change | HCLF Week 24 | Change | p value |
|---|---|---|---|---|---|
| Body weight (kg) | 88.1 | -12.0 | 89.9 | -11.5 | 0.57 |
| BMI (kg/$m_2$) | 30.0 | -4.0 | 30.9 | -4.0 | 0.74 |
| Waist circumference (cm) | 100.5 | -10.6 | 103.2 | -9.1 | 0.25 |
| Total FFM (kg) | 58.8 | -1.7 | 57.7 | -1.9 | 0.66 |
| Total FM (kg) | 29.1 | -10.2 | 32.2 | -9.6 | 0.64 |
| FM-to-FFM ratio (kg/kg) | 0.5 | -0.2 | 0.6 | -0.1 | 0.76 |

Tay J et al. Metabolic Effects of Weight Loss on a Very-Low-Carbohydrate Diet Compared With an Isocaloric High-Carbohydrate Diet in Abdominally Obese Subjects. JACC 2008;51:59–67.

# Serum Lipids Before and After a 24-Week Dietary Intervention

| | VLCHF | | | HCLF | | |
|---|---|---|---|---|---|---|
| | Wk 0 | Wk 24 | Change | Wk 0 | Wk 24 | Change |
| Total Chol (mmol/l) | | 5.39 | 5.37 | -0.02 | 5.39 | 4.85 | -0.54 |
| LDL-C (mmol/l) | 3.24 | 3.19 | 0.06 | 3.26 | 2.80 | -0.46 | |
| HDL-C (mmol/l) | 1.42 | 1.67 | 0.25 | 1.33 | 1.41 | 0.08 | |
| TAG (mmol/l) | 1.60 | 0.96 | -0.64 | 1.78 | 1.43 | -0.35 | |
| ApoB (g/l) | 0.98 | 0.96 | -0.02 | 1.00 | 0.95 | -0.05 | |

Tay J et al. Metabolic Effects of Weight Loss on a Very-Low-Carbohydrate Diet Compared With an Isocaloric High-Carbohydrate Diet in Abdominally Obese Subjects. JACC 2008;51:59–67.

# Carbohydrate Restriction Treats Metabolic Syndrome


- **Volek JS, Feinman RD. Carbohydrate restriction improves the features of Metabolic Syndrome: Metabolic syndrome may be defined by the response to carbohydrate restriction. Nutr Metab 2005;2:31.**
- **Feinman RD, Volek JS. Carbohydrate restriction as the default treatment for type 2 diabetes and metabolic syndrome. Scand Cardiovasc J 2008;42:256-63.**
- **Accurso A et al. Dietary carbohdyrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. Nutr Metab 2008;5:9.**
- **Volek JS, Fernandez ML, Feinman RD, Phinney SD. Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome. Prog Lipid Res 2008;47:307-18.**
- **Volek JS et al. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids 2009;44:297-309.**

# The transient hypercholesterolemia of major weight loss[1–3]

*Stephen D Phinney, Anna B Tang, Carolyn R Waggoner, Rita G Tezanos-Pinto, and Paul A Davis*

**ABSTRACT** Serum lipoproteins, body composition, and adipose cholesterol contents of six obese women were studied during and after major weight loss by very-low-calorie diets (VLCDs). Subjects started at 168 ± 11% of ideal body weight, lost 30.3 ± 3.7 kg in 5–7 mo, followed by 2+ mo in weight maintenance. Serum cholesterol fell from a prediet (baseline) value of 5.49 ± 0.32 to 3.62 ± 0.31 mmol/L ($P < 0.01$) after 1–2 mo of VLCDs (nadir), after which it rose to 5.95 ± 0.36 mmol/L (peak, $P < 0.01$ compared with nadir and baseline) as weight loss continued. With weight maintenance, serum cholesterol fell to 4.92 ± 0.34 mmol/L ($P < 0.05$ compared with peak). Adipose cholesterol content did not change in peripheral (arm and leg) biopsy sites but rose significantly in abdominal adipose tissue with weight loss. We conclude that major weight loss was associated with a late rise in serum cholesterol, possibly from mobilization of adipose cholesterol stores, which resolved when weight loss ceased. *Am J Clin Nutr* 1991;53:1404–10.

**KEY WORDS** Very-low-calorie diets, serum cholesterol, adipose cholesterol

## Introduction

Both elevated serum cholesterol concentration and obesity vation (9). Further, a tendency for a late rise in serum cholesterol was observed in patients undergoing therapeutic weight loss with very-low-calorie diets (VLCDs) (10–12). Although weight loss by either dieting or exercise was shown to reduce serum total cholesterol and raise high-density-lipoprotein (HDL) cholesterol (13), this is not a uniform response in all patient groups studied (14). This variability could be due to differences in methodology between these studies, such as diet composition, amount of weight lost, and timing of sample acquisition, but the underlying etiology of this variability has not been explained.

A particularly intriguing variability in serum cholesterol is the rise seen when VLCDs are taken for > 3 mo. In the course of other outpatient research, we observed that 88% of 44 adult patients experienced a diet-induced fall in cholesterol within 2 mo, 73% showed a late rise > 0.5 mmol/L, and 36% had serum cholesterol concentrations rise above prediet values while they were still losing weight.

To explore more carefully the dynamics of serum cholesterol and its subfractions during major weight loss, we obtained serum, adipose tissue, and body composition data from six moderately obese women during and after major weight loss induced by a VLCD administered in a multidisciplinary outpatient weight-management clinic.

# Transient Hypercholesterolemia of Weight Loss

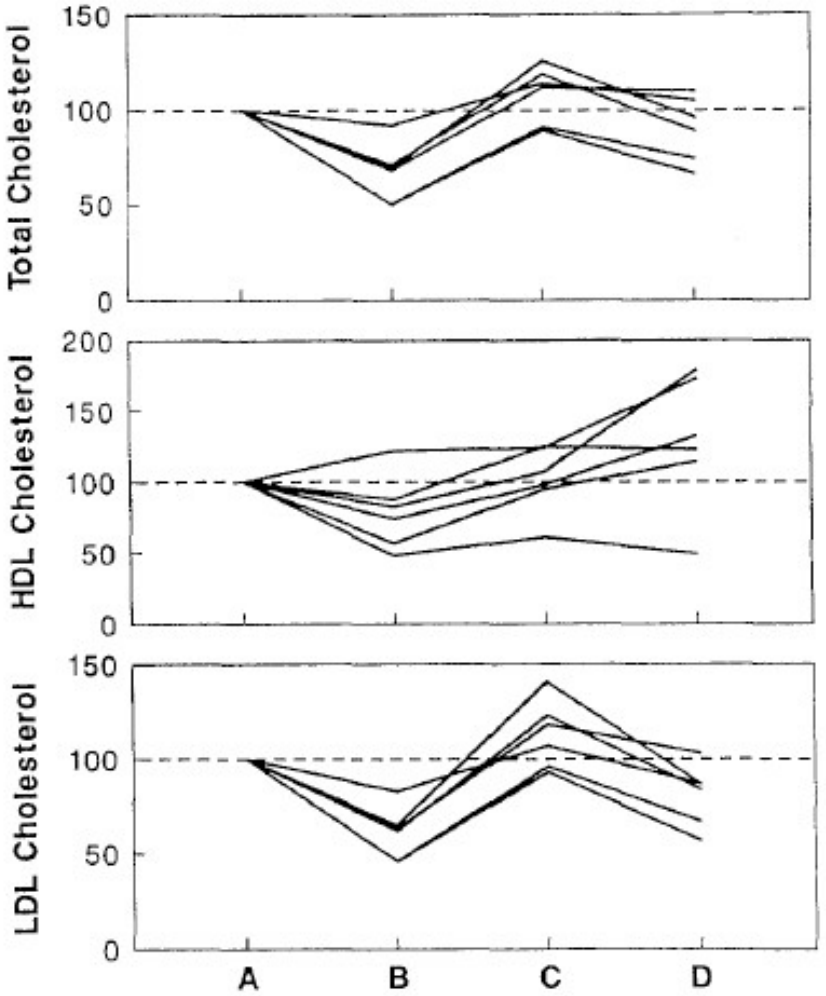



FIG 3. Serum total, HDL, and LDL cholesterol. Selected values were taken for each subject at baseline (A), at total cholesterol nadir (B), at total cholesterol peak (C), and in postweight-loss maintenance (D). All values are normalized as percent of the baseline value A.

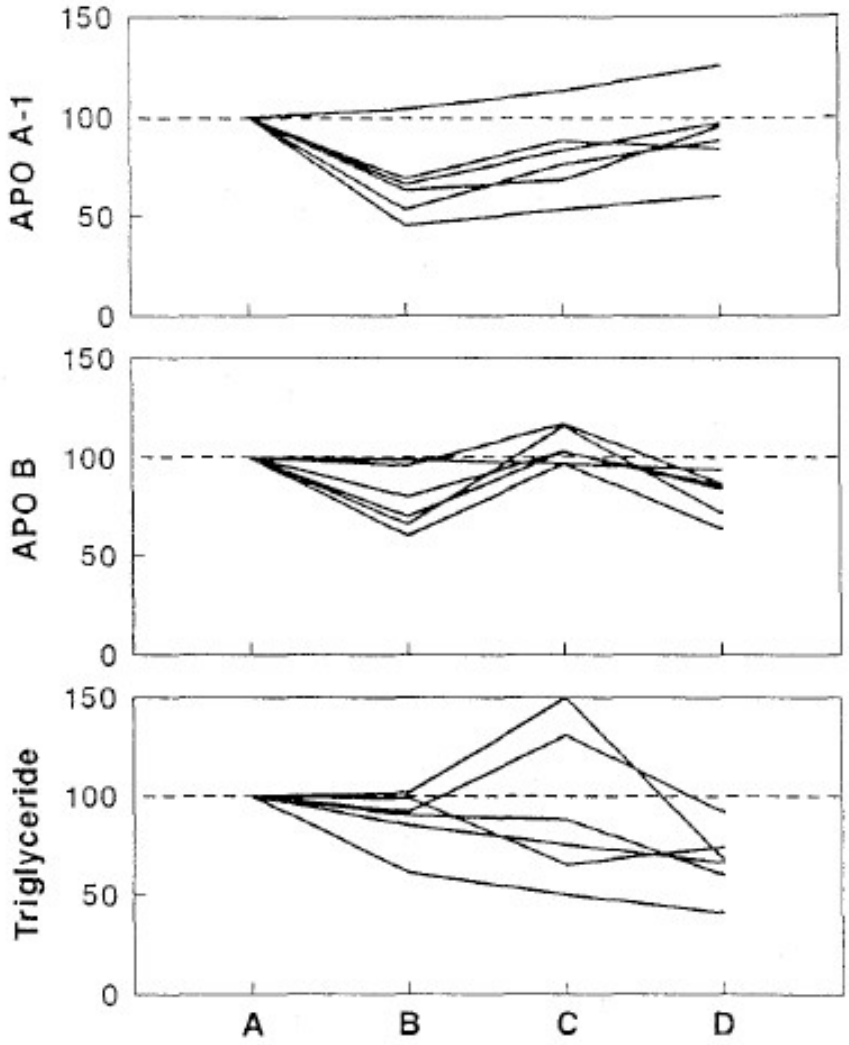
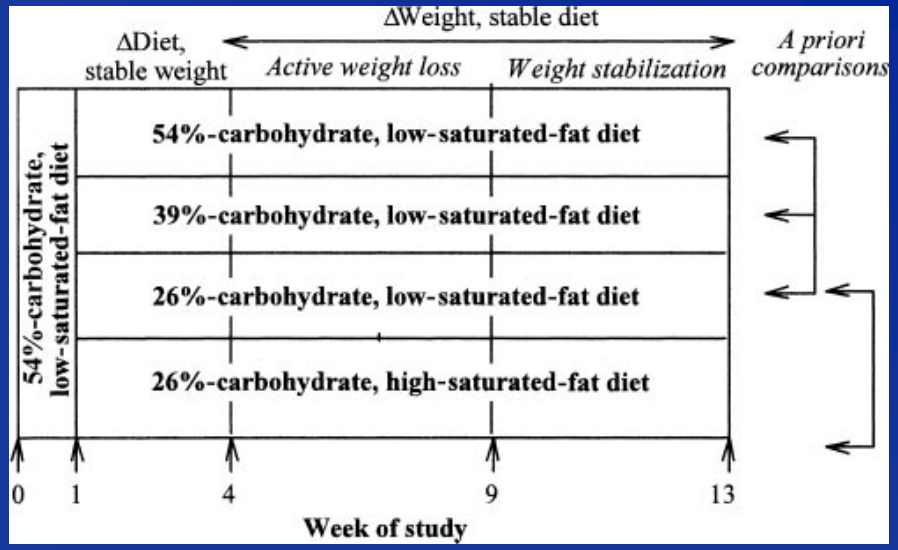
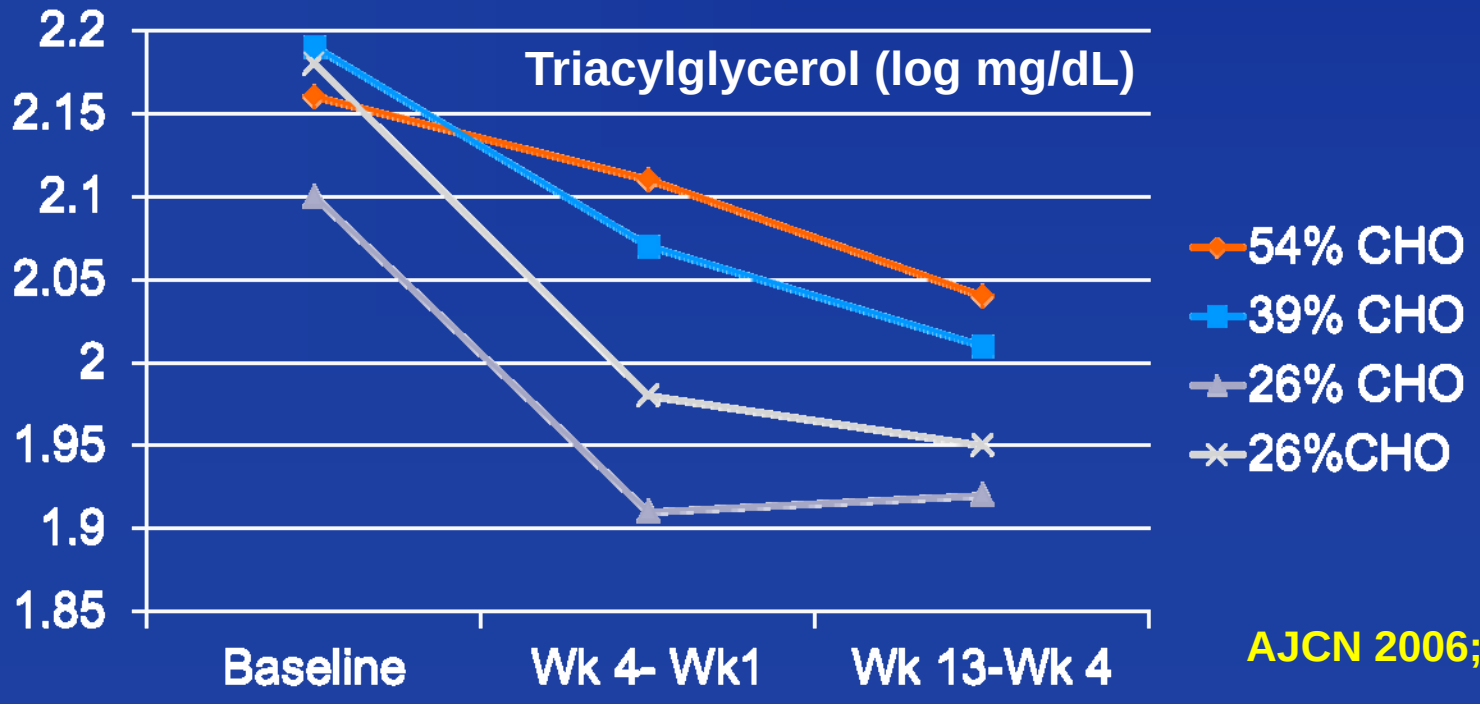



FIG 4. Serum apolipoproteins A-I and B and triglycerides. Selected values for each subject were taken at the same time points as in Figure 3. All values are normalized as percent of the baseline value A.

# Effects of Diet, 5 kg Weight Loss

**N = 178**
**All males**
**BMI 29 kg/m2**




AJCN 2006;83:1025-31.

# Effects of Diet, 5 kg Weight Loss

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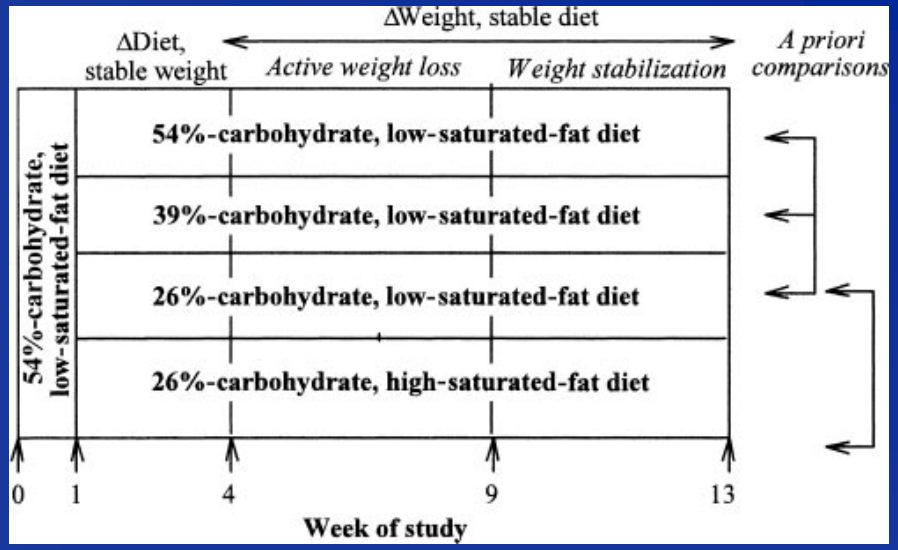
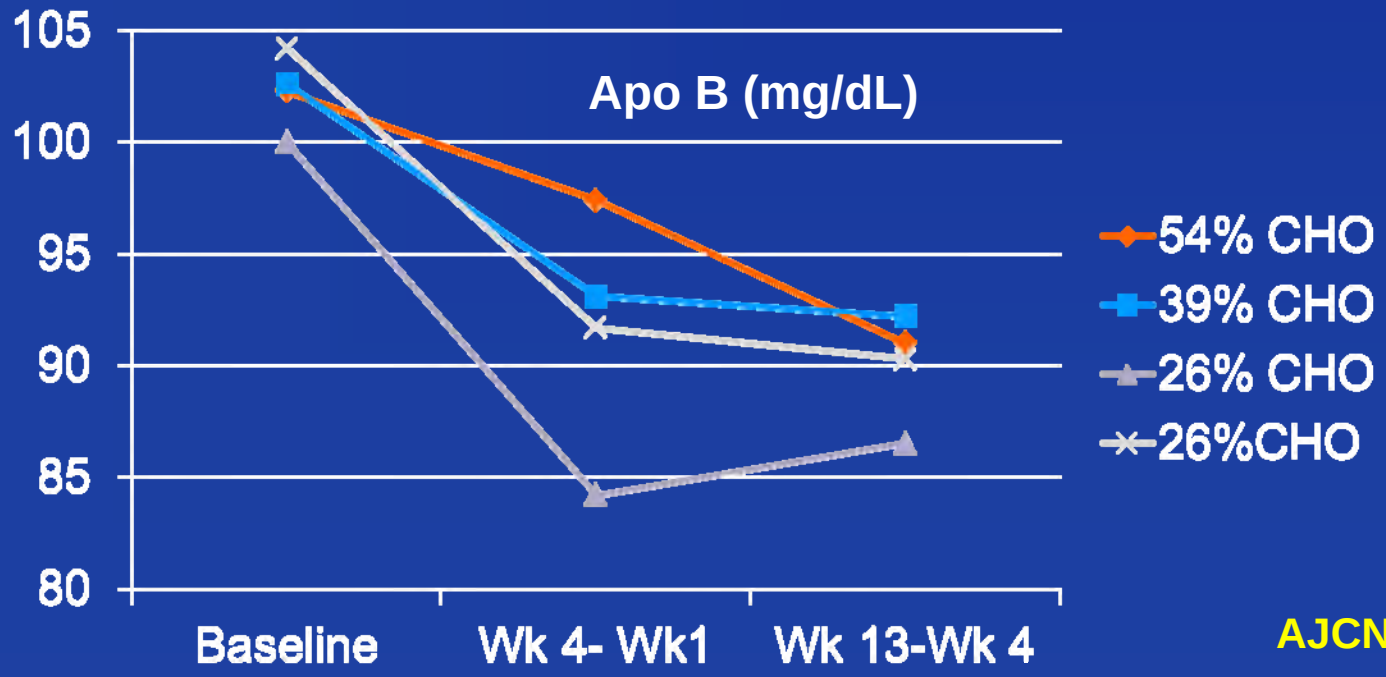
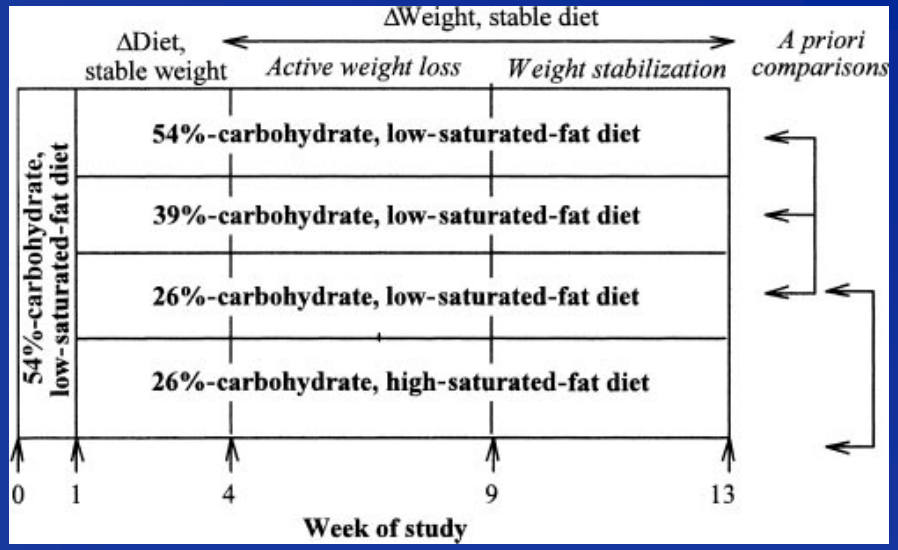


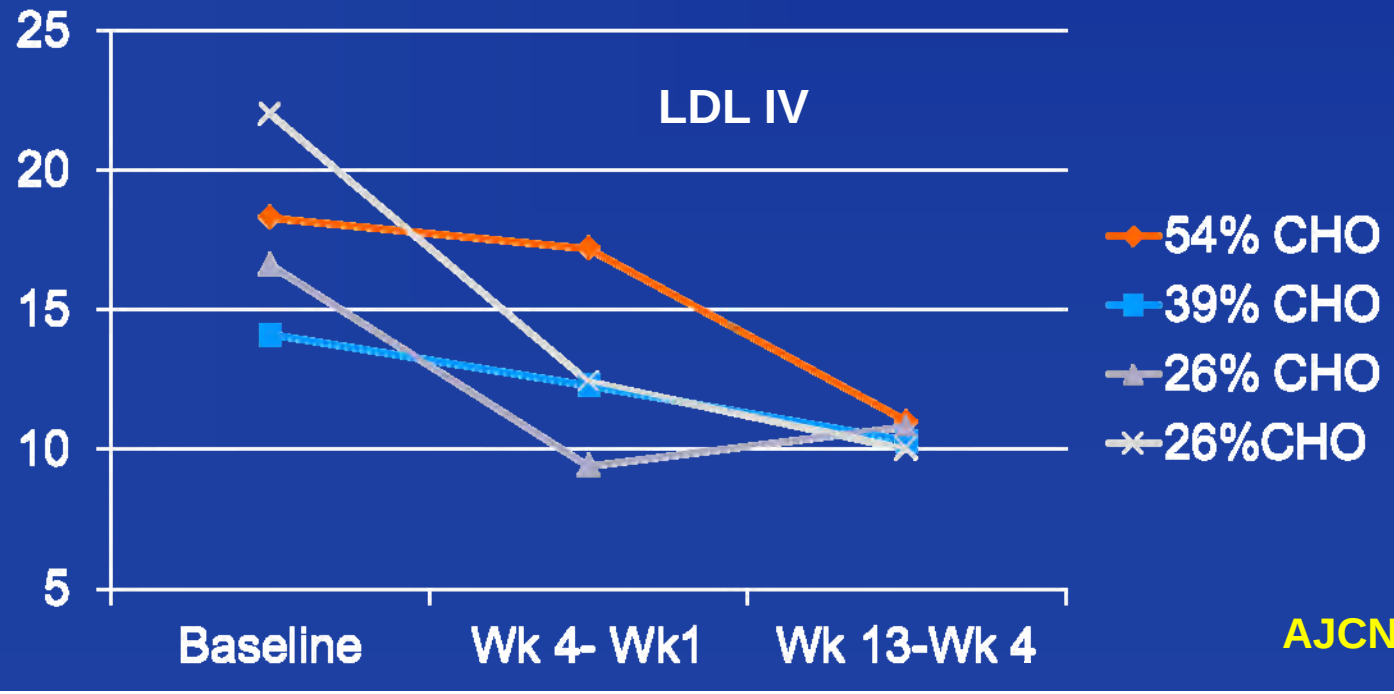




AJCN 2006;83:1025-31.

# Effects of Diet, 5 kg Weight Loss

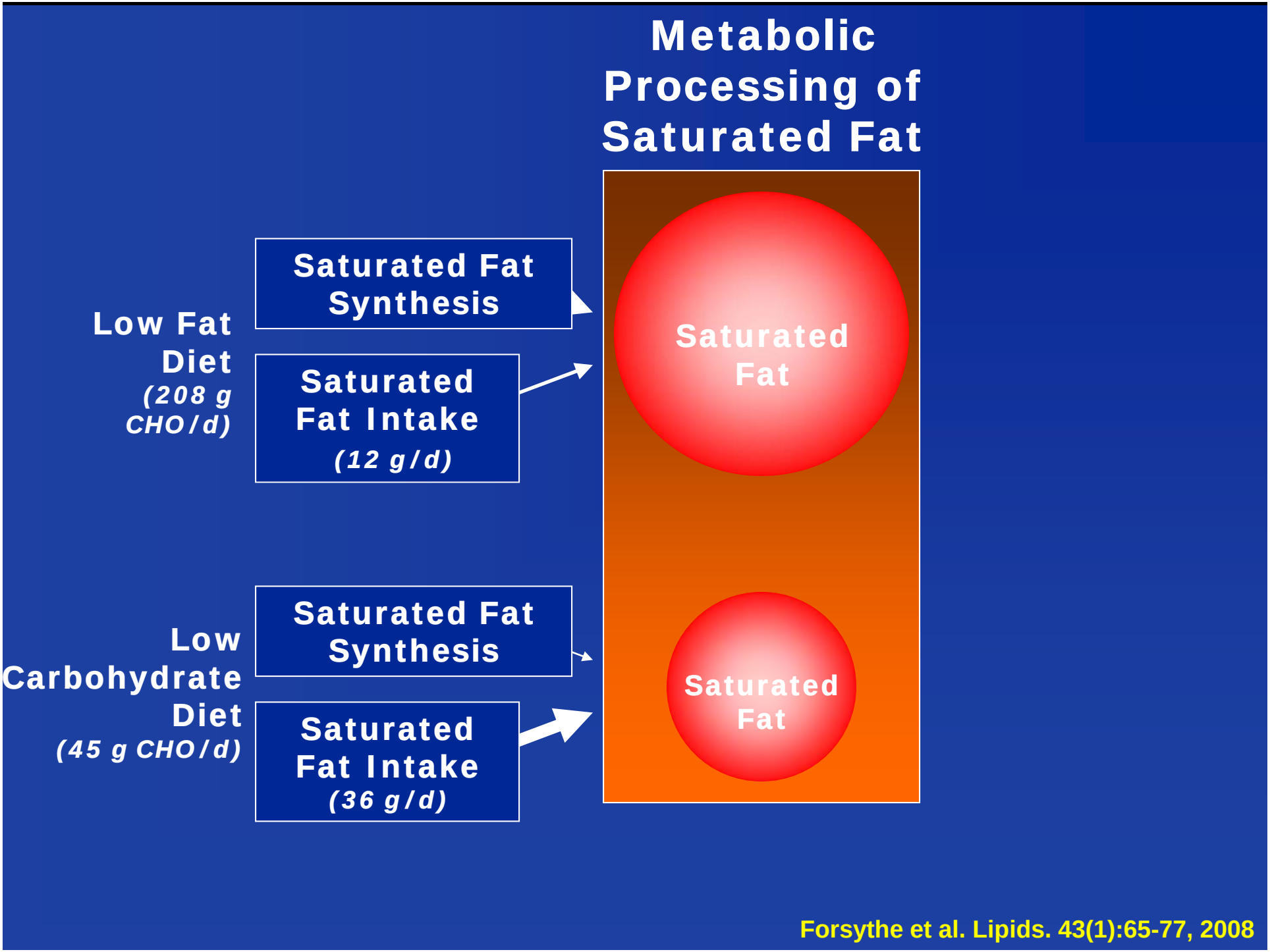
**N = 178**
**All males**
**BMI 29 kg/m2**



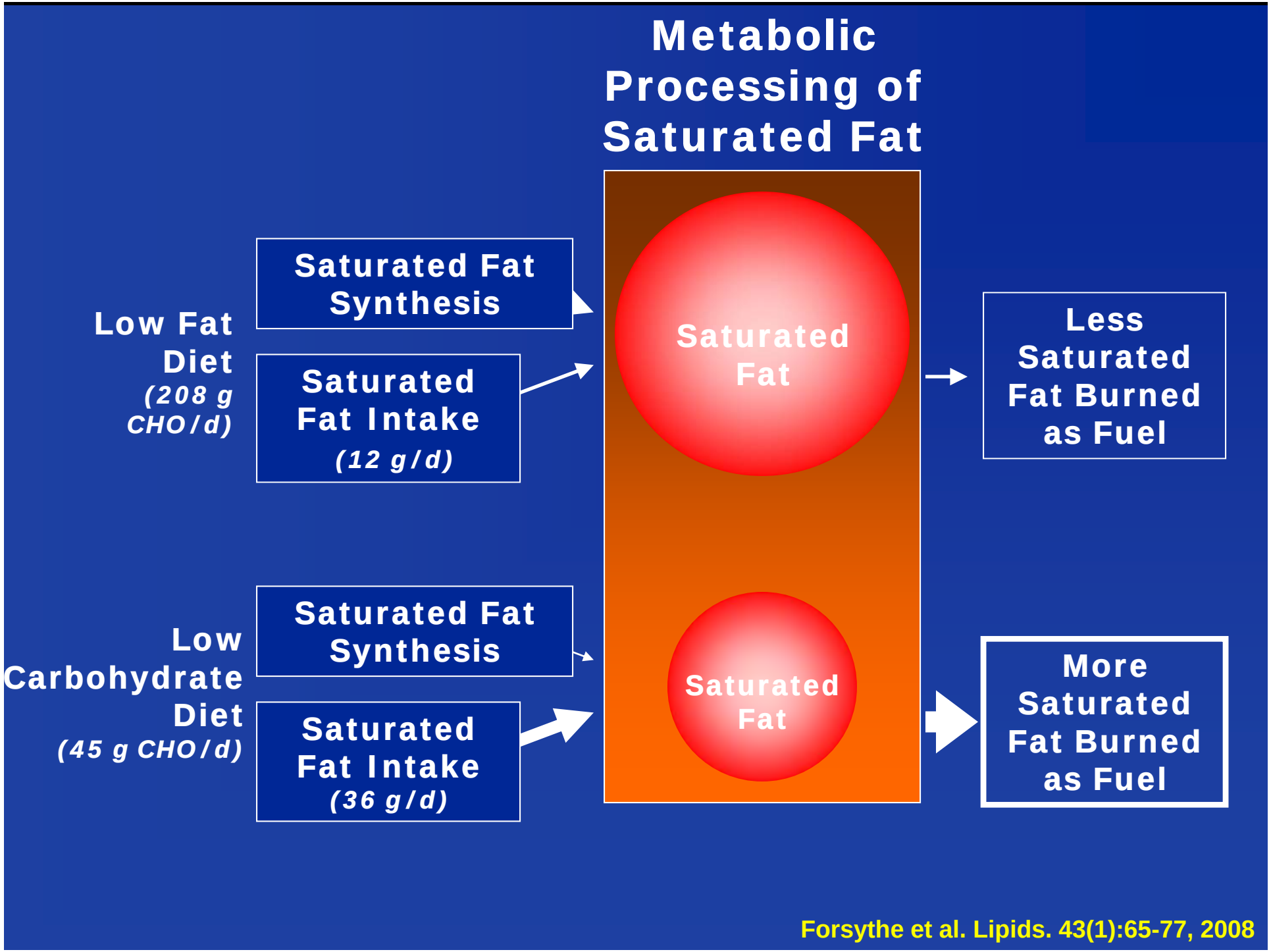

AJCN 2006;83:1025-31.

# Metabolic Processing of Saturated Fat




Forsythe et al. Lipids. 43(1):65-77, 2008

# Metabolic Processing of Saturated Fat




Forsythe et al. Lipids. 43(1):65-77, 2008

# Does Insulin Reduction Explain Changes in Lipoproteins after Body Fat Loss?

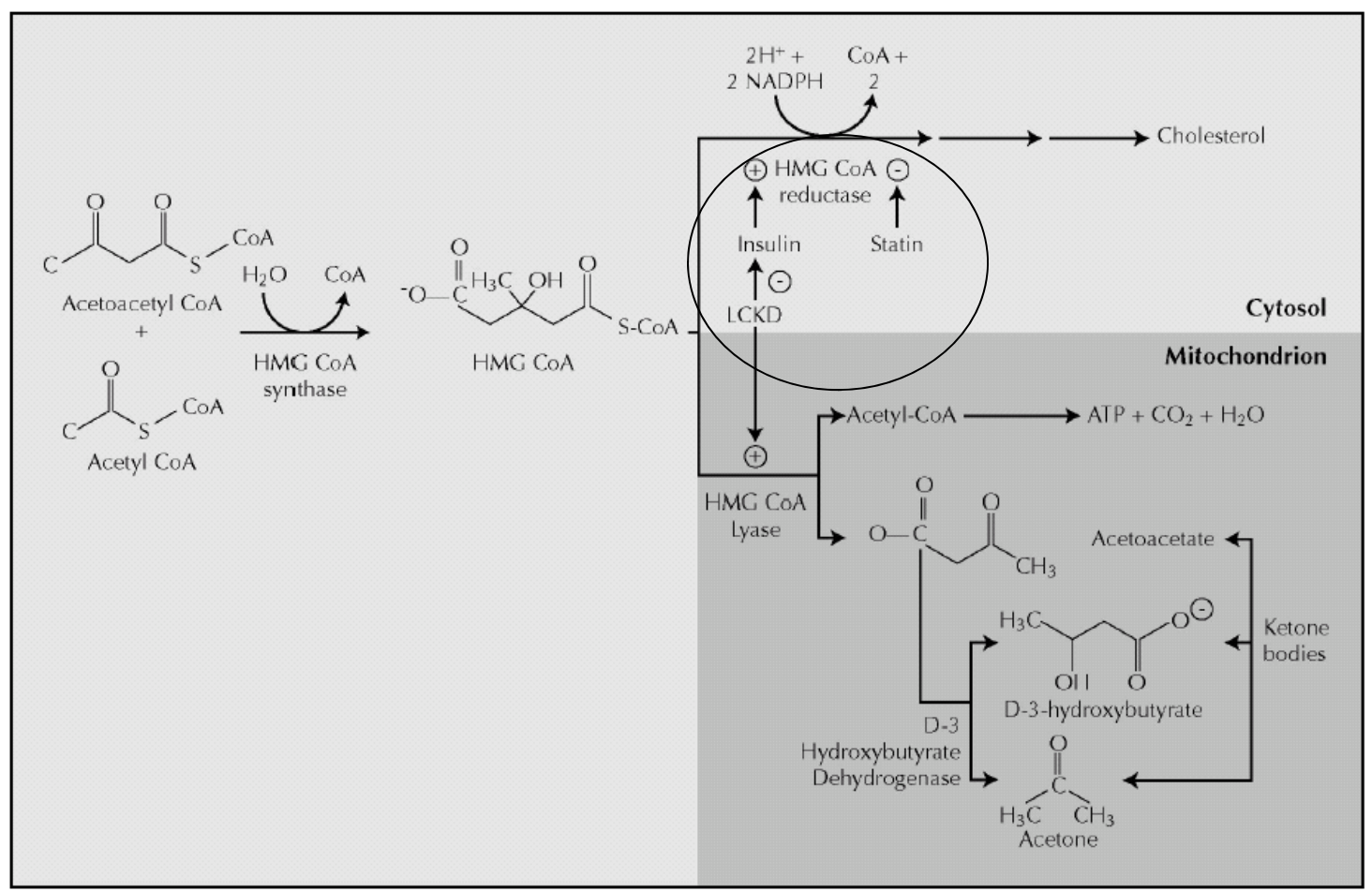



**Figure 2.** Potential biochemical mechanism of cholesterol reduction of a low-carbohydrate ketogenic diet (LCKD). (ATP—adenosine triphosphate; HMG CoA—3-hydroxy-3-methylglutaryl coenzyme A.)

**Kennedy AR et al. A high fat, ketogenic diet induces a unique metabolic state in mice. Am J Physiol Endocrinol Metab 2007, February 13.**

# Relationship Between Large VLDL and Small LDL

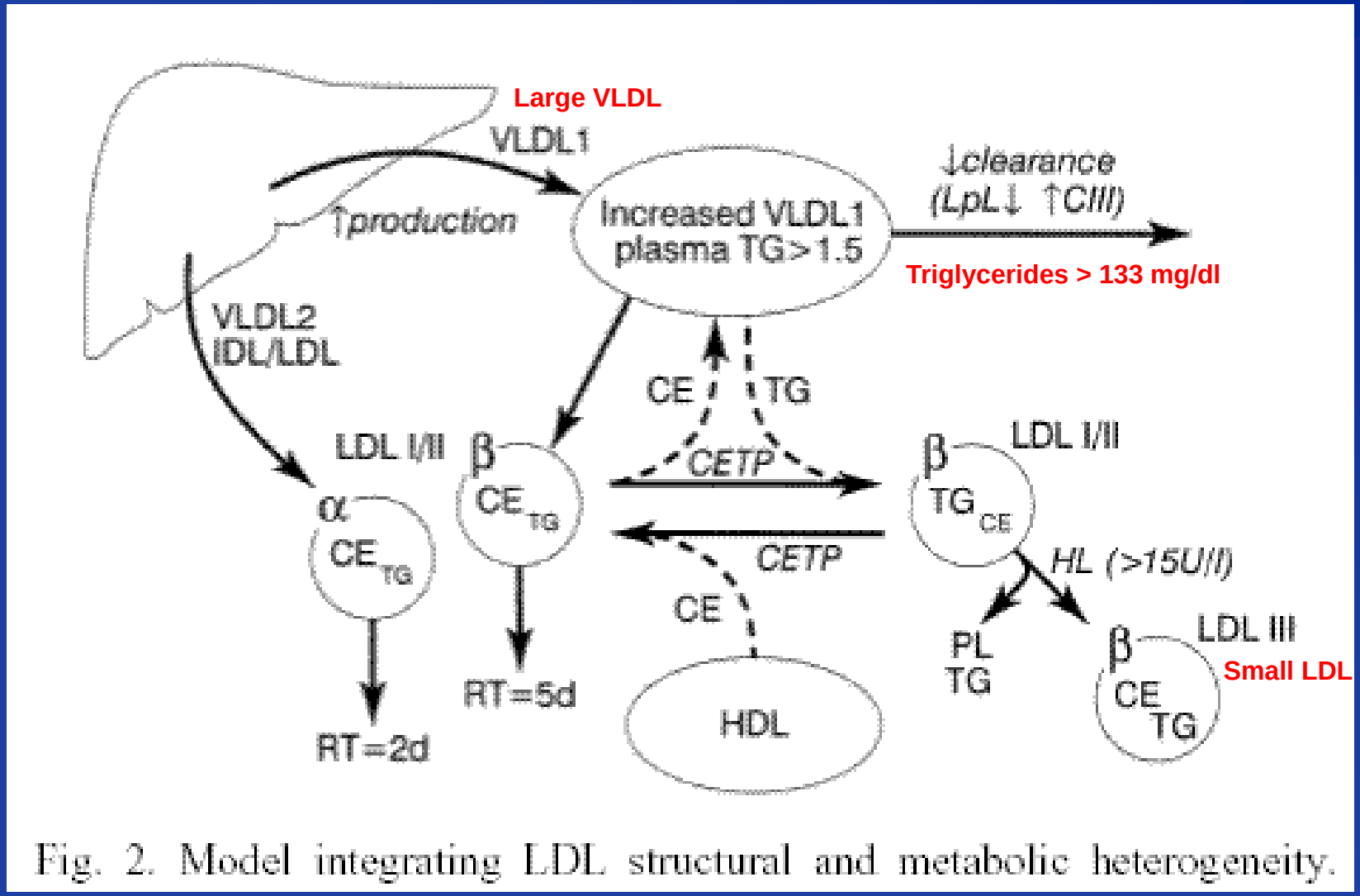



Fig. 2. Model integrating LDL structural and metabolic heterogeneity.

Packard C et al. Int J Card 2000;74:S17–S22.

# Dietary Carbohydrate, Large VLDL and Small LDL

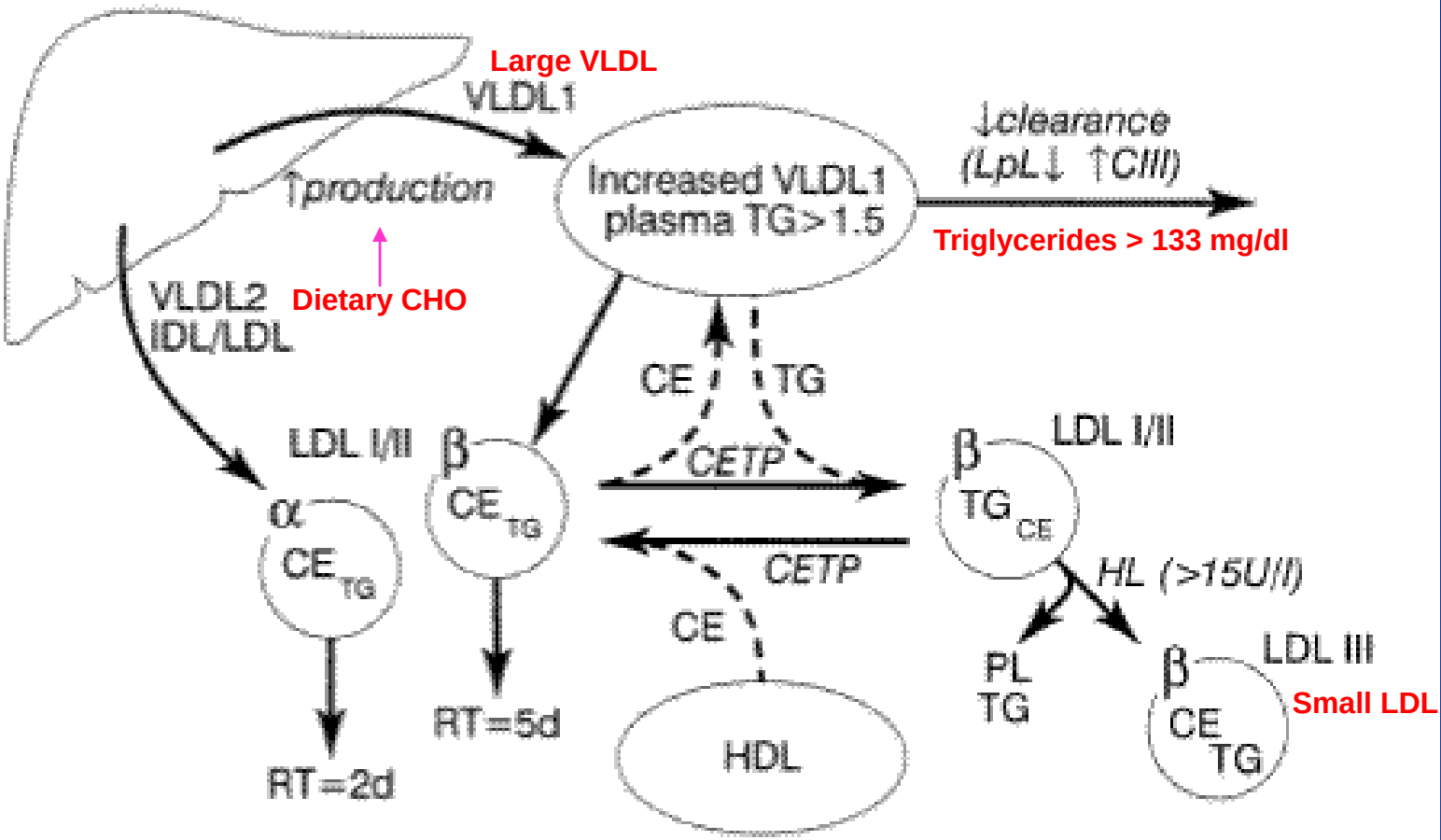
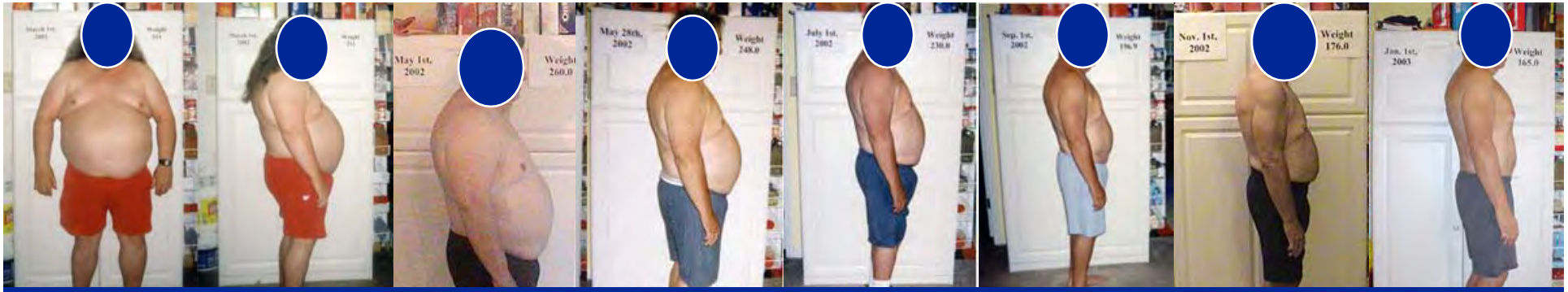


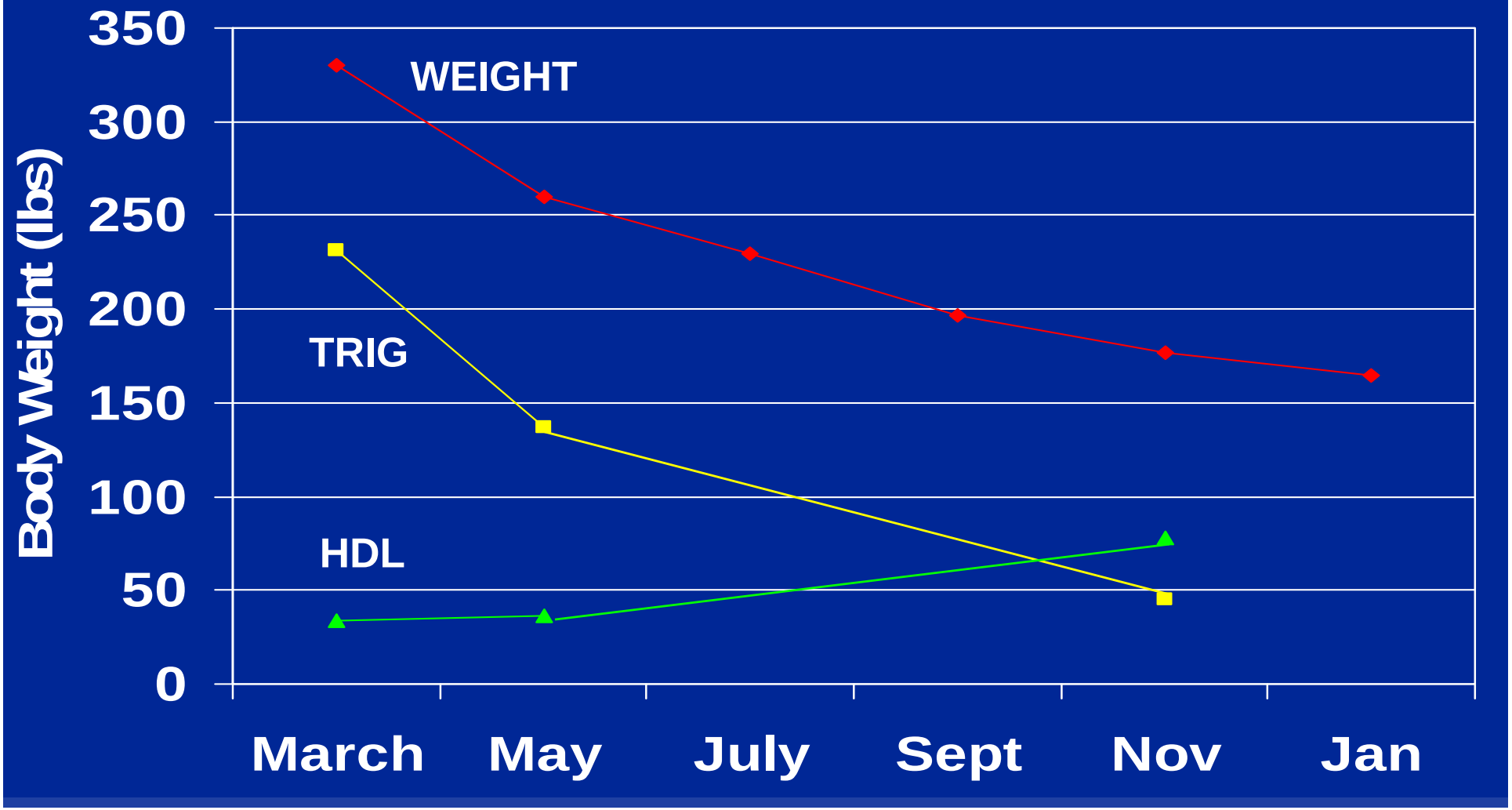

Fig. 2. Model integrating LDL structural and metabolic heterogeneity.

Volek JS, Feinman RD. Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction. Nutrition & Metabolism 2005, 2:31.



Spironolactone, coumadin d/c'd

CPAP d/c'd



# Weight Loss, Improvements in Lipids

**A 50 year old white female with obesity (BMI = 31.3) wants to lose weight.**

| | | | Fasting lab tests: | | | | |
|---|---|---|---|---|---|---|---|
| **Date** | **BMI** | **Wt (lbs)** | **Chol** | **Trig** | **LDL** | **HDL** | **Glucose** |
| **6/10** | **31.3** | **178** | **245** | **247** | **141** | **54** | **92** |
| | ***Initiation of Carbohydrate Restricted Diet*** | | | | | | |
| **8/10** | **29.1** | **164** | | | | | |
| **2/11** | **24.5** | **141** | | | | | |
| **5/11** | **23.5** | **138** | **209** | **46** | **119** | **81** | **88** |

# Summary

- There is considerable variability in the effect of fat mass loss on serum lipoproteins.
- During the fat mass loss process, measurement of serum lipoproteins may not reflect the steady state after weight stability.
- Low fat, low calorie diets lower cardiovascular risk factors by mainly lowering LDL-C; low carbohydrate diets lower cardiovascular risk factors by mainly lowering triglyceride and raising HDL-C.
- The dietary pattern and loss of body fat both can influence dyslipidemia.

# What is the Effect of Changes in Body Fat on Dyslipidemia

Eric C. Westman, M.D. M.H.S.

Duke University Medical Center

Durham, North Carolina

ewestman@duke.edu

Associate Professor of Medicine

President, Obesity Medicine Association (formerly ASBP)

Director, Duke Lifestyle Medicine Clinic

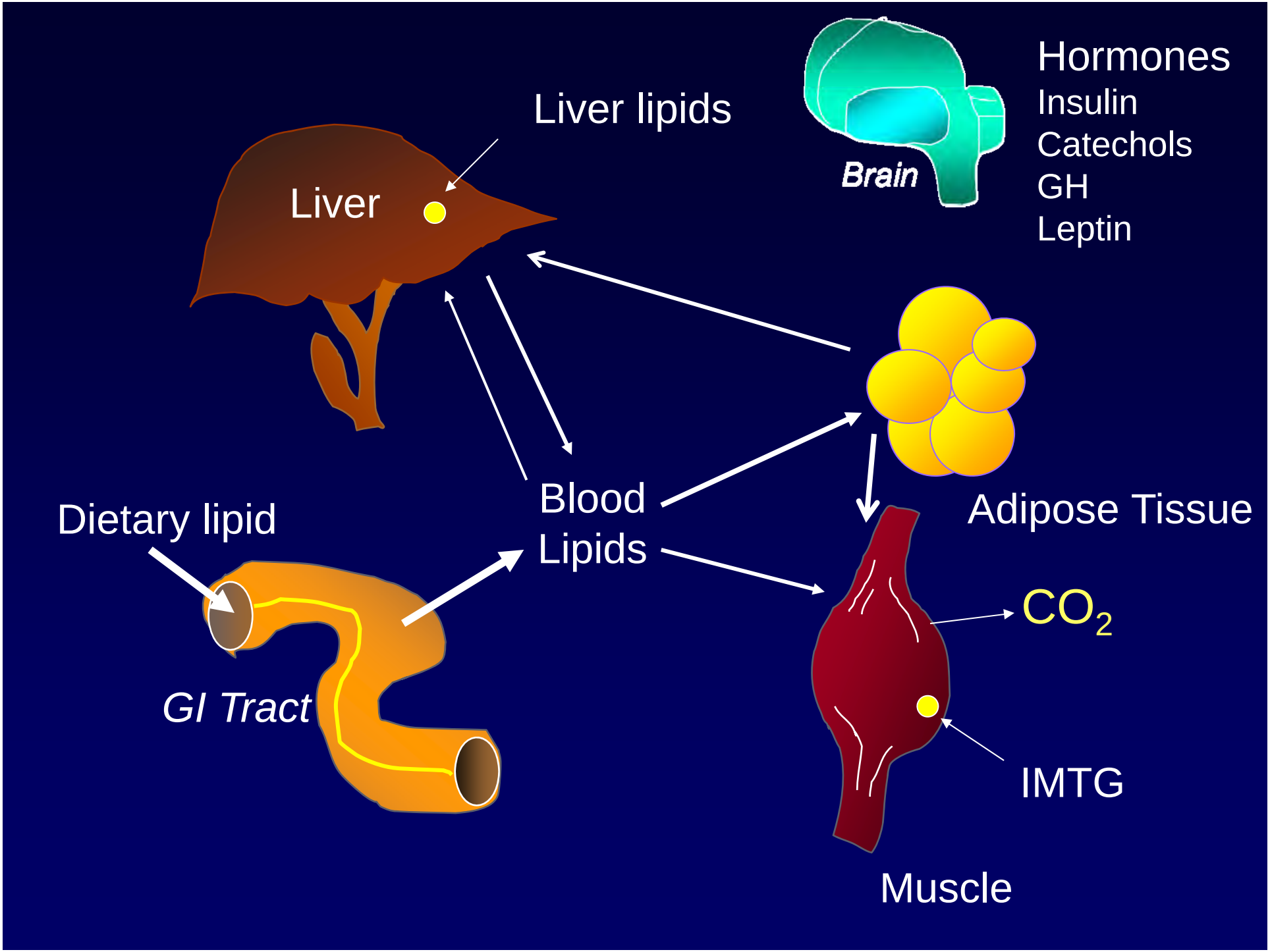
Course Director, Medical Management of Obesity

Fellow, The Obesity Society

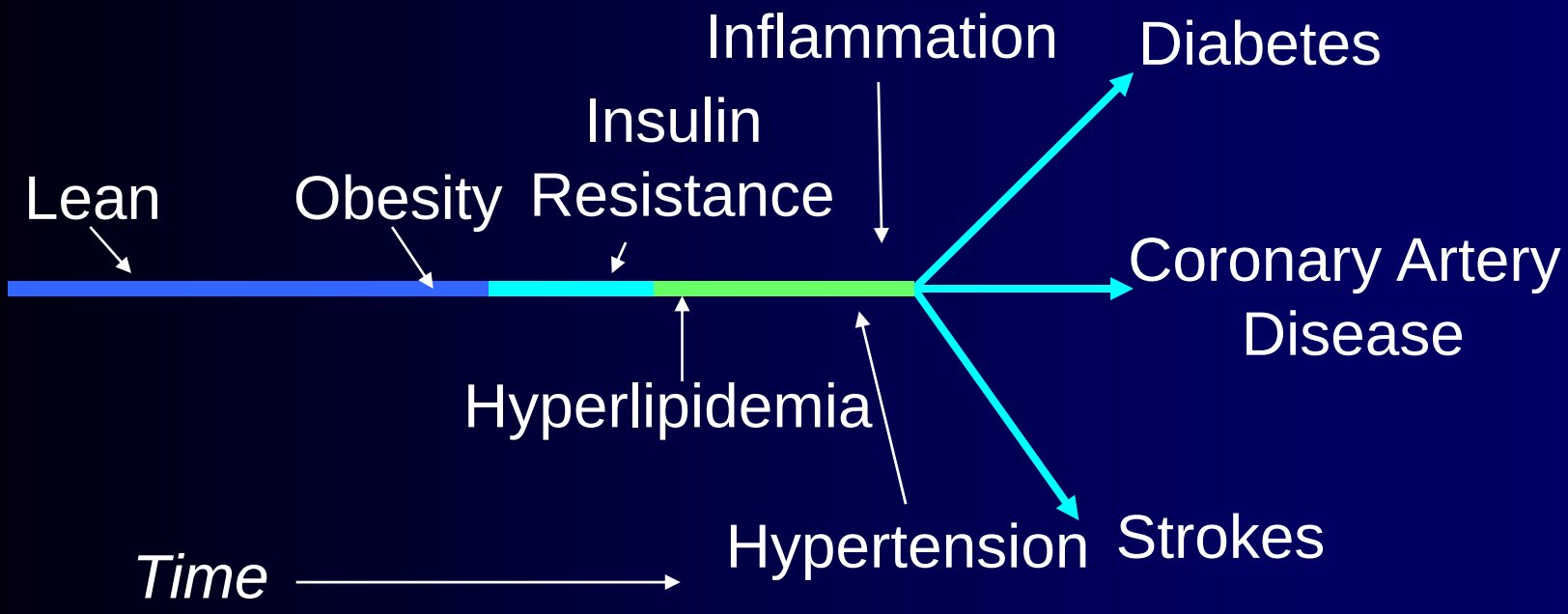
Author of The New Atkins for a New You

# What Are the Effects of Weight Management Pharmacotherapy on Lipid Metabolism and Lipid Levels?

Daniel Bessesen, MD
Professor of Medicine
University of Colorado School of Medicine
Chief of Endocrinology, Denver Health Medical Center
Daniel.Bessesen@ucdenver.edu


Hormones
Insulin
Catechols
GH
Leptin
Brain
Liver lipids
Liver
Adipose Tissue
Dietary lipid
Blood
Lipids
$CO_2$
GI Tract
IMTG
Muscle

# Weight Gain and CVD



# Summary Points

- Lipid lowering drugs have a bigger effect on serum lipid levels than obesity treatments.
- Obesity treatments are not FDA approved for lipid lowering.
- Obesity is likely involved in the pathogenesis of CVD and other diseases and treatment is advocated widely in guidelines.
- Patients often inquire about help with weight loss
- As lipid specialists you should decide what role. weight loss plays in your practice and how to talk to your patients about their options.

# Game plan

- Phen/fen as a model…lessons?
- Sibutramine as a model…lessons?
- Weight loss agents
  - Orlistat
  - Phentermine/topiramate ER
  - Lorcasarin
  - Naltrexone ER/Bupropion ER
  - Liraglutide 3mg
- Some final thoughts

# Phen/fen Weight loss

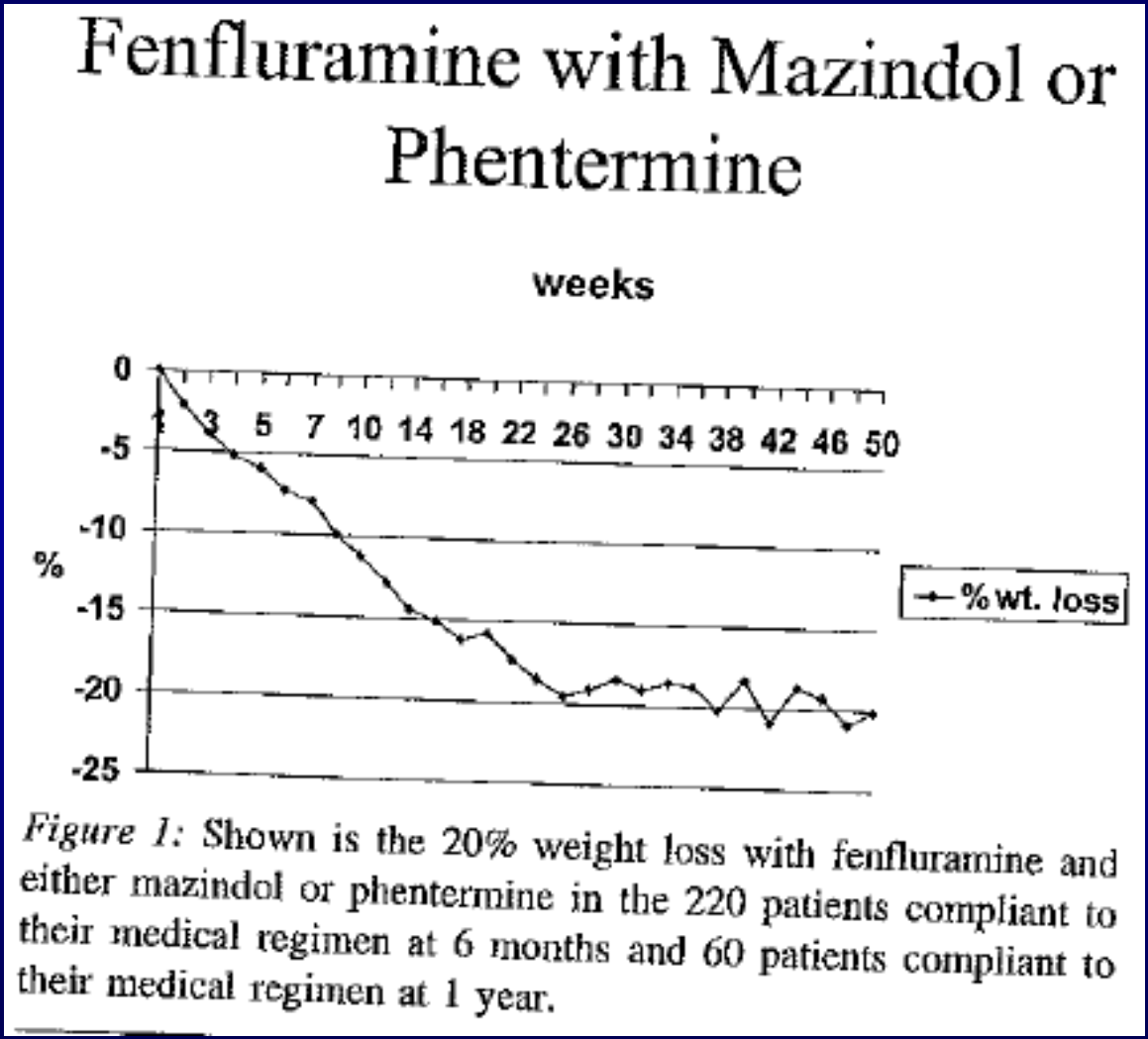



*Figure 1:* Shown is the 20% weight loss with fenfluramine and either mazindol or phentermine in the 220 patients compliant to their medical regimen at 6 months and 60 patients compliant to their medical regimen at 1 year.

Obesity Research 1999: 7; 523-531

# Phen/fen: Lipids

- Tg levels went down 2.5%/% weight lost
- LDL levels went down 0.9%/% weight lost

**Table 2.** Medication status, weight loss, percent weight loss, and time of minimal medication dose

| | Time (weeks) | Weight loss | | Medication status (%) | | |
|---|---|---|---|---|---|---|
| | | kg | % | Discontinued | Reduced | Unchanged |
| Diabetes (Rx with insulin) | 8.0±2.1 | 9.9±1.9 | 9.0±1.7 | 100 | 0 | 0 |
| Diabetes (Rx with sulfonylurea) | 5.7±1.1 | 7.6±.08 | 8.2±1.1 | 100 | 0 | 0 |
| Hyperlipidemia (Rx with meds) | 6.0±2.4 | 8.2±1.7 | 9.7±2.1 | 64 | 0 | 36 |
| Hypertension (Rx with meds) | 10.9±1.2 | 13.2±0.6 | 10.6±0.9 | 56 | 30 | 14 |

The amount of weight loss and the time at which the optimal improvement occurred in subjects on medications for obesity associated disease.

Obesity Research 1999: 7; 523-531

# Sibutramine: Weight loss

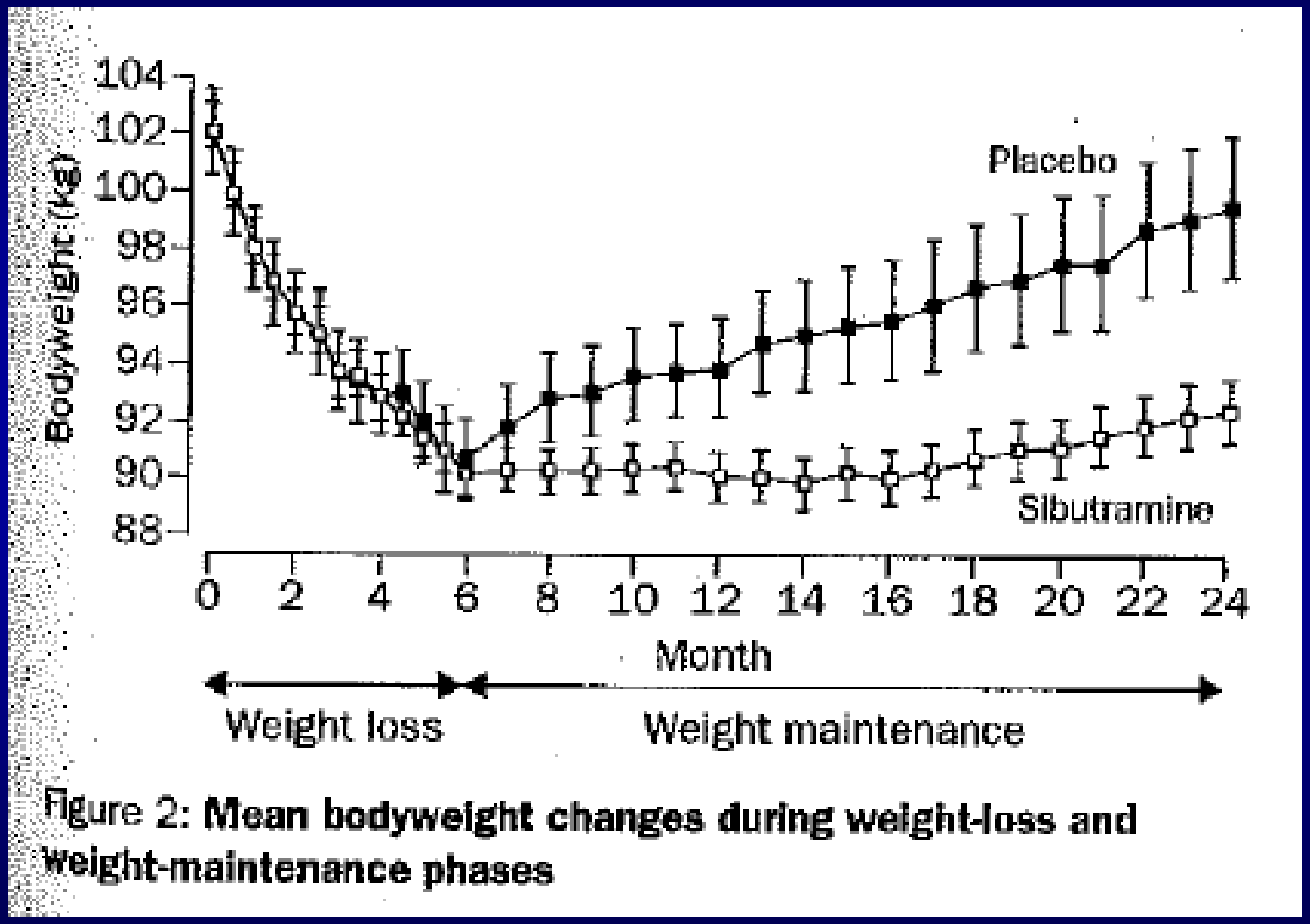
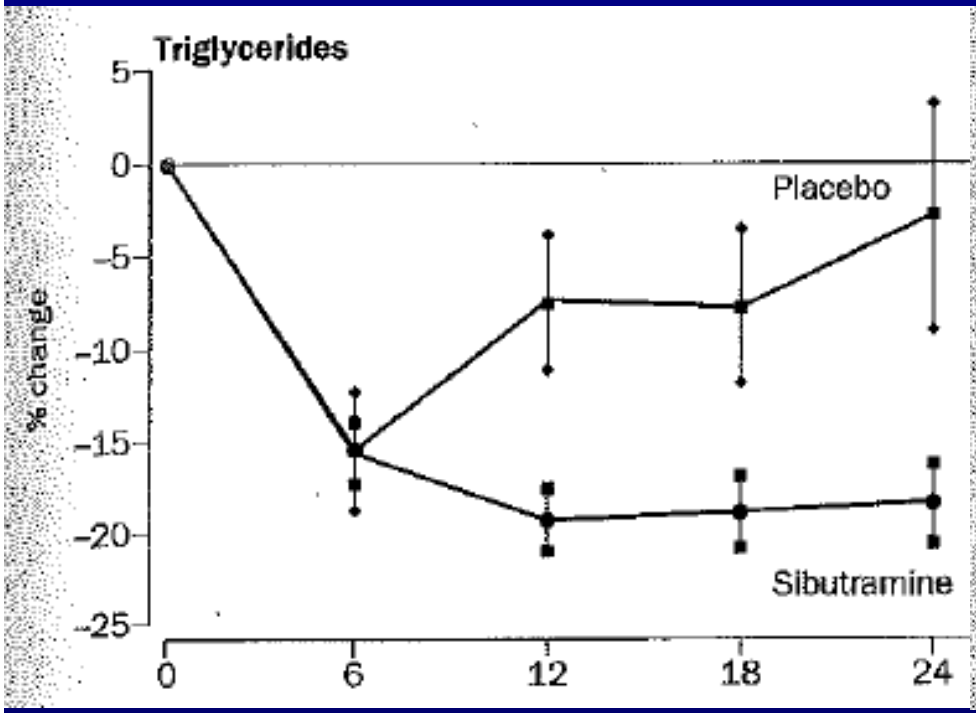
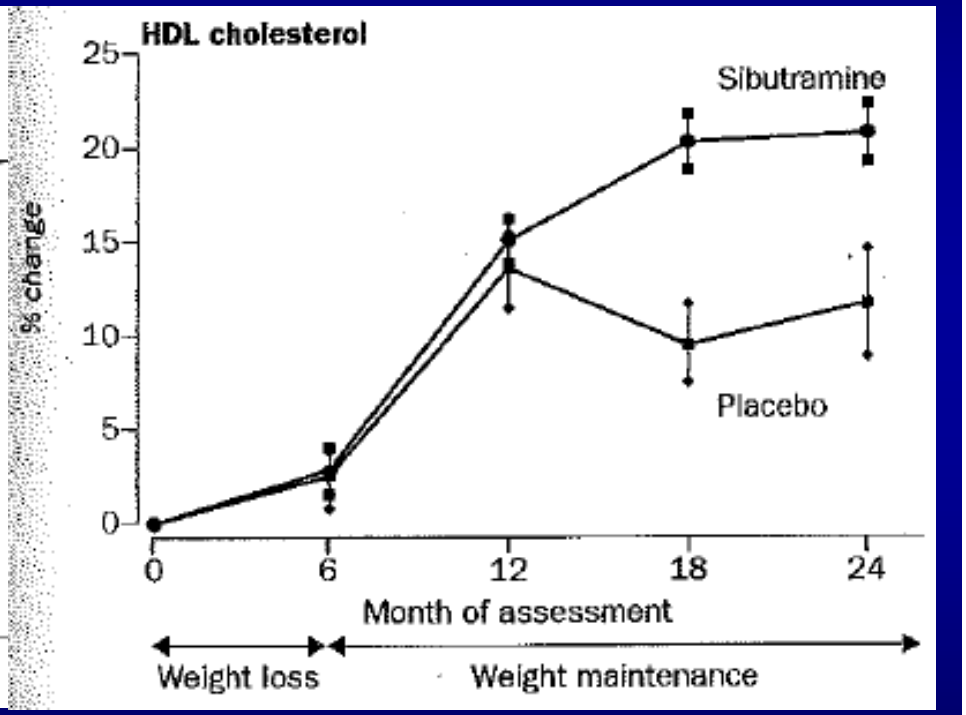



Figure 2: **Mean bodyweight changes during weight-loss and weight-maintenance phases**

Lancet 2000:356; 2119-25

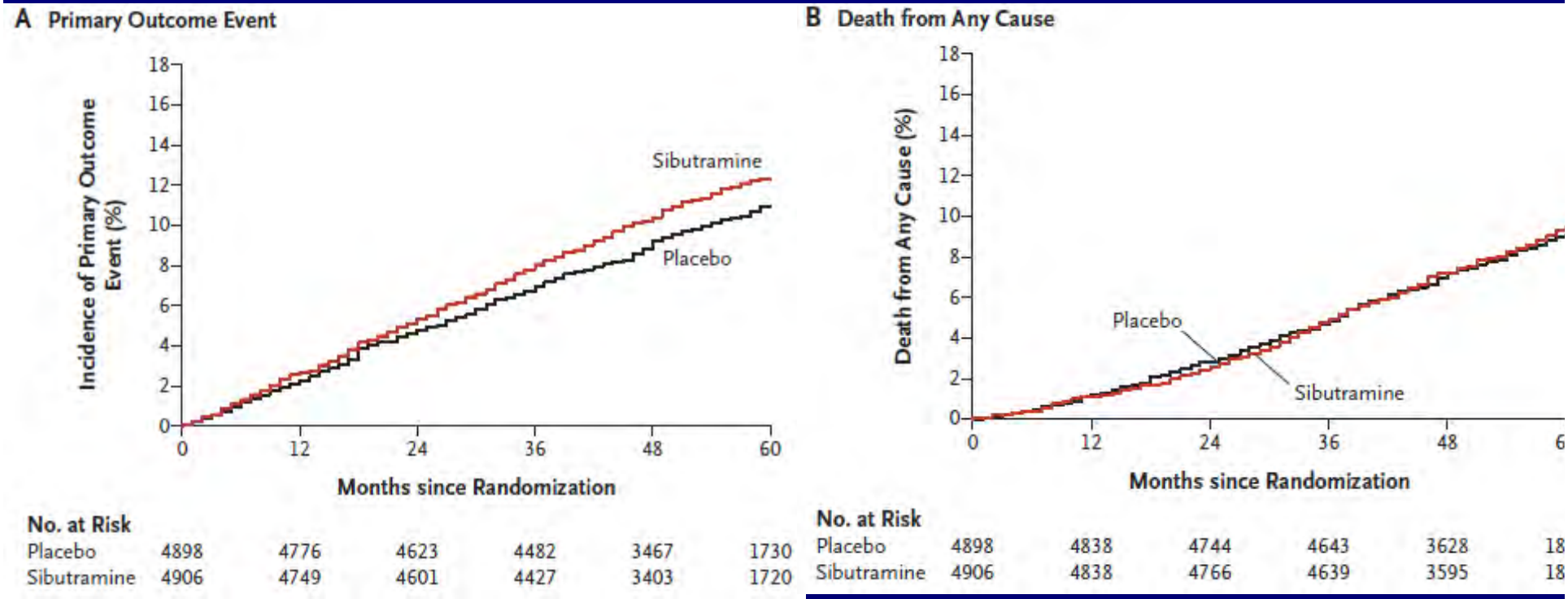
# Sibutramine: Lipids




Lancet 2000:356; 2119-25

# Sibutramine: CVD risk the SCOUT trial




N Engl J Med 2010;363:905-17.

# Sibutramine: Lessons learned?

- SCOUT trial included high risk patients that would not otherwise have been treated.
- Continued medication even if they did not lose weight
- 2012 Case/control study >6000 pts in UK and Germany showed significantly lower ASCVD risk in sibutramine users
- 2015 case/control study >23,000 pts in UK increased risk in those with CVD (DM, DM+1RF) but not in those without.

Tyczynski Drug Saf 2012. 35:629-44
Hayes Int J Obesity (2015), 1–6doi:10.1038/ijo.2015.86

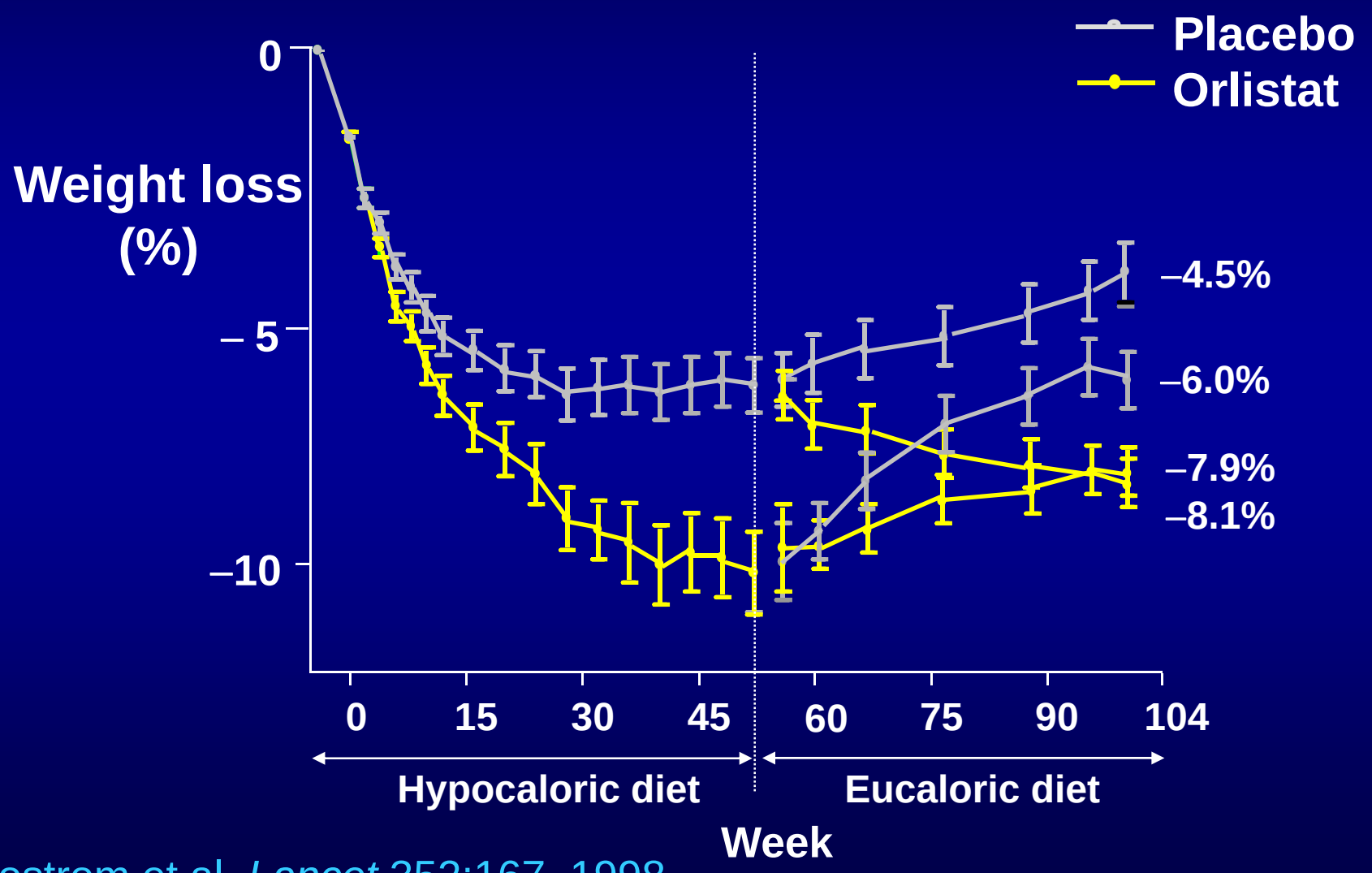
# 1º Drug Treatment of Obesity

- Current medications 5-12% wt loss
- Likely will need to use long term.
- Typically not paid for by insurance so cost is a big issue for patients.
- Issues of FDA approval, long term safety, and efficacy.
- Meds: phentermine, orlistat, phentermine/ topiramate ER, lorcasarin,

# Orlistat

- Thousands of patients studied up to 4 years of exposure.
- Approved for long term use
- 5-8% weight loss on average
- Side effects: Oily stools, diarrhea, urgency, theoretically fat soluble vitamin deficiency
- Safest weight loss medication

# Effect of Orlistat on Body Weight




Sjostrom et al. *Lancet* 352:167, 1998

# Orlistat + Fenofibrate effects on sdLDL-C

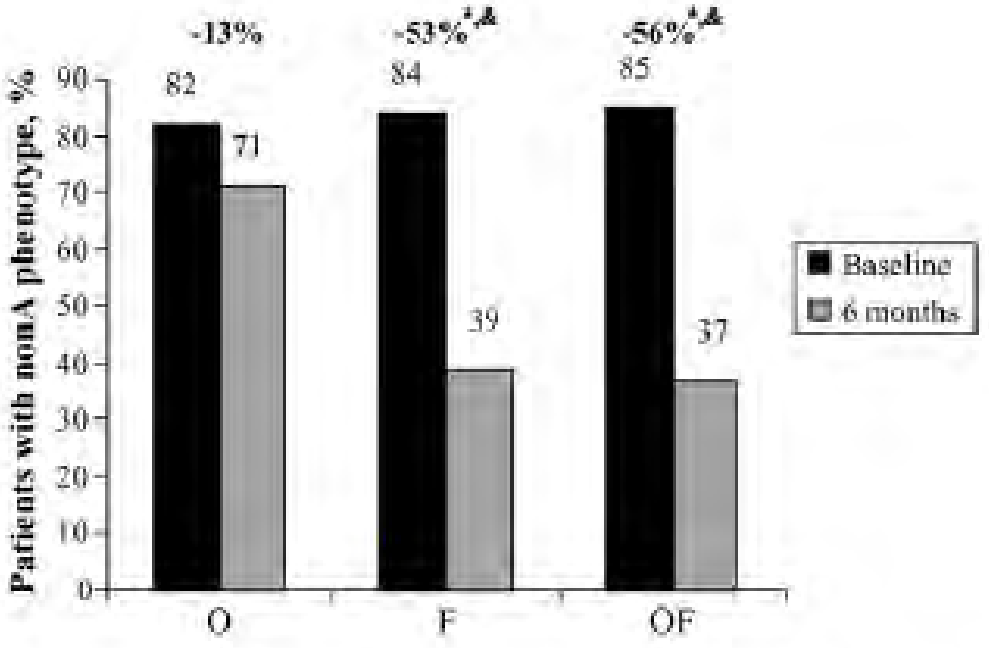



Fig. 1. Subjects with phenotype nonA at baseline and after 6 months of treatment (the six patients who did not complete the study are not included). O: orlistat; F: micronised fenofibrate; OF: orlistat + micronised fenofibrate. $^{*}p < 0.001$ vs. baseline. $^{\&}p < 0.05$ vs. O group.

Atherosclerosis 193 (2007) 428–437

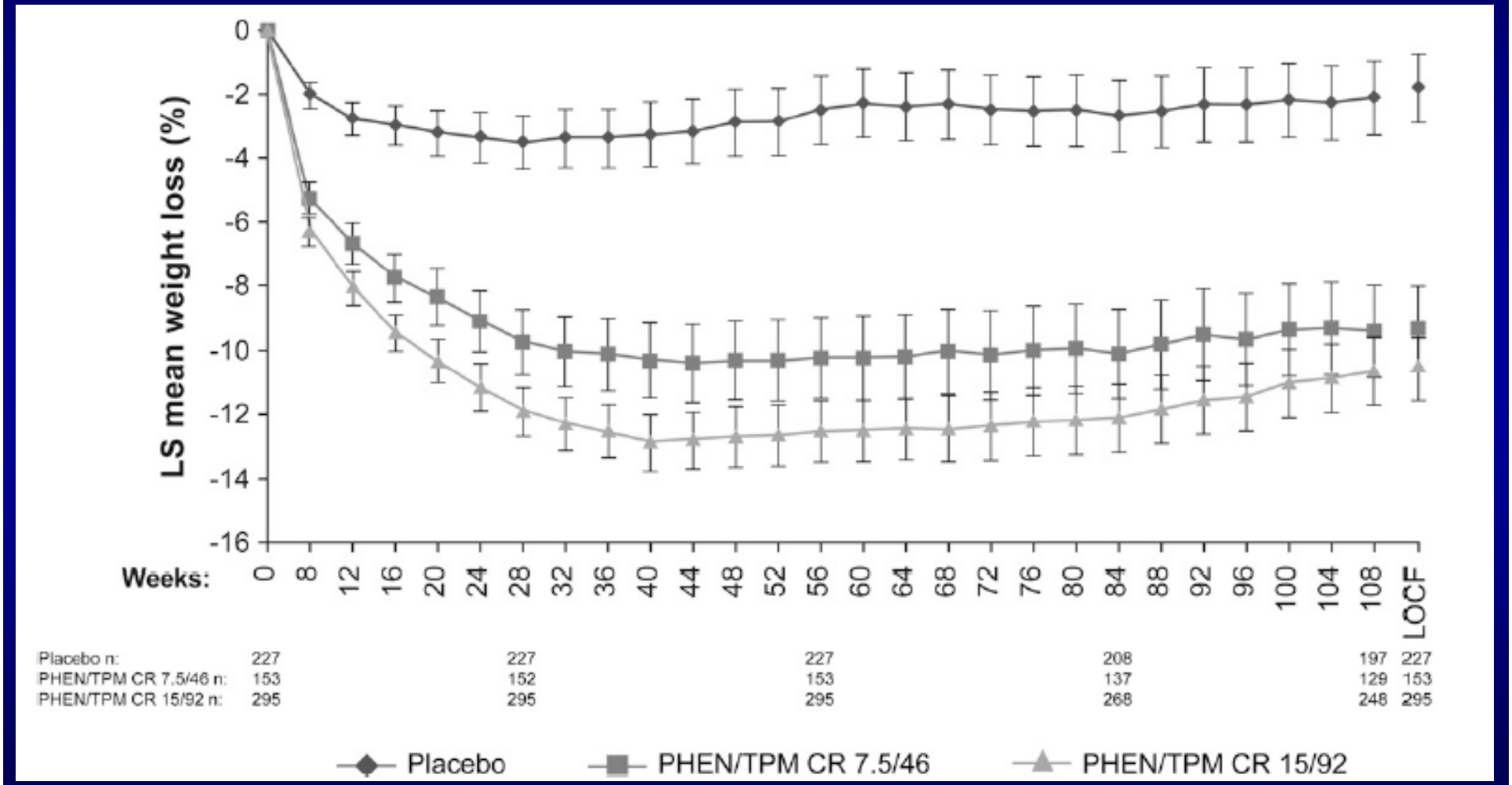
# Phentermine/Topiramate (Qsymia, Vivus)

- Combination gives greater efficacy with fewer side effects
- Doses 7.5/46 mg and 15/92 mg phentermine/topiramate
- Side effects: dry mouth, paraesthesias, insomnia, dizziness, anxiety, irritability and disturbance in attention

# Phentermine/Topiramate

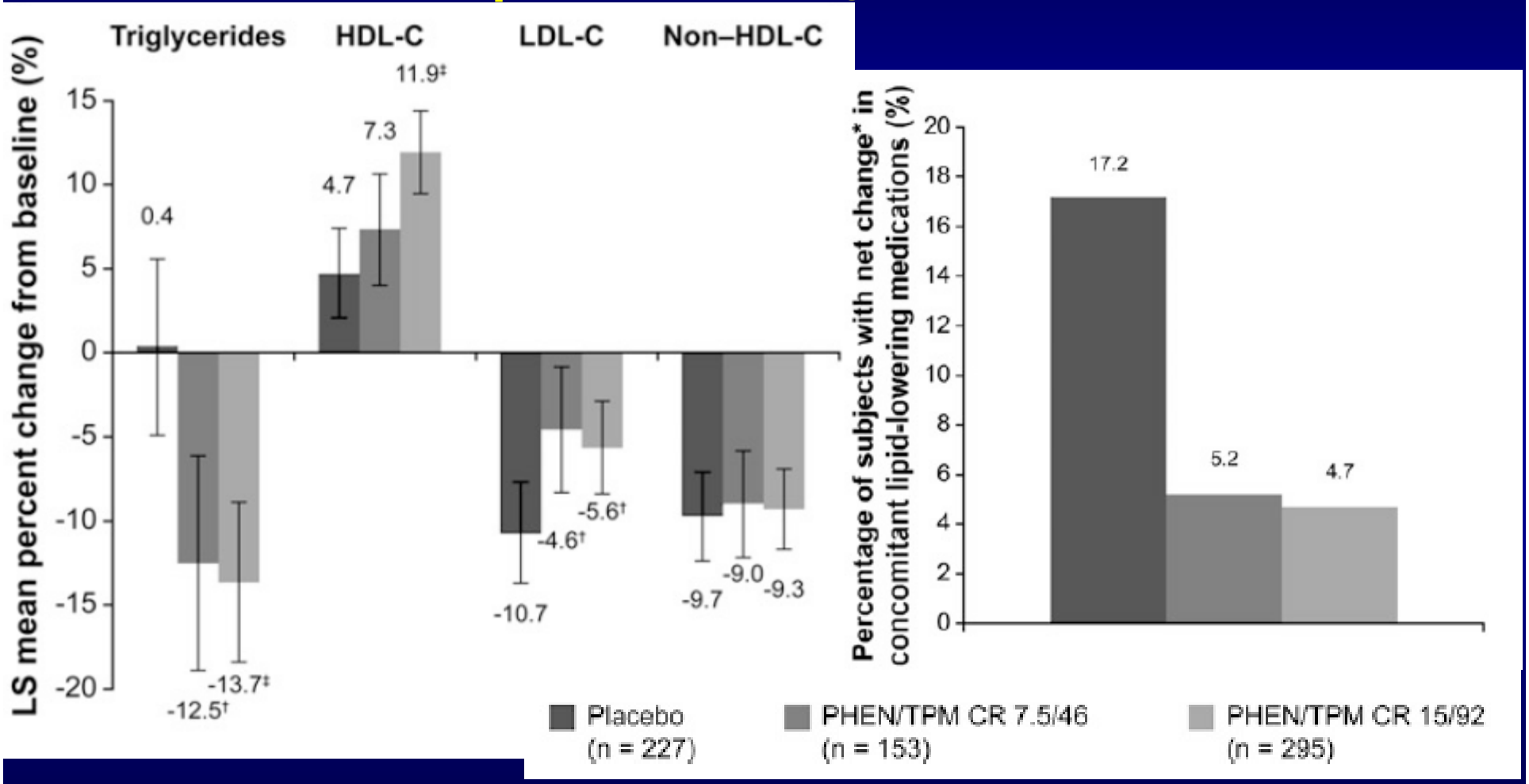
- Topiramate teratogenic risk: pregnancy test on starting and monthly while using.
- Most effective medication available 10-12% weight loss.
- Reduces blood pressure, glucose, insulin, triglycerides and raises HDL
- Unclear if physicians will prescribe off label using generic phentermine and topiramate.

# Phen/Top (Qsymia) 2 year data on Weight: SEQUEL Trial




Am J Clin Nutr 2012;95:297–308

# Phen/Top (Qsymia) 2 year data on Lipids: SEQUEL Trial




Am J Clin Nutr 2012;95:297–308

# Lorcasarin

- Serotonin 2C receptor agonist, activates POMC neurons which leads to $\alpha$–MSH activation of MC4R leading to satiety
- Dose: 10 mg twice daily
- Previous serotonin agonists fenfluramine and dexfenfluramine caused cardiac valve disease
- 2C receptor only in the brain not in heart
- Studies in 1-2,000 people for up to 2 years do not show evidence of valvulopathy with lorcasarin.

Yanovski SZ, Yanovski JA. JAMA. 2014;311:74-86

# Lorcasarin

- Weight loss: 4-6% not much better than phentermine or orlistat
- Side effects: minimal, headache, dizziness and nausea (rare priapism, monitor for depression), best side effect profile

# Lorcasarin (Belviq): Weight Effects BLOOM Study

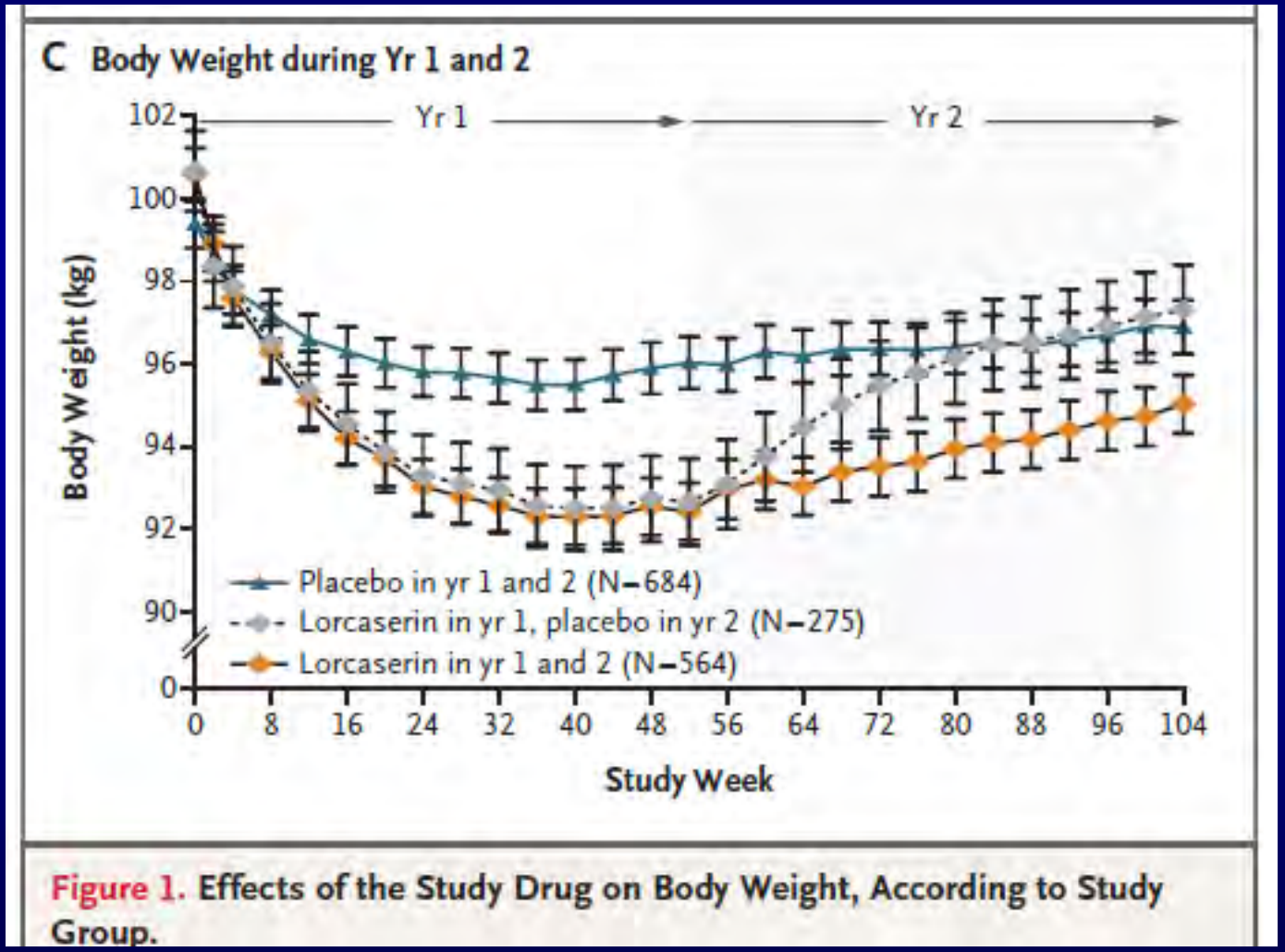



Figure 1. Effects of the Study Drug on Body Weight, According to Study Group.

N Engl J Med. 2010 Jul 15;363(3):245-56

# Lorcasarin: Lipid Effects
# BLOOM Study

**Table 2. Changes in Efficacy and Safety End Points between Baseline and 1 Year.***

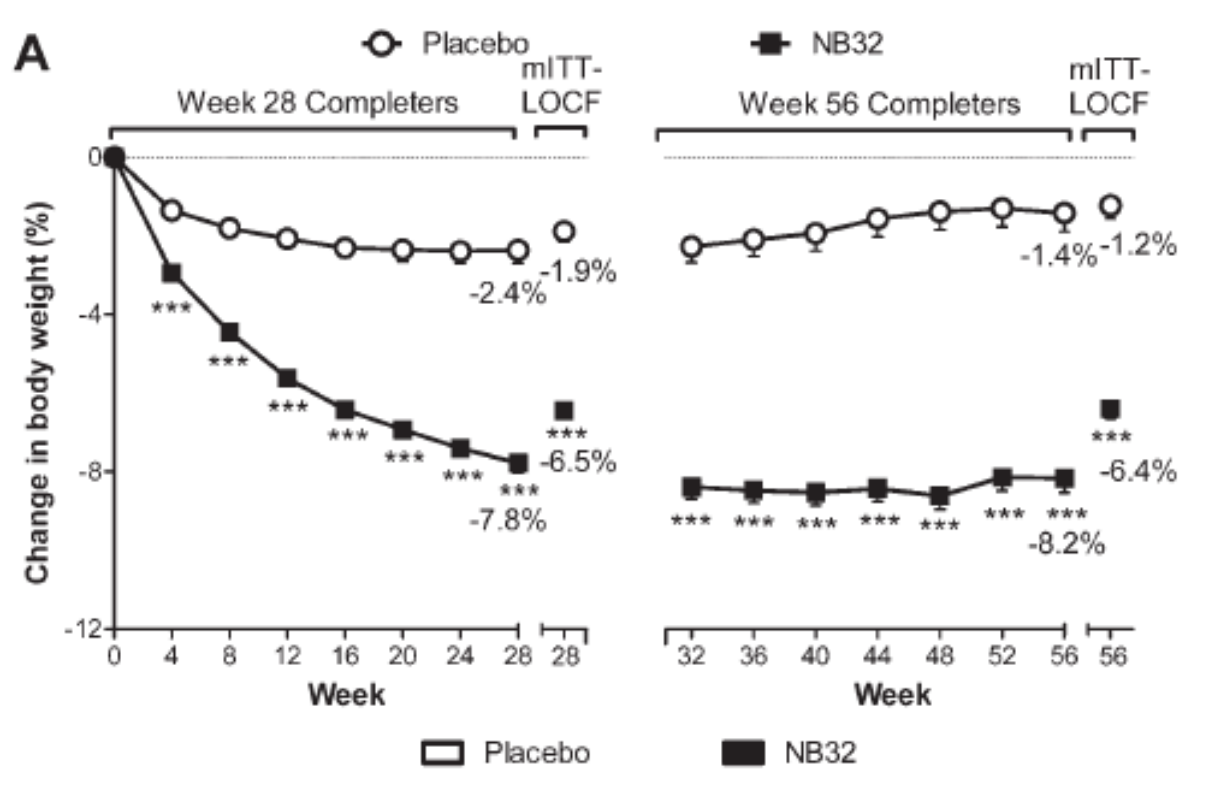
| End Point | Intention-to-Treat Analysis with LOCF Imputation | | | Repeated-Measures Analysis | | |
|---|---|---|---|---|---|---|
| | Lorcaserin (N=1538) | Placebo (N=1499) | P Value | Lorcaserin (N=1538) | Placebo (N=1499) | P Value |
| Blood pressure (mm Hg) | | | | | | |
| Systolic | −1.4±0.3 | −0.8±0.3 | 0.04 | −1.5±0.3 | −0.7±0.4 | 0.10 |
| Diastolic | −1.1±0.2 | −0.6±0.2 | 0.01 | −1.3±0.3 | −0.6±0.3 | 0.055 |
| Cholesterol (%) | | | | | | |
| Total | −0.90±0.33 | 0.57±0.34 | 0.001 | −1.37±0.39 | 0.57±0.43 | 0.001 |
| LDL | 2.87±0.56 | 4.03±0.58 | 0.049 | 4.10±0.64 | 5.90±0.70 | 0.04 |
| HDL | 0.05±0.33 | −0.21±0.34 | 0.72 | −0.93±0.40 | −1.90±0.43 | 0.08 |
| Triglycerides (%) | −6.15±1.03 | −0.14±0.99 | <0.001 | −9.58±1.15 | −1.82±1.26 | <0.001 |

N Engl J Med. 2010 Jul 15;363(3):245-56

# Naltrexone SR/Bupropion SR

- Concerning side effects: increased blood pressure and pulse, seizures, suicidal ideation.
- Common side effects: nausea, constipation, diarrhea, headache, dry mouth
- Stop if clinically significant increase in BP or P
- Weight loss 5-8% on average
- Intermediate effectiveness and side effects

# Naltrexone SR/Bupropion SR: COR II Trial




TG decreased 9.8%
HDL increased 3.6%
LDL decreased 6.2%

1,496 subjects, 54% follow up at 1 year

Obesity (2013) 21, 935-943.

# Liraglutide 3mg

- GLP-1 agonist already used for glucose lowering in diabetes
- 3 mg dose approved for weight loss by FDA on 12/23/2014
- 6-8% weight loss
- Side effects: nausea, diarrhea, vomiting, pancreatitis, questions about medullary thyroid carcinoma risk
- Intermediate effectiveness, clinicians used to prescribing for diabetes

# Liraglutide: Effects on Weight

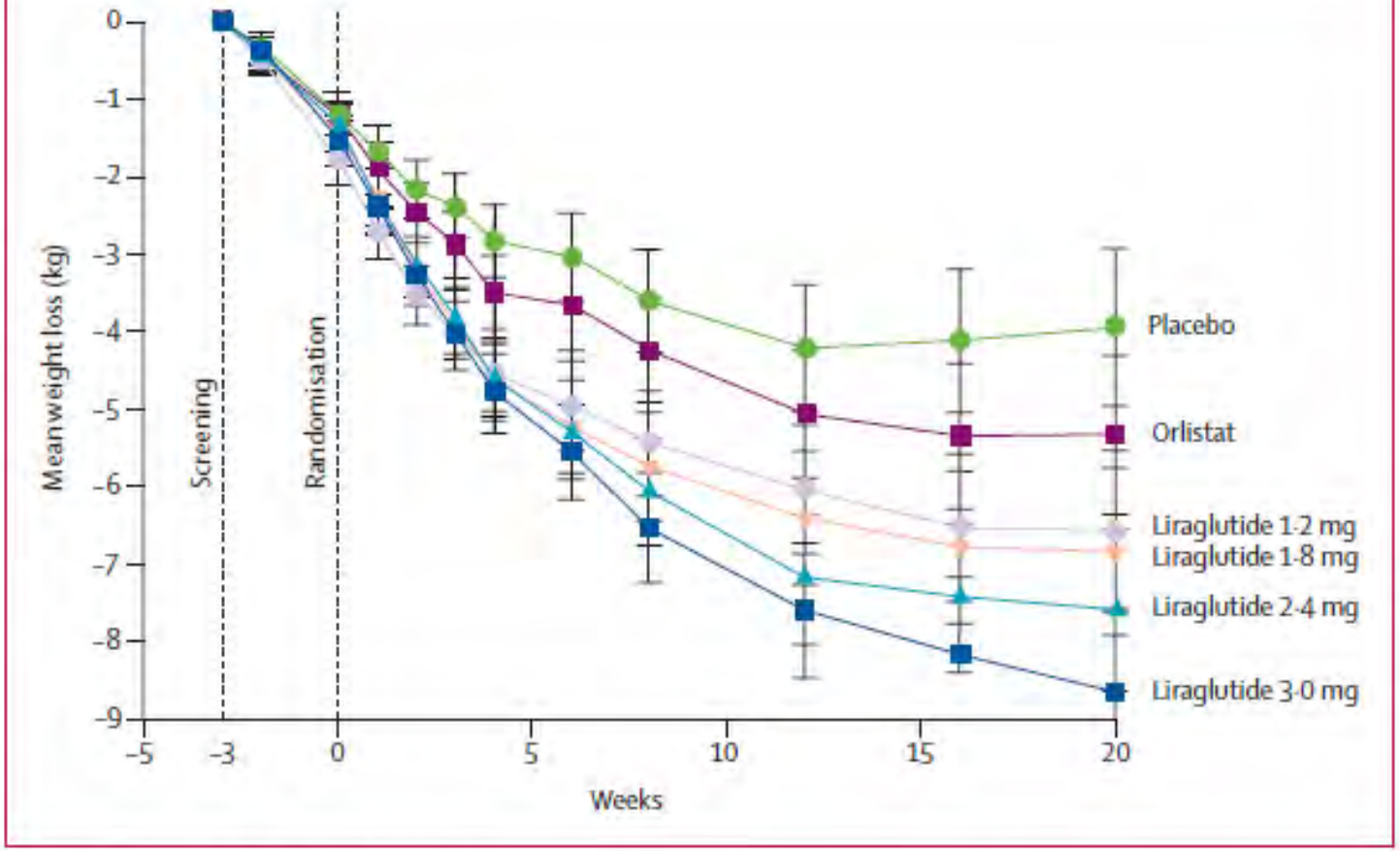
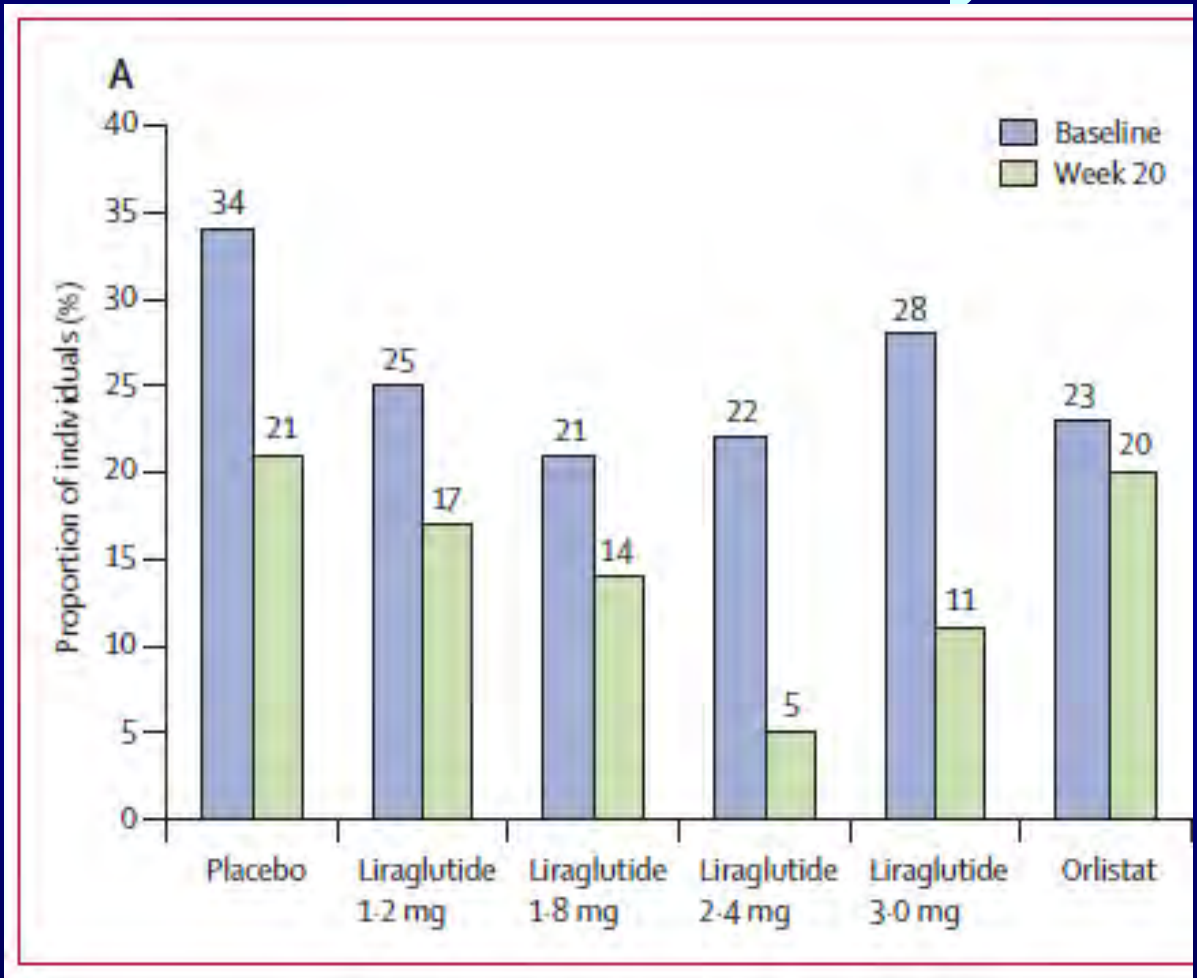



***Figure 2:*** **Change in bodyweight**
Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward.

Lancet 2009; 374: 1606–16

# Liraglutide: Effects on "Metabolic Syndrome"

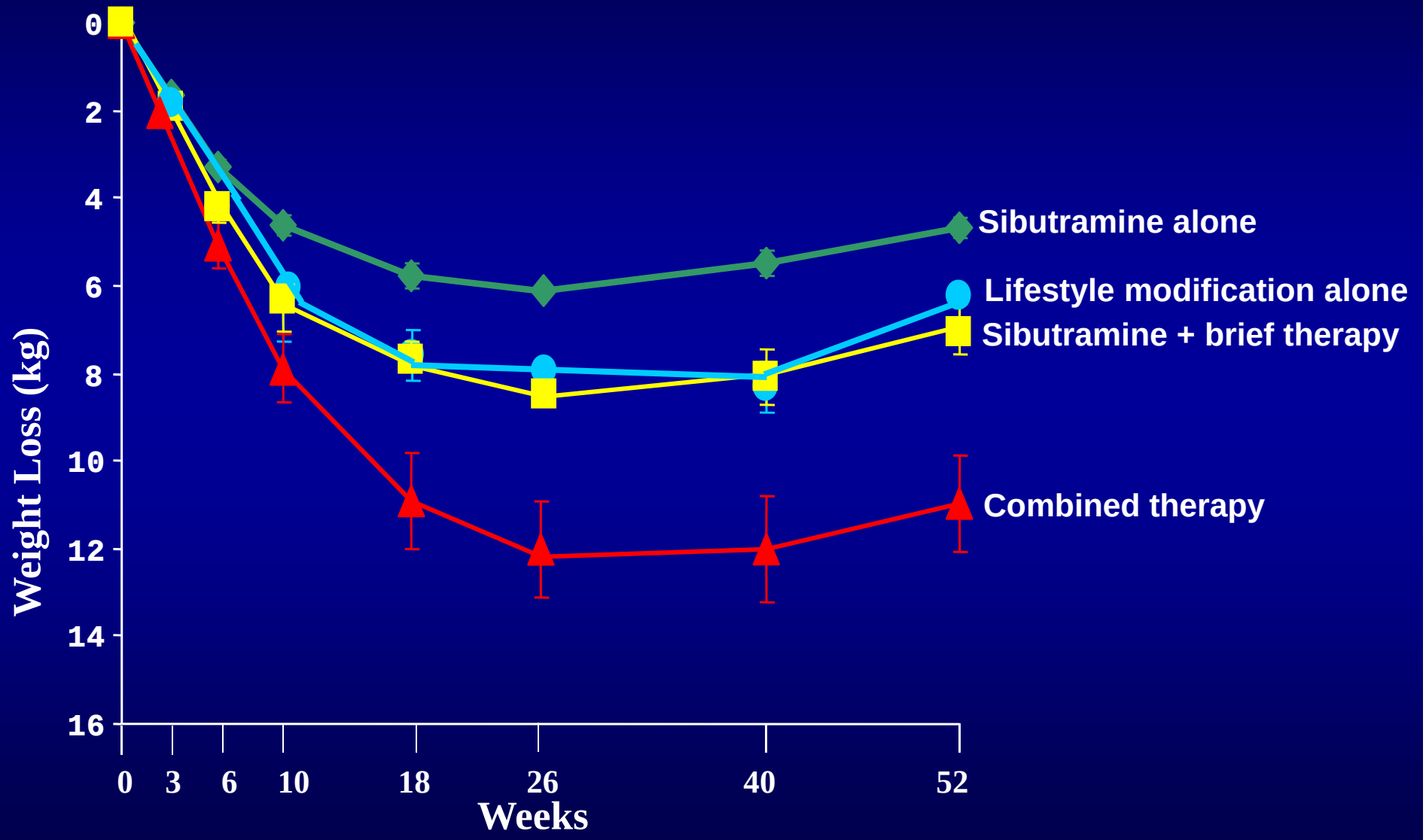



"no significant effect on lipids"

14 week study
Tg decreased 19%
LDL decreased 9.6%
HDL decreased 3%

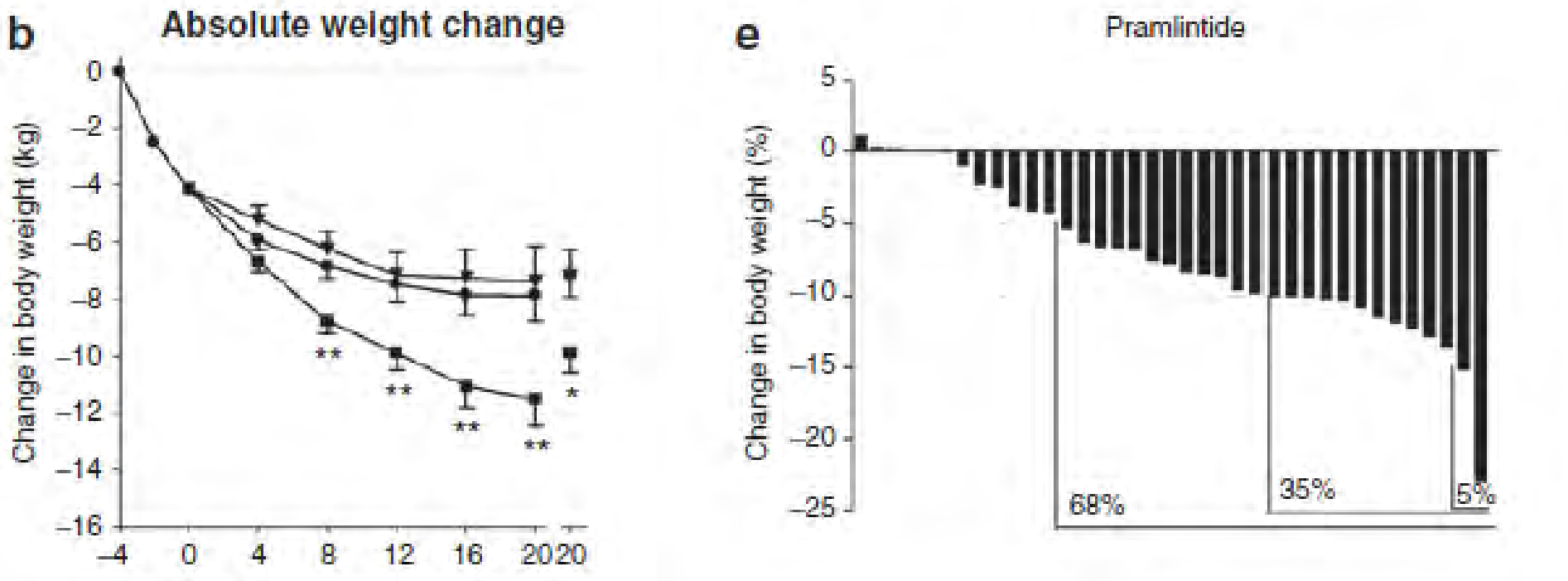
Lancet 2009; 374: 1606–16 Nutr Metab Cadio Dis 2014 24: 1317

# Behavior+Medication better than either alone




Wadden, et al. *N Engl J Med*. 2005;35:2111-20.

# Variability in Response to a Weight Loss Intervention




Ravussin E; Obesity (Silver Spring). 2009 Sep;17(9):1736-43

# How to Think about Weight loss Then?

- Obesity might be thought of as one of several cardiovascular risk factors that you could choose to treat.
- Obesity is likely important early in the course of the development of CVD and may become less important later
- There is tremendous variability in the response to treatments and so individualizing is important
- Patients may value weight loss more than the treatment of other CVD risk factors.

# Summary of data

**Table 2. Summary of percent changes in cardiovascular and metabolic risk factors***

| Drug | Reference | SBP (mm Hg) | DBP (mm Hg) | FG (mg/dL) | HbA1c (%) | LDL (%) | TGL (%) |
|---|---|---|---|---|---|---|---|
| Phentermine | Randomized controlled trials: no 1-year data, none since 1980s | | | | | | |
| Orlistat | XENDOS[49] | 7.3† (5.2) | −3.6† (−2.6) | 1.8† (3.6) | NA | −11.4† (−1.6) | −6.2 (−6.3) |
| Lorcaserin (10 mg BID) | BLOOM[46] | 1.4† (0.8) | −1.1† (−0.6) | −0.8† (1.1) | −0.04† (0.03) | 2.87† (4.03) | −6.15† (−0.14) |
| Lorcaserin (10 mg BID) | BLOSSOM[48] | 1.9 (1.2) | −1.9 (−1.4) | NA | 0.19 (-0.14) | 0.3 (1.7) | −4.3 (−0.9) |
| Lorcaserin (10 mg BID) | BLOOM-DM[47] | 0.8 (0.9) | −1.1 (−0.7) | −27.4† (−11.9) | −0.9† (−0.4) | 4.2 (5.0) | −10.7 (−4.8) |
| Phentermine/Topiramate (15/92 mg) | EQUIP[50] | 2.9† (0.9) | −1.5† (0.4) | −0.6† (1.9) | NA | −8.4† (−5.5) | −5.2† (9.1) |
| Phentermine/Topiramate (15/92 mg) | CONQUER[51] | 5.6† (2.4) | −3.8† (−2.7) | −1.26† (0.54) | −0.1† (0.1) | −6.9† (−4.1) | −10.6† (4.7) |
| Bupropion/naltrexone (32/360 mg) | COR-I[52] | 0.1† (1.9) | 0.0 (−0.9) | −3.24† (−1.26) | NA | −2.0 (−0.5) | −12.7† (−3.1) |
| Bupropion/naltrexone (32/360 mg) | [77] COR-II[53] | 0.6† (0.5) | 0.4 (0.3) | −2.8 (−1.3) | NA | −6.2† (−2.1) | −9.8† (−0.5) |
| Bupropion/naltrexone (32/360 mg) | COR-BMOD[54] | 1.3† (3.9) | −1.4† (−2.8) | −2.4 (−1.1) | NA | 7.1 (10.0) | −16.6† (−8.5) |
| Bupropion/naltrexone (32/360 mg) | COR-D[55] | 0.0 (1.1) | −1.1 (−1.5) | −11.9 (−4.0) | −0.6† (−0.1) | −1.4 (0.0) | −11.2† (−0.8) |
| Liraglutide (3 mg) | Phase II[56] | 4.9 (1.6) | −2.8 (−0.2) | −5.77† (1.44) | −0.26† (0.01) | −0.43§† (−0.28) mmol/L | −0.14†,‡ (0.01) mmol/L |
| Liraglutide (3 mg) | SCALE Maintain[57] | 0.2† (2.8) | 1.4 (1.2) | −9.0† (−3.6) | −0.1† (0.1) | 0.2† (0.3) | 0.0‡ (0.1) |
| | | −2.7 | −0.3 | −7.2 | −0.3 | −0.09 mmol/L | −0.11 mmol/L |
| Liraglutide | SCALE Obesity[60] | Estimated treatment differences: SBP, −2.8, DBP, −0.9 mm Hg† Low-density lipoprotein cholesterol −2%,† high -density lipoprotein cholesterol 2%,† triglyceride levels, 9%† Progression to prediabetes: liraglutide 3 mg, 6.9%; placebo,19.9%† | | | | | |

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# Long term phentermine prescribing

- If patient has no evidence of serious cardiovascular disease
- No serious psychiatric disease
- Has been told of the other FDA approved weight loss medications and has been told that phentermine does not have long term safety or efficacy data and that prescribing is ‘off label’
- No clinically significant increase in pulse of BP
- Pt loses at least 5% of baseline weight

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# Bariatric Surgery and Lipids

**Lipids and Bariatric Procedures Part 1 of 2: Scientific Statement from the National Lipid Association (NLA), American Society for Metabolic and Bariatric Surgery (ASMBS)**

**Lipids and Bariatric Procedures Part 2 of 2: Scientific Statement from the American Society for Metabolic and Bariatric Surgery (ASMBS) and the National Lipid Association (NLA)**

# Learning Objectives:

- Explain how adipose tissue is an active endocrine and immune organ
- Discuss how an increase in body fat causes fat dysfunction (adiposopathy) which contributes to metabolic disease
- Provide overview of the ASMBS and NLA Scientific Statement regarding the effects of bariatric surgery on lipid blood levels

Table 1. Outline of adiposopathic anatomic, functional, histological, endocrine, and immune changes that may contribute to metabolic diseases such as dyslipidemia among patients with obesity. 23

**Anatomic changes:**

- Adipocyte hypertrophy with variable increases in adipocyte number, as regulated by intracellular proteins:
  - Sterol regulatory element binding protein 1 (SREBP1), which is the human analogue to adipocyte determination and differentiation-dependent factor 1 (ADD1)
  - Peroxisome proliferator activated receptor (PPAR) gamma
  - CCAAT-enhancer-binding proteins (C/EBPs)

- When adipogenesis (proliferation and differentiation) in peripheral subcutaneous adipose tissue (SAT) is inadequate to store excess energy, this may:
  - Further worsen adipocyte hypertrophy of existing adipocytes
  - Contribute to energy overflow with increased circulating free fatty acid blood levels, increasing size of other adipose tissue depots, including:
    - Visceral adipose tissue (VAT) accumulation
    - Subcutaneous abdominal adipose tissue accumulation
    - Pericardiac adipose tissue accumulation
    - Perivascular adipose tissue accumulation
  - Contribute to energy overflow with increased circulating free fatty acid blood levels, increasing fatty infiltration and lipotoxicity to:
    - Liver, resulting in nonalcoholic fatty liver disease (NAFLD), with subsets including hepatic steatosis, which may contribute in insulin resistance, and nonalcoholic steatohepatitis (NASH), an inflammatory state that may lead to insulin resistance, fibrosis, and cirrhosis
    - Muscle, resulting in intramyocellular triglycerides and insulin resistance
    - Pancreas, resulting in beta cell dysfunction, macrophage infiltration, and β-cell failure
    - Heart, resulting in fat accumulation within cardiomyocytes, mitochondrial dysfunction, inflammation, and cardiac dysfunction
    - Kidney, resulting in renal fat accumulation, immune cell infiltration, increased glomerular capillary wall tension, podocyte dysfunction, focal and segmental glomerulosclerosis, proteinuria, and progressive renal dysfunction

Table 1. Outline of adiposopathic anatomic, functional, histological, endocrine, and immune changes that may contribute to metabolic diseases such as dyslipidemia among patients with obesity. 23

| **Histological and functional changes:** |
|---|
| • Adipocyte and adipose tissue hypoxia because of:<br>  o Growth of adipose tissue beyond vascular supply<br>  o Inadequate angiogenesis<br>  o Impaired blood flow<br>• Increased adipocyte apoptosis<br>• Increased reactive oxygen species and oxidative stress<br>• Extracellular matrix abnormalities<br>• Intraorganelle dysfunction<br>  o Mitochondrial stress*<br>  o Endoplasmic reticulum stress*<br>• Changes in adipose tissue neural network and innervations |

Table 1. Outline of adiposopathic anatomic, functional, histological, endocrine, and immune changes that may contribute to metabolic diseases such as dyslipidemia among patients with obesity. 23

| **Adiposopathic endocrinopathies resulting from dysfunctional adipocyte and adipose tissue processes involving:** |
|---|
| • Angiogenesis |
| • Adipogenesis |
| • Extracellular matrix dissolution and reformation |
| • Lipogenesis |
| • Growth factor production |
| • Glucose metabolism |
| • Production of factors associated with the renin-angiotensin system |
| • Lipid metabolism |
| • Enzyme production |
| • Hormone production |
| • Steroid metabolism |
| • Immune response |
| • Hemostasis |
| • Element binding (e.g., sterol regulatory element binding proteins, calcium, etc.) |
| • Adipose tissue has multiple receptors, such as receptors for traditional peptides and glycoprotein hormones, receptors for nuclear hormones, other nuclear receptors, receptors for cytokines or adipokines with cytokine-like activity, receptors for growth factors, and catecholamine receptors |

Table 1. Outline of adiposopathic anatomic, functional, histological, endocrine, and immune changes that may contribute to metabolic diseases such as dyslipidemia among patients with obesity. 23

| **Adiposopathic immunopathies resulting from dysfunctional adipocyte and adipose tissue processes involving:** |
| --- |
| • Proinflammatory adipose tissue factors<br>  o Factors with cytokine activity<br>  o Acute-phase response proteins<br>  o Proteins of the alternative complement system<br>  o Chemotactic or chemoattractants for immune cells<br>  o Eicosanoids and prostaglandins<br>• Anti-inflammatory adipose tissue factors |

# Adipose Tissue Anatomy

| | | |
|---|---|---|
| **Adipocyte number** | **Limitations in adipogenesis (fat cell proliferation and differentiation) in peripheral subcutaneous adipose tissue may contribute to adipocyte hypertrophy of existing fat cells, adipose tissue dysfunction, and metabolic disease. Conversely, an increase in subcutaneous adipocyte number correlates to decreased TG levels, increased HDL cholesterol levels, increased insulin sensitivity, and decreased insulin levels.** | **While bariatric surgery clearly reduces fat cell volume, it is unclear that bariatric surgery (or other methods of weight loss) reduces adipocyte number.** |
| **Adipocyte size** | If during positive caloric balance, adipogenesis is impaired, then existing fat cells may undergo hypertrophy, which is an anatomic finding of adiposopathy. Adipocyte dysfunction, contributes to metabolic diseases such as dyslipidemia and fatty liver (with or without elevated liver transaminases). | Bariatric surgery may reduce adipocyte size, which may improve adipocyte function and metabolic diseases such as dyslipidemia, high glucose levels, and fatty liver, (at least partially due to improved insulin sensitivity), possibly involving an adipocyte volume threshold. |

| | | |
|---|---|---|
| **Subcutaneous adipose tissue** | Positive caloric balance increases fat deposition in multiple fat depots, with adipose tissue dysfunction promoting metabolic diseases such as dyslipidemia. | Bariatric surgery reduces subcutaneous fat cell volume. Compared to a reduction in total fat mass, a reduction in subcutaneous adipocyte size more strongly associates with improved insulin sensitivity, which is a mechanism that helps explain how bariatric surgery improves dyslipidemia and non-alcoholic fatty liver disease. |
| **Visceral adipose tissue** | Positive caloric balance increases fat deposition in multiple fat depots, which may promote metabolic diseases such as dyslipidemia. An increase in visceral adipose tissue may be a marker for global fat dysfunction, and is often clinically assessed by measuring waist circumference. | Bariatric surgery reduces visceral adiposity and generally improves the components of the metabolic syndrome, which in addition to increased waist circumference, includes elevated TG levels, reduced HDL cholesterol levels, as well as high glucose levels and high blood pressure. |
| **Pericardiac and perivascular adipose tissue *** | Positive caloric balance increases fat deposition in multiple fat depots, including pericardiac and perivascular adipose tissue, which may directly contribute to atherosclerosis. | Bariatric surgery may reduce paracardial and epicardial fat, with limited effects upon myocardial triglycerides. The reduction in epicardial fat volume loss may be more limited in patients with sleep apnea** |

# Adipose Tissue Dysfunction

| | | |
|---|---|---|
| Oxidative stress | Adipocyte hypertrophy can produce mitochondrial and endoplasmic reticulum dysfunction, which in turn promotes oxidative stress.*** Increased oxidative stress may cause adipocyte dysfunction leading to dyslipidemia. | Bariatric surgery may reduce adiposopathic markers of oxidative stress, which may improve metabolic diseases such as dyslipidemia. |

# Endocrine Factors

# Receptors

# Lipid parameters

# Transfer & transport proteins

# Inflammatory factors

# Bile acid metabolism

# Microbiota and microbiome

# Hormones affecting nutrient metabolism and lipid blood levels

**Adverse cardiovascular health consequences of adiposopathy, which may be improved with weight loss, such as through bariatric procedures**

# Potential effects of bariatric procedures on illustrative non-lipid atherosclerotic cardiovascular disease (ASCVD) risk factors and adiposopathic markers which may contribute to metabolic disease

| Lipid parameters | Effect of bariatric procedure |
|---|---|
| | |
| **Adjustable Gastric Banding** | |
| | |
| Low density lipoprotein cholesterol | ↓ |
| Non-high density lipoprotein-cholesterol | - |
| Apolipoprotein B | - |
| Lipoprotein particle number | ↓ - |
| Total cholesterol | ↓ |
| Triglycerides | ↓ |
| High density lipoprotein cholesterol | ↑ |
| Lipoprotein remnants | Not reported |
| Lipoprotein (a) | - |
| LDL particle size | - |

| **Gastric Sleeve** | |
|---|---|
| | |
| Low density lipoprotein cholesterol | ↓ |
| Non-high density lipoprotein-cholesterol | ↓ |
| Apolipoprotein B | ↓ |
| Lipoprotein particle number | ↓ |
| Total cholesterol | ↓ |
| Triglycerides | ↓ |
| High density lipoprotein cholesterol | ↑ |
| Lipoprotein remnants | ↓ |
| Lipoprotein (a) | ??? |
| LDL particle size | - |

| **Gastric Bypass** | |
|---|---|
| | |
| Low density lipoprotein cholesterol | ↓ |
| Non-high density lipoprotein-cholesterol | ↓ |
| Apolipoprotein B | ↓ |
| Lipoprotein particle number | ↓ |
| Total cholesterol | ↓ |
| Triglycerides | ↓ |
| High density lipoprotein cholesterol | ↑ |
| Lipoprotein remnants | ↓ |
| Lipoprotein (a) | - |
| LDL particle size | ↑ |

| **Biliopancreatic diversion/duodenal switch** | |
|---|---|
| | |
| Low density lipoprotein cholesterol | ↓ |
| Non-high density lipoprotein-cholesterol | ↓ |
| Apolipoprotein B | ↓ |
| Lipoprotein particle number | Not reported |
| Total cholesterol | ↓ |
| Triglycerides | ↓ |
| High density lipoprotein cholesterol | ↑ |
| Lipoprotein remnants | Not reported |
| Lipoprotein (a) | Not reported |
| LDL particle size | Not reported |

Potential lipid effects of selected vitamins deficiencies that sometime occur with bariatric procedures

Potential lipid effects of selected minerals and trace element deficiencies that sometime occur with bariatric procedures

Replacement of select post-operative vitamin and mineral deficiency

## General Observations

(1) The greater the fat mass loss, the greater the improvement in dyslipidemia.

(2) Data regarding the lipid effects of biliopancreatic diversion/duodenal switch is less reported than with laparoscopic gastric banding, roux-en-y gastric bypass, and sleeve gastrectomy, probably because it is a less common bariatric procedure.

(3) Bariatric procedures allow for a decrease in the use of drugs for treatment of dyslipidemia, 131 132 as well as decreased in drugs used for treatment of diabetes mellitus and blood pressure, compared to medical therapy. 133 134

(4) High density lipoprotein cholesterol may decrease during active weight loss (particularly the first six months after bariatric surgery), and then may ultimately increase above baseline.

(5) Data on bariatric procedures is scarce on some of the lipid parameters of most interest to lipidologists.

- Non-high density lipoprotein cholesterol
- Apolipoprotein B
- Lipoprotein particle number
- Remnant lipoproteins
- Lipoprotein (a) & lipoprotein particle size


# Bariatric Surgery and Lipids