

# Hyperlipidemia

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**HARVARD**  
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Postgraduate  
Medical Education

# Disclosures

- **Research Grants:**
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- **Advisory Committees:**
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# Learning Objectives

- **Review effects of diet on lipids and cardiovascular risk**
- **Review value and limitations of statin therapy**
- **Review new 2018 lipid guidelines to reduce cardiovascular risk**
- **Review the new evidence on PCSK9 agents**

# Decreasing Cardiovascular Risk



## Healthy Lifestyles

- Some lipid effects
- Non-lipid effects
  - Vascular compliance
  - Cardiac mechanics
  - Muscle metabolism

# Fats and Coronary Artery Disease

- **1960-1980 Coronary Epidemic**
- **Response focused on fat as a the causal “nutrient”**
- **Recommended dietary allowances for saturated fat and dietary cholesterol**
- **The food industry response was predictable...**



# Low Fat Processed Foods

**An Explosion of Processed  
Foods with Refined Sugar  
Instead of Fat**



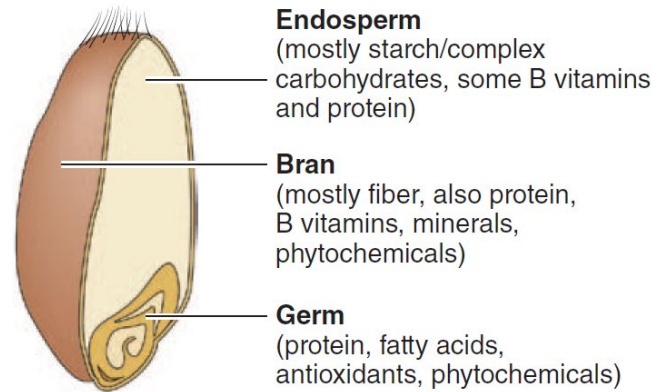
# Fat versus Sugar?

- Fat is a lubricant and more satiating
- Sugar is less satiating so the tendency is to eat more → more calories → obesity



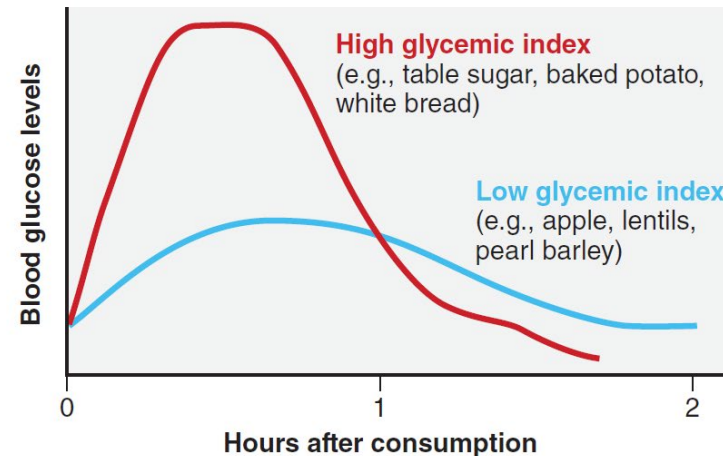
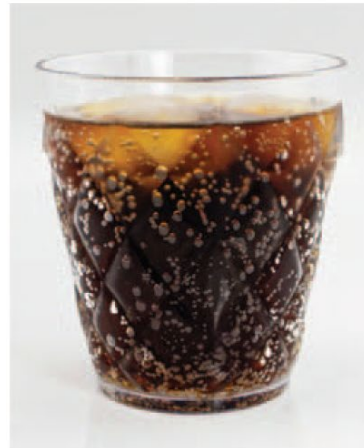
# Modulators of High COH Diet Effects

**Whole Grain  
Content**



**Fiber  
Content**

**Liquid versus  
Solid COH**



**Glycemic  
Index  
Accessibility  
of Starch  
and Sugars**

## Low COH $\approx$ “Ketogenic Diets”

- **Atkins – 4 Phase Diet**

- Very low COH, unlimited protein/fat

- **Paleo Diet**

- Low COH and low or no dairy, grains, sugars, legumes

- High protein, fruits, nuts, vegetables, organ meats, lard



## Other Weight Loss Diets

**Modest Effect on LDL  
Effect on CV Risk ??**

### Zone Diet and South Beach (3 Phase) Diets

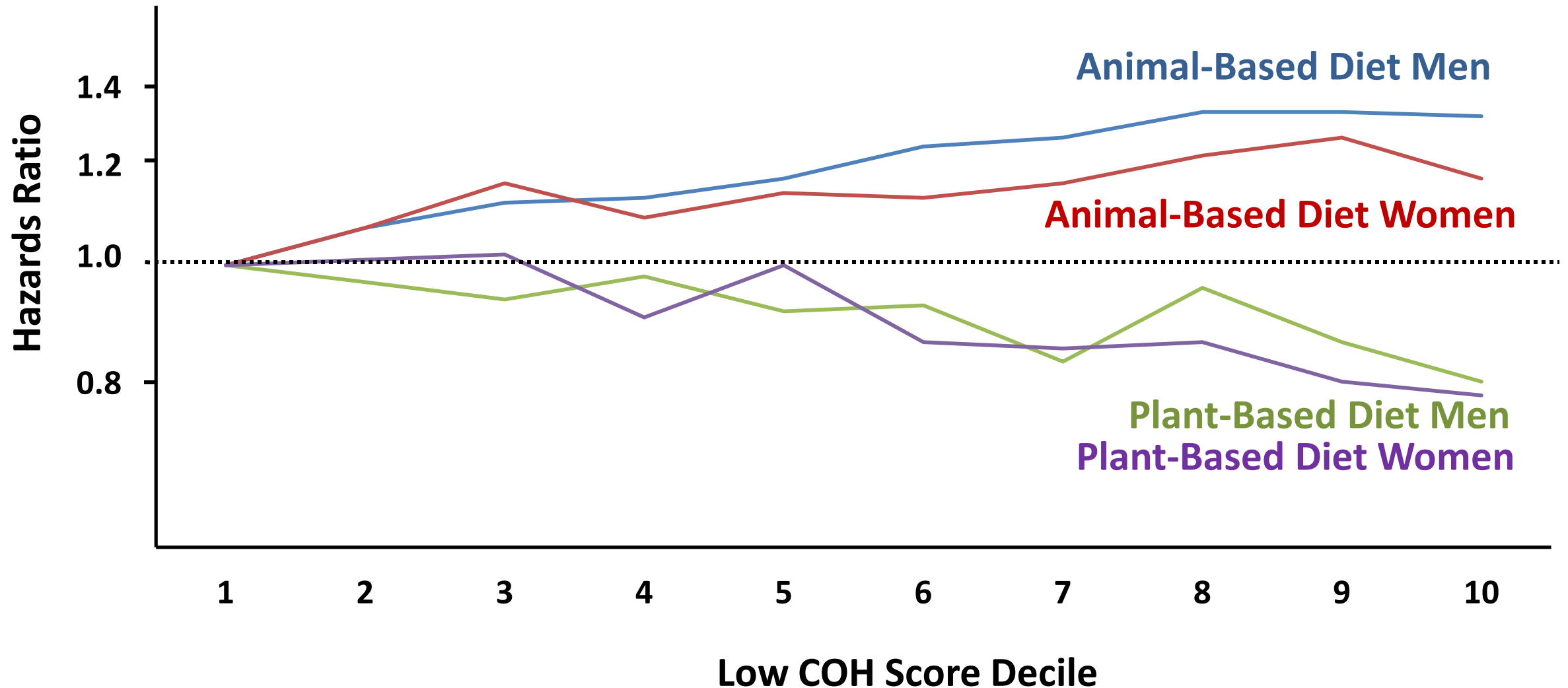
Low glycemic COH, Low-fat proteins, some monounsaturated FA

### Weight Watchers

Calorie restriction by Physical Activity/Behav Modification,

# Risk of All Cause Mortality with Low COH Diet

Women's Health Study and Physician Health Study



# Getting Enough Protein Without Much Meat?



**Spinach**  
49% protein



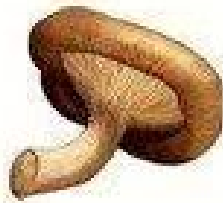
**Kale**  
45% protein



**Broccoli**  
45% protein



**Cauliflower**  
40% protein



**Mushrooms**  
38% protein



**Parsley**  
34% protein



**Cucumbers**  
24% protein



**Green Pepper**  
22% protein

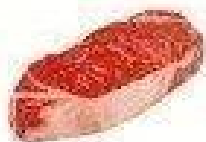


**Cabbage**  
22% protein



**Tomatoes**  
18% protein

## Protein in Meat:



**Beef**  
25.8% protein



**Chicken**  
23% protein



**Eggs**  
12% protein

# Eggs

- Dietary cholesterol: 40% from meat, 25% from eggs
- Adjusting for dietary fat, no relationship to serum LDL or to CV Risk



- Healthy individuals: “No harm in eating up to 1 egg/ day...  
..incorporated in a heart-healthy dietary pattern”

# More Diets

- **Gluten-free diets**
  - For celiac disease
  - Gluten insensitivity – is it a real thing?
- **DASH Diet**
  - Designed to lower BP, but also lowers CVD
- **Vegetarian diet**
  - Associated with low CVD if low in saturated fats
- **Mediterranean diet...**



# “Mediterranean Diet”

- Food-based not nutrient-based diet
- High intake: fruits, nuts, non-starchy vegetables, legumes, monounsaturated fats (olive/canola)
- Modest intake: whole grains, fish, chicken,
- Low intake: red meat, refined grains, starches, sugars



Life Magazine  
Greece January 1948.  
“Lunch! bread, one onion,  
and olives”

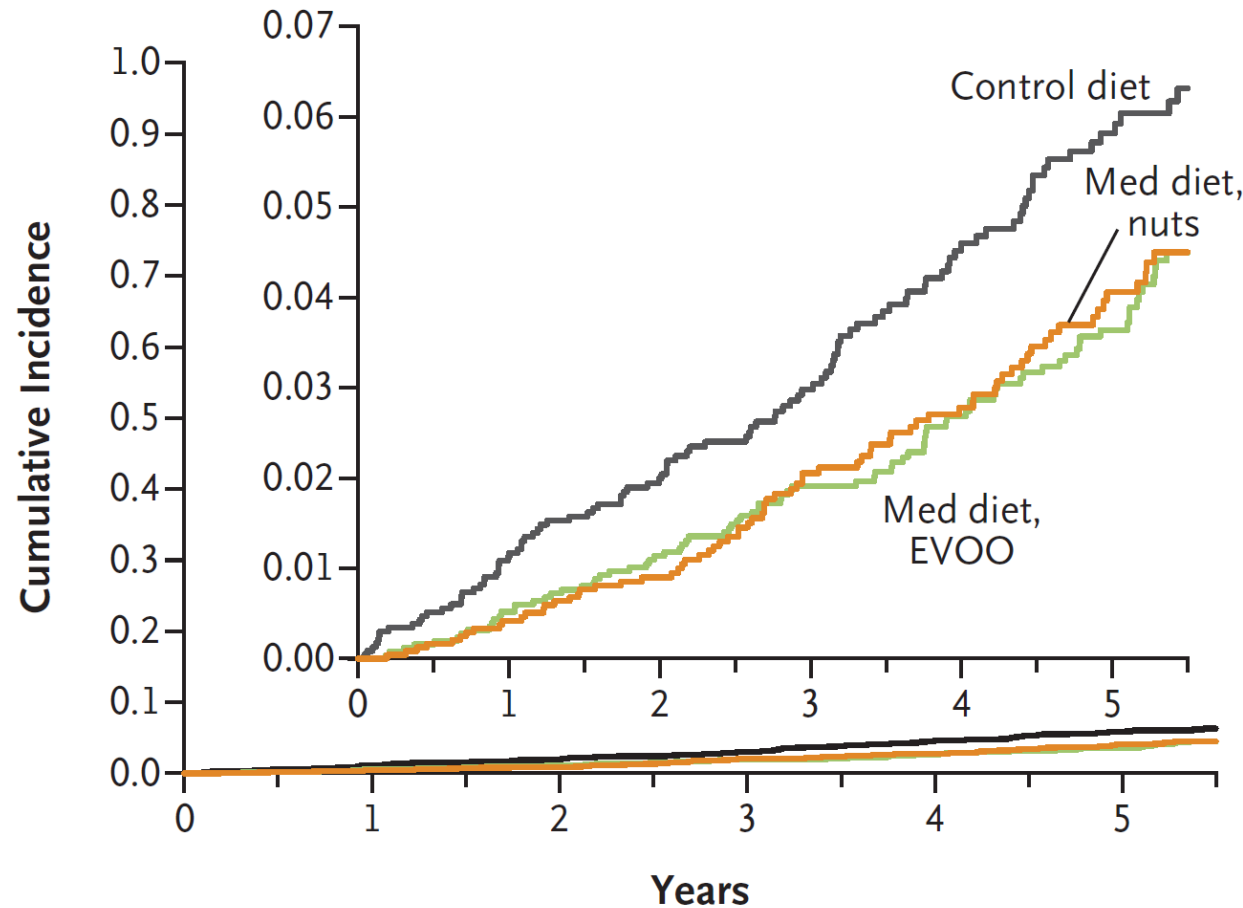
# PREDIMED: Mediterranean Diet

**Primary Endpoint: Myocardial Infarction, Stroke, CV Death**

Med diet, EVOO: hazard ratio, 0.69 (95% CI, 0.53–0.91)

Med diet, nuts: hazard ratio, 0.72 (95% CI, 0.54–0.95)

**Control Diet**



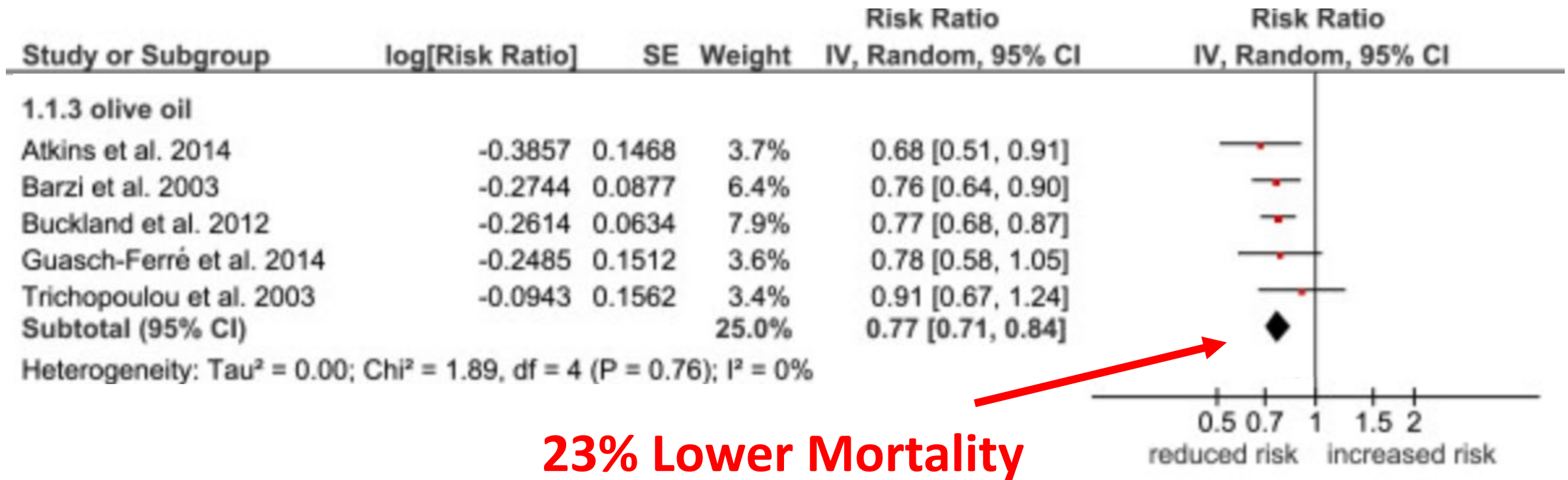
**Med Diet + Nuts**  
**HR = 0.72 (95% CI, 0.54, 0.95)**

**Med Diet + Extra Virgin Olive Oil**  
**HR = 0.69 (95% CI, 0.53, 0.91)**

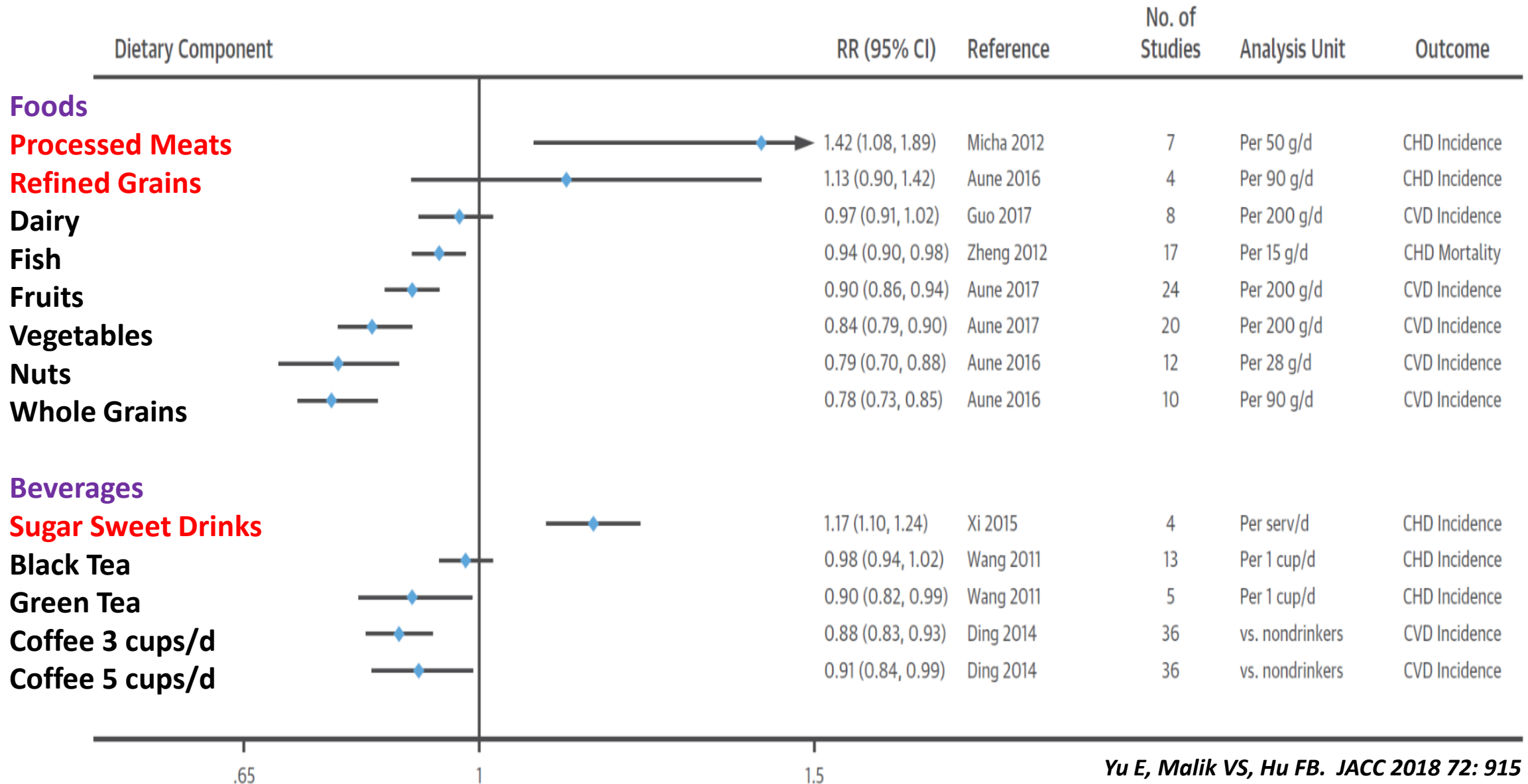
*Estruch R, et al. NEJM 2013; 368: 1279*  
*Correction: NEJM 2018; 378: e34*

# Meta-Analysis Olive Oil and Total Mortality

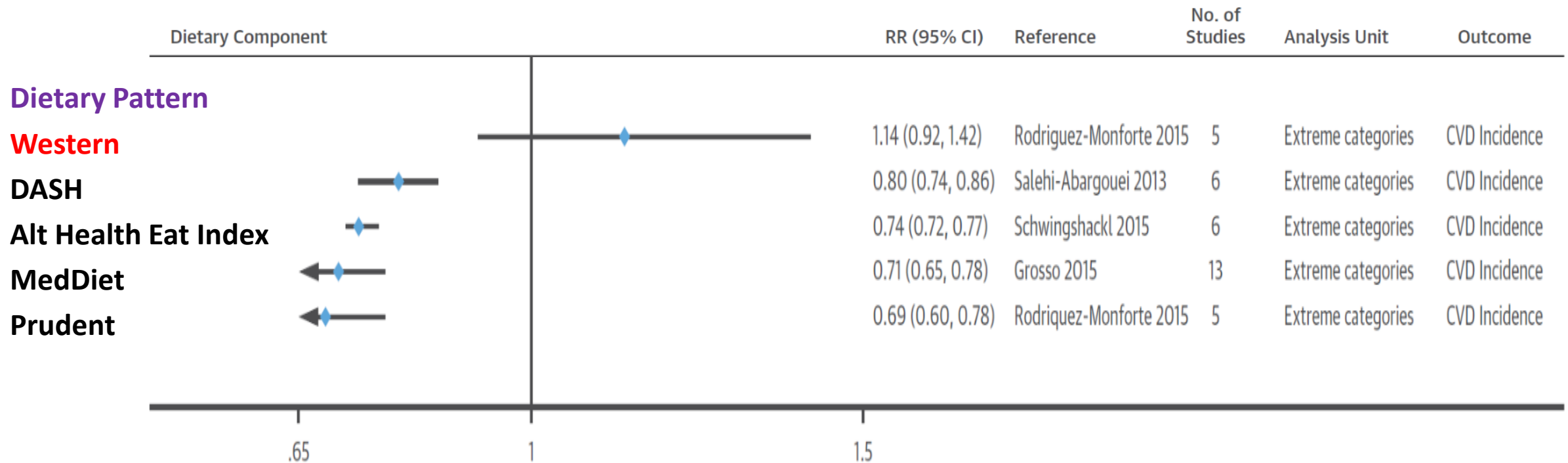
Top versus Bottom Third  
Olive Oil Consumption



# Meta-Analyses Food Groups and CVD Risk



# Meta-Analyses Dietary Pattern and CVD Risk



# US Dietary Guidelines Advisory Committee 2015

- The overall body of evidence identifies that a healthy dietary pattern is
  - Diets **higher** in vegetables, fruits: Strong Evidence
  - Diets **higher** whole grains: Moderate to Strong Evidence
  - Diets **higher** low- or non-fat dairy, seafood, legumes, and nuts: Moderate Evidence
  - Diets with **some** alcohol (only among adults), but increased risks of accidents: Moderate Evidence
  - Diets **lower** in red and processed meat: Strong Evidence
  - Diets **low** in sugar-sweetened foods and drinks and refined grains: Strong Evidence

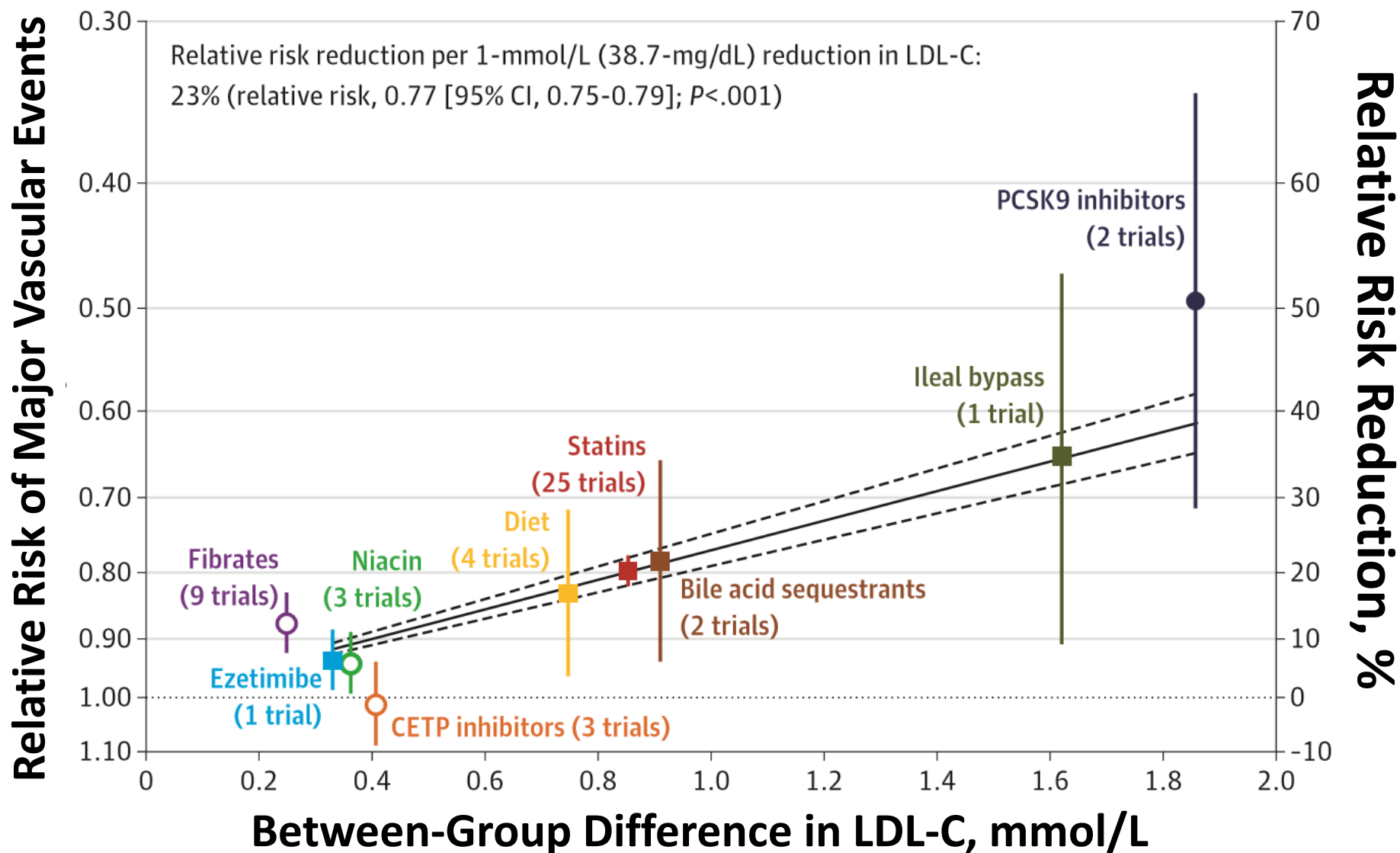
# LDL Lowering Medications

## Important Adjunct to Healthy Lifestyle in Higher Risk Groups

- **Familial Hypercholesterolemia**
- **Clinically Evident Atherosclerosis**
  - CAD, PAD, CVD
- **Diabetes Mellitus**
- **Multiple Risk Factors**

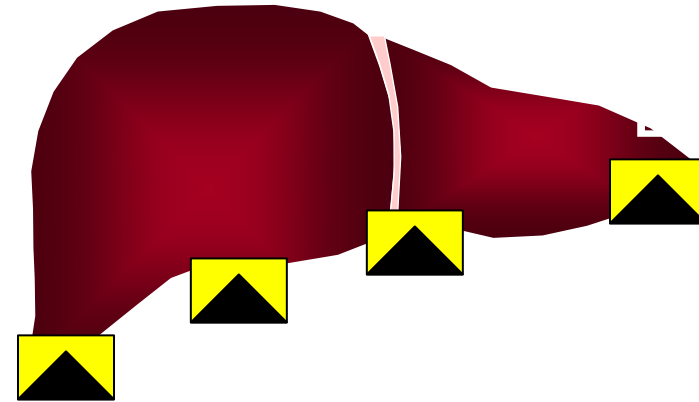


# Decrease in LDL and Decrease in Risk



# LDL Lowering Therapies

All LDL lowering therapies increase the expression of LDL receptors on the liver to increase LDL uptake, and drive down serum LDL levels.



Statins  
Bile salt Binders  
Ezetimibe  
PCSK9 inhibitors

# **Familial Hypercholesterolemia**

## **Disorders of the LDL Receptor**

- **Autosomal dominant**
- **Strong association - premature CAD**
- **> 200 LDL receptor mutations:**
  - **Phenotype influences course of disease**
- **Founder effect in certain populations:**
  - **French Canadians, Lebanon**
- **Clinical diagnosis: Xanthomas, high LDL, FH**

# Homozygous vs Heterozygous FH

|                       | Homozygous                               | Heterozygous                              |
|-----------------------|------------------------------------------|-------------------------------------------|
| Mutant Alleles        | Both                                     | One                                       |
| Frequency             | 1 : 1 million                            | 1 : 500                                   |
| LDL Receptor Activity | < 2%                                     | 2 – 25%                                   |
| Cutaneous             | Xanthomas as Child                       | Xanthomas as Adult                        |
| LDL                   | >> 190 mg/dL*                            | > 190 mg/dL*                              |
| Myocardial Infarct    | Childhood – Early Adult                  | 40% by 50 years age                       |
| Treatment             | Apheresis,<br>Liver Transplant,<br>Drugs | Drugs ± Apheresis<br>Genetic Counselling? |

\* LDL 190 mg/dL ≈ 5.0 mmol/L

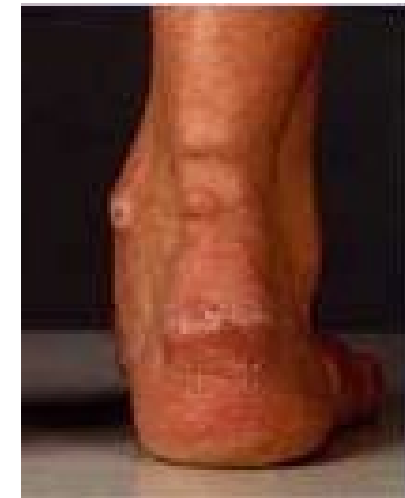


# Dutch Lipid Clinic Network Score

|                                                                      |   |
|----------------------------------------------------------------------|---|
| Patient History and Physical                                         |   |
| Premature CAD (<55 men, < 60 women)                                  | 2 |
| Premature cerebral or PVD                                            | 1 |
| Tendon xanthoma                                                      | 6 |
| Arcus cornealis < 45 years old                                       | 4 |
| First-degree relative                                                |   |
| Premature CVD or LDL > 95 <sup>th</sup> centile                      | 1 |
| Xanthoma, arcus cornealis, or children w LDL > 95 <sup>th</sup> cent | 2 |
| LDL Cholesterol                                                      |   |
| > 330 mg/dL (8.5 mmol/L)                                             | 8 |
| 250-329 mg/dL (6.5-8.4 mmol/L)                                       | 5 |
| 190-249 mg/dL (5.0-6.4 mmol/L)                                       | 3 |
| 155-189 mg/dL (4.0-4.9 mmol/L)                                       | 1 |
| DNA functional mutation of LDLR, apoB, or PCSK9 gene                 | 8 |

# Dutch Lipid Clinic Network Score

| Diagnosis   | Total Points |
|-------------|--------------|
| Definite FH | > 8          |
| Probable FH | 6 – 8        |
| Possible FH | 3-5          |
| Unlikely FH | < 3          |



# **Statins & Cardiovascular Risk**

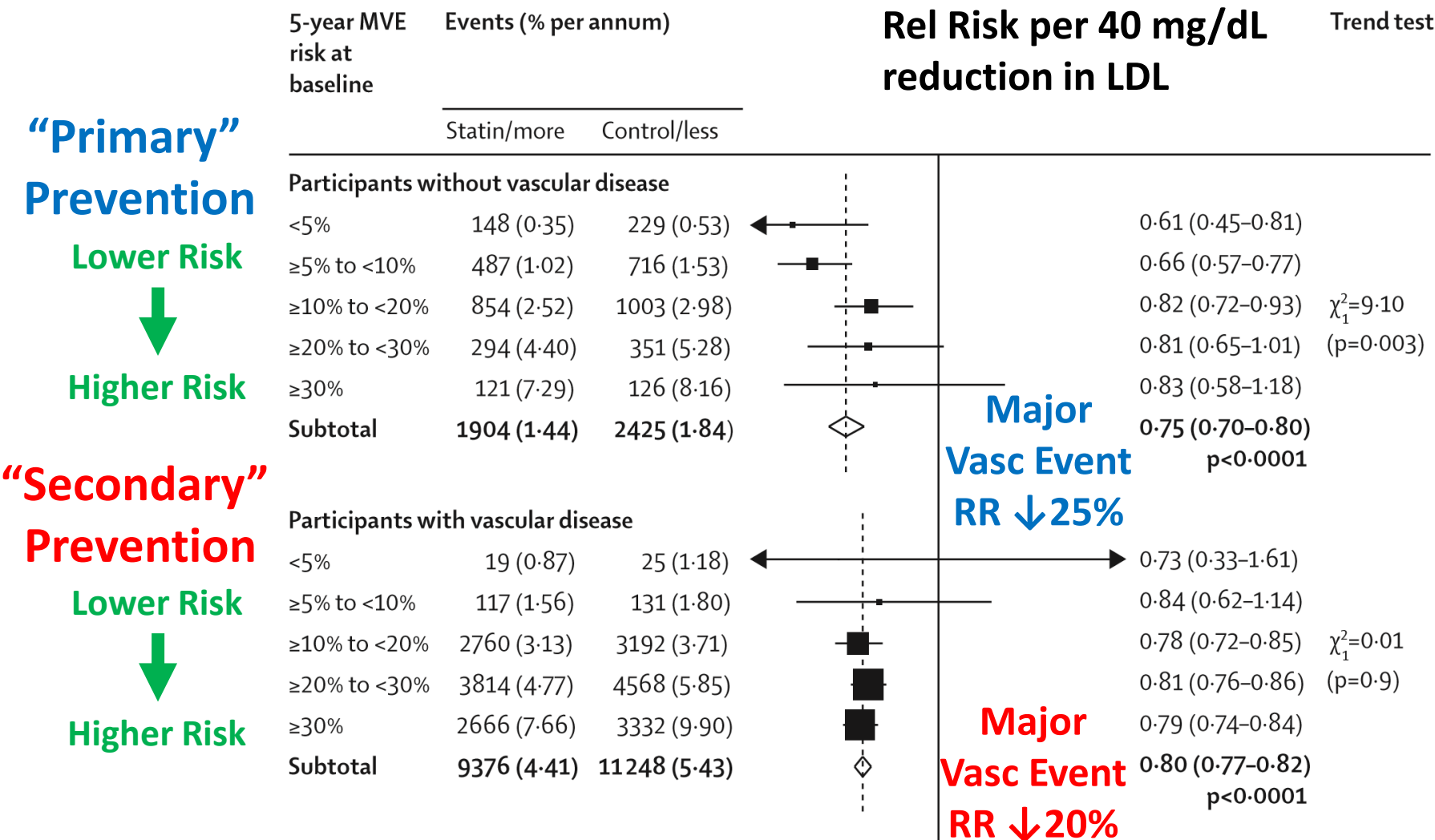
**They Work...**

# Statins Work In....

- **Acute coronary syndromes**
- **Stable coronary syndromes**
- **Coronary equivalent syndromes**
  - **Diabetes**
  - **Hypertension and other risk factors**
  - **Peripheral artery disease**
- **Multiple risk factors with moderate to high risk of cardiovascular disease over 10yrs**

# Statins and Primary vs Secondary Prevention in 27 Trials

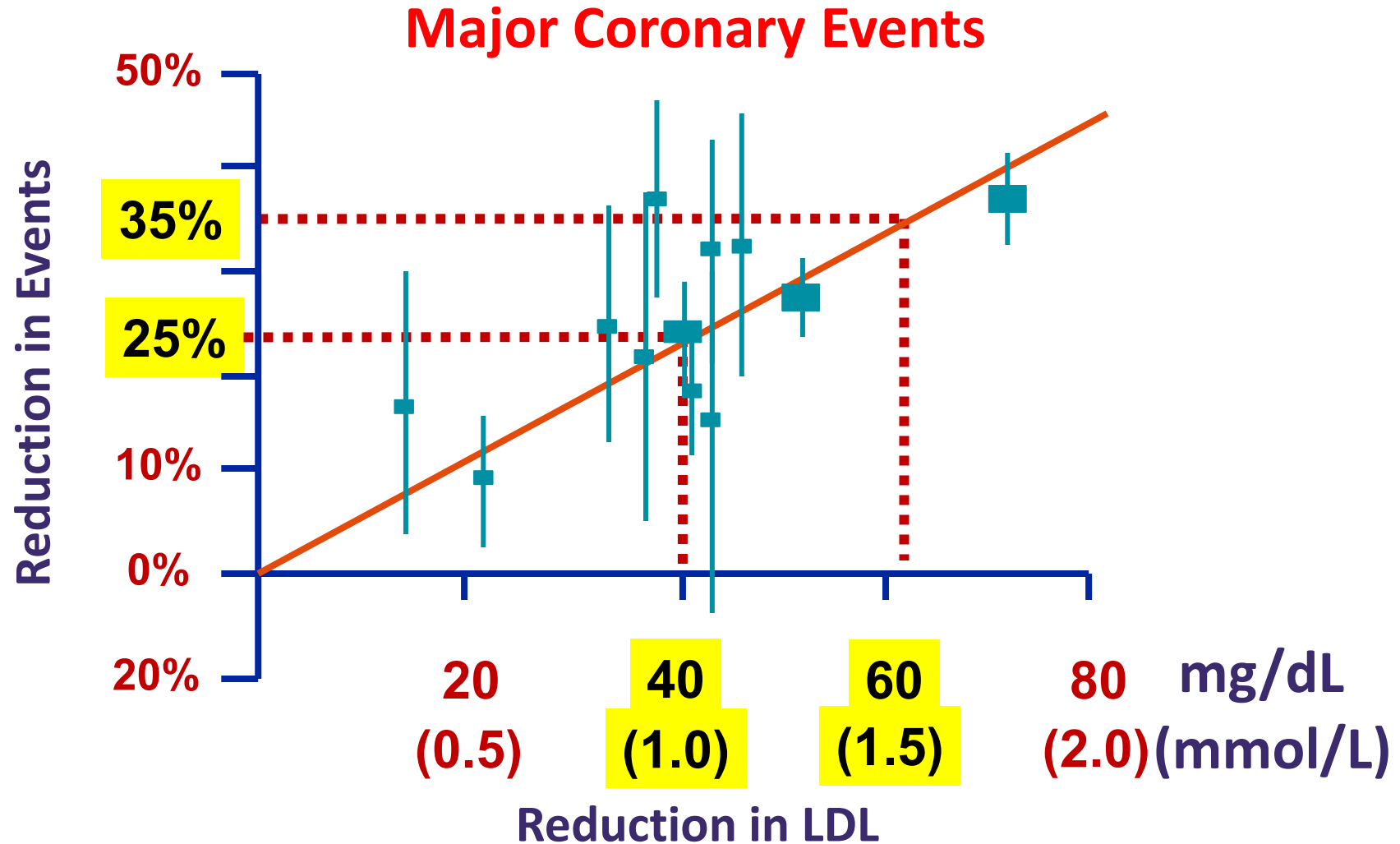
~175K Subjects



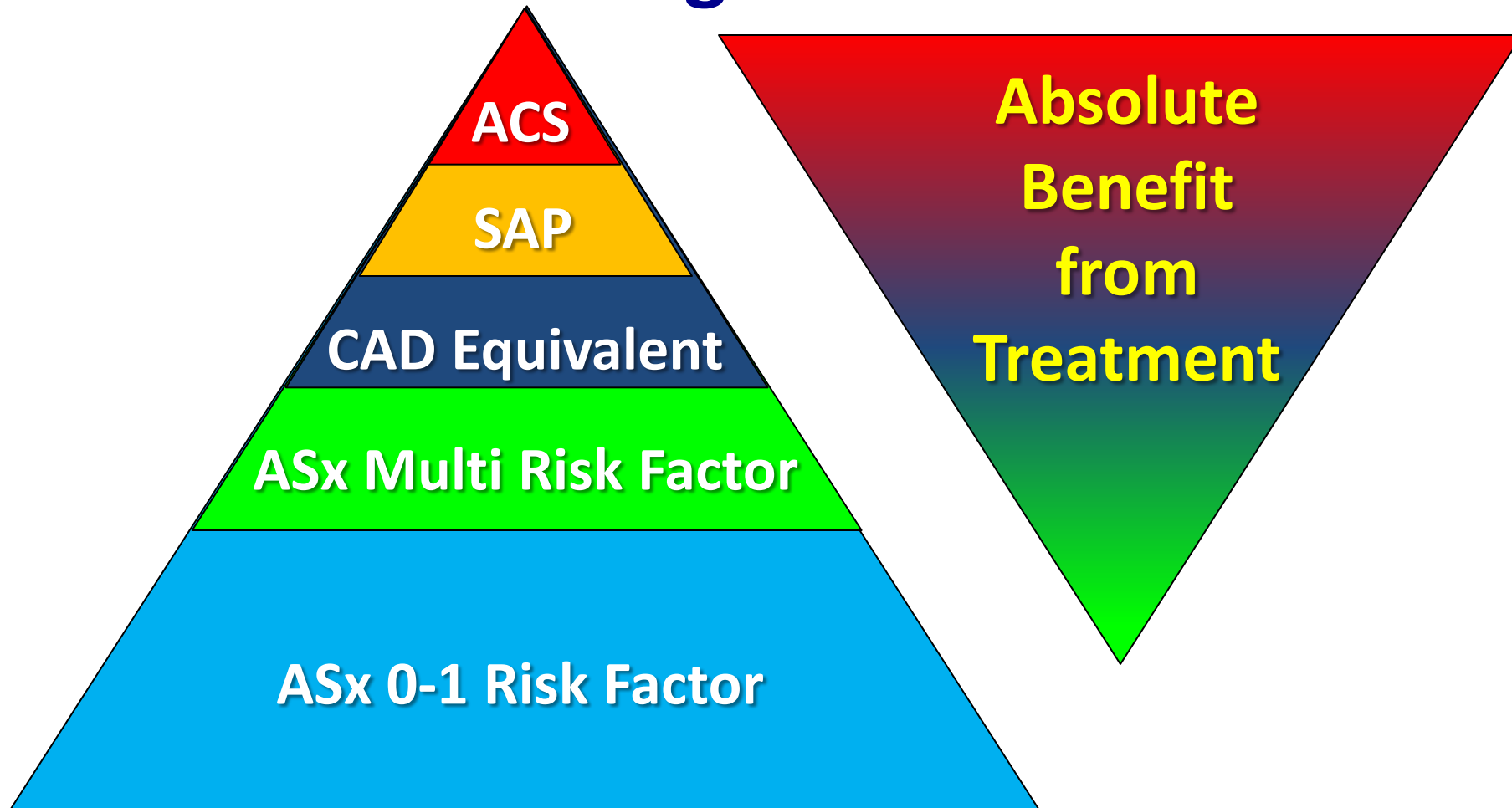
CTT Collaborators. Lancet. 2012;380:581.

# **How to Use Statins**

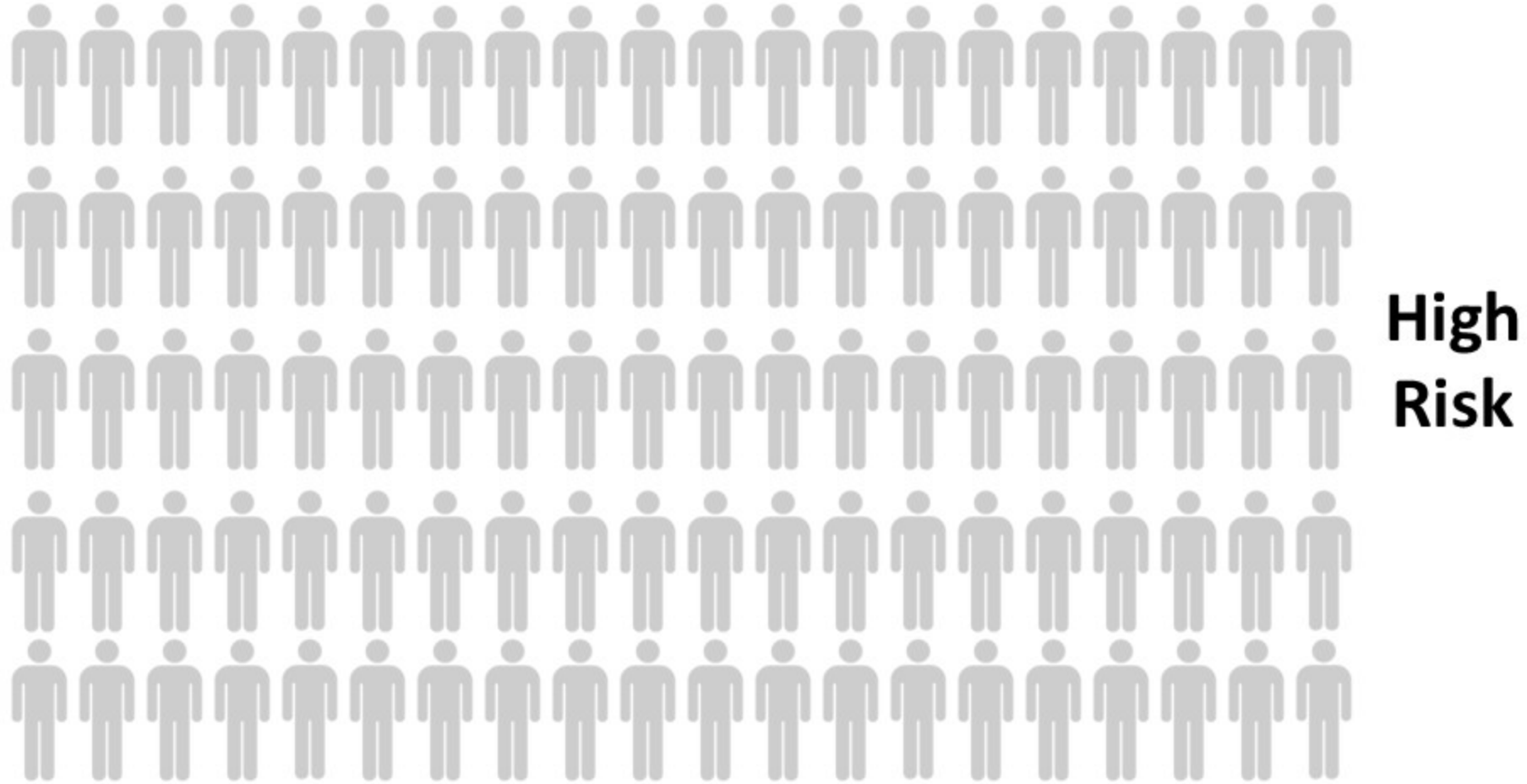
# Absolute LDL Change at 1 Year and Percentage Reduction in Events



# **35% Relative Reduction Yields a Higher Absolute Risk Reduction For Higher Risk Patients**

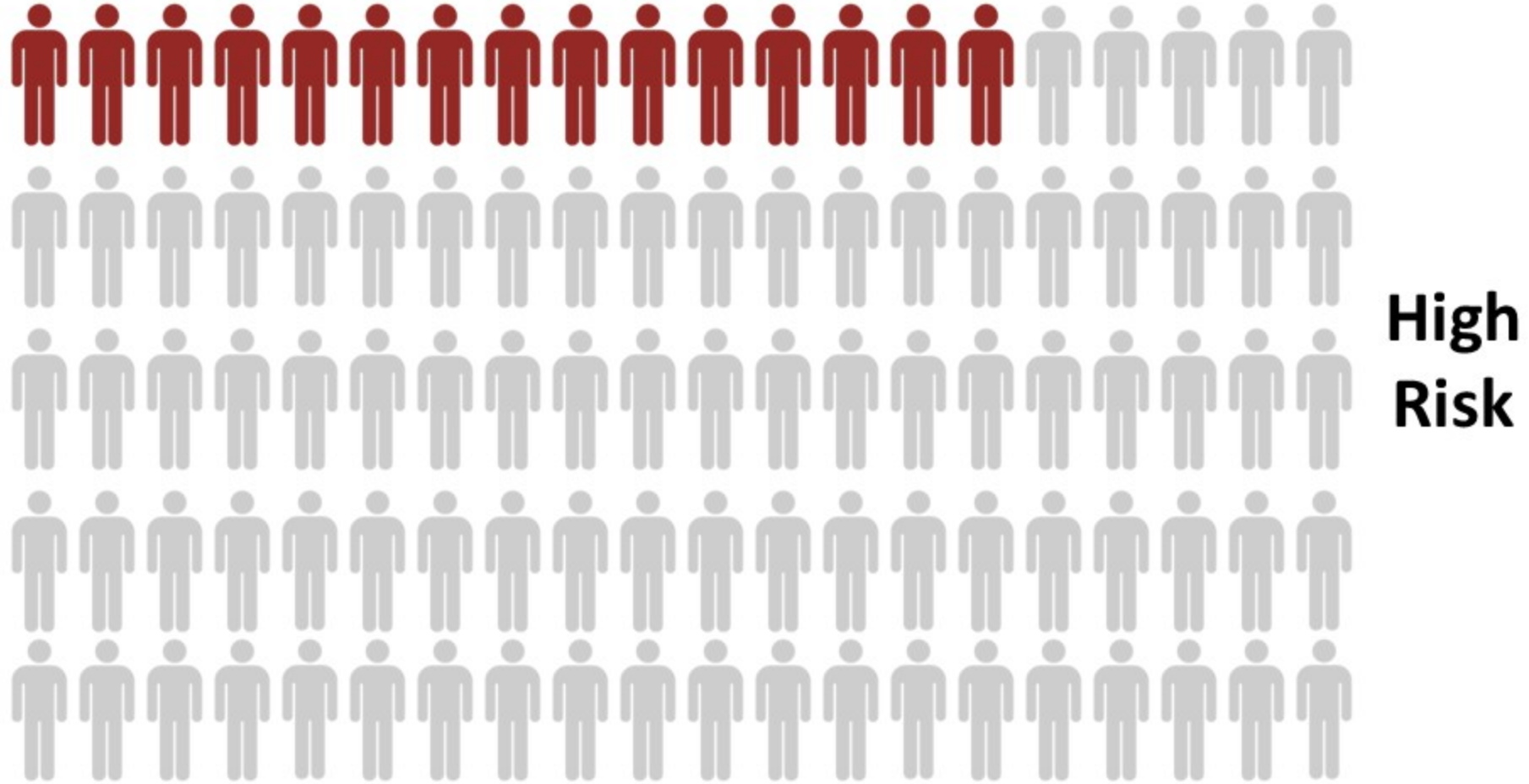


# Absolute Risk and Benefit in 100 Men

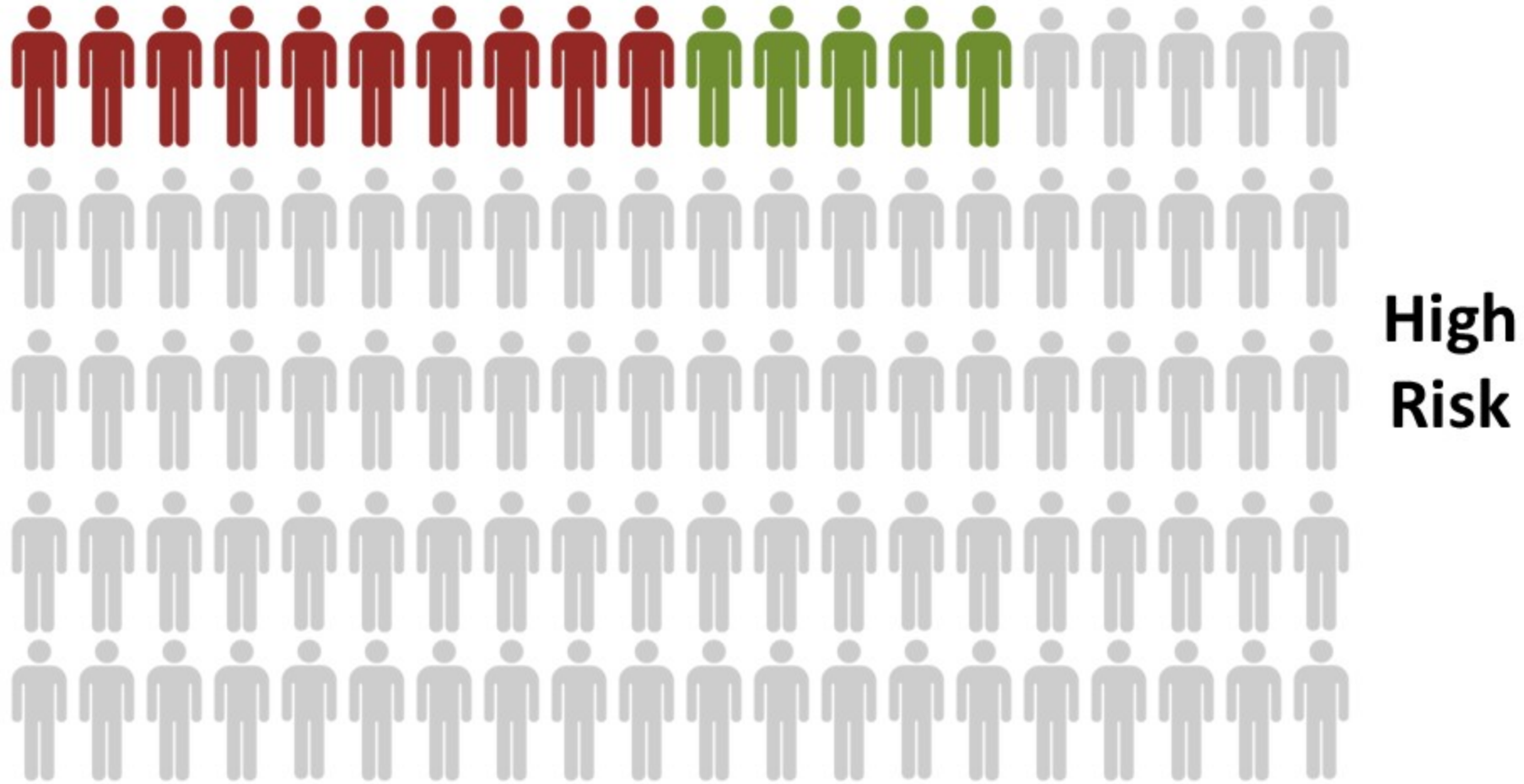


**High Risk of a CV Event  $\approx$  3% Per Year**

# Absolute Risk and Benefit in 100 Men

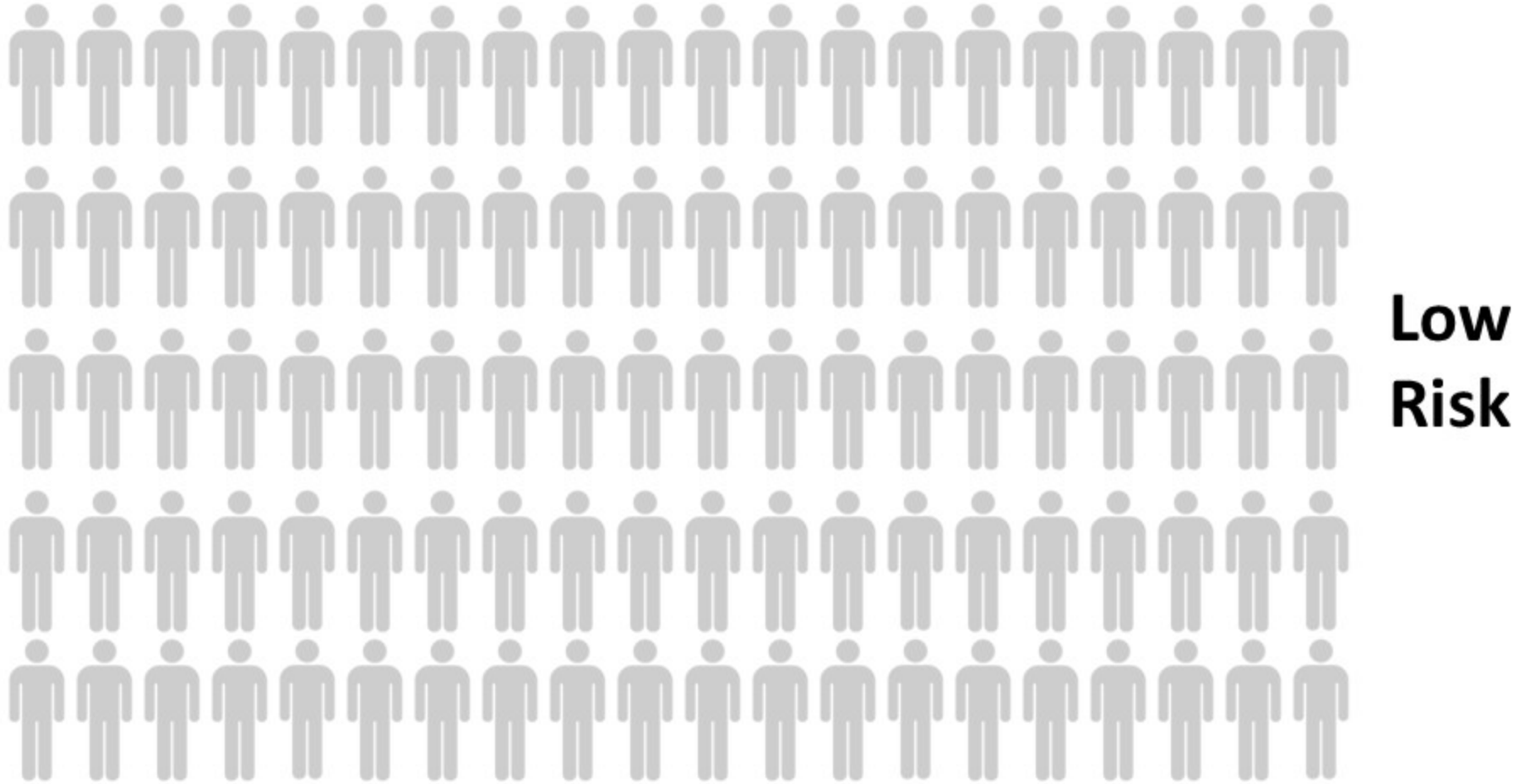


# Absolute Risk and Benefit in 100 Men



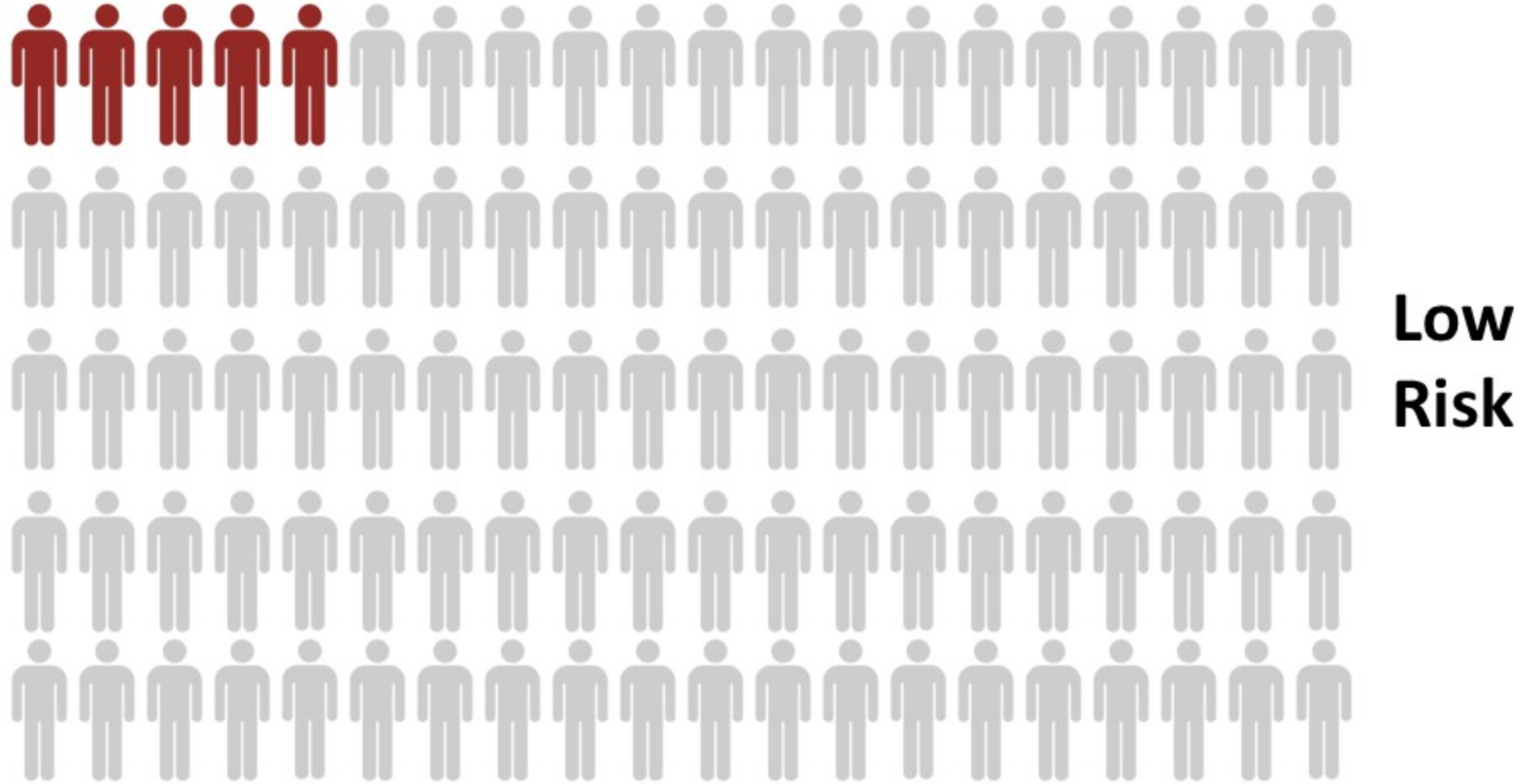
**35% RR over 5 Years = 5 CV Events Prevented  
Per 100 Men Treated**

# Absolute Risk and Benefit in 100 Men



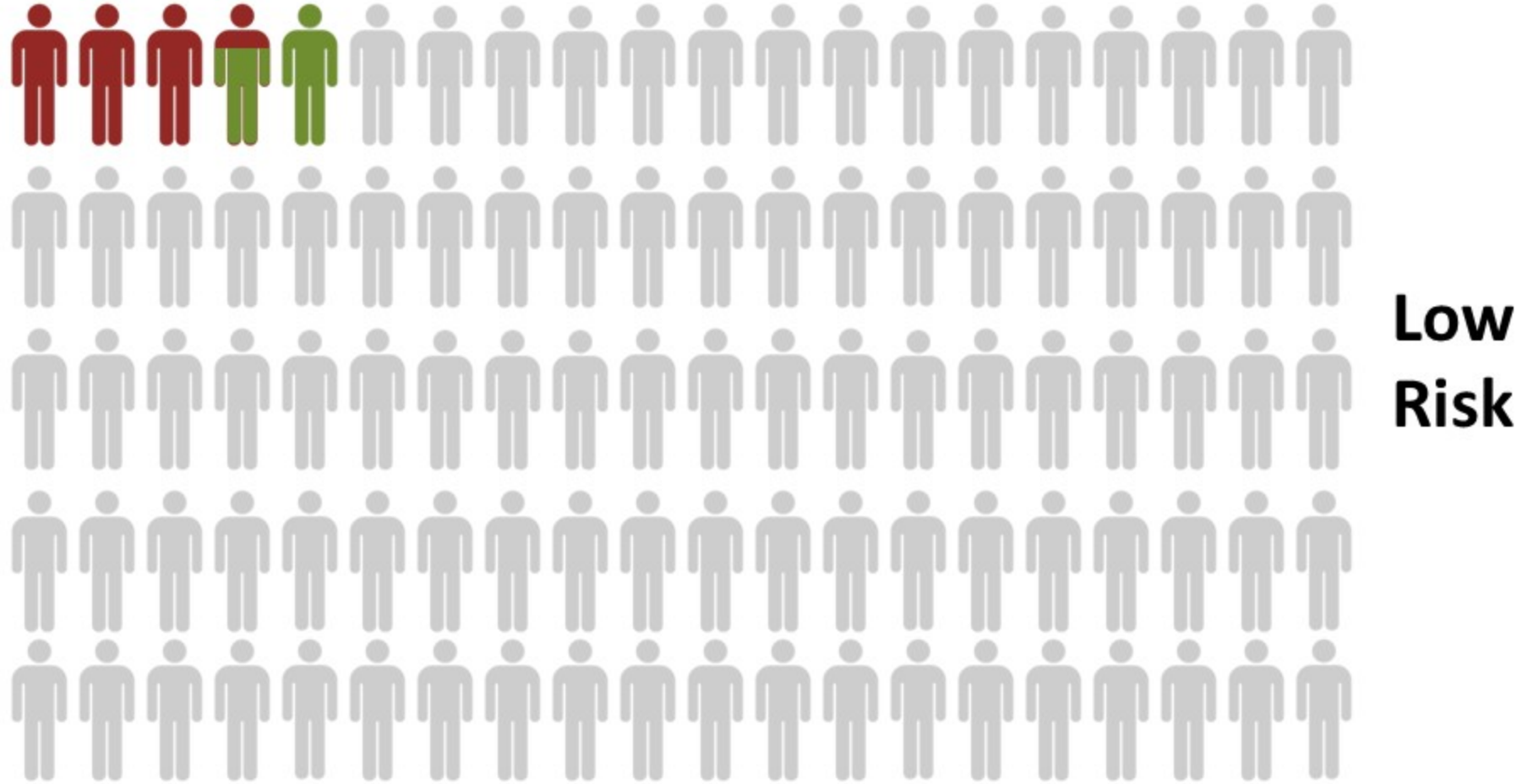
**Low Risk of a CV Event  $\approx$  1% Per Year**

# Absolute Risk and Benefit in 100 Men



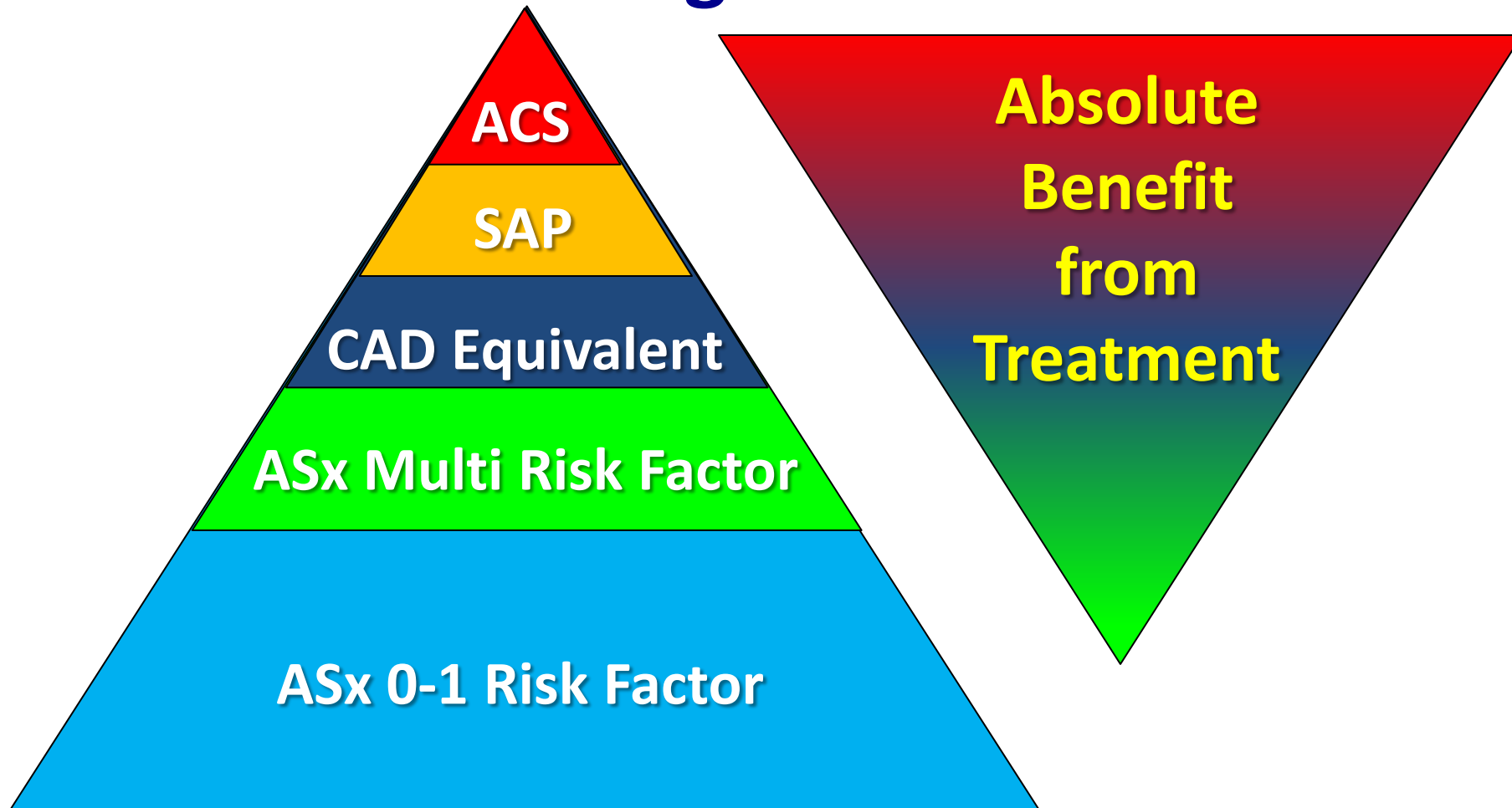
**5 Years = 5 CV Events**

# Absolute Risk and Benefit in 100 Men



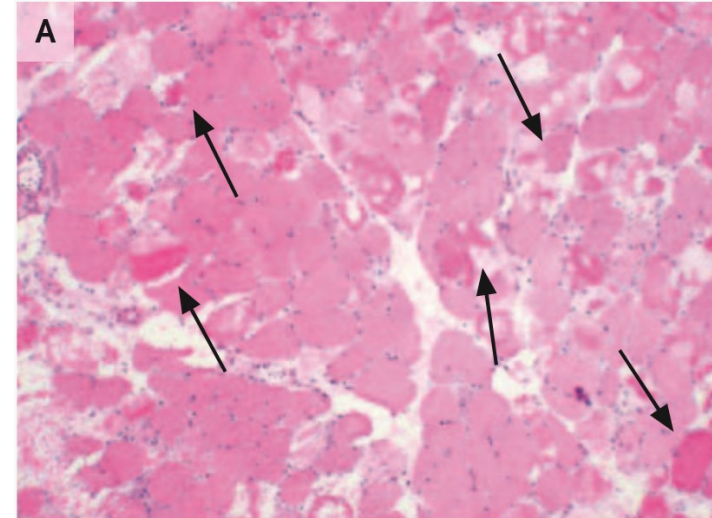
**35% RR over 5 Years = 1.7 CV Events Prevented  
Per 100 Men Treated**

# 35% Relative Reduction Yields a Higher Absolute Risk Reduction For Higher Risk Patients



# Adverse Effects Statins

- **Myopathy**
  - Myositis ↔ Rhabdo
  - Myalgia
- **Cancer (No)**
- **Diabetes Mellitus**
- **Cognitive Changes**
- **Hepatitis (so rare only test if symptoms/signs)**
- **Use in the Elderly**



*Bosch X, et al. NEJM 2009; 361: 62*

# Myositis

- **Myositis (1:100)**

- Muscle weakness/pain,  $\uparrow$ CK 5-10x ULN
- Without renal involvement

- **Rhabdomyolysis (1:10,000)**

- Profound weakness,  $\uparrow$ CK > 10x ULN
- Renal involvement and/or myoglobinuria

- **Statin-Induced Necrotizing Autoimmune Myopathy (1:100,000)**

- Profound proximal weakness
- Ab to HMG CoA Reductase
- ELISA test & Consider immunotherapy

Symptoms/ CK  
Rapidly  
Reversible on  
Statin  
Withdrawal

Persistence of  
Symptoms/ CK  
on Statin  
Withdrawal

# **Risk Factors for Myositis**

- **Hypothyroidism**
- **Vit D deficiency?**
- **High dose statins (esp. simvastatin)**
- **Advanced age**
- **Lower BMI**
- **Cytochrome P450 Inhibition**
  - **Increases serum statin concentration but unpredictable effect on risk of myositis**
- **Rare NSLCO1B1 polymorphisms**
  - **Decrease statin uptake by the liver**

# Factors that Decrease CYP-450 3A4

Potentially ↑ Statin Concentrations but Side-Effects Unpredictable

- Gemfibrozil (esp with simvastatin)
- Cyclosporine
- Macrolide antibiotics
- Azole antifungals
- ART drugs in HIV (esp protease inhibitors)
- Grapefruit juice
  - Inhibits GI but not Liver CYP-450



# Other Potential Causes of CK↑

- **Hypothyroid** (also increases lipids)
- **Idiopathic Hyper-CK-emia**
  - Benign elevation of CK (100's to 1000's)
- **Injury or Excessive Exercise**
  - Focal muscle tear vs Diffuse myositis
- **Alcoholism**
  - Pressure necrosis and dehydration
- **Other Inflammatory Myopathies\***
  - Polymyositis, Dermatomyositis (heliotrope)
  - Also present with ↑CK and Myopathic EMG

*\* Check out Clinical Problem Solving: NEJM 2016: 374: 1774  
<http://www.nejm.org/doi/full/10.1056/NEJMimc1508369>*

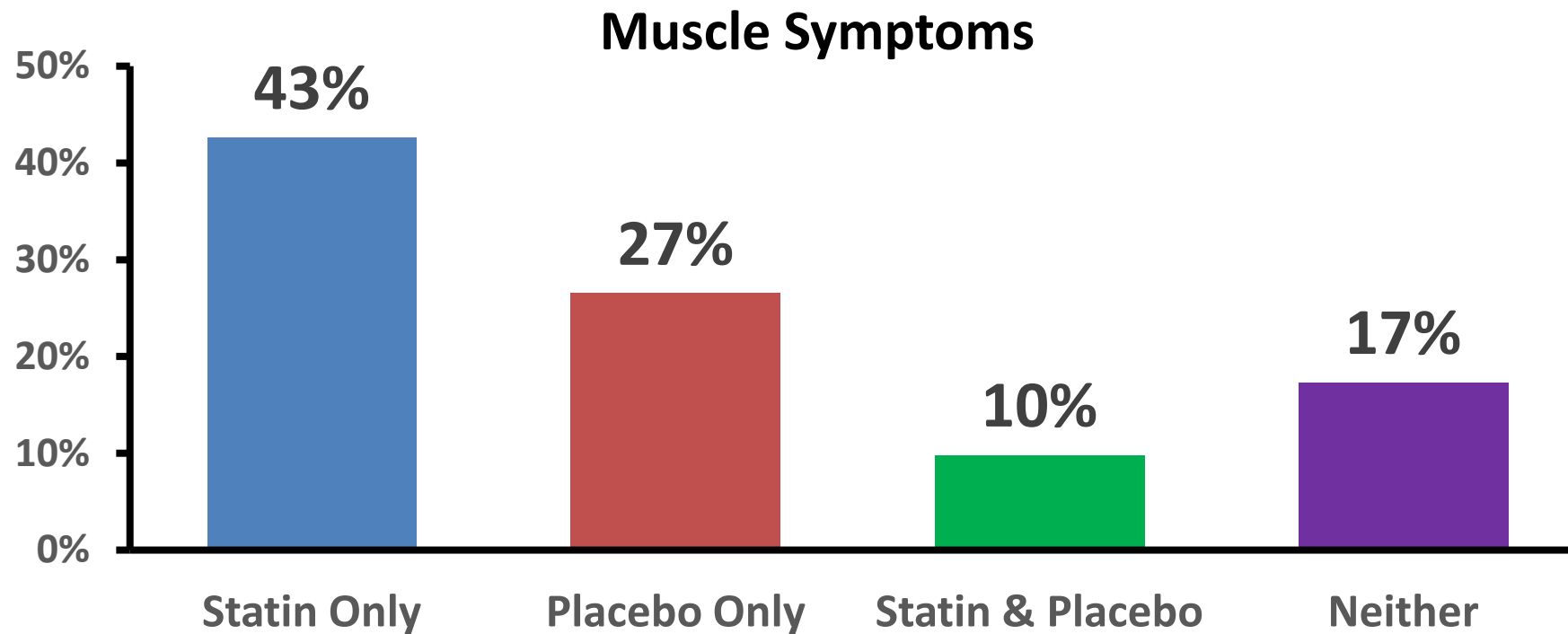
# STOMP Trial: Statin Myalgia Without Myositis

- Muscle pain/ aching starting about 1 month after starting statin
- CK normal or  $< 4 \times$  ULN
- Incidence:
  - 10% in atorva 80/d vs 5% in placebo
  - So an incidence of 5% attributable to drug
- Resolved within 2 weeks of stopping drug
- Returned within 4 weeks of re-challenge
- Coenzyme Q10 not effective & not recommended in 2018 Guidelines

*STOMP: Parker BA, et al. Circulation 2013; 27: 96  
Taylor BA, et al. Atherosclerosis 2015; 238: 329*

# GAUSS-3 Statin Intolerance

- 491 patients intolerant of Atorva 10mg/d or another statin
- Rechallenged with Atorva 20mg/d or Placebo



# Management of Statin Myopathy

- **Stop Statin until symptoms resolve**
- **Check for contributing factors**
  - Hypothyroidism, Vit D deficiency
  - Drug interactions – e.g. new drugs
- **Reassure patients of the safety of statins**
  - Try at least 2 other statins or lower doses
  - Use alternate day dosing ( e.g. atorva/rosuva)
- **Non-statin alternatives**
  - Ezetimibe 10mg/d (20% LDL lowering)
  - PCSK9 inhibitors if FH or CVD “not at goal”

# **Case: HyperCK and Myopathy**

- **75 yr old African American man seen for lymphedema**
- **Right CEA 2014, DM on diet, HT, HL**
- **Rosuvastatin 40mg/d since 2013**
- **Mar 2016: ER visit for palpitations, no muscle ache**
  - **CK 1083 → Rosuva stopped. TSH/VitD/ESR normal**
- **Apr 2016: Felt well and in retrospect he had mild muscle aches and difficulty climbing stairs over 1 year “old age”**

# Statin, Hyper-CK and LDL

| Date                | Rosuva<br>mg/d | Muscle Sx   | CK<br>U/L | LDL<br>mg/dL |
|---------------------|----------------|-------------|-----------|--------------|
| Nov 2012            | 0              |             |           | 153          |
| Feb 2016            | 40             | Yes (retro) |           | 44           |
| Mar 2016 (ER Visit) | Stopped        | Yes         | 1084      | 42           |
| May 2016            | 0              | No          | 1036      | 120          |
| Jun 2016            | 10             | No          | 1296      | 72           |
| Oct 2016            | 5              | No          | 1334      | 94           |
| Oct 2019            | 5              | No          | ?         | 85           |

# **Case: Myopathy on High Dose Statin**

- **46 yr old man with moderate renal artery stenosis**
- **Strong FH: Father SCD 45yrs, Mother CAD**
- **Simva and Prava caused mild increase in LFTs**
- **Oct 2015: Atorva 20/d → Myalgias → stopped**
- **Apr-Jun 2016: Dose ranging Rosuva**

# Statin Dose, Myalgia Symptoms, Lab Work

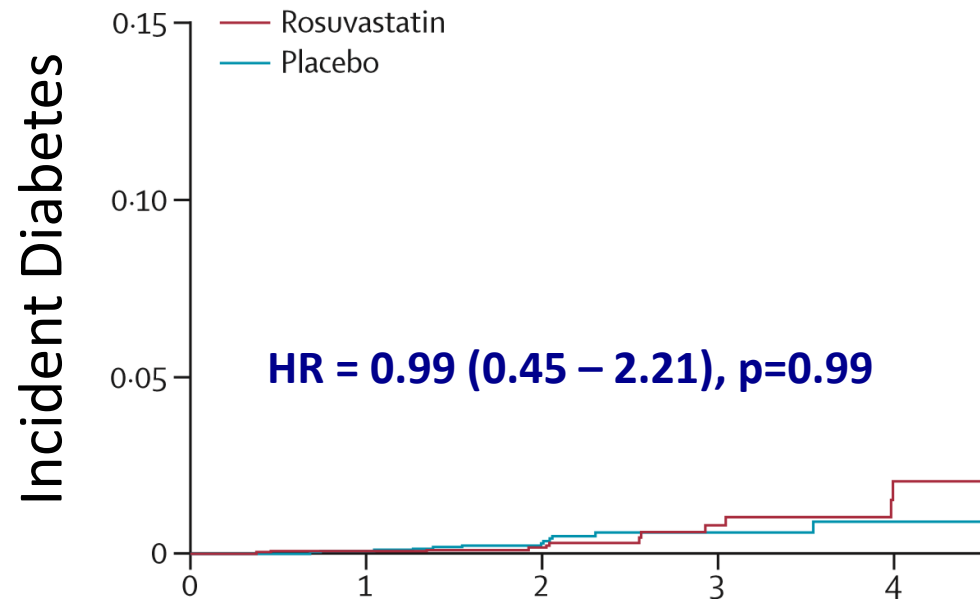
| Date       | Statin mg/d     | LDL mg/dL | Myalgias | CK           |
|------------|-----------------|-----------|----------|--------------|
| Aug 2015   | 0               | 177       | No       |              |
| Oct 2015   | Atorva 20       | 77        | Yes      |              |
| Feb 2016   | 0               | 172       | No       | ETT OK 11min |
| April 2016 | Rosuva 10       | 71        | No       | 91           |
| May 2016   | Rosuva 20       | 65        | Yes      | 730          |
| May 2016   | 0               |           | No       |              |
| Jun 2016   | Rosuva 5        |           | No       |              |
| Oct 2016   | Rosuva 5        | 85        | No       | 251          |
| Jul 2019   | Rosuva 5 + Ez 5 | 73        | No       | ?            |

# Statins and Risk of New Diabetes

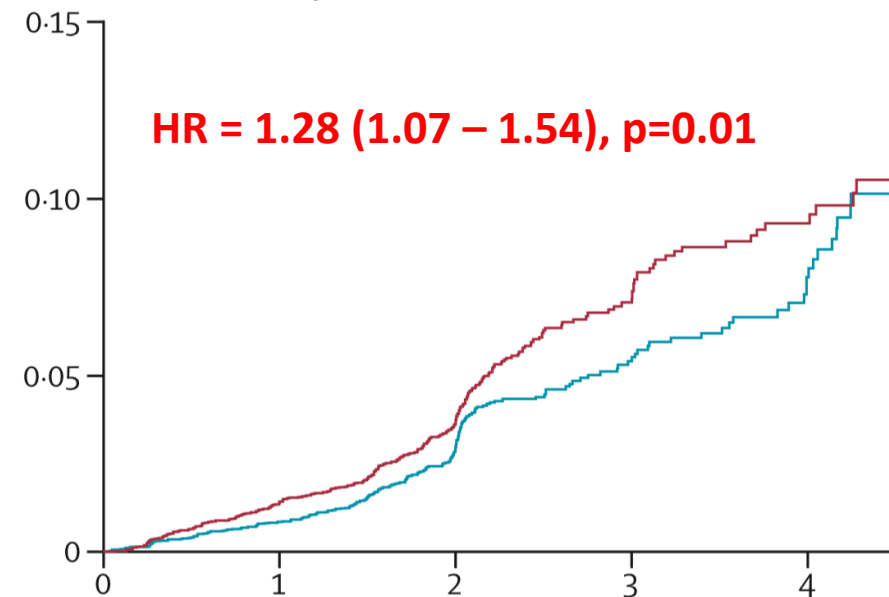
Jupiter Study: Rosuva vs Placebo

## Major Risk Factors for Diabetes Mellitus

### No major risk factors for diabetes



### One or more risk factors for diabetes



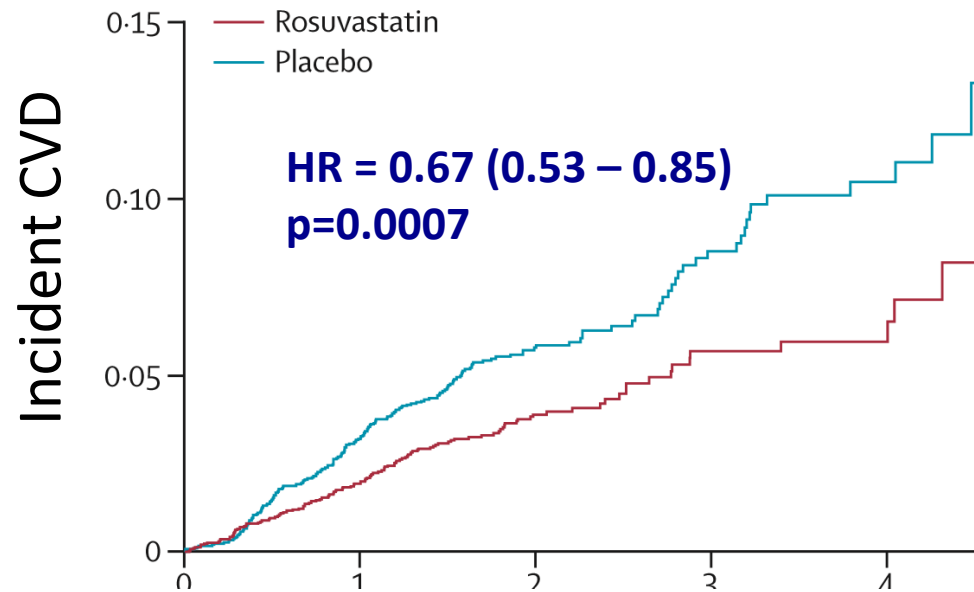
Years of Follow-up

# Statins and Diabetes: Impact on CVD

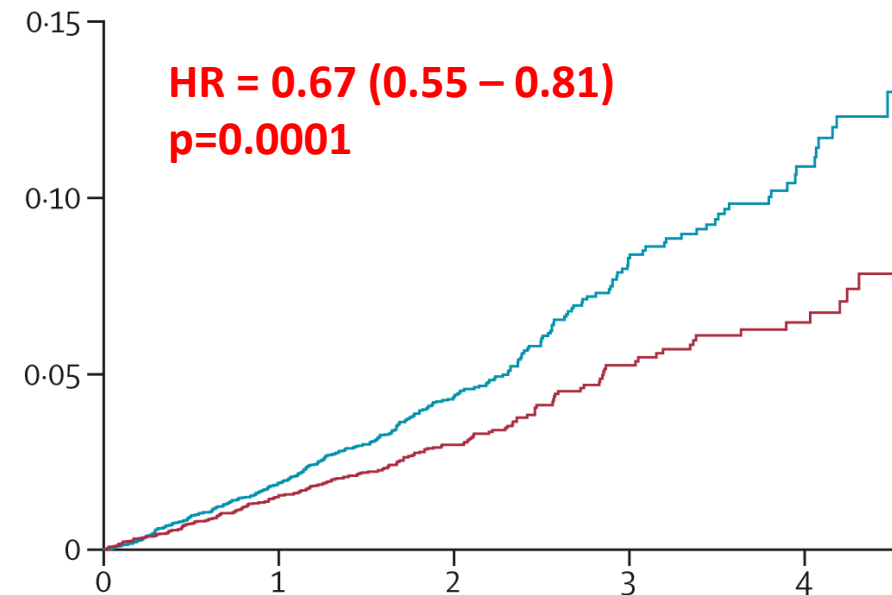
Jupiter Study: Rosuva vs Placebo

## Major Risk Factors for Diabetes Mellitus

No major risk factors for diabetes



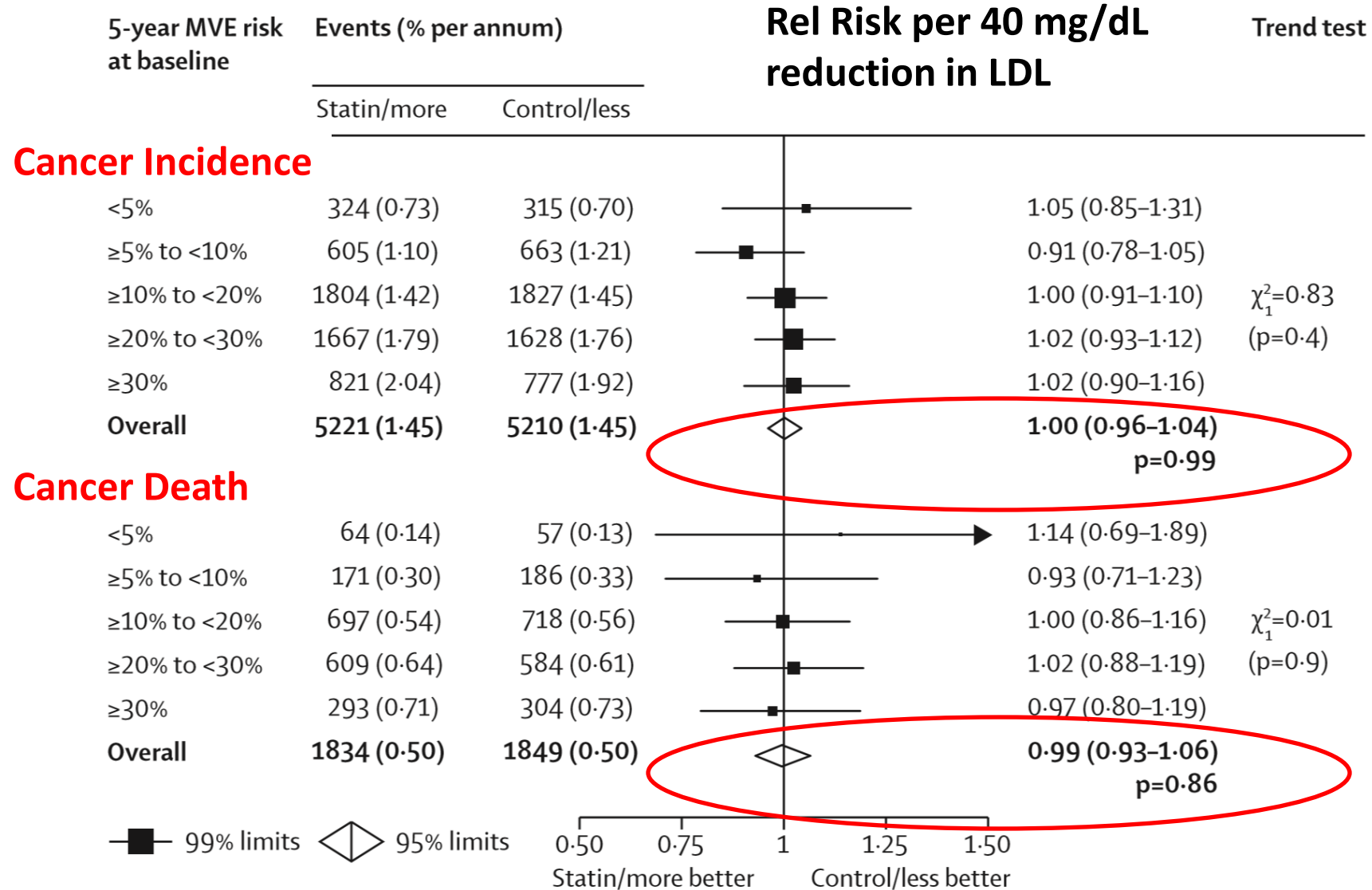
One or more risk factors for diabetes



Years of Follow-up

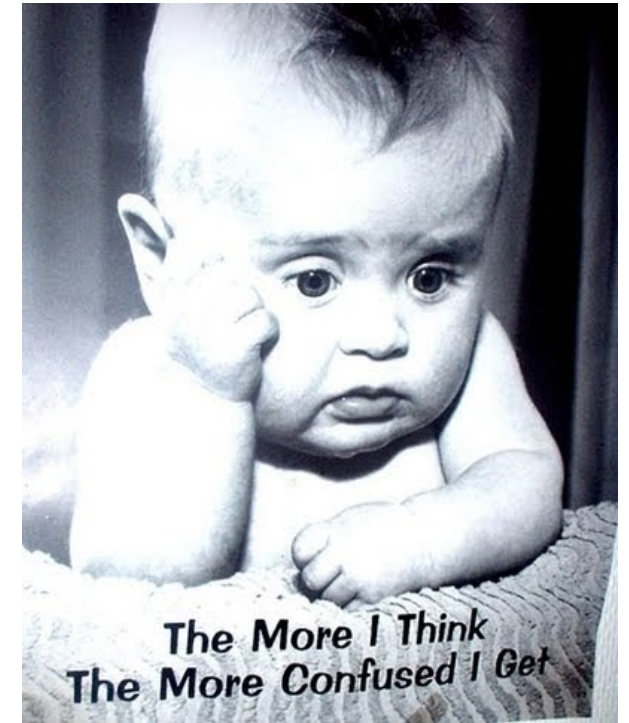
# Statins and Cancer

~175K Subjects



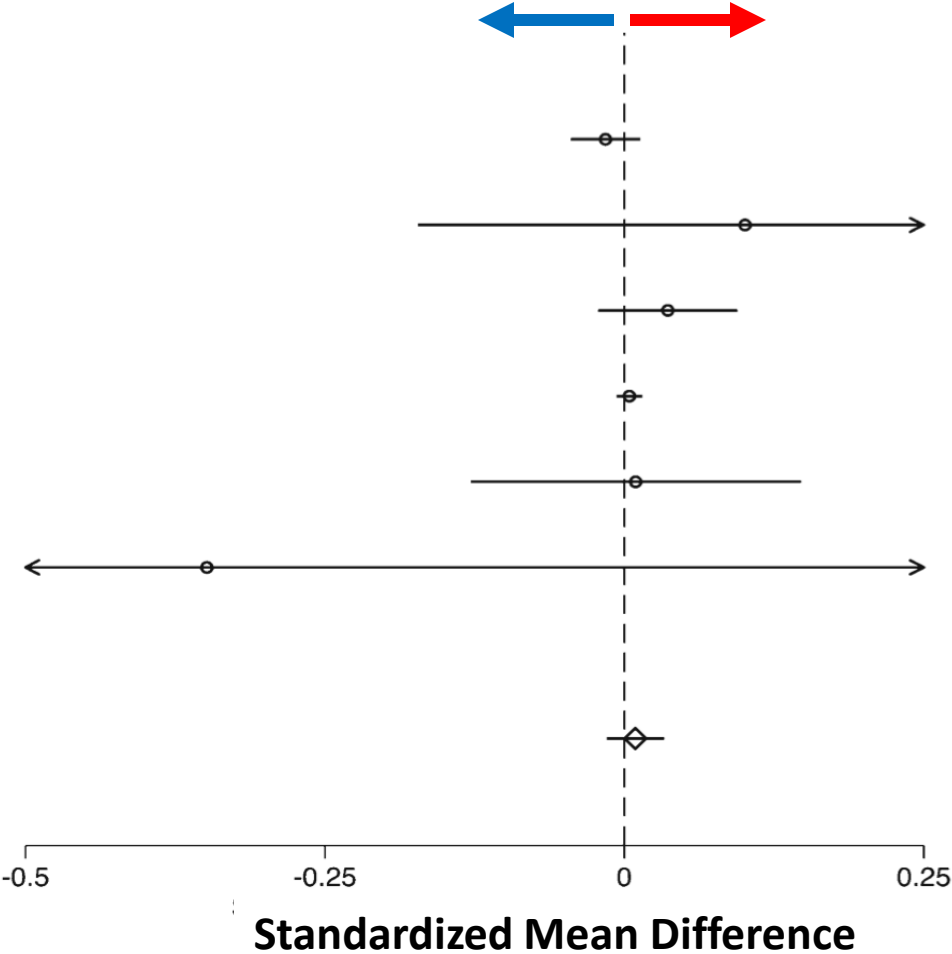
# Statins and Cognition

- High LDL a risk factor for stroke, multi-infarct dementia, and Alzheimer's disease
- 60 cases reported to the FDA of reversible cognitive dysfunction with statins
- Observational meta-analyses fail to show an effect of statins on cognition
- In animal models, statins decrease neuroinflammation and amyloid- $\beta$  concentrations



# 25 Statin RCTs and Cognition

Statins Better    Statins Worse



| Domain           | N (n)       |
|------------------|-------------|
| Global           | 5 (26,515)  |
| Attention        | 7 (732)     |
| Executive        | 7 (26,926)  |
| Memory           | 8 (26,850)  |
| Processing Speed | 10 (6,630)  |
| Working Memory   | 3 (83)      |
|                  |             |
| All Domains      | 14 (27,643) |

# Statins in the Elderly Over 75 Years

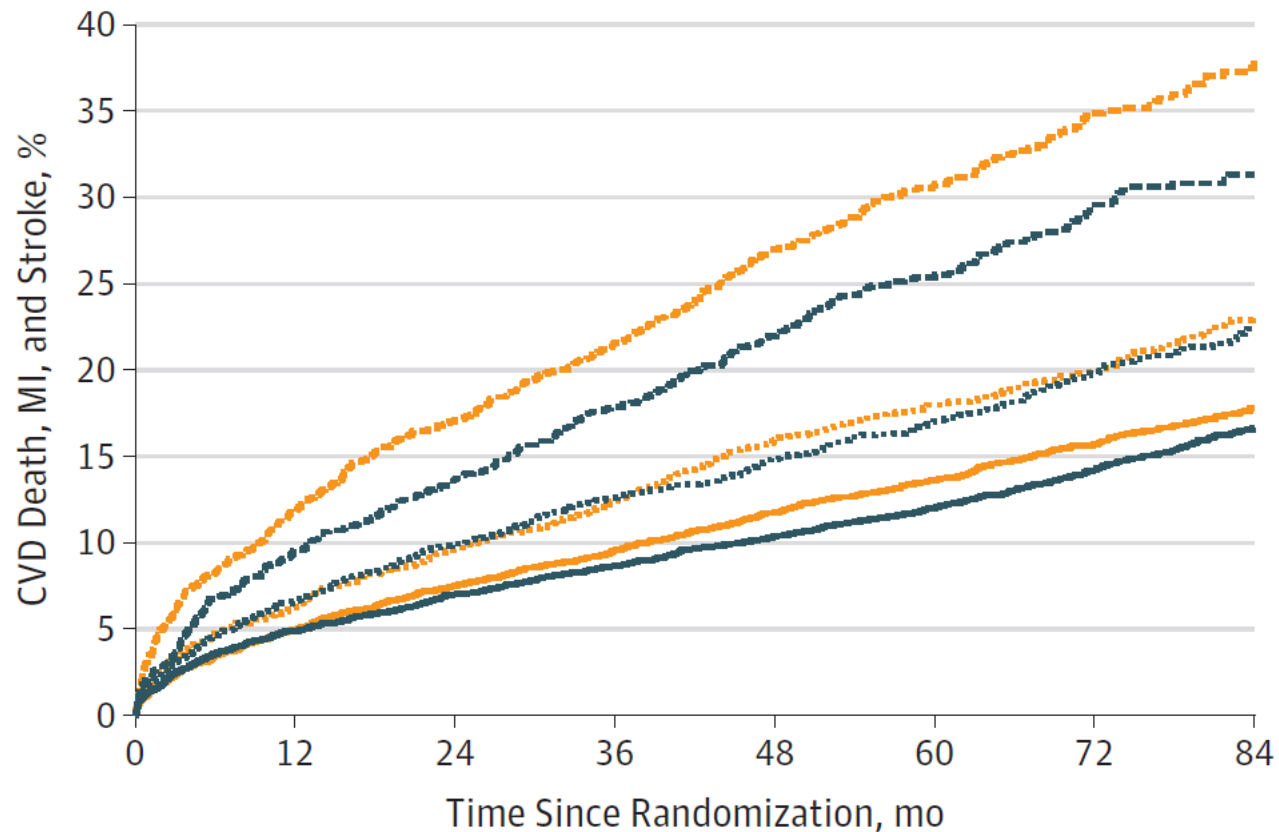
- Clinical trials mostly < 75 yrs
- **Over 75 yrs age group**
- Large number of CVD events
- Many trials support continued statins in patients > 75 yrs
- But, acute pharmacokinetics/dynamics
  - Very old have higher serum statin concentrations
  - Cmax 50% higher, AUC 25% higher
  - ?higher risk of side effects with maximum doses



# IMPROVE-IT and the Elderly

> 75 years old subgroup with stable angina mean age of 80 years

**B** CVD death, MI, and stroke > 75 Years, HR=0.79 (0.69, 0.91)



> 75 Years, Simvastatin Alone  
median LDL = 64 mg/dL (1.7 mmol/L)

> 75 Years, Simvastatin + Ezetimibe  
median LDL = 46 mg/dL (1.2 mmol/L)

**Cholesterol Treatment Trialist  
Meta-analysis**  
Intensive LDL Lowering Benefits  
Patients > 75 yrs **WITH**  
Cardiovascular disease

*Bach RG. JAMACardiol 2019; 4: 846*

*CTT Collaboration. Lancet 2019; 393: 407*

# Statins Over 75 Years of Age



**Good Life Expectancy**  
**Clinically Evident CAD**  
**Diabetes, PVD, isch CVA**

**Poor Life Expectancy**  
**Muscle Weakness**  
**Frailty or Dementia**  
**Drug Interactions**

**Consider Intermediate Dose**

# **Where Statins May Not Work**

# RCTs No Benefit From Statins

- **End-Stage Renal Disease on Dialysis 2+ yrs**
  - AURORA (Rosuva), 4D (Atorva)
  - InSHARP (Simva/Ezet) benefit, but some pre-HDx
- **Aortic Stenosis**
  - Saltire (Atorva), SEAS (Simva/Ezet), Astronomer (Rosuva)
- **CHF no CAD**
  - CORONA (Rosuva), GISSI-HF (Rosuva) all Negative
- **ARDS/ COPD**
  - ARDS & COPD Clinical Research Networks - No benefit
- **CABG**
  - STICS No benefit Rosuva 20mg for post-op AFib or MI
- **Pre-PCI in ACS versus within 24 hours**
  - SECURE-PCI No benefit

*Fellstrom B et al. N Engl J Med 2009;360:1395-1407*

*Kjekshus J et al. N Engl J Med 2007;357: 2248*

*Zheng Z, et al. N Engl J Med 2016; 374: 1744*

*SALTIRE: Cowell JS, et al. NEJM 2005; 352: 2389*

*SEAS: Rossebø AB, et al. NEJM 2008; 359: 1343*

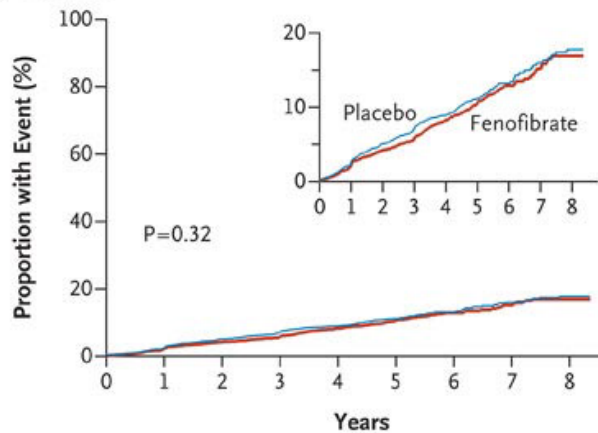
*Astronomer: Chan KL, et al. Circulation 2010; 121: 306*

*Berwanger O, et al. JAMA 2018. March 11*

# **Therapies for Low HDL and High TGs**

# Fibrates, Niacins, CETP Inhibitors

## Fibrates: ACCORD

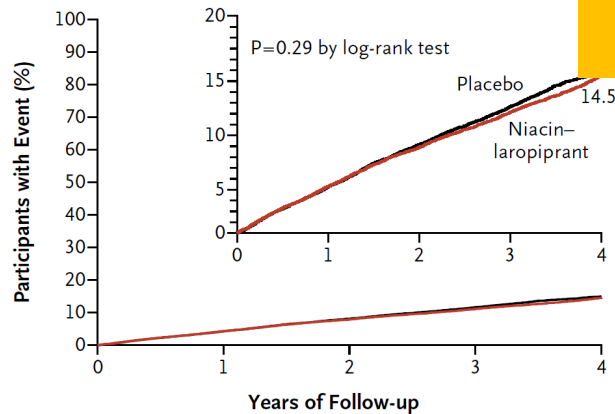


The ACCORD Study Group. *NEJM* 2010;363:2537-2544

## Niacin: AIM-HIGH

Percentage of Patients  
with Outcome

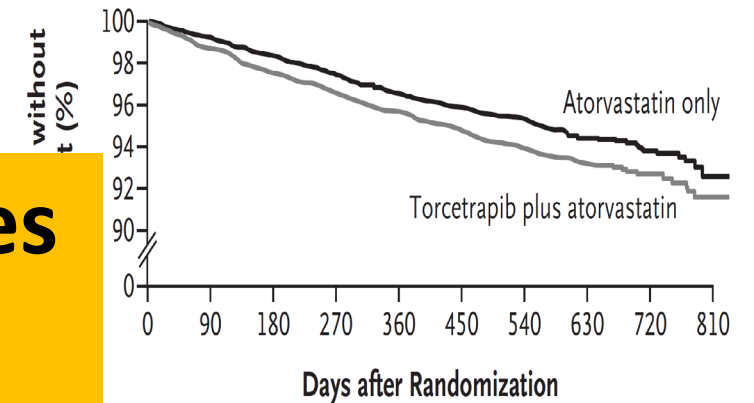
**No Significant Differences  
(or Worse)  
In CV Events When Used  
With Statins**



HPS2-THRIVE Investigators. *NEJM* 2014; 371: 203

## Torcetrapib: ILLUMINATE

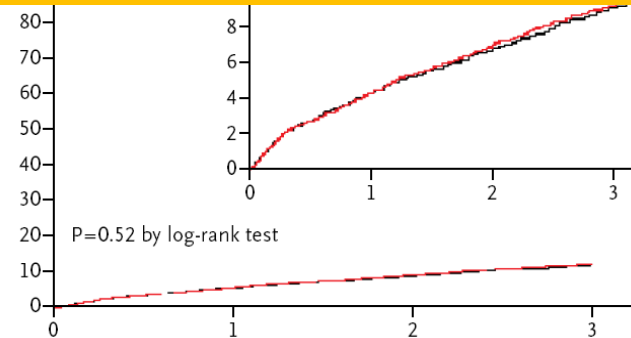
Cardiovascular Events



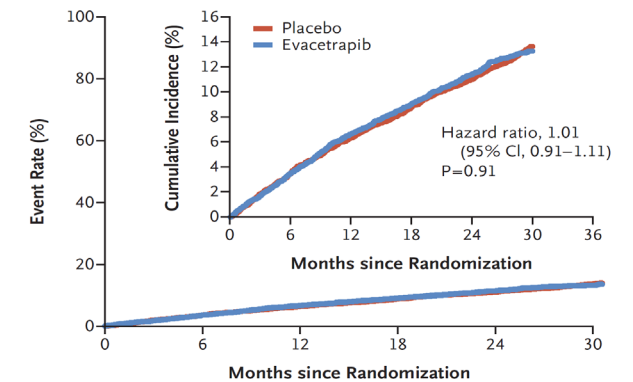
Barter PJ, et al. *NEJM* 2007; 357: 2109

## Evacetrapib: ACCELERATE

Cumulative Incidence of Primary  
Outcome (% of patients)



Schwartz GG, et al. *NEJM* 2012; 367: 2089



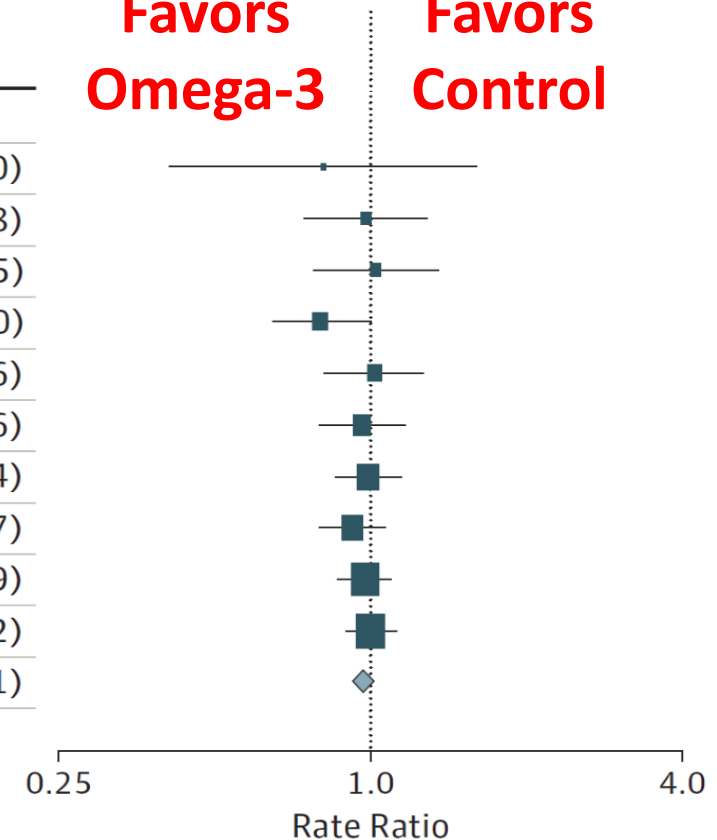
Lincoff AM, et al.. *NEJM* 2017; 376: 1933

# Meta-Analysis Omega-3 FA and Fish Oil

|                       | No. of Events (%) |             | Rate Ratios (CI) |
|-----------------------|-------------------|-------------|------------------|
| Source                | Treatment         | Control     |                  |
| Major vascular events |                   |             |                  |
| DOIT                  | 29 (10.3)         | 35 (12.5)   | 0.81 (0.41-1.60) |
| AREDS-2               | 213 (9.9)         | 208 (10.1)  | 0.98 (0.75-1.28) |
| SU.FOL.OM3            | 216 (17.2)        | 211 (16.9)  | 1.02 (0.78-1.35) |
| JELIS                 | 262 (2.8)         | 324 (3.5)   | 0.80 (0.65-1.00) |
| Alpha Omega           | 332 (13.8)        | 331 (13.6)  | 1.02 (0.82-1.26) |
| OMEGA                 | 534 (27.7)        | 541 (28.6)  | 0.96 (0.80-1.16) |
| R&P                   | 733 (11.7)        | 745 (11.9)  | 0.99 (0.86-1.14) |
| GISSI-HF              | 783 (22.4)        | 831 (23.9)  | 0.92 (0.80-1.07) |
| ORIGIN                | 1276 (20.3)       | 1295 (20.7) | 0.98 (0.87-1.09) |
| GISSI-P               | 1552 (27.4)       | 1550 (27.3) | 1.00 (0.90-1.12) |
| All                   | 5930 (15.2)       | 6071 (15.6) | 0.97 (0.93-1.01) |

$P = .10$

**Favors  
Omega-3**      **Favors  
Control**



|                  |            |            |                         |
|------------------|------------|------------|-------------------------|
| <b>ASCEND</b>    | <b>882</b> | <b>887</b> | <b>1.00 (0.91-1.09)</b> |
| <b>VITAL</b>     | <b>527</b> | <b>567</b> | <b>0.93 (0.82-1.04)</b> |
| <b>REDUCE-IT</b> | <b>705</b> | <b>901</b> | <b>0.75 (0.68-0.83)</b> |

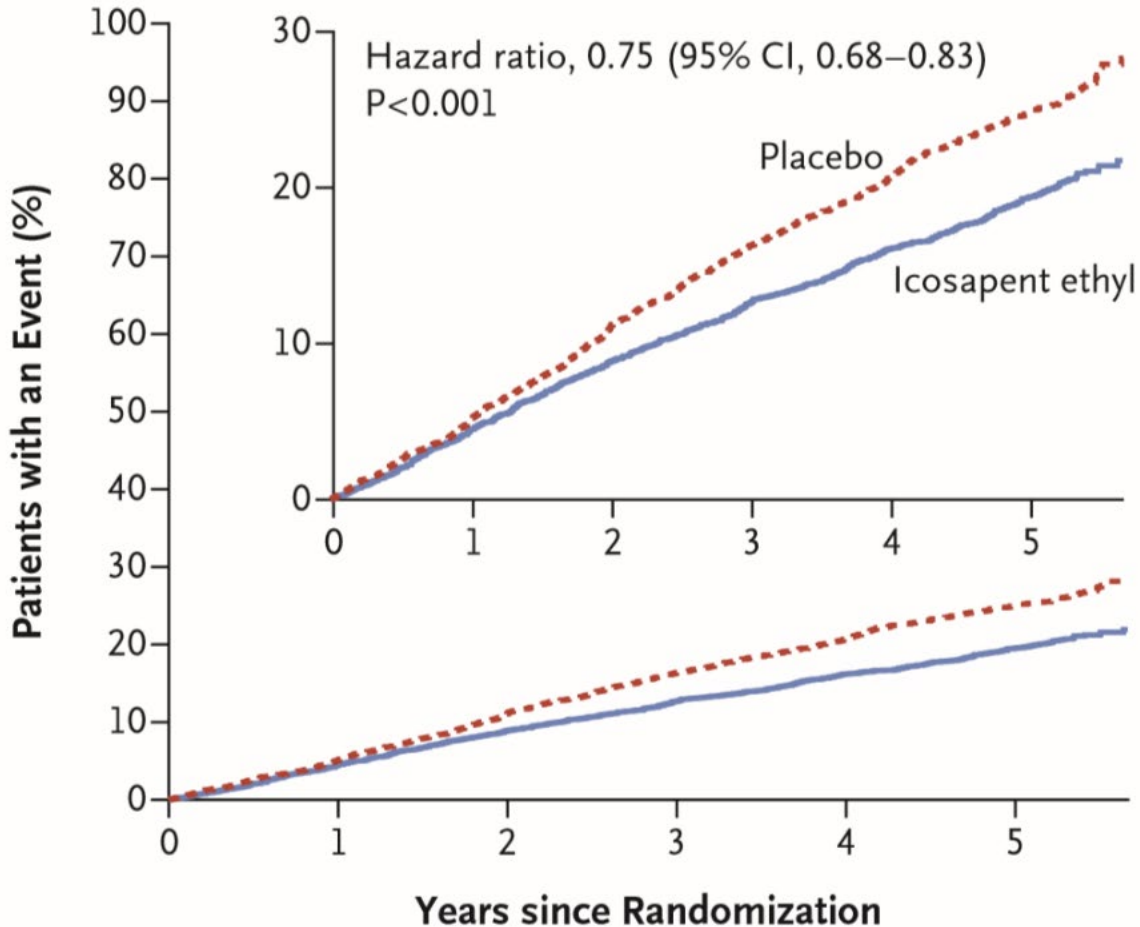


**ASCEND. NEJM 2018; 379: 1540**  
**VITAL. NEJM 2019; 380: 33**  
**REDUCE-IT. NEJM 2019; 380: 11**

# REDUCE-IT

Eicosapent ethyl – refined EPA ethyl ester

## A Primary End Point



## Secondary Prevention Trial

Trigs 18% lower in EPA  
LDL 6.6% higher in placebo  
hsCRP 21% lower in EPA

Explain less than half the  
25% reduction in CV risk

Mechanism uncertain  
Dose of EPA very high (10x)

# Role for Non-LDL Lowering

- No role in combination with statins
- Maybe a role in statin intolerant subjects
  - Gemfibrozil: Helsinki, VA-HIT
  - Niacin: CDP, HATs
  - Omega 3 FA: Secondary prevention with EPA?
- Better drugs available



# **Ezetimibe and Statins**

# IMPROVE-IT: Ezetimibe & Simva

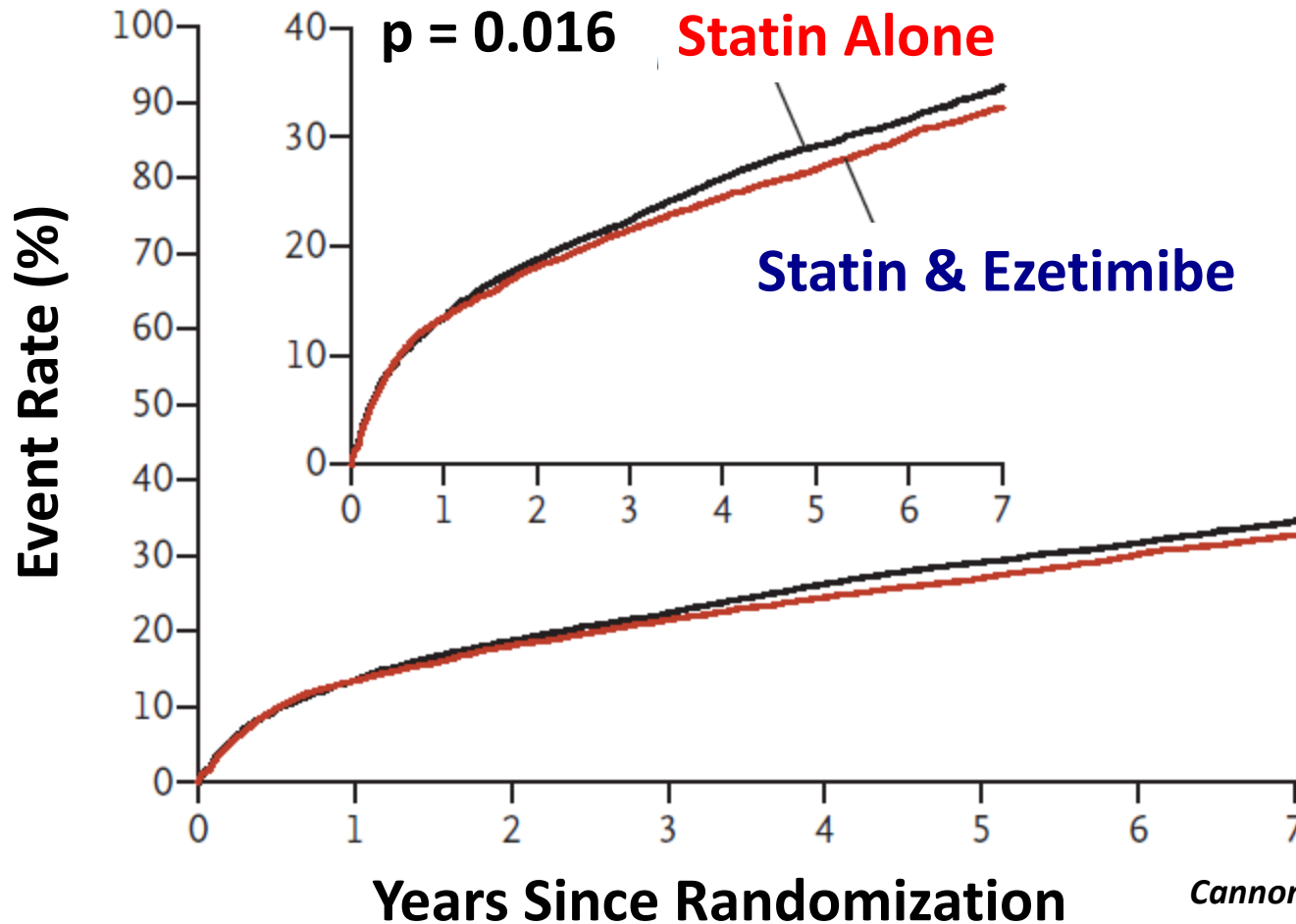
Ezetimibe/Simva 10/40mg versus Simva 40-80mg

HR = 0.936 (95%CI: 0.89, 0.99)

p = 0.016 **Statin Alone**

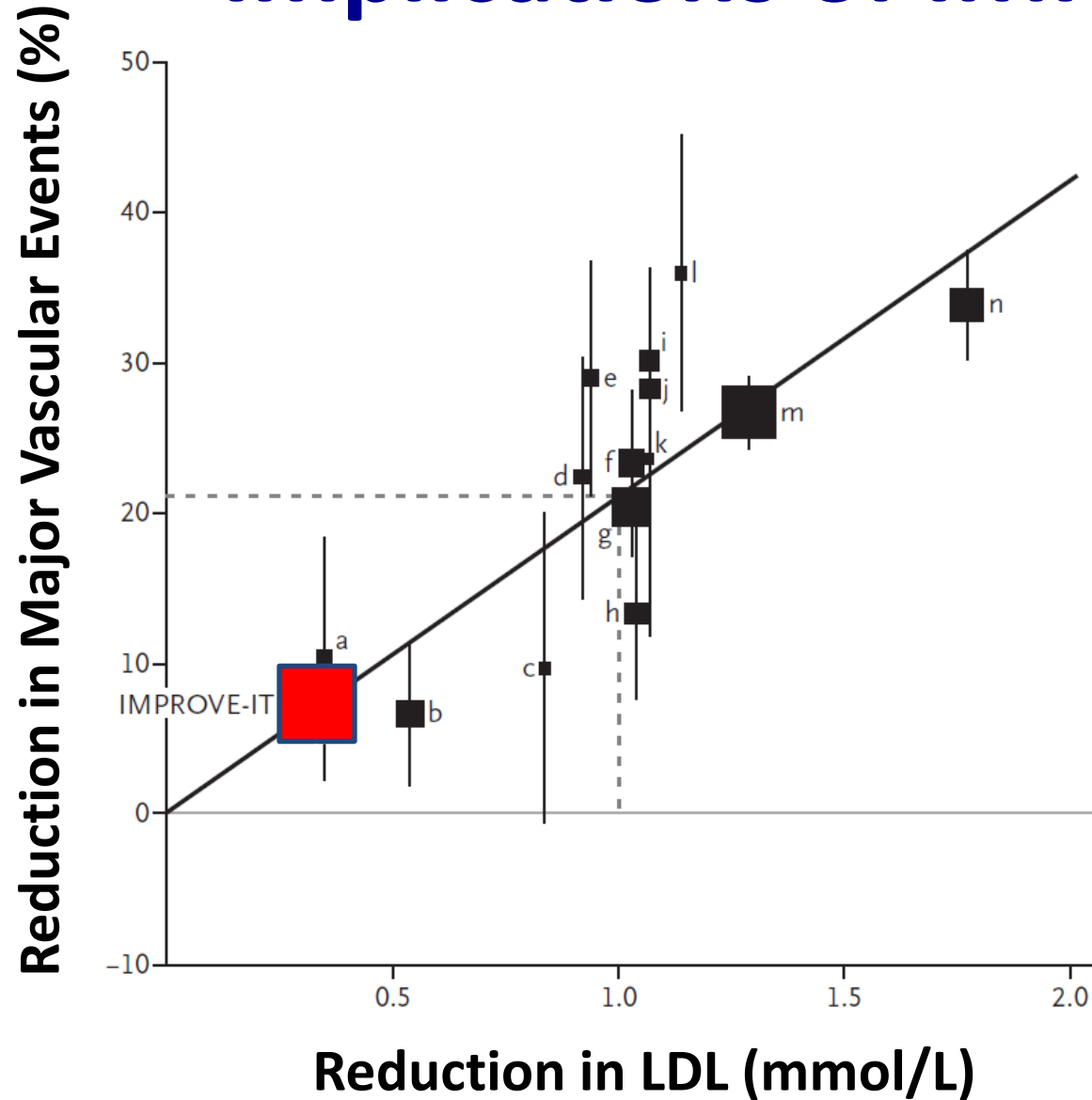
**Statin & Ezetimibe**

**ΔLDL**  
**26% vs 43%**



Cannon C, et al. NEJM 2015

# Implications of IMPROVE-IT



Implies the main effect of statins and non-statins is through LDL lowering

Regenerates interest in LDL targets?

Supports novel LDL lowering therapies

*Cannon C, et al. NEJM 2015*

*Jarcho JA, Keaney, JF. NEJM 2015*

# 2018 Multidisciplinary Lipid Guidelines

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**2018**

## **AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol**

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Scott M. Grundy, Neil J. Stone, Alison L. Bailey, Craig Beam, Kim K. Birtcher, Roger S. Blumenthal, Lynne T. Braun, Sarah de Ferranti, Joseph Faiella-Tommasino, Daniel E. Forman, ... [Show all Authors](#)

Originally published 10 Nov 2018 | *Circulation*. 2018;0:CIR.0000000000000625

Grundy SM, et al.  
2018 Cholesterol Clinical Practice Guidelines

**Circulation. 2018;000:e000–e000.  
DOI: 10.1161/CIR.0000000000000625**

**Build on the 2013 Guidelines**

**Clinical ASCVD:  
ACS, MI, Coronary Revasc, CVA,  
TIA, PAD, AAA**

**Primary Prevention: Risk  
Estimators in Specific Groups**

 **ESC**  
European Society  
of Cardiology  
European Heart Journal (2019) 00, 1–78  
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

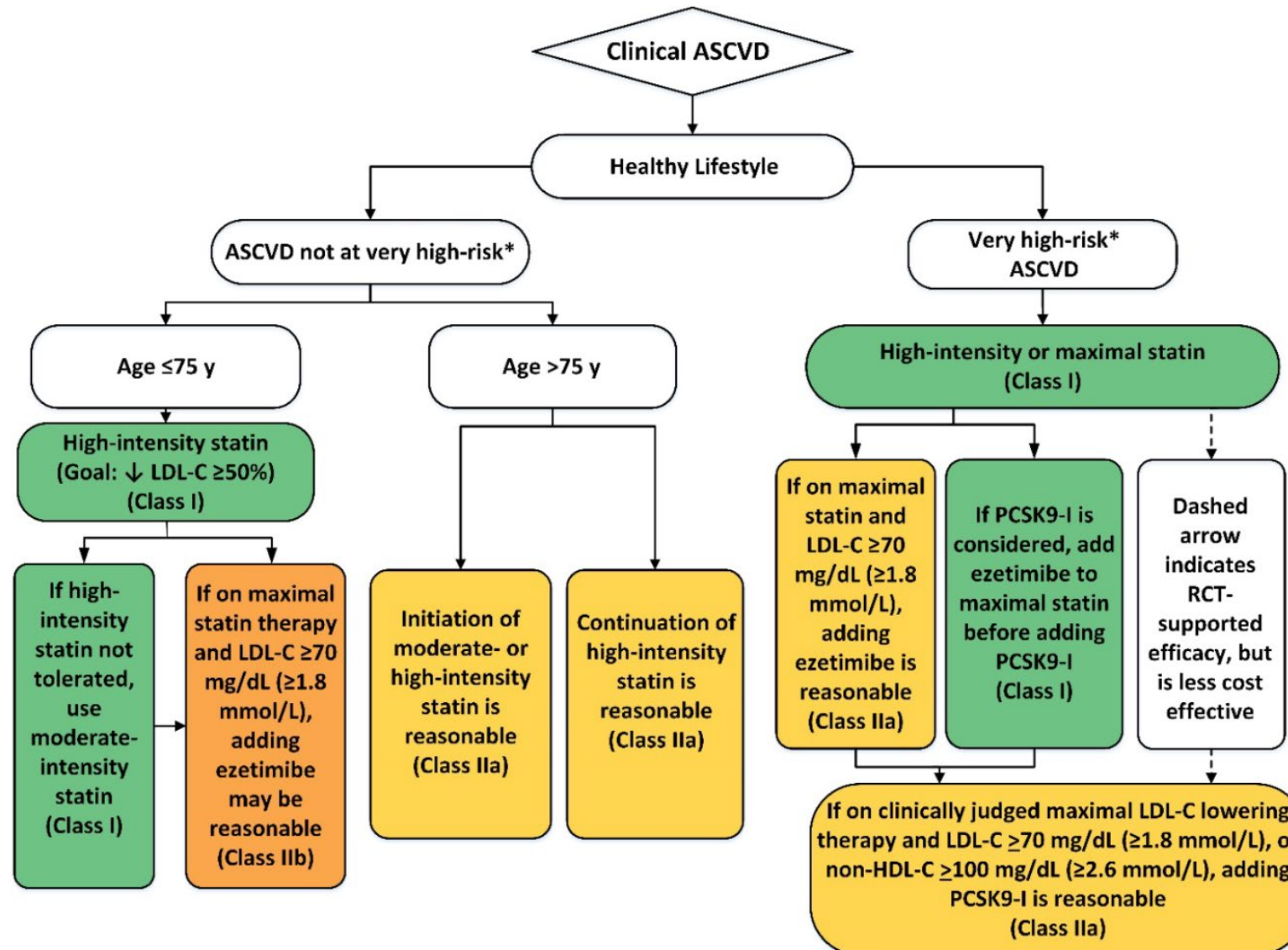


**2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk***

**New ESC 2019 Guidelines Very Similar**

doi:10.1093/eurheartj/ehz455

# 2018: Approach in Patients with Clinical CVD



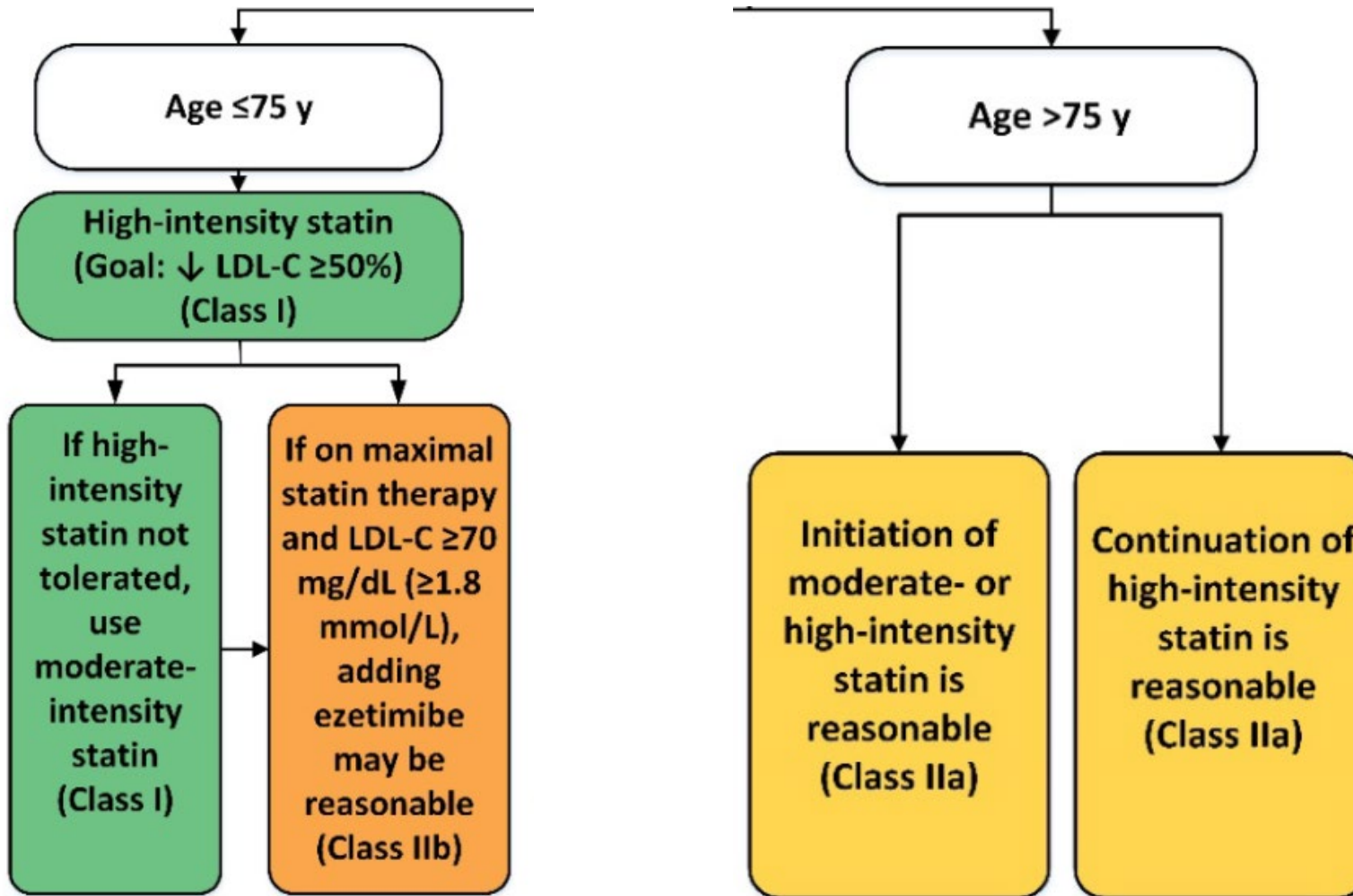
...Let's Break  
This Down...

Grundy SM, et al. 2018 Cholesterol  
Clinical Practice Guidelines  
Circulation. 2019;139:e1082–e1143.  
DOI: 10.1161/CIR.0000000000000625  
Also JACC 2018

# Features of Very High-Risk of Future CVD Event

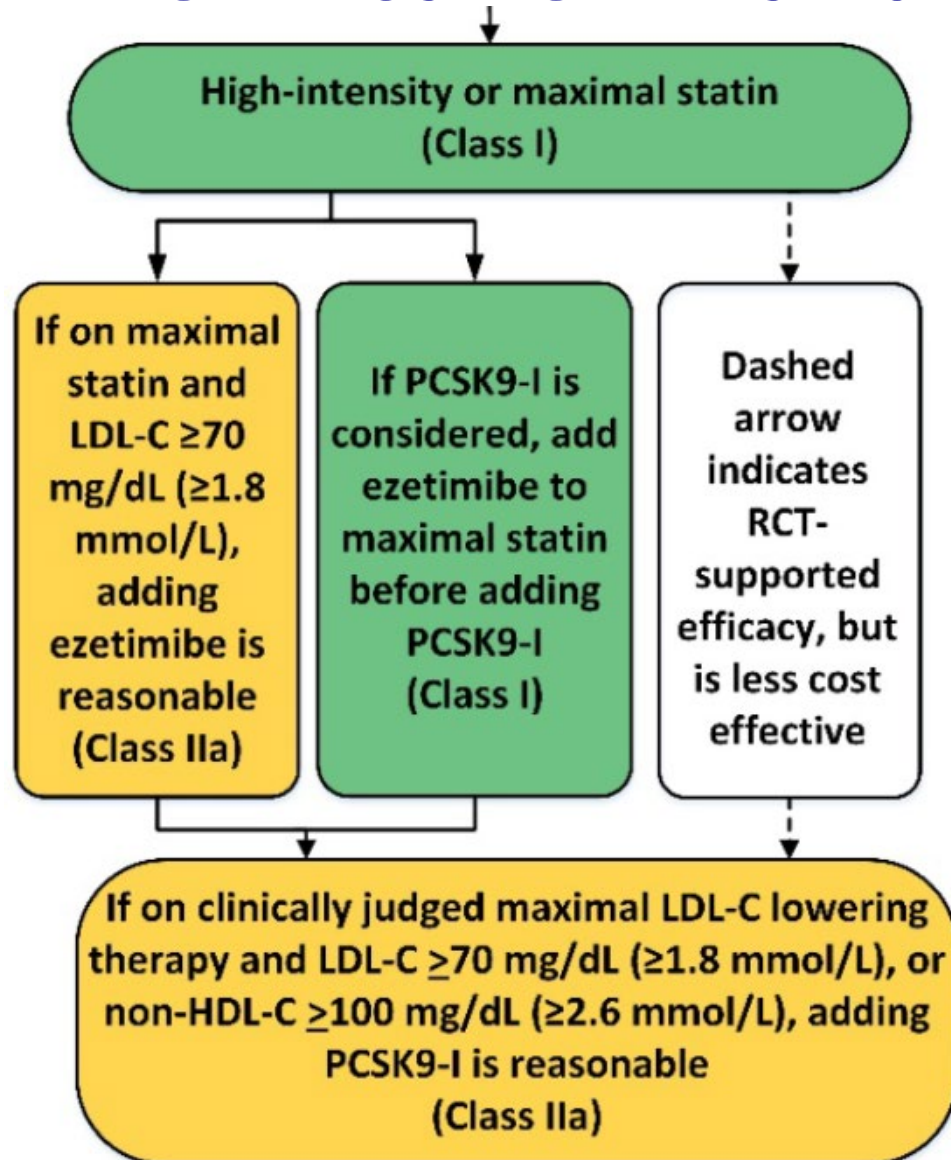
| Major ASCVD Events                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------|
| Recent ACS (within the past 12 mo)                                                                                                      |
| History of MI (other than recent ACS event listed above)                                                                                |
| History of ischemic stroke                                                                                                              |
| Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39)) |
| High-Risk Conditions                                                                                                                    |
| Age ≥65 y                                                                                                                               |
| Heterozygous familial hypercholesterolemia                                                                                              |
| History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)               |
| Diabetes mellitus                                                                                                                       |
| Hypertension                                                                                                                            |
| CKD (eGFR 15-59 mL/min/1.73 m <sup>2</sup> ) (S4.1-15, S4.1-17)                                                                         |
| Current smoking                                                                                                                         |
| Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe                   |
| History of congestive HF                                                                                                                |

# Clinical CVD and Not Very High Risk



*Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines  
Circulation. 2019;139:e1082–e1143.  
DOI: 10.1161/CIR.0000000000000625  
Also JACC 2018*

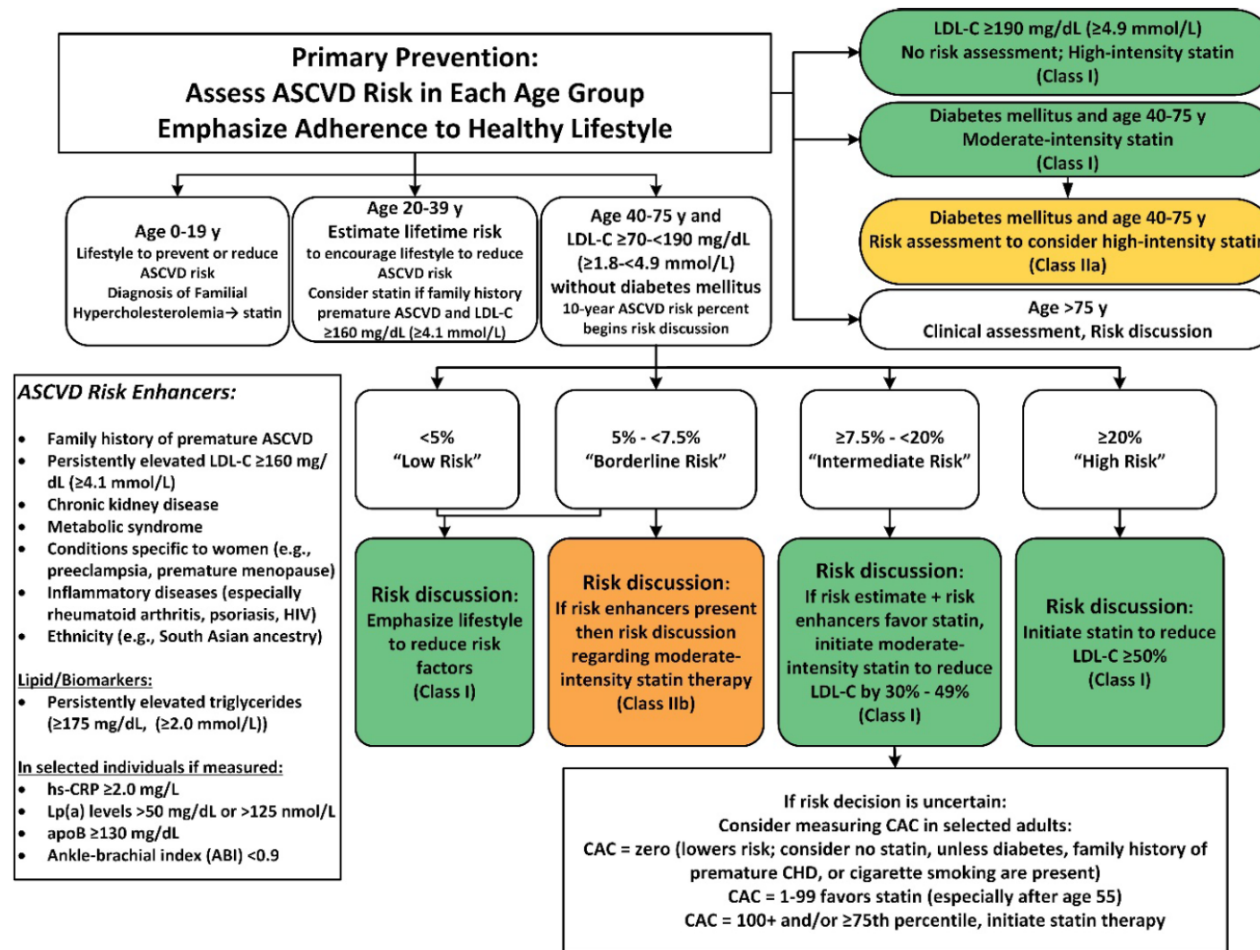
# Clinical CVD and Very High Risk



The 2018 Guidelines acknowledge that the indications for PCSK9 Inhibitors are uncertain in patients on a max statin dose

*Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines Circulation. 2019;139:e1082–e1143. DOI: 10.1161/CIR.0000000000000625 Also JACC 2018*

# Approach to Patients for Primary Prevention



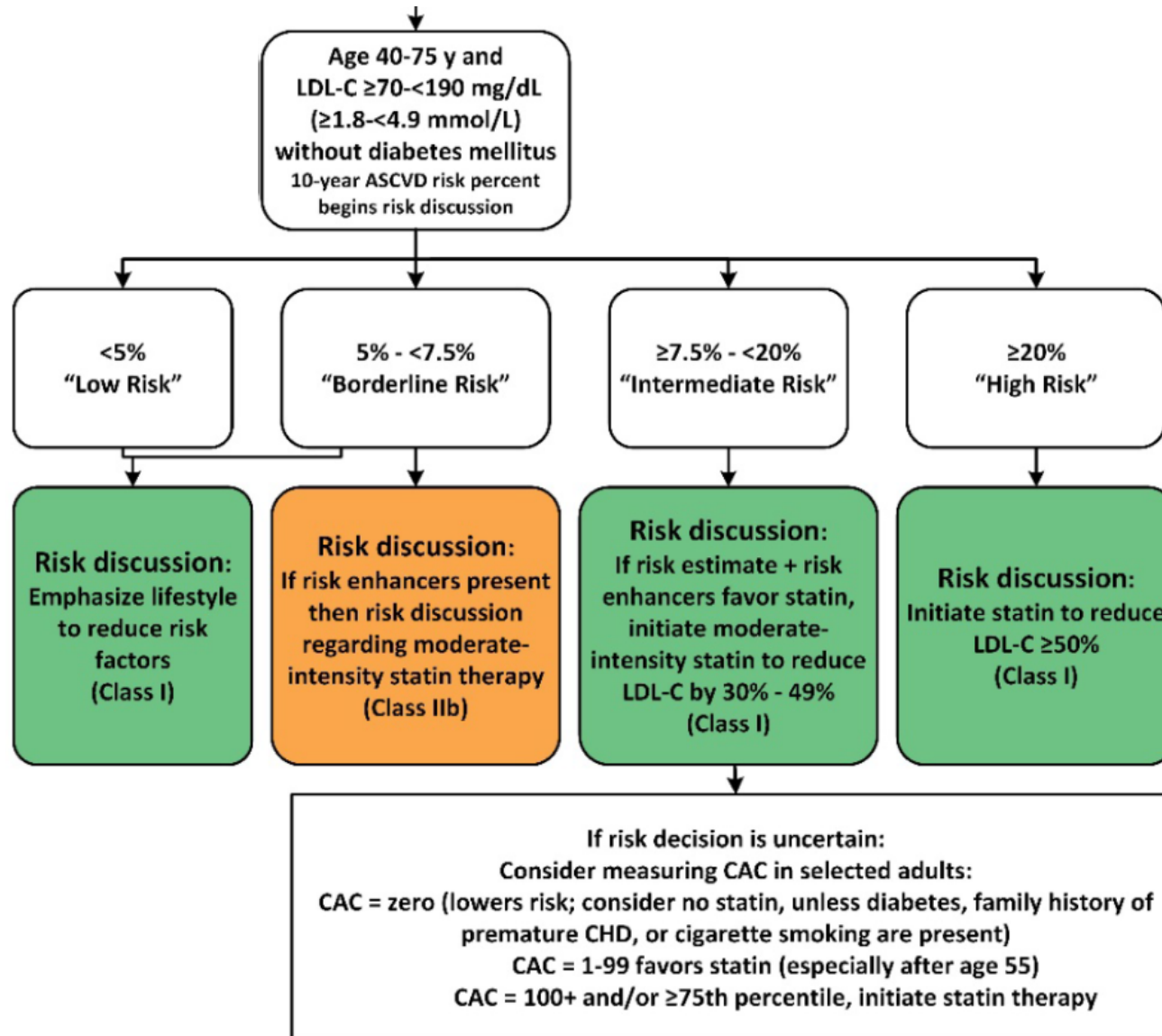
**Diabetes vs No Diabetes  
Estimate Risk**

Colors correspond to Class of Recommendation in Table 2.

apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein (a).

*Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines Circulation. 2019;139:e1082–e1143. DOI: 10.1161/CIR.0000000000000625 Also JACC 2018*

# Patients 40-75 Years of Age No Diabetes



**Estimate Risk**

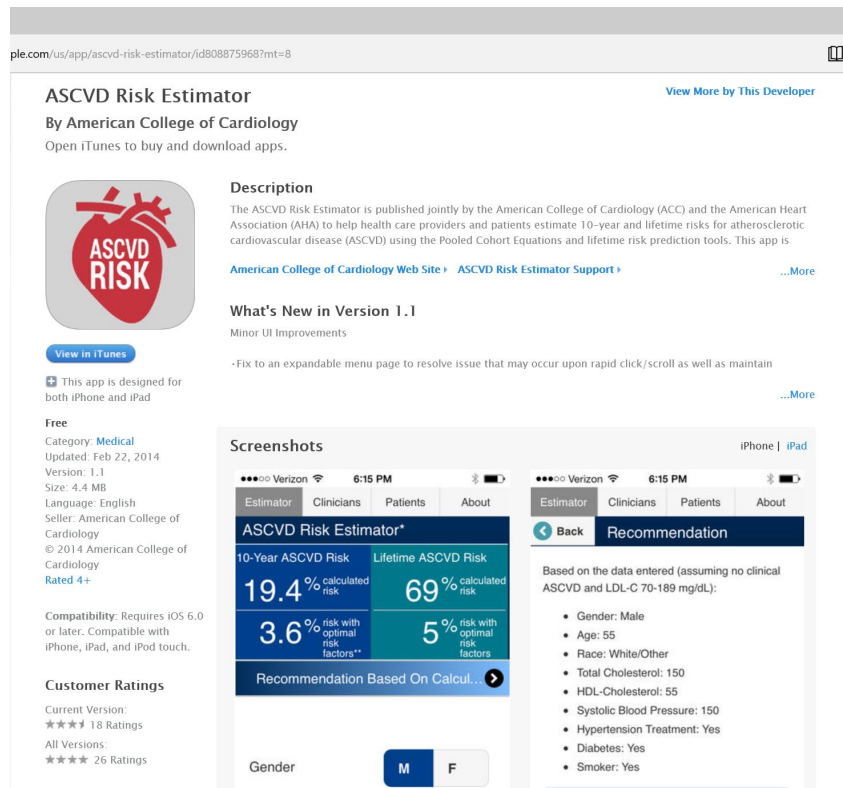
*Grundy SM, et al. 2018 Cholesterol  
Clinical Practice Guidelines  
Circulation. 2019;139:e1082–e1143.  
DOI: 10.1161/CIR.0000000000000625  
Also JACC 2018*

# iPhone App

<https://itunes.apple.com/us/app/ascvd-risk-estimator/id808875968?mt=8>

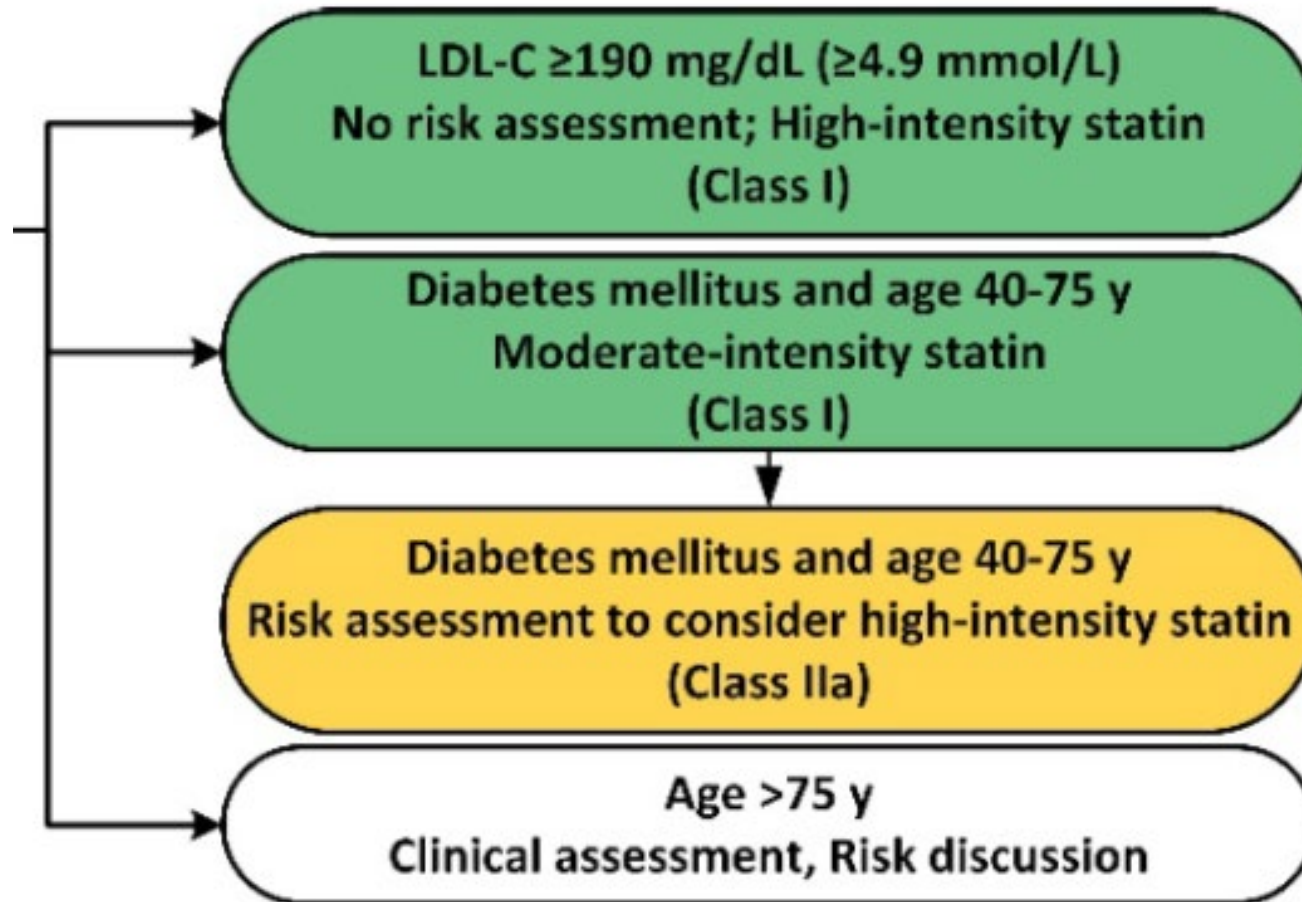
# Android App

<https://play.google.com/store/apps/details?id=org.acc.cvrisk&hl=en>



<http://www.acc.org/tools-and-practice-support/mobile-resources/features/2013-prevention-guidelines-ascvd-risk-estimator>

# Patients 40-75 Years Other Conditions



**Very high LDL (i.e. FH)**  
**Diabetes Mellitus**  
**Age over 75 yrs**

*Grundy SM, et al. 2018 Cholesterol  
Clinical Practice Guidelines  
Circulation. 2019;139:e1082–e1143.  
DOI: 10.1161/CIR.0000000000000625  
Also JACC 2018*

# Risk Enhancers in Patients with Diabetes Mellitus

| Risk Enhancers                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• Long duration (<math>\geq 10</math> years for type 2 diabetes mellitus (S4.3-20) or <math>\geq 20</math> years for type 1 diabetes mellitus (S4.3-6))</li><li>• Albuminuria <math>\geq 30</math> mcg of albumin/mg creatinine (S4.3-25)</li><li>• eGFR <math>&lt; 60</math> mL/min/<math>1.73 \text{ m}^2</math> (S4.3-25)</li><li>• Retinopathy (S4.3-19)</li><li>• Neuropathy (S4.3-16)</li><li>• ABI <math>&lt; 0.9</math> (S4.3-22, S4.3-24)</li></ul> |

ABI indicates ankle-brachial index; and eGFR, estimated glomerular filtration rate.

**= Diabetes and End-Organ Damage**

# Triglycerides and Pancreatitis

- **2018 AHA/ACC Lipid Guidelines**

- Trigs 0-999 mg/dL (0-11.3 mmol/L)

- Lifestyle changes (obesity, DM2)
    - Consider statin if risk of ASCVD > 7.5%

- Trigs > 1000 mg/dL (>11.3 mmol/L): Pancreatitis risk

- **Loose weight** if obese, **low ETOH** and low simple COH (i.e. sugars) diet
    - Omega 3 FA, consider fibrate

- **2012 Endocrine Society Clinical Guidelines Committee**

- Risk of pancreatitis increases above 1000 mg/dL and consider treatment with concentrations higher than this

*Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines Circulation. 2019;139:e1082–e1143. DOI: 10.1161/CIR.0000000000000625 Also JACC 2018*

*Endocrine Society Clinical Guidelines Committee. JClinEndocrMetab 2012; 97: 2969*

# Novel Therapies for LDL Lowering

- **PCSK9 Monoclonal Ab Inhibitors**

- Alirocumab (Praluent)
- Evolocumab (Repatha)

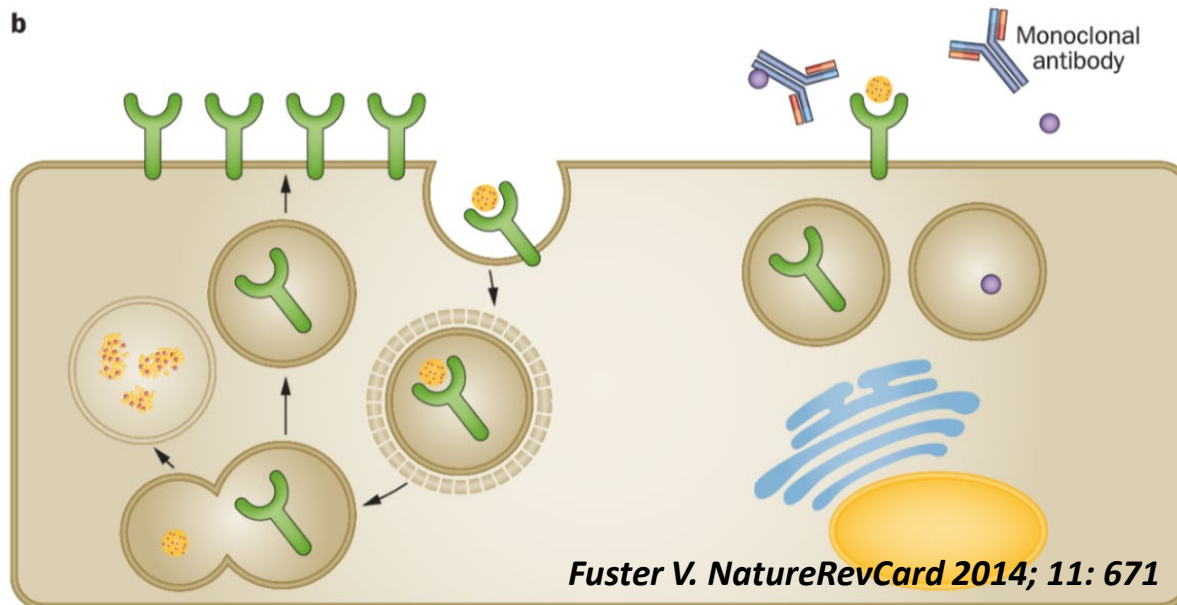
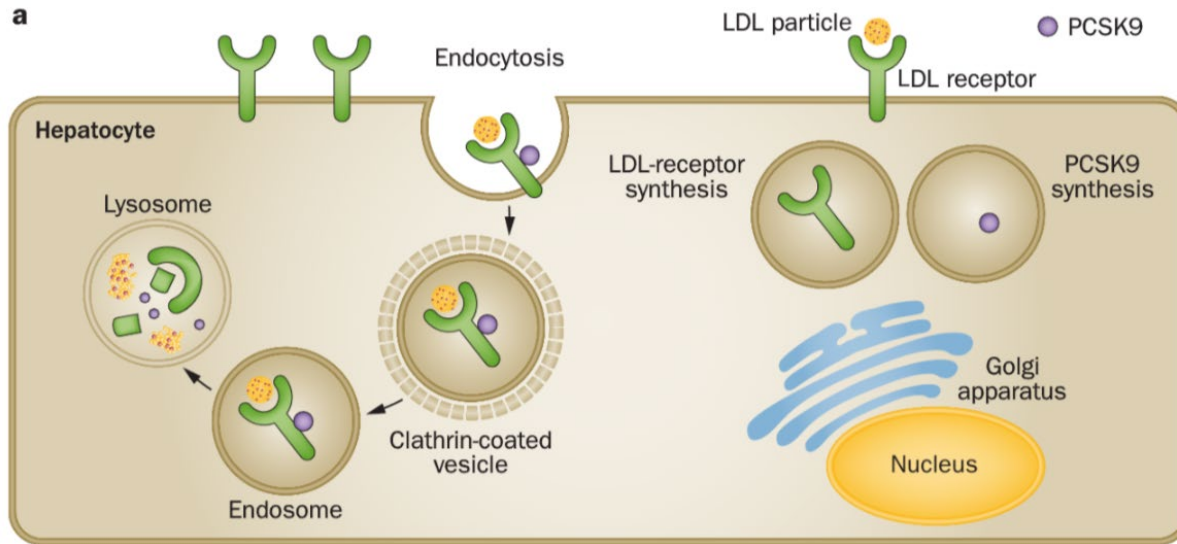


Available  
for Use

- **PCSK9 RNA Interference Drugs**

- Inclisiran – 6mth action in phase 1 trial

# PCSK9 & LDL-Receptor Expression

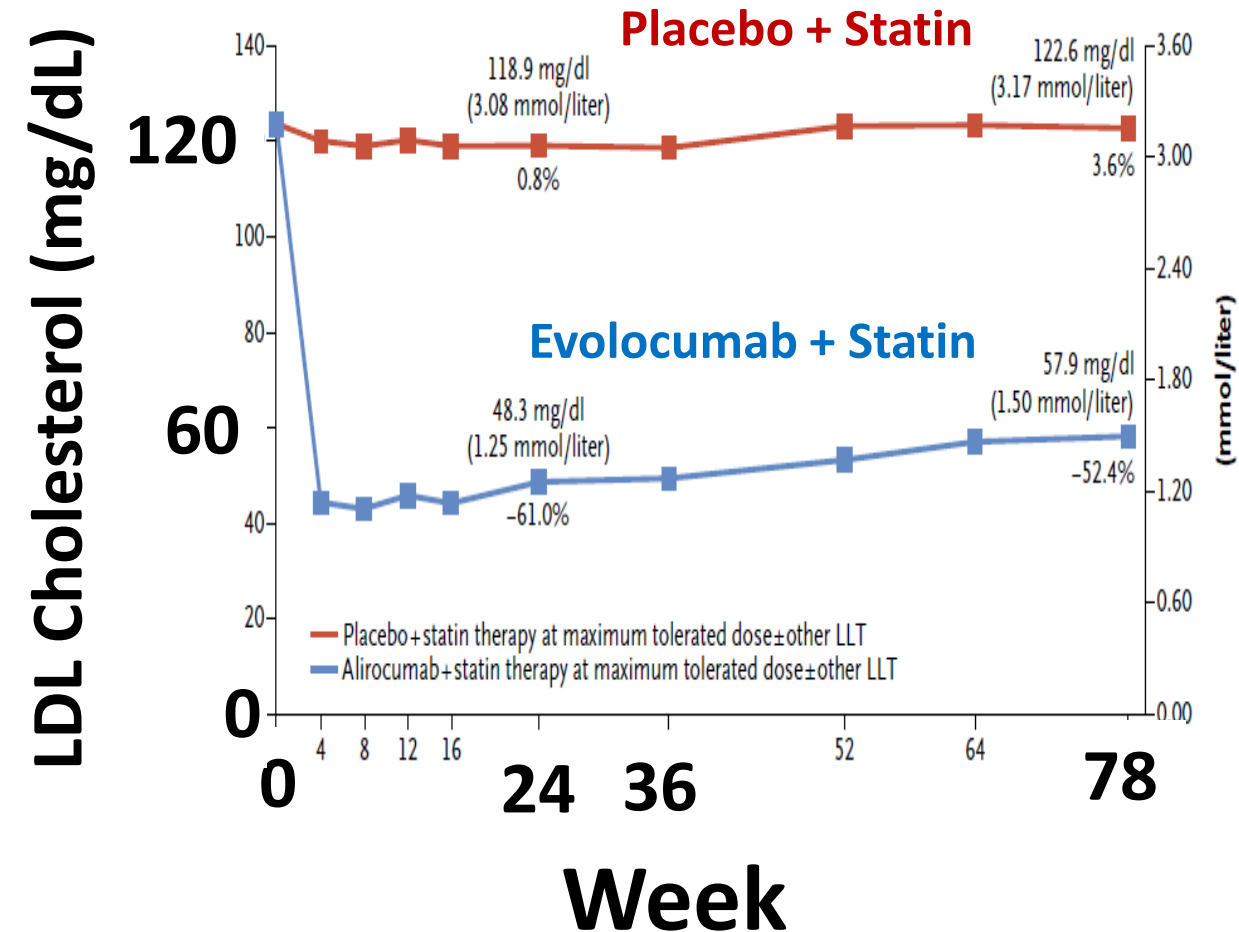


- PCSK9 binds to the LDL receptor
- LDL receptor degrades
- Prevents LDL receptor recycling

- PCSK9 inhibitors block PCSK9 binding to LDL receptors
- Increase LDL receptor recycling and expression

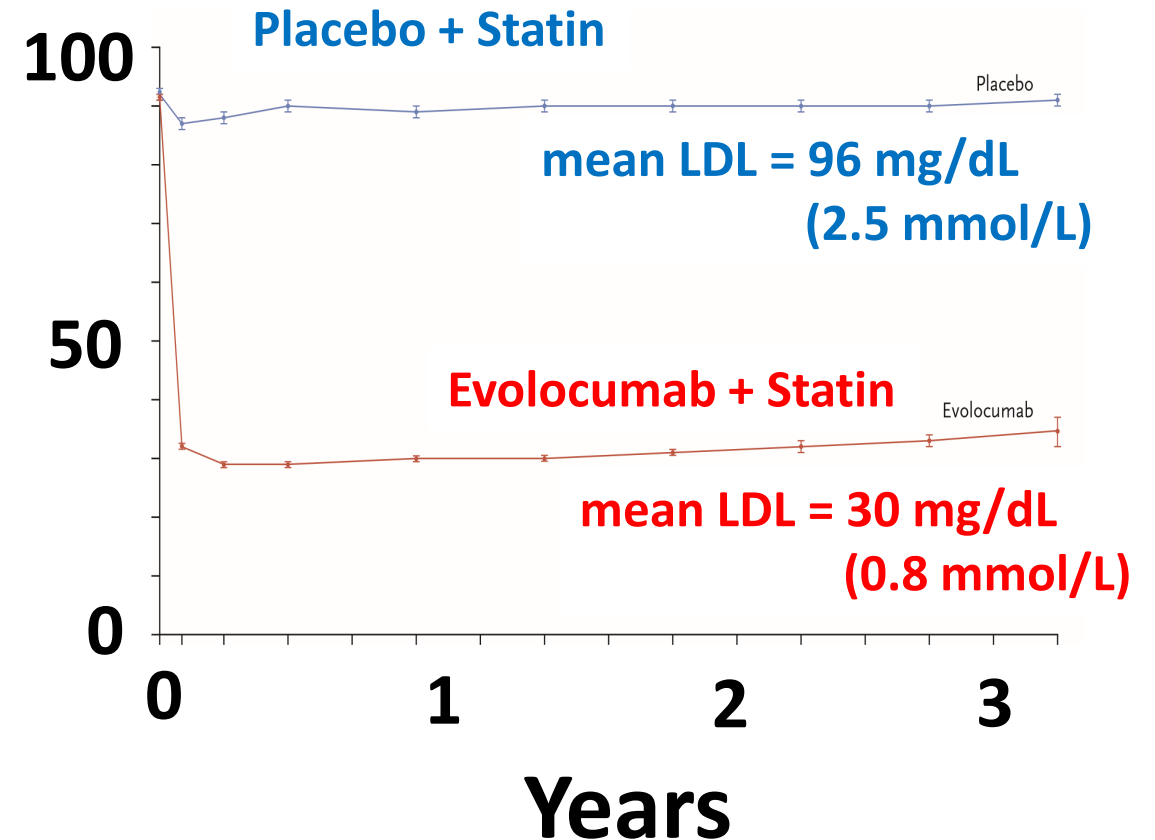
# PCSK9i and LDL Cholesterol Response

## ODYSSEY LONG TERM: Alirocumab



Robinson JG, et al. NEJM 2015; 372: 1489

## FOURIER: Evolocumab

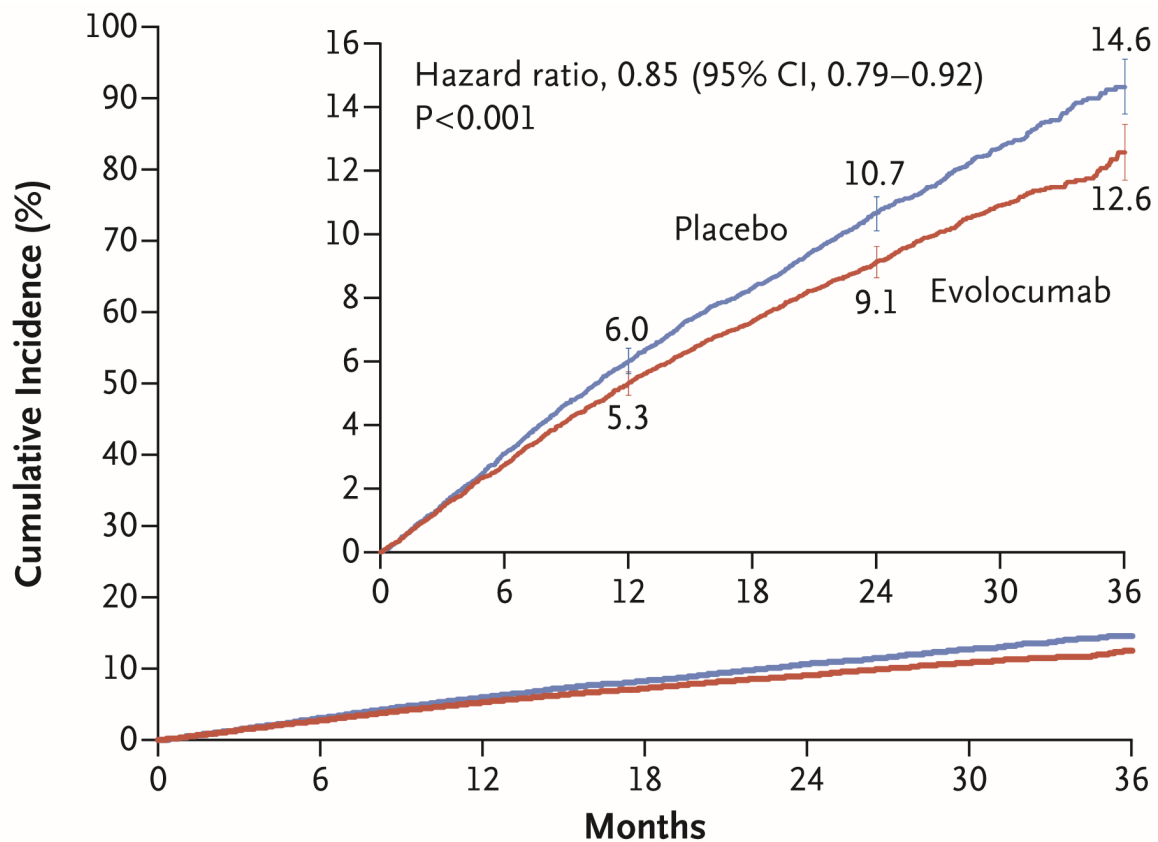


Sabatine MS, et al. NEJM 2017; 376: 1713

# PCSK9i Cardiovascular Outcomes

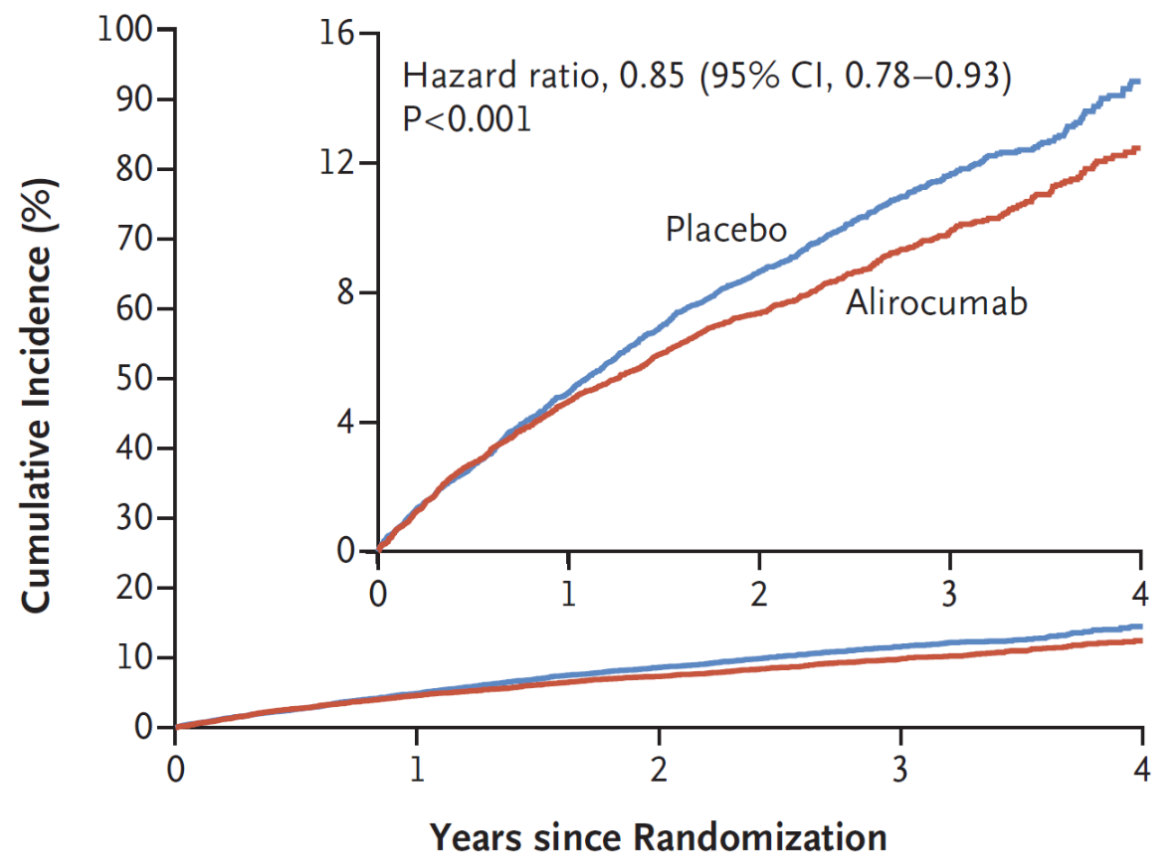
MACE: CV Events, Hospitalization UAP, Revascularization

## FOURIER: Evolocumab



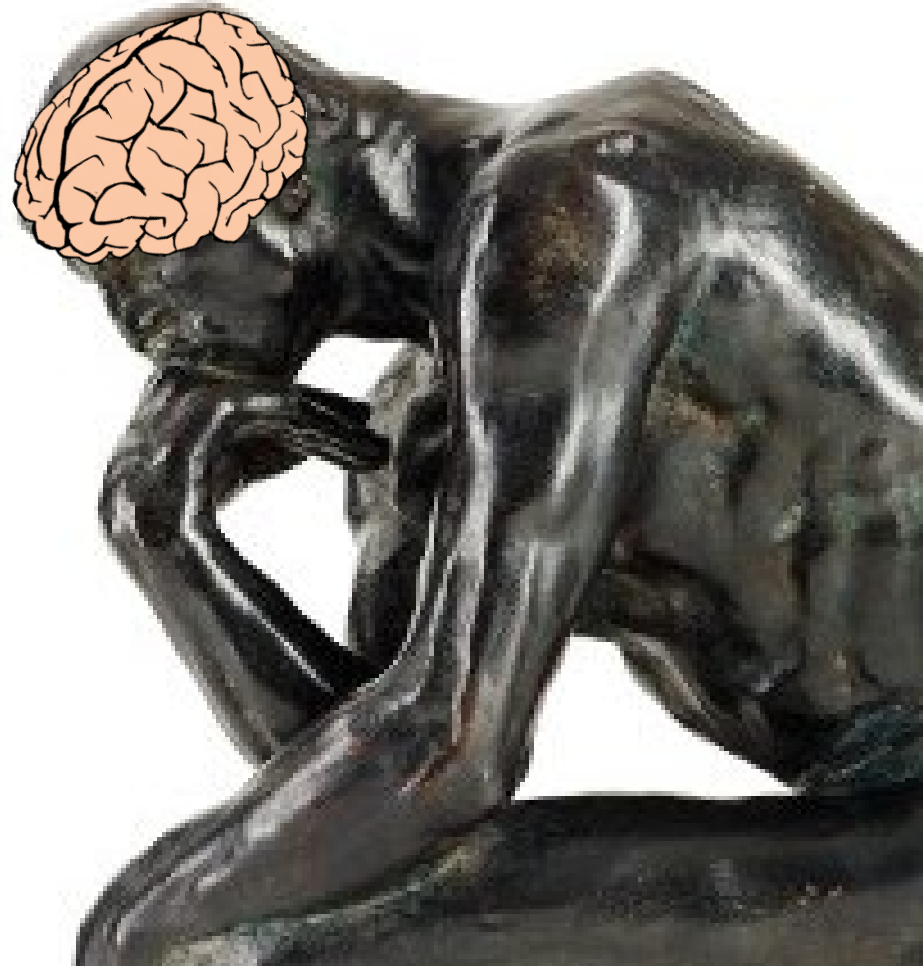
*Sabatine MS, et al. NEJM 2017; 376: 1713*

## ODYSSEY Outcomes: Alirocumab

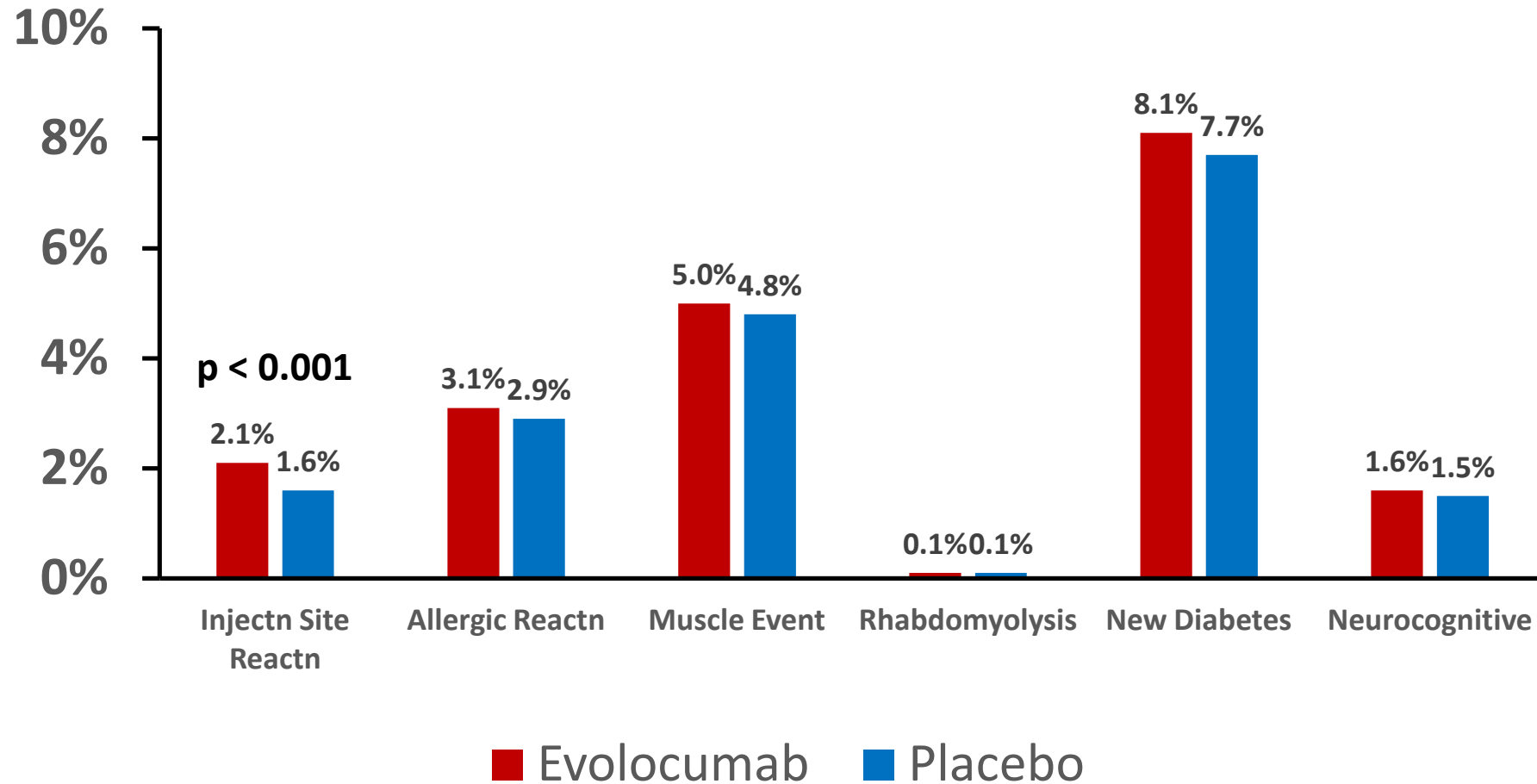


*Schwartz GG, et al. N Engl J Med 2018;379:2097-107*

# What Happens with an Average LDL of 30mg/dL (0.8 mmol/L)?



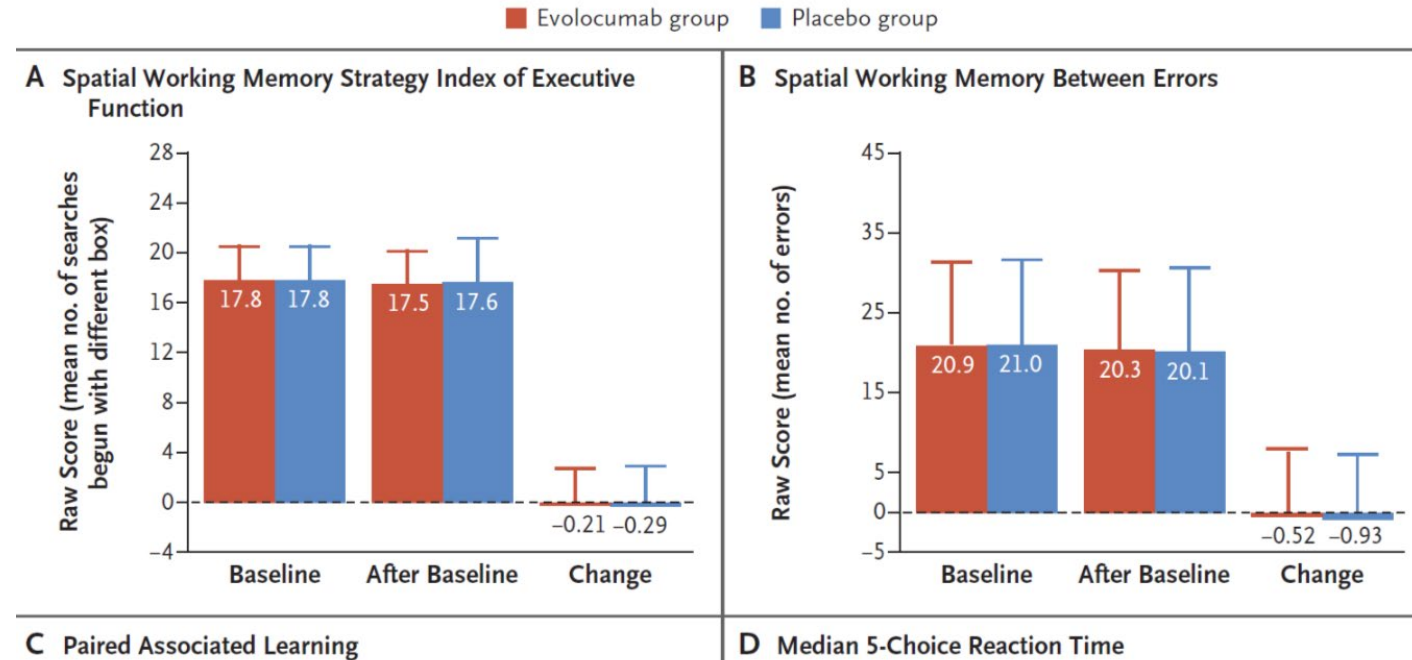
# FOURIER: Adverse Events



# EBBINHAUS Substudy of FOURIER

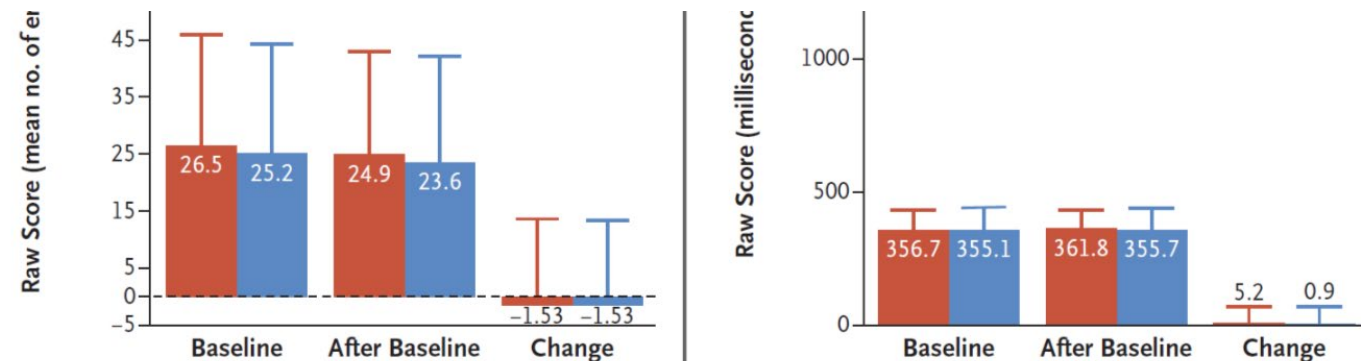
## Cambridge Neuropsychological Test Automated Battery

- 1974 Subjects
- 40-85 Years



**No Difference in Cognitive Function Over 19 months**

*Giugliano R, et al.*  
*NEJM 2017; 377: 633*



# FDA Recommended Doses



- **Alirocumab (Praluent)**
  - 75 mg subcut every 2 weeks
  - 150 mg s/c every 2 weeks if inadequate response
- **Evolocumab (Repatha)**
  - 140 mg s/c every 2 weeks, OR
  - 420 mg s/c every month (3 x 140mg over 30 min)
- **Measure LDL at 4-8 weeks and 6 monthly**

# Cost of PCSK-9 Inhibitors



- Low uptake of Alirocumab and Evolocumab @ \$14,600/ person/ year → Oct 2018 drop in the list price to \$5,850/p/yr
- Cost-effectiveness only acceptable if annual cost drops to ≈ \$4,500 per person
- 2019: Cost-effective for **very high risk patients** with a baseline event rate of 6.9 or more events per 100 patient years

*Schulman KA, et al. N Engl J Med 2015; 373:1591*

*Kazi DS, et al. JAMA 2016;11004 Nov 2016*

*Fonarow GC, et al. JAMA Cardiol 10.1001/jamacardio.2019.1647*

# PCSK9: Prior Authorization



## PCSK9 INHIBITORS (PRALUENT®/REPATHA™) PRIOR AUTHORIZATION Physician Fax Form

Clear Data

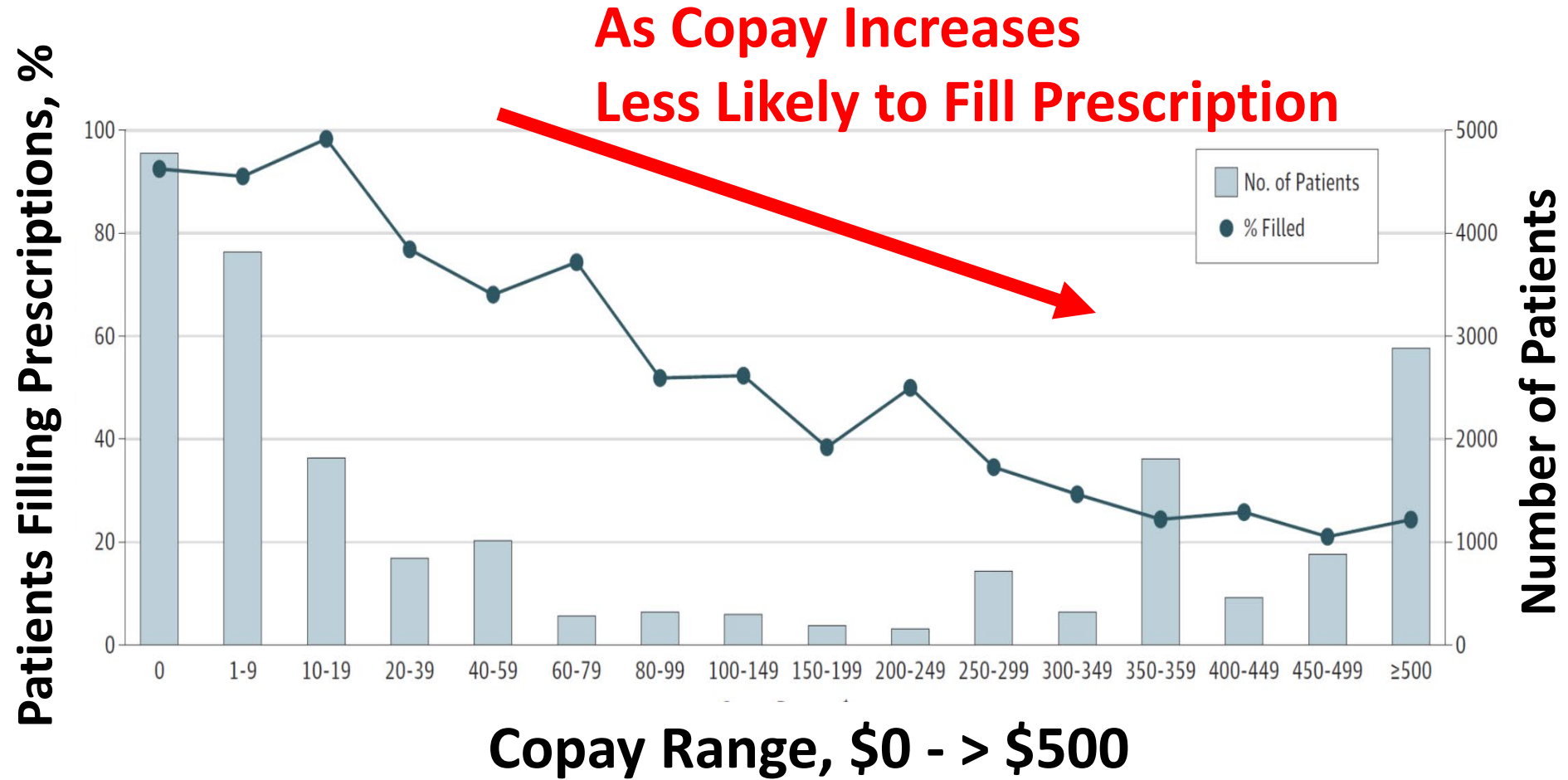
BCBS Kansas **REQUIRES** that this form be completed by the prescriber. This form is for prospective, concurrent and retrospective reviews.

The following documentation is **REQUIRED** for prior authorization. Incomplete forms will be returned for additional information. To ensure you are submitting this form correctly, you can complete and submit it directly to us online at [www.covermymeds.com](http://www.covermymeds.com). For formulary information, please visit the Blue Cross and Blue Shield of Kansas website at <http://www.bcbsks.com>.

|                                                                                                                                                                                      |                 |                                                 |                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------------------------------------------------|-------------------|
| <b>PATIENT INFORMATION</b>                                                                                                                                                           |                 | <b>Today's Date:</b>                            |                   |
| Patient Name (First):                                                                                                                                                                | Last:           | M:                                              | DOB (mm/dd/yyyy): |
| Patient Address:                                                                                                                                                                     |                 | City, State, Zip:                               |                   |
|                                                                                                                                                                                      |                 | Patient Telephone:                              |                   |
| <b>INSURANCE INFORMATION</b>                                                                                                                                                         |                 |                                                 |                   |
| ID Number:                                                                                                                                                                           |                 | Group Number:                                   |                   |
| <b>PHYSICIAN/CLINIC INFORMATION</b>                                                                                                                                                  |                 |                                                 |                   |
| Prescriber Name:                                                                                                                                                                     | Physician NPI#: | Specialty:                                      | Contact Name:     |
| Clinic Name:                                                                                                                                                                         |                 | Clinic Address:                                 |                   |
| City, State, Zip:                                                                                                                                                                    |                 | Phone #:                                        | Secure Fax #:     |
| <b>PLEASE ATTACH ANY ADDITIONAL INFORMATION THAT SHOULD BE CONSIDERED WITH THIS REQUEST</b>                                                                                          |                 |                                                 |                   |
| Medication Requested:                                                                                                                                                                |                 | Strength:                                       |                   |
| Dosing Schedule:                                                                                                                                                                     |                 | Quantity per Month:                             |                   |
| <b>Please provide the following labs (Please note: medical records such as chart notes or labs are REQUIRED).</b>                                                                    |                 |                                                 |                   |
| <b>Untreated values:</b>                                                                                                                                                             |                 | <b>Values on non-PCSK9 cholesterol therapy:</b> |                   |
| LDL-C level: ____ mg/dL                                                                                                                                                              | Date: ____      | LDL-C level: ____ mg/dL                         | Date: ____        |
| Total Cholesterol: ____ g/dL                                                                                                                                                         | Date: ____      | Total Cholesterol: ____ g/dL                    | Date: ____        |
| <b>Current values:</b>                                                                                                                                                               |                 |                                                 |                   |
| LDL-C level: ____ mg/dL                                                                                                                                                              | Date: ____      | LDL-C level: ____ mg/dL                         | Date: ____        |
| Total Cholesterol: ____ mg/dL                                                                                                                                                        | Date: ____      | Total Cholesterol: ____ mg/dL                   | Date: ____        |
| <b>ALL REQUESTS (Chart notes and laboratory documentation are required for review):</b>                                                                                              |                 |                                                 |                   |
| 1. What is the patient's diagnosis?                                                                                                                                                  |                 |                                                 |                   |
| <input type="checkbox"/> <b>Homozygous familial hypercholesterolemia (HoFH)</b>                                                                                                      |                 |                                                 |                   |
| Has the diagnosis been confirmed by any of the following?(check all that apply)..... <input type="checkbox"/> Yes <input type="checkbox"/> No                                        |                 |                                                 |                   |
| <input type="checkbox"/> Genetic confirmation of <b>two</b> mutant alleles at the <i>LDLR</i> , <i>Apo-B</i> , <i>PCSK9</i> , <i>ARH</i> adaptor protein <i>1/LDLRAP1</i> gene locus |                 |                                                 |                   |
| <input type="checkbox"/> Cutaneous or tendon xanthoma before age 10 years                                                                                                            |                 |                                                 |                   |
| <input type="checkbox"/> History of untreated LDL-C >500 mg/dL (>13 mmol/L) or treated LDL-C ≥300 mg/dL (≥7.76 mmol/L)                                                               |                 |                                                 |                   |
| <input type="checkbox"/> Untreated elevated LDL-C levels consistent with heterozygous FH in both parents [untreated LDL-C >190 mg/dL (>4.9 mmol/L)]                                  |                 |                                                 |                   |
| <input type="checkbox"/> <b>Heterozygous familial hypercholesterolemia (HeFH)</b>                                                                                                    |                 |                                                 |                   |
| Has the diagnosis been confirmed by any of the following?(check all that apply)..... <input type="checkbox"/> Yes <input type="checkbox"/> No                                        |                 |                                                 |                   |
| <input type="checkbox"/> Genetic confirmation of <b>one</b> mutant allele at the <i>LDLR</i> , <i>Apo-B</i> , <i>PCSK9</i> , <i>ARH</i> adaptor protein <i>1/LDLRAP1</i> gene locus  |                 |                                                 |                   |
| <input type="checkbox"/> History of total cholesterol greater than 290 mg/dL (>7.5 mmol/L) or LDL-C greater than 190 mg/dL (>4.9 mmol/L)                                             |                 |                                                 |                   |
| Does the patient have a history of tendon xanthomas? ..... <input type="checkbox"/> Yes <input type="checkbox"/> No                                                                  |                 |                                                 |                   |
| If no, is there history of tendon xanthomas in any of the following?                                                                                                                 |                 |                                                 |                   |
| <input type="checkbox"/> Patient's first degree relative (i.e. parent, sibling, or child) <input type="checkbox"/> Patient's second degree relative (i.e. grandparent, uncle, aunt)  |                 |                                                 |                   |
| Does the patient have any of the following (please check all that apply):                                                                                                            |                 |                                                 |                   |



# PCSK9 Access



# Prescribing PCSK9 Inhibitors

Cost Often Covered by 3<sup>rd</sup> Party Payers

- **Familial Hypercholesterolemia**

- Abnormal gene or LDL > 250 with xanthomas or a family history of premature ASCVD or Dutch Score > 8
- AND, High dose atorva/rosuva and ezetimibe not resulted in a > 50% reduction in LDL
- AND, Counseled on healthy lifestyle, other RF changes

- **Very High Risk Patients with Multiple CV Events**

- Recurrent MI, Revascularization, and LDL > 70-100 mg/dL on statin and Ezetimibe (or sometimes if intolerant to multiple statins)
- AND, Counseled on healthy lifestyle, other RF changes
- FDA is concerned that patients will skip statins and go straight to PCSK9i

# Key Points & Summary

- Lifestyle changes are fundamental
- Describe food groups *not* fats/COH/protein to patients
- New 2018 lipid guidelines build on 2013 guidelines
  - Clinical CVD versus No Clinical CVD +/- Diabetes
  - Emphasize statin therapy of two intensities
  - Use of statin, ezetimibe, and PCSK9 inhibitors
- Avoid statins where they are of no benefit
- PCSK9 Inhibitors are powerful novel agents but limited in their availability mainly to very high risk patients

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