Landmark Clinical Trials

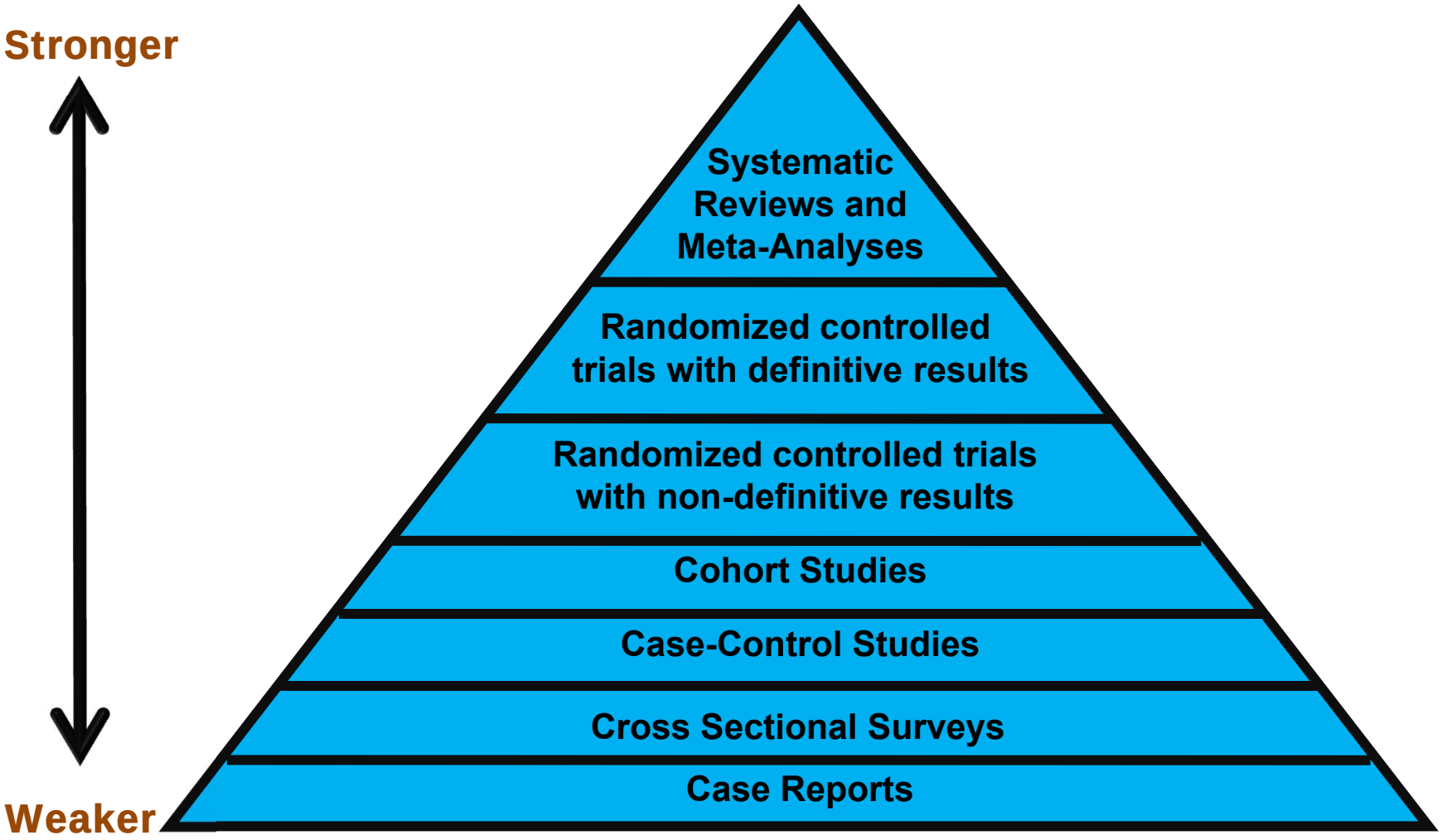
Learning Objectives

- Discuss clinical trials and their role in lipid and lipoprotein treatment in cardiovascular prevention.
- Review the clinical trials of lipid-altering drug therapies used in cardiovascular disease prevention.
- Apply basic principles of statistics to enhance understanding of clinical trials related to lipid management.

Outline

- Overview of Basic Study Design and Biostatistics
- Prominent Landmark Clinical Trials:
  - Statin trials
  - LDL-C focused nonstatin trials
  - Mixed lipid modification focused nonstatin trials
  - Triglyceride/HDL-C focused nonstatin trials
- Other Landmark Trials
- Trials on the Horizon

Hierarchy of Evidence



Guyatt GH, et al. *JAMA.* 1995;274:1800-1804.

Clinical Trials: Endpoint Analysis

- **Primary Endpoints**:
  - Prospectively determined outcome
  - Main purpose of study, basis of power calculation
  - Results should be definitive
- **Secondary Endpoints**:
  - Prospectively determined outcome
  - Study may not have power to detect a difference
  - Results not designed to definitive
- **Subgroup Analyses**:
  - Results are speculative and hypothesis generating

Significance of Study Findings

Statistical Significance

- **P-value** represents the probability that an association occurred due to chance
  - P = 0.05 = 5% or 5/100 chance that the association occurred due to random variation
- **Confidence Interval** (CI)
  - 95% CI = range within which one can be 95% confident that the true value lies
  - Smaller 95% CI indicates greater precision in the point estimate of the effect

Clinical Significance

- Difference is meaningful to patient care

Interpreting Study Results

- **Relative risk reduction (RRR)**:

$$RRR = \frac{(control\ event\ rate) - (treatment\ event\ rate)}{(control\ event\ rate)}$$

- **Absolute risk reduction (ARR)**:

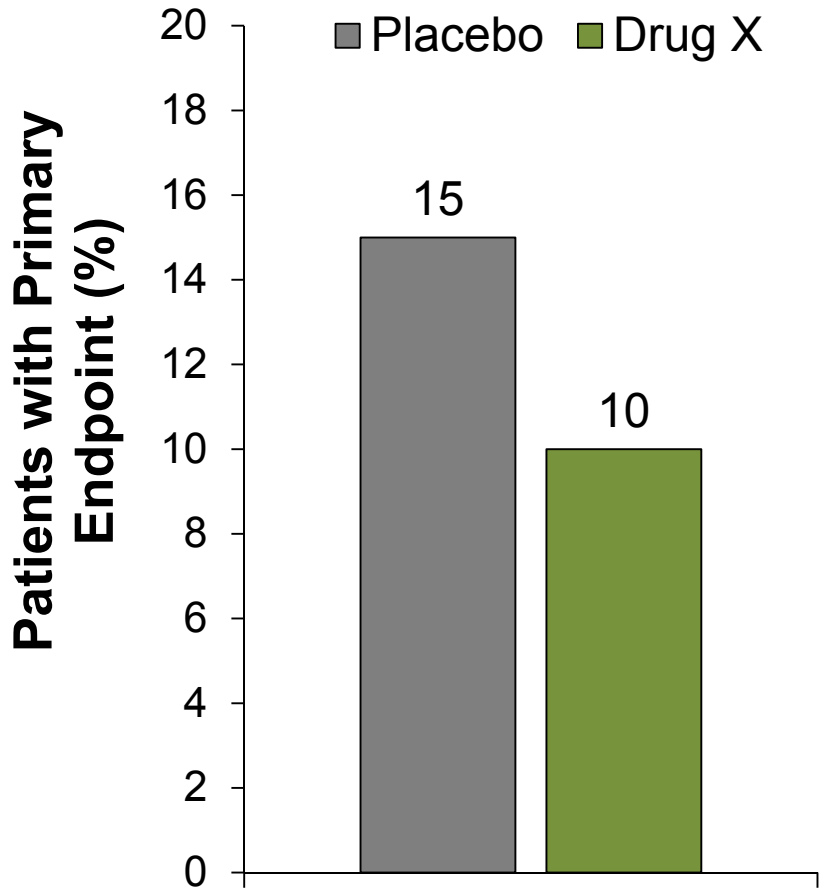
$$ARR = (control\ event\ rate) - (treatment\ event\ rate)$$

- **Number Needed to Treat (NNT)**:
  - Number of patients that must be treated with studied therapy to prevent one event/endpoint

$$NNT = \frac{1}{ARR}$$

Number needed to harm can be calculated to assess serious adverse effects

Example Clinical Trial



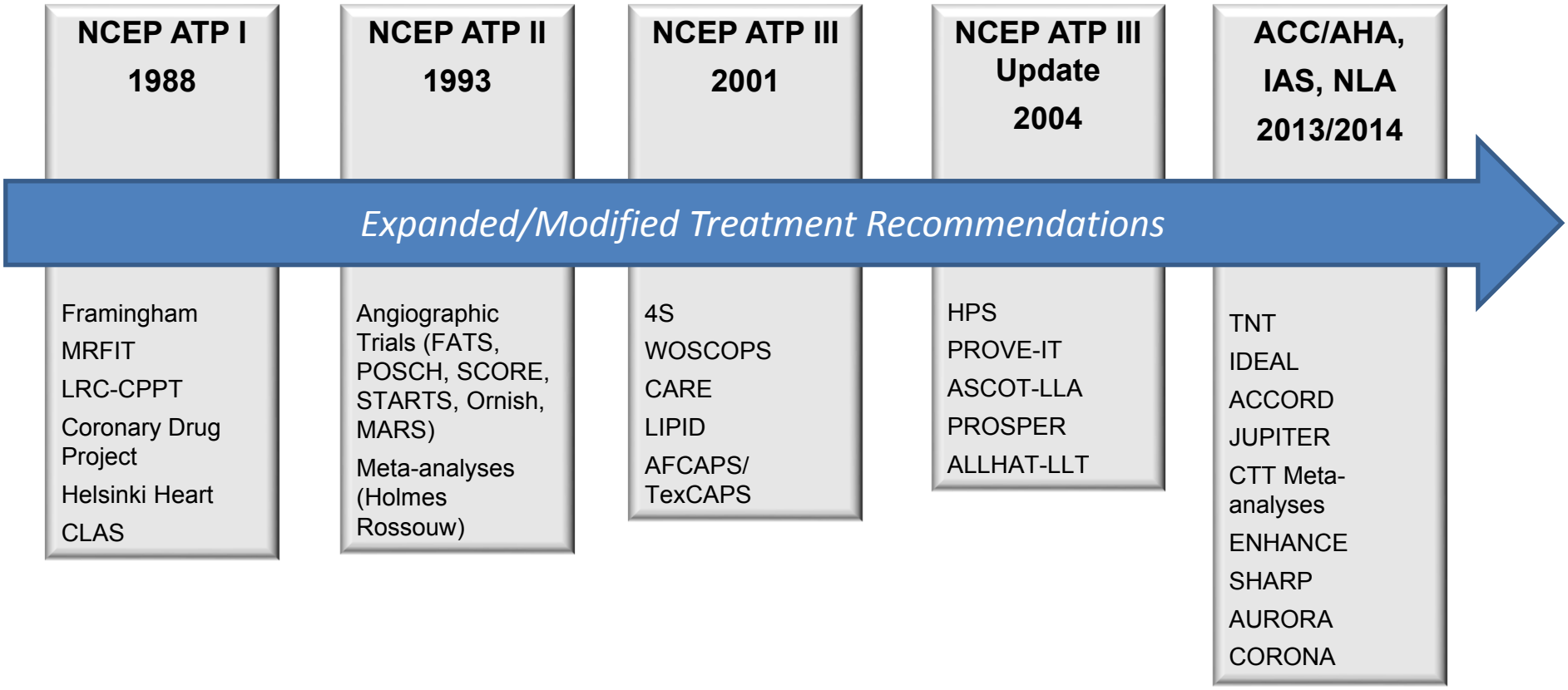
$$RRR = \frac{15\%-10\%}{15\%} = 33\%$$

$$ARR = 15\%-10\% = 5\%$$

$$NNT = \frac{1}{5\%} = \frac{1}{0.05} = 20$$

Amarenco P, et al. *N Engl J Med* 2006;355:549-59.

Evolution of Guidelines and Landmark Trials



NHLBI = National Heart, Lung, and Blood Institute
NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel
AHA = American Heart Association
ACC = American College of Cardiology
IAS = International Atherosclerosis Society

EXAMPLE: ACC/AHA Evidence-Based Recommendation Ranking Format

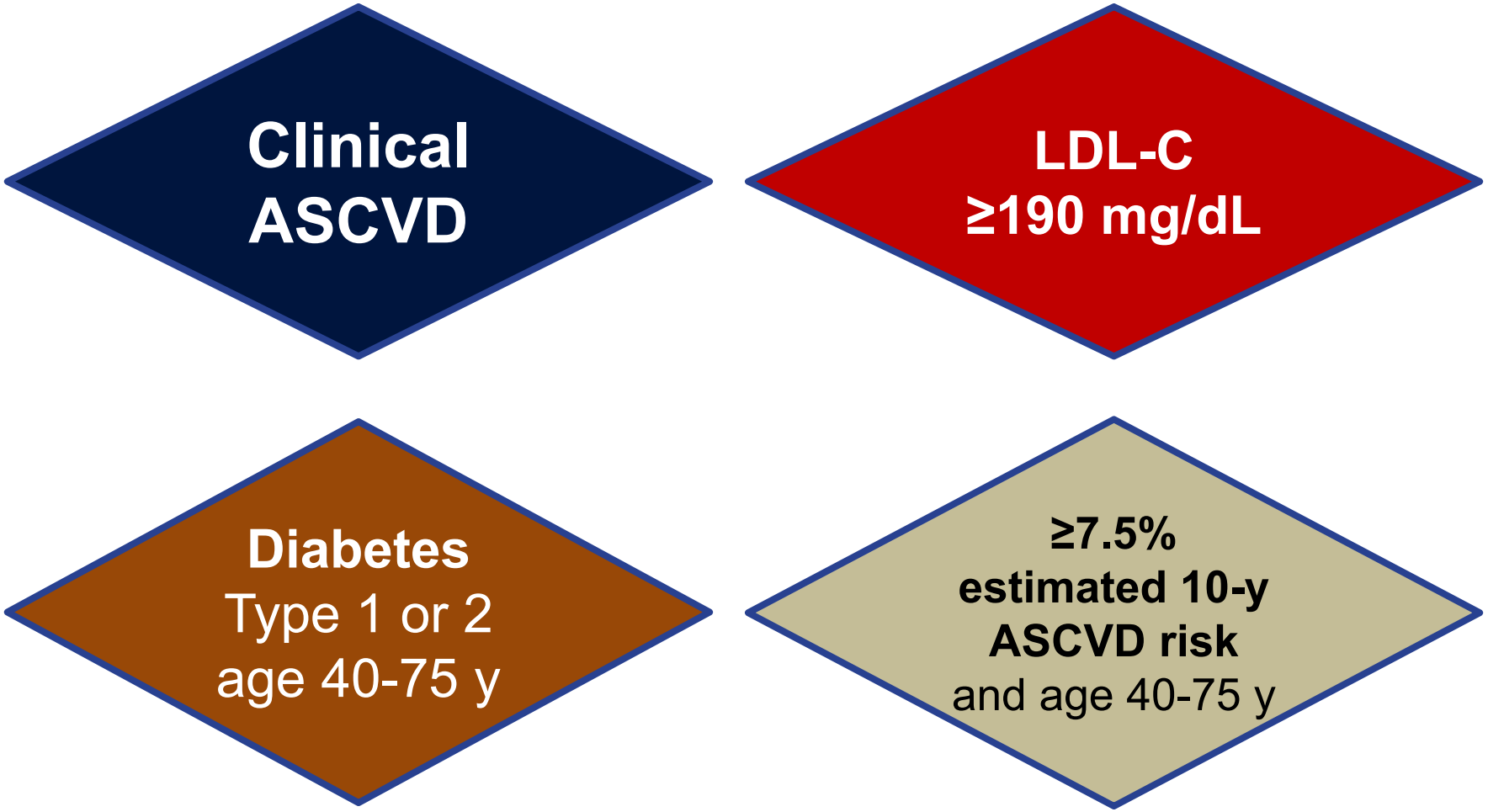
- **Class of Recommendations**
  - Class I: Benefits >>> Risk
  - Class IIa: Benefits >> Risk
  - Class IIb: Benefit ≥ Risk
- **Level of Evidence**
  - Level A: Multiple populations; data from multiple RCTs or meta-analyses
  - Level B: Limited populations and single RCT or non-controlled studies
  - Level C: Very limited populations; consensus opinion

Stone NJ, et al. Circulation. 2013: published online before print November 12, 2013.

Statin Trials

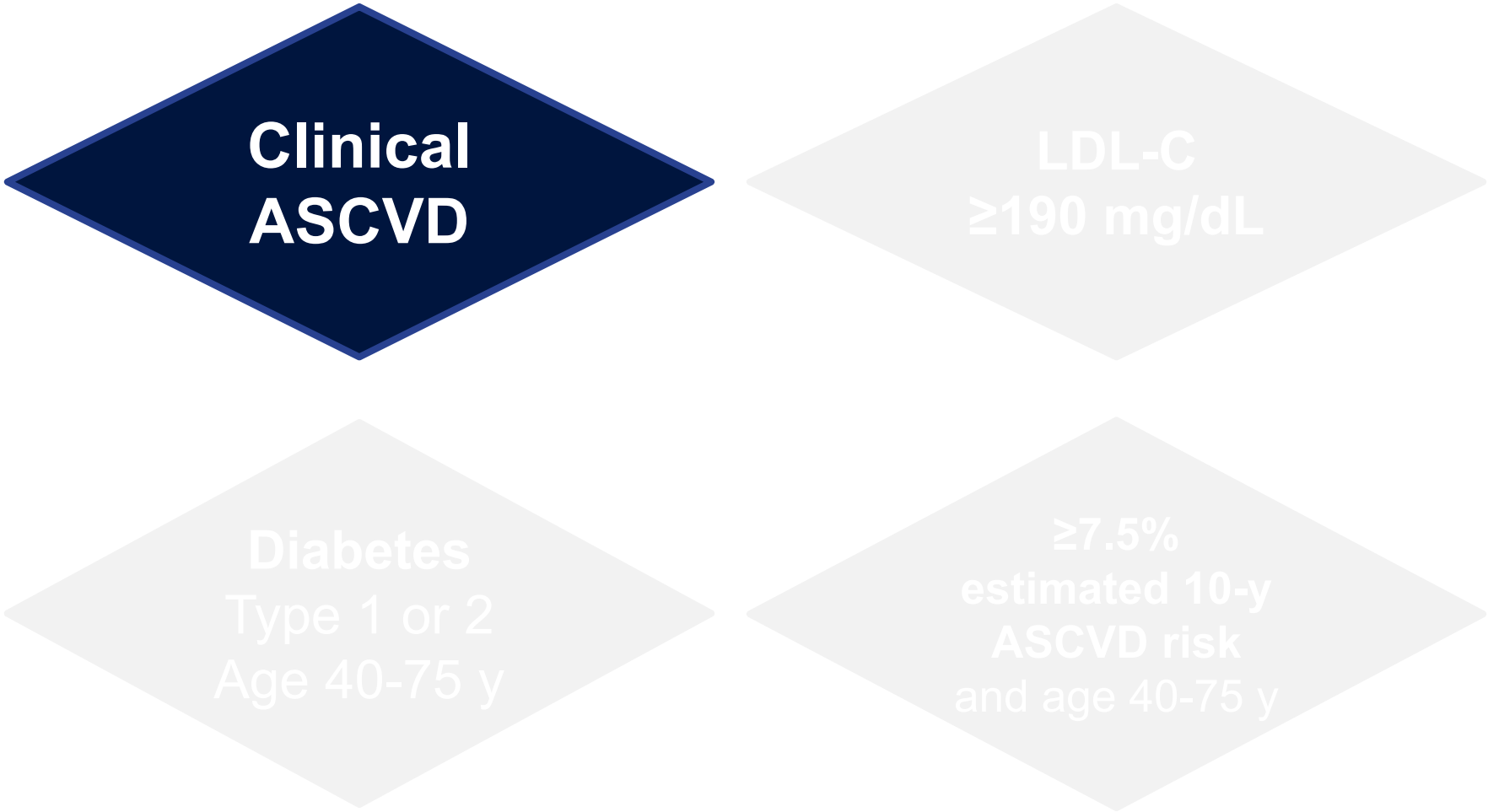
- AFCAPs/TexCAPs
- 4S
- HPS
- PROVE-IT
- ASCOT-LLA
- WOSCOPS
- CARE
- LIPID
- MEGA
- A to Z
- REVERSAL
- ASTEROID
- CARDS
- TNT
- JUPITER
- SEARCH
- METEOR
- IDEAL
- SPARCL
- ALLHAT-LLT
- PROSPER
- 4D
- MIRACLE
- AURORA
- CORONA

2013 ACC/AHA Blood Cholesterol Guideline 4 Statin Benefit Groups



Stone NJ, et al. Circulation. 2013: published online before print November 12, 2013.

2013 ACC/AHA Blood Cholesterol Guideline 4 Statin Benefit Groups



Stone NJ, et al. Circulation. 2013: published online before print November 12, 2013.

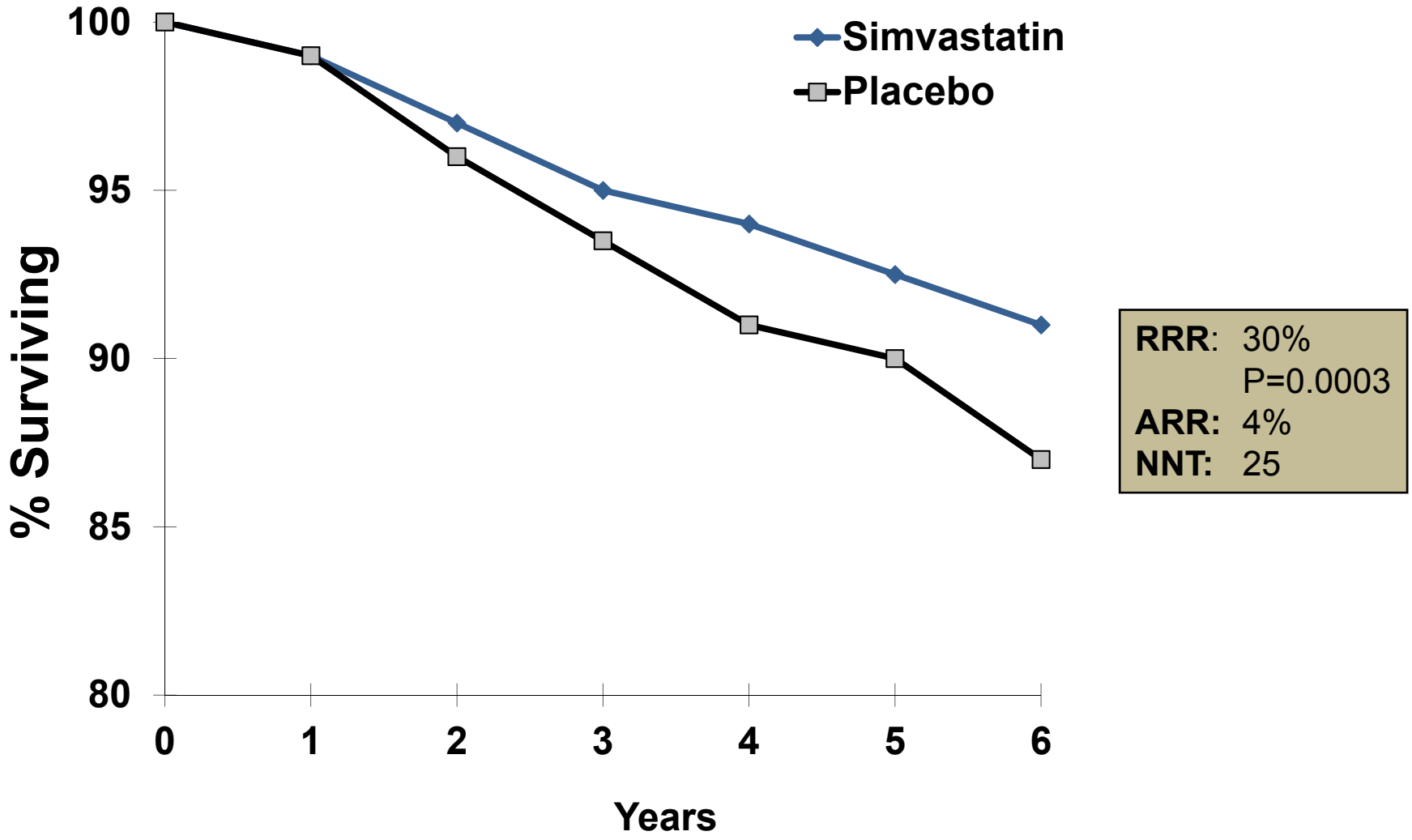
Scandinavian Simvastatin Survival Study (4S)

- Double-blind trial in 4444 men and women 35 to 70 years of age with prior MI and/or angina pectoris and total cholesterol (TC) of 212-309 mg/dL
- Randomized to simvastatin 20 mg daily or placebo; simvastatin increased to 40 mg daily if TC > 200 mg/dL
- Median duration was 5.4 years

- Primary Endpoint: All cause mortality

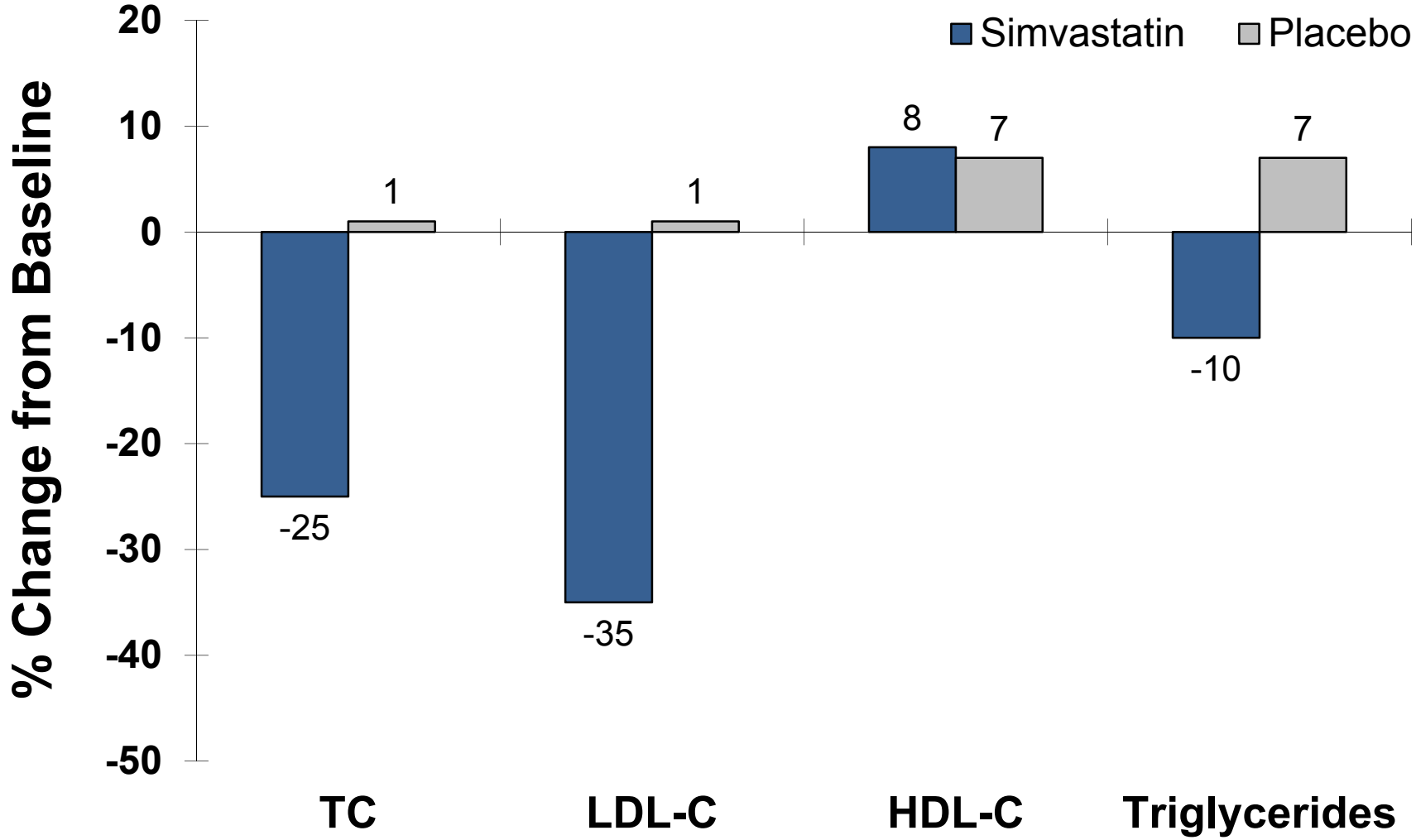
The Scandinavian Simvastatin Survival Study Group. *Lancet.* 1994;344:1383-1389.

4S Primary Endpoint



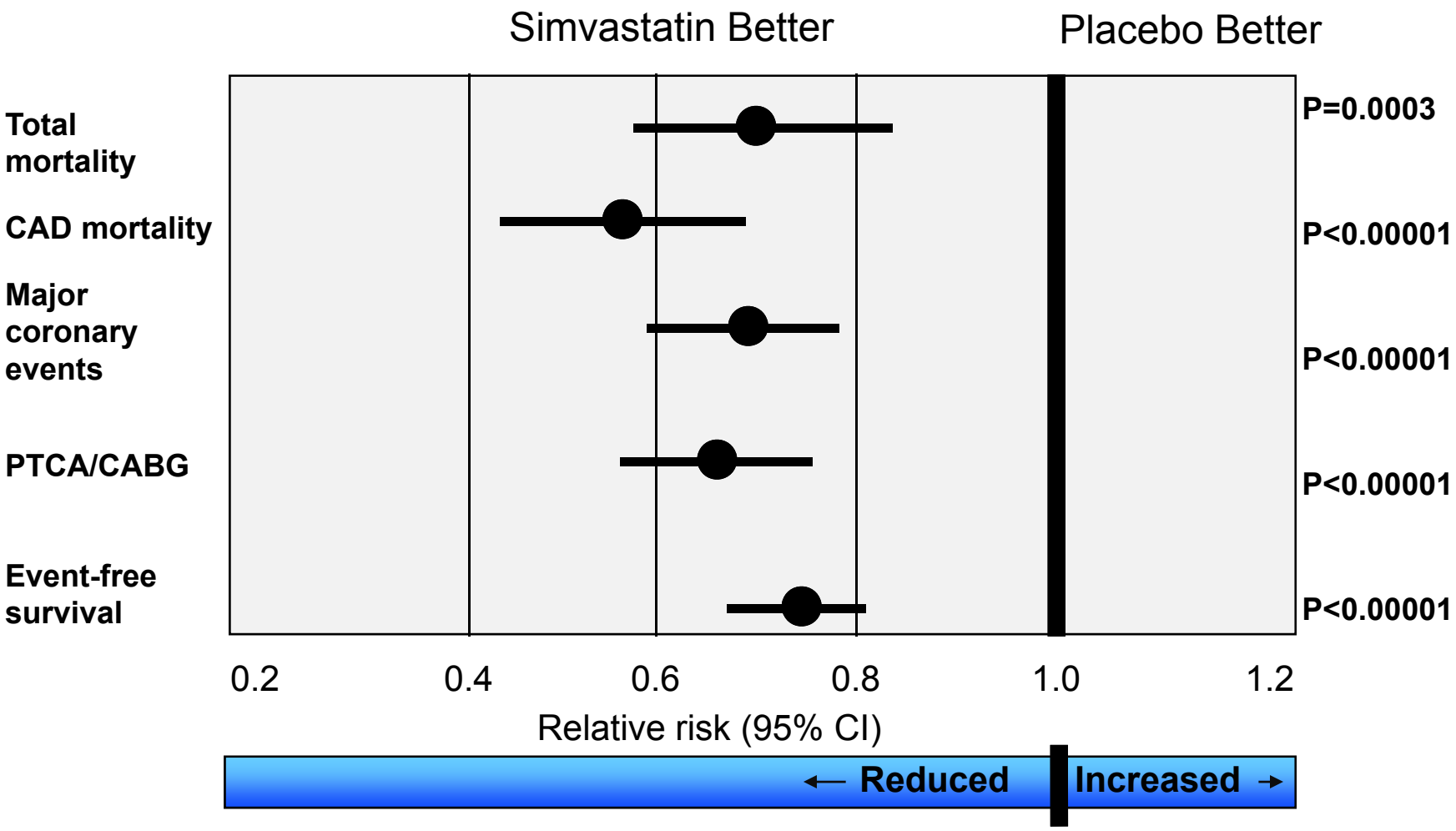
The Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344:1383-1389.

4S: Changes in Lipoprotein Levels



The Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344:1383-1389.

4S: Results of Key End-points



The Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344:1383-1389.

Heart Protection Study (HPS)

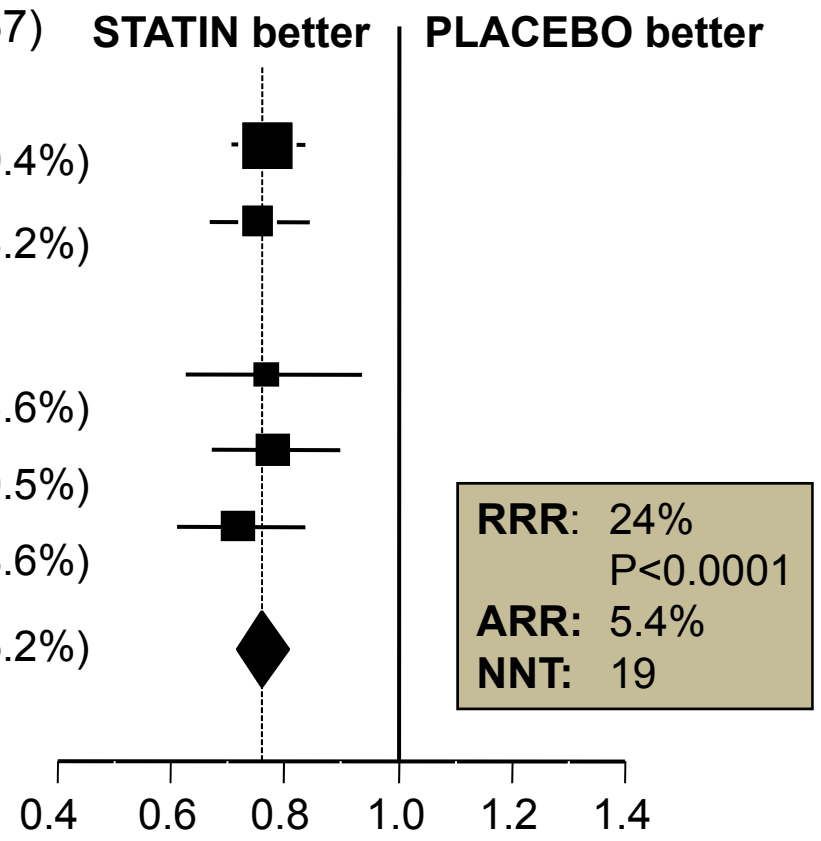
- Double-blind trial in 22,536 patients, age 40-80 years, at increased risk of CHD death due to prior disease:
  - MI or other CHD
  - Occlusive disease of non-coronary arteries, or
  - Diabetes mellitus or treated hypertension
- Total cholesterol was >3.5 mmol/L (>135 mg/dL)
- Randomized to simvastatin 40 mg daily or placebo
- Scheduled 5 year treatment period

- Primary Endpoint: Major vascular events

Heart Protection Study Collaborative Group. *Lancet.* 2002;360:7-22.

HPS: Primary Endpoint Results by Group

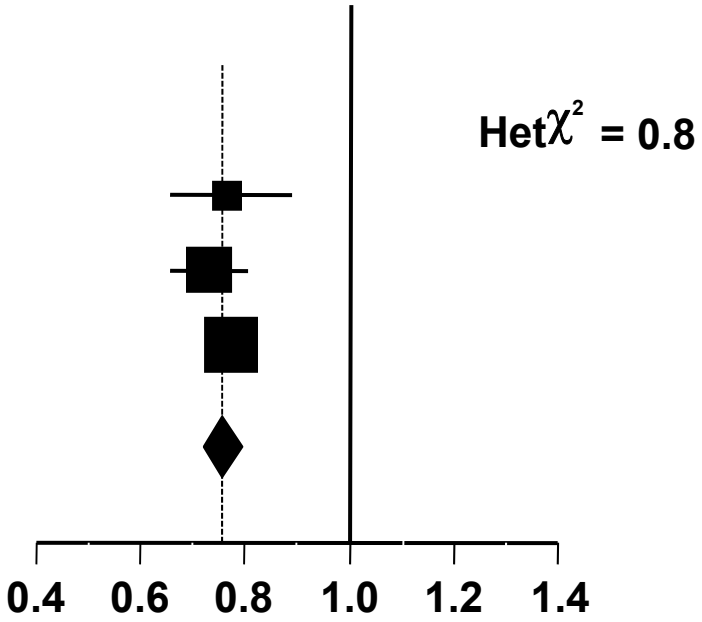
	SIMVASTATIN (10,269)		PLACEBO (10,267)	
Previous MI	999	(23.5%)	1250	(29.4%)
Other CHD (not MI)	460	(18.9%)	591	(24.2%)
No prior CHD				
CVD	172	(18.7%)	212	(23.6%)
PVD	327	(24.7%)	420	(30.5%)
Diabetes	276	(13.8%)	367	(18.6%)
ALL PATIENTS	2033	(19.8%)	2585	(25.2%)



Heart Protection Study Collaborative Group. *Lancet.* 2002;360:7-22.

HPS: Primary Endpoint Results by LDL-C

Baseline feature	STATIN (10,269)	PLACEBO (10,267)
LDL-C		
< 100 (2.6 mmol/L)	285	360
100 to 129	670	881
≥ 130 (3.4 mmol/L)	1087	1365
ALL PATIENTS	2042 (19.9%)	2606 (25.4%)



Heart Protection Study Collaborative Group. *Lancet.* 2002;360:7-22.

Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction (PROVE IT –TIMI 22)

- Double-blind trial in 4162 patients hospitalized for ACS within 24 hours of acute coronary syndrome (ACS)
- Randomized to pravastatin 40 mg or atorvastatin 80 mg daily within 10 days of ACS for a mean of 24 months

- Primary endpoint: Composite of all cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization, stroke

Cannon C, et al. *Am J Cardiol.* 2002;89:860-861.
Cannon C, et al. *N Engl J Med*. 2004;350:1495-1504.

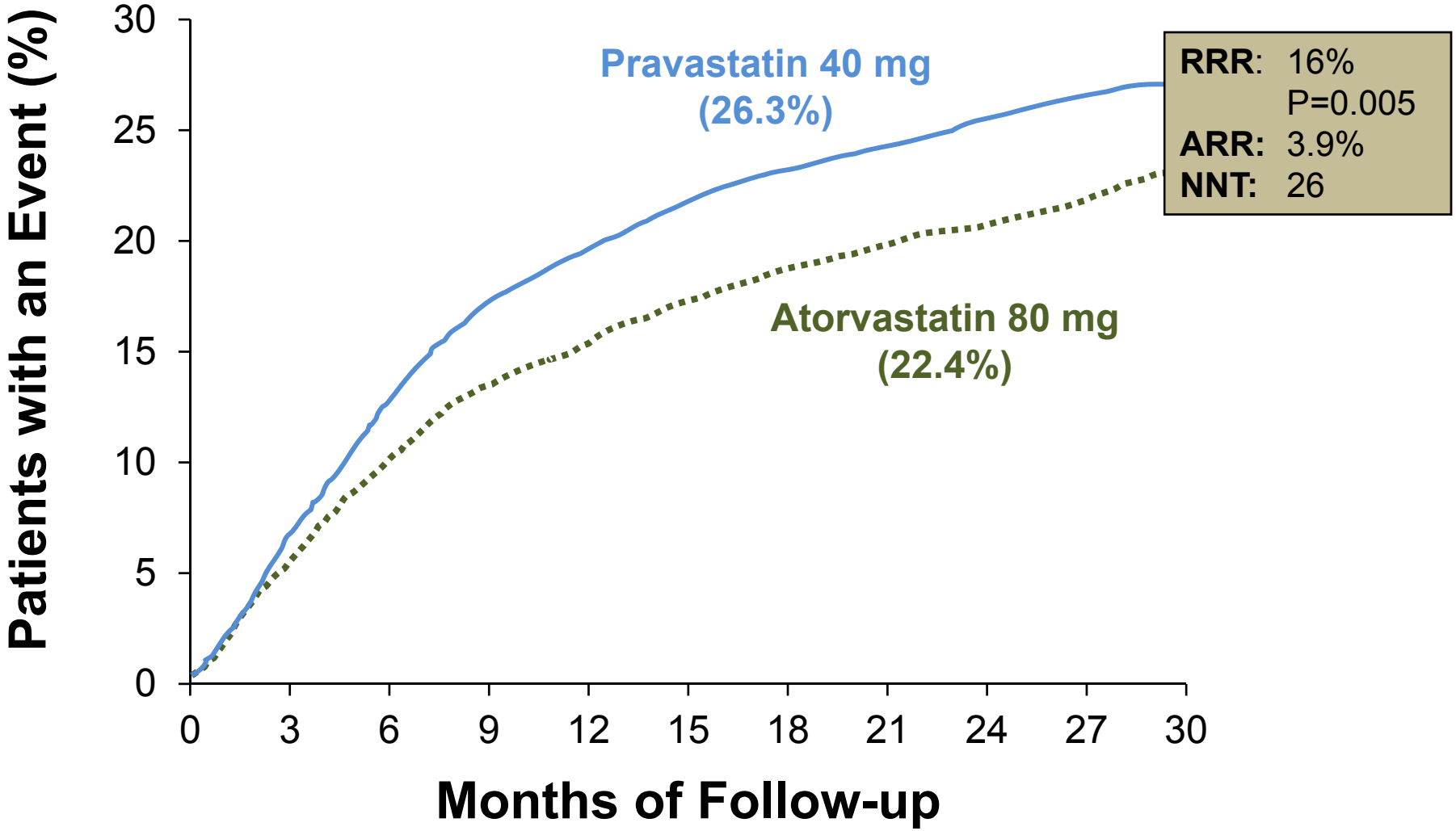
PROVE IT – TIMI 22: Lipid Results

- Median starting LDL-C was 106 mg/dL
- Median treated LDL-C values were:
  - Atorvastatin 62 mg/dL
  - Pravastatin 95 mg/dL (P<0.001)

- ACS response lowers LDL-C from the true baseline and 25% of patients were receiving statins before ACS event

Cannon C, et al. *N Engl J Med.* 2004;350:1495-1504.

PROVE IT: Primary Endpoint



Cannon C, et al. *N Engl J Med.* 2004;350:1495-1504.

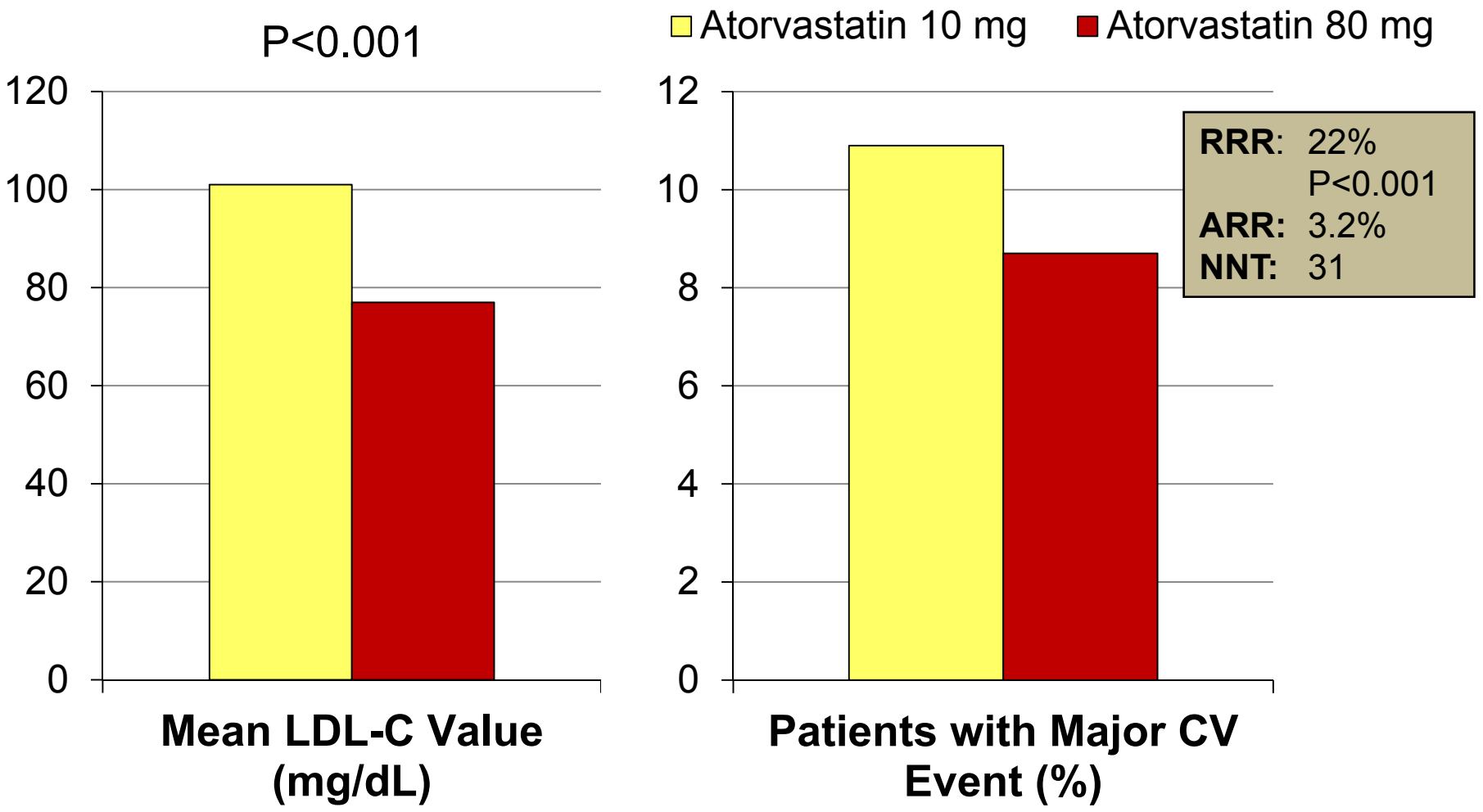
Treating to New Targets (TNT): Study Design

- Double-blind controlled trial in 10,001 men and women age 35-75 years
- All patients had clinically evident CHD and LDL-C <130 mg/dL while taking atorvastatin 10 mg daily
- Patients randomized to atorvastatin 80 mg or 10 mg
- Median duration was 4.9 years

- Primary end point: Time to first major CV event (CHD death, non-procedural myocardial infarction, resuscitation after cardiac arrest, or stroke)

LaRosa JC, et al. *N Engl J Med.* 2005;352:1425-1435.

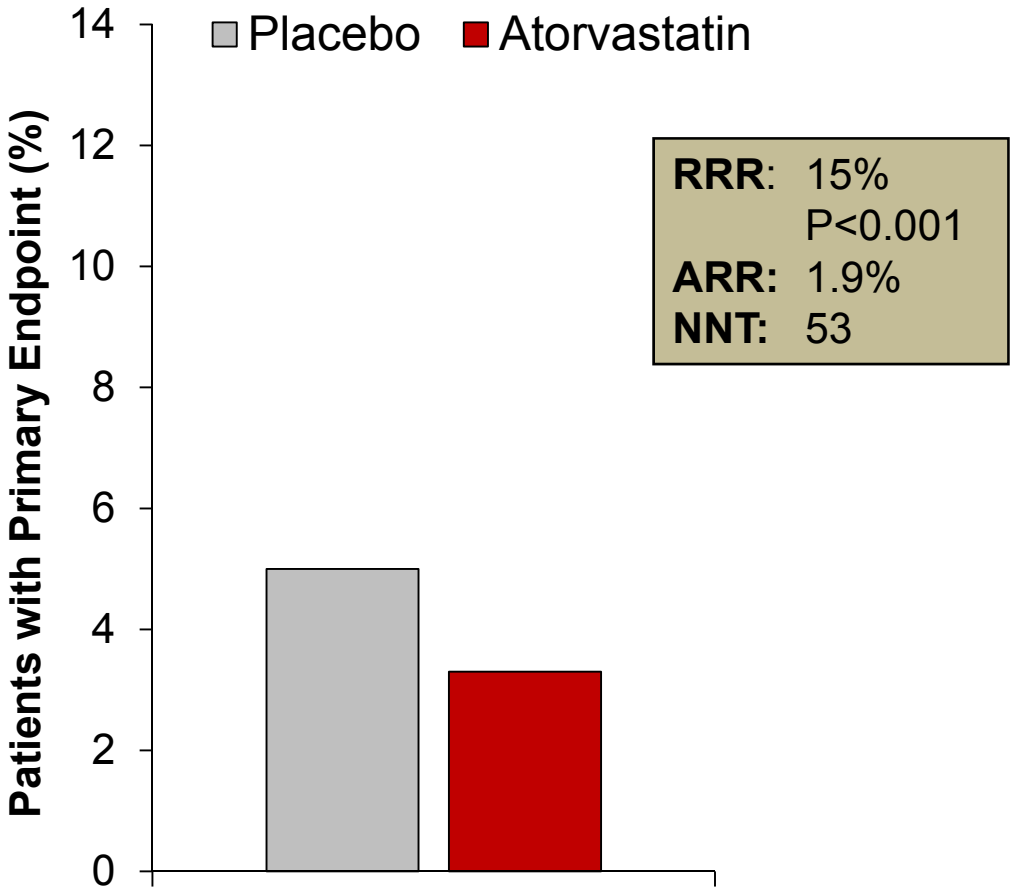
Treating to New Targets (TNT): LDL-C Results and Primary Endpoint



LaRosa JC, et al. *N Engl J Med.* 2005;352:1425-1435.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

- Randomized, double-blind trial in 4731 patients with stroke or TIA in past 1 to 6 months
- Randomized to atorvastatin 80 mg daily or placebo
- Mean follow-up 4.9 years
- Primary endpoint: Stroke



Amarenco P, et al. *N Engl J Med* 2006;355:549-59.

Cholesterol Treatment Trialists' (CTT) Collaboration

- Meta-analysis of large (n>1000), randomized clinical trials that were at least 2 yrs in duration
  - More vs. Less intensive statin therapy:
    - 5 trials (n=39,612), median 5 yr follow-up
  - Statin vs. control:
    - 21 trials (n=129,526), median 4.8 yr follow-up
- Average CV event risk reductions per 1.0 mmol/L LDL-C reduction at 1 year after randomization were calculated

Baigent C, et al. *Lancet* 2010; 376: 1670–81.

CTT Collaboration: More vs. Less Statin Therapy

- Weighted mean further reduction in LDL-C was 0.51 mmol/L (~19 mg/dL)

	Further Event Reduction
Major Vascular Events	15% (P<0.001)
CHD Death or Non-Fatal MI	13% (P<0.001)
Coronary Revascularization	19% (P<0.001)
Ischemic Stroke	16% (P=0.005)

- CV event reductions proportionate to LDL-C reductions, even when baseline LDL-C was <2 mmol/L (77 mg/dL)

Baigent C, et al. *Lancet* 2010; 376: 1670–81.

2013 ACC/AHA Blood Cholesterol Guideline 4 Statin Benefit Groups

Clinical ASCVD

LDL-C ≥190 mg/dL

Diabetes
Type 1 or 2
age 40-75 y

≥7.5% estimated 10-y ASCVD risk and age 40-75 y

Stone NJ, et al. Circulation. 2013: published online before print November 12, 2013.

Collaborative AtoRvastatin Diabetes Study (CARDS)

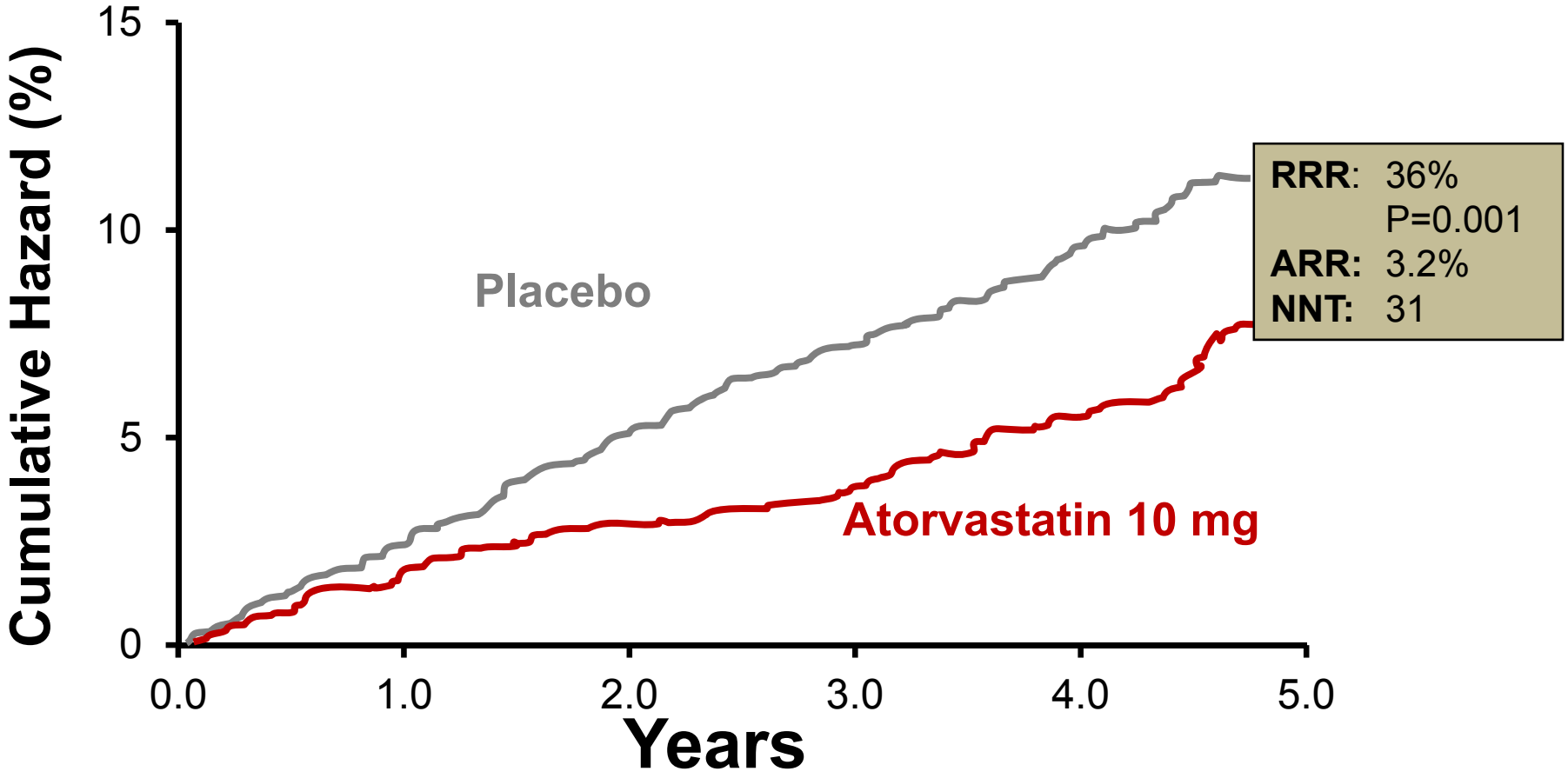
- 2838 primary prevention patients (no ASCVD) with type 2 diabetes
  - At least 1 other CV risk factor such as smoking, hypertension, retinopathy, or microalbuminuria
  - LDL-C levels ≤160 mg/dL and TG levels ≤600 mg/dL
- Randomized to placebo or atorvastatin 10 mg daily

- Primary endpoint:
  - Time to first major CV event (CHD death, nonfatal MI, revascularization, stroke)
- Trial stopped at a median of 3.9 years, 2 years early

Colhoun HM, et al. *Lancet.* 2004;364:685-696.

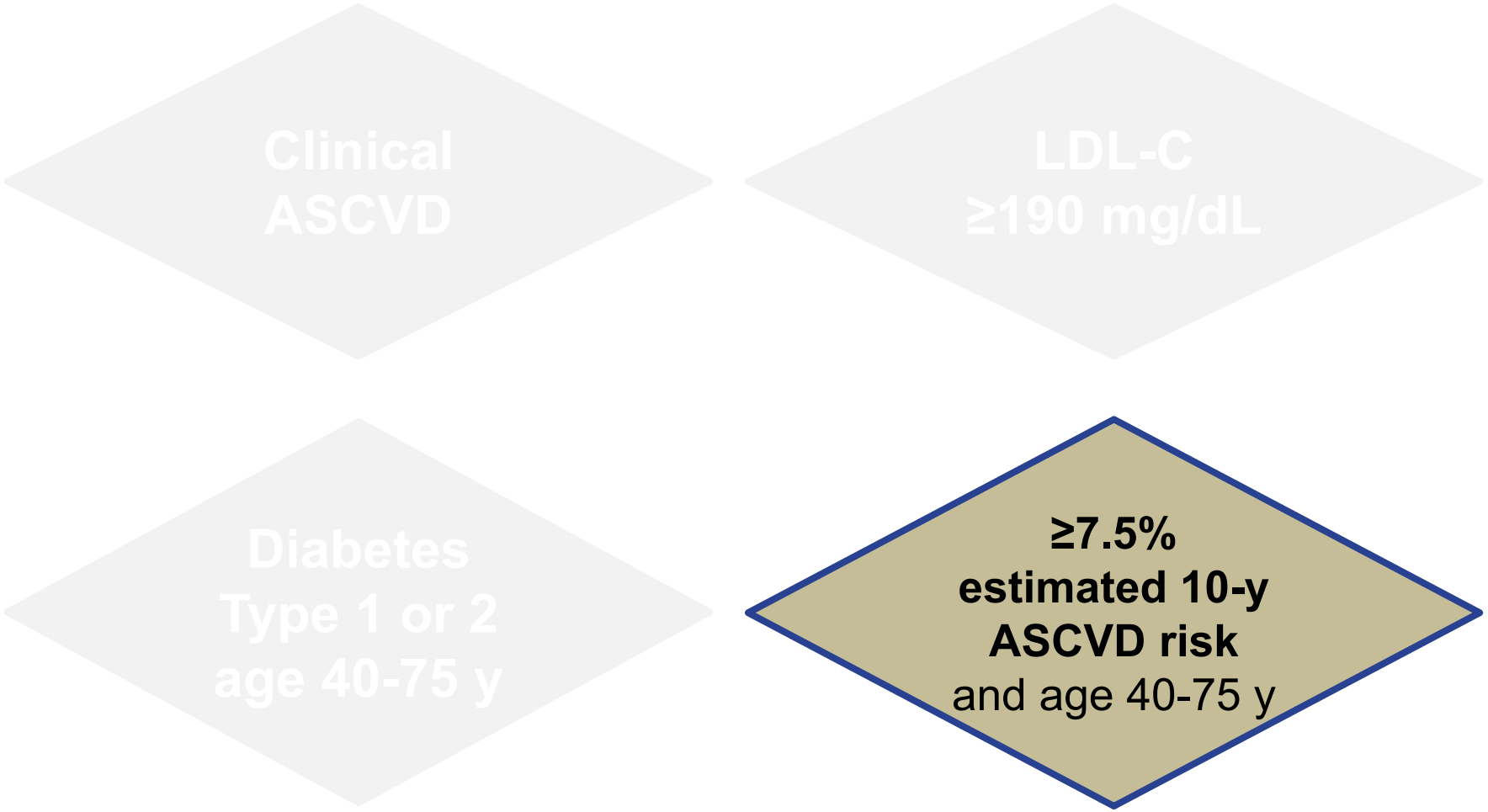
CARDS: Primary End Point Results

- Mean baseline LDL-C 117 mg/dL reduced 40% with atorvastatin (P<0<0001)



Colhoun HM, et al. *Lancet.* 2004;364:685-696.

2013 ACC/AHA Blood Cholesterol Guideline 4 Statin Benefit Groups



Stone NJ, et al. Circulation. 2013: published online before print November 12, 2013.

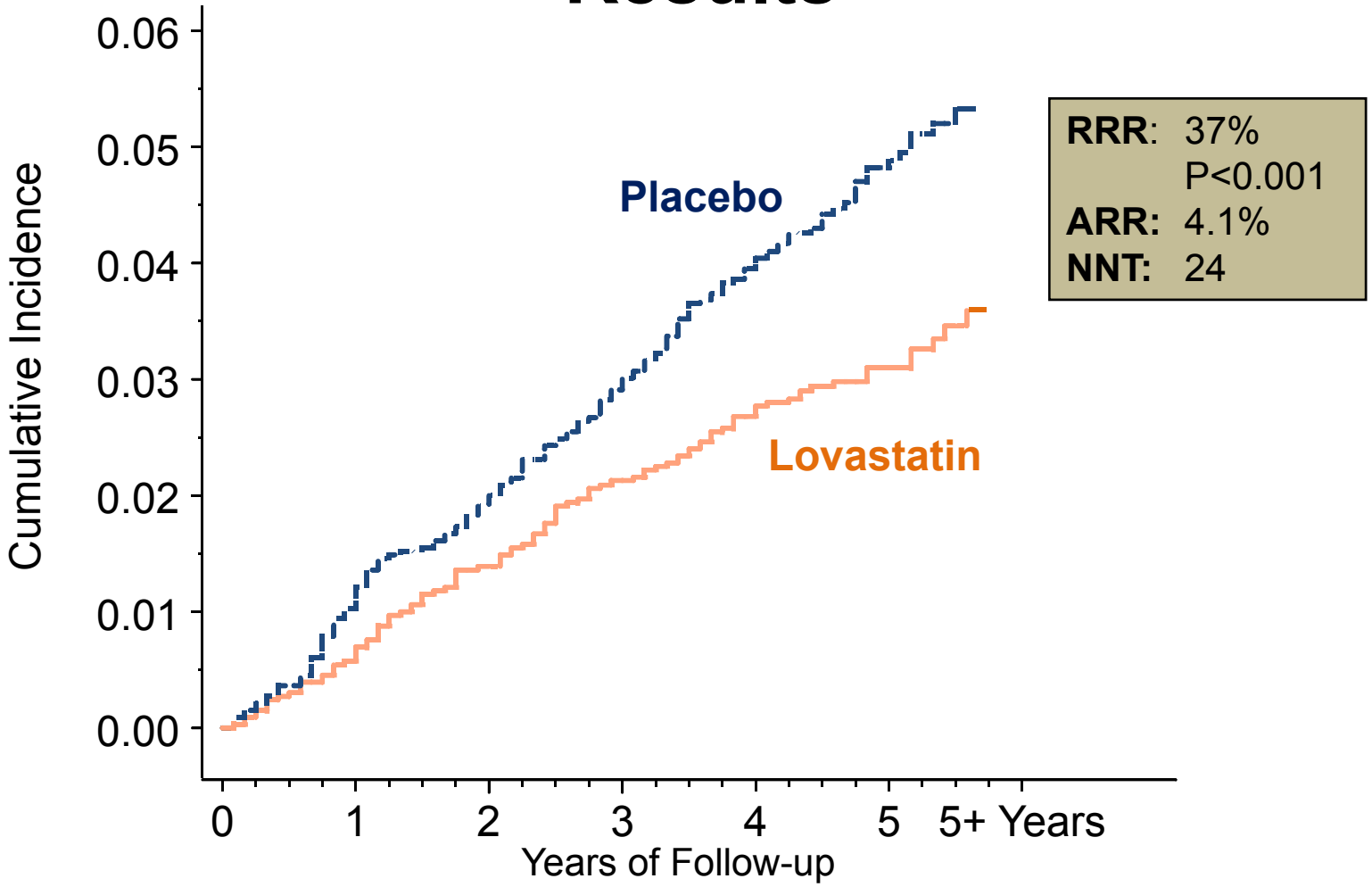
AFCAPS/TexCAPS

- Randomized, double-blind trial in 5608 men and 997 women with no history of CHD (primary prevention)
  - Baseline LDL-C was 150 mg/dL
  - Baseline HDL-C was 37 mg/dL
- Randomized to lovastatin 20-40 mg daily (titrated to achieve an LDL-C of <110 mg/dL) or placebo
- Mean follow-up was 5.2 years

- Primary endpoint: First acute major coronary event (unstable angina pectoris, fatal or non-fatal MI, or sudden cardiac death)

Downs JR, et al. *JAMA*. 1998;279:1615-1622.

AFCAPS/TexCAPS: Primary Endpoint Results



Downs JR, et al. *JAMA*. 1998;279:1615-1622.

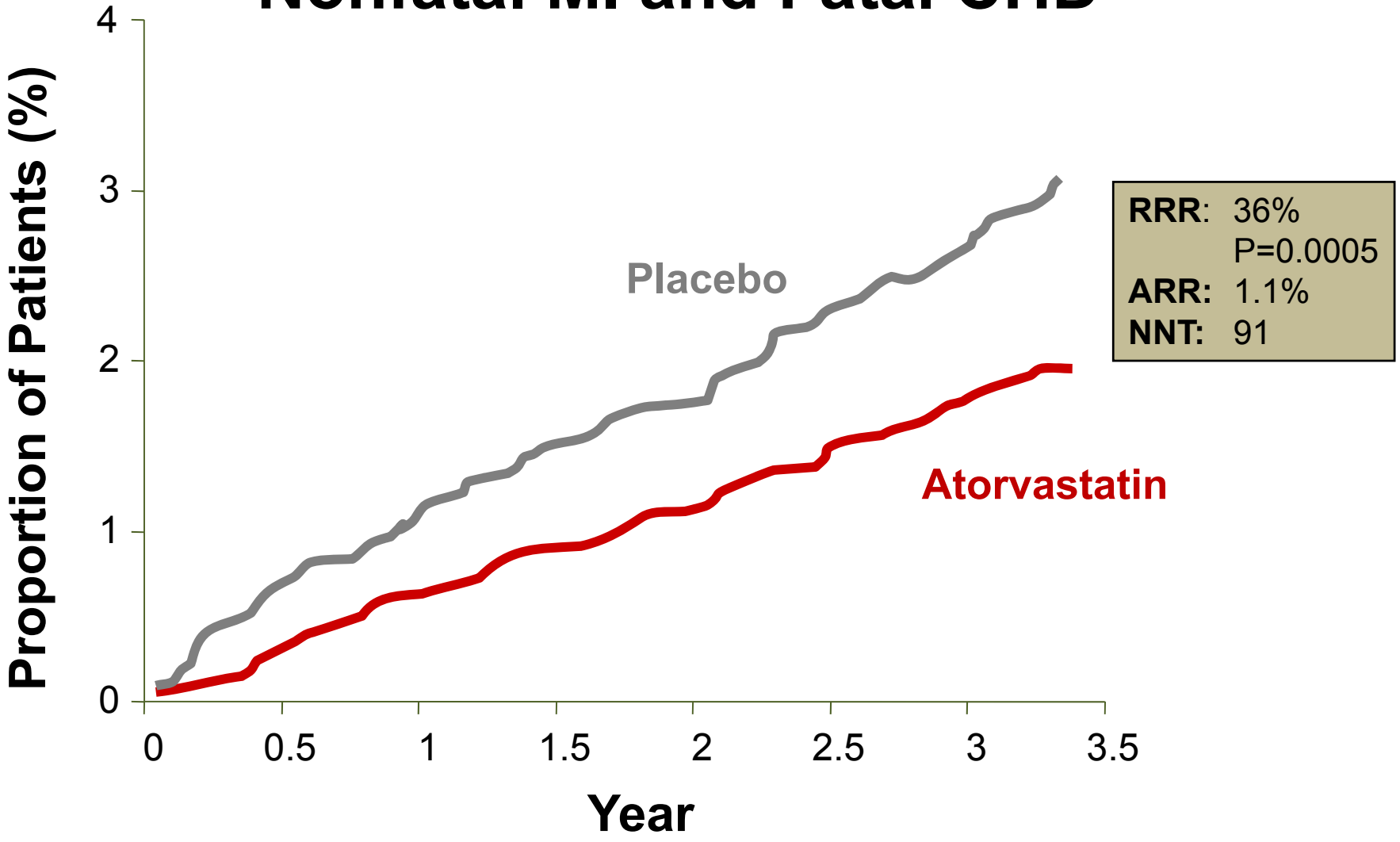
Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA)

- Double-blind trial in 10,305 patients with multiple CV risk factors including diabetes mellitus, but not CHD
- Randomized to placebo or atorvastatin 10 mg daily

- Primary Endpoint was non-fatal MI and fatal CHD
- Treatment stopped after a median follow-up of 3.3 year
- Mean baseline LDL-C 133 mg/dL:
  - Reduced 33% to a mean LDL of 90 mg/dL

Sever P, et al. *Lancet.* 2003;361:1149-1158.

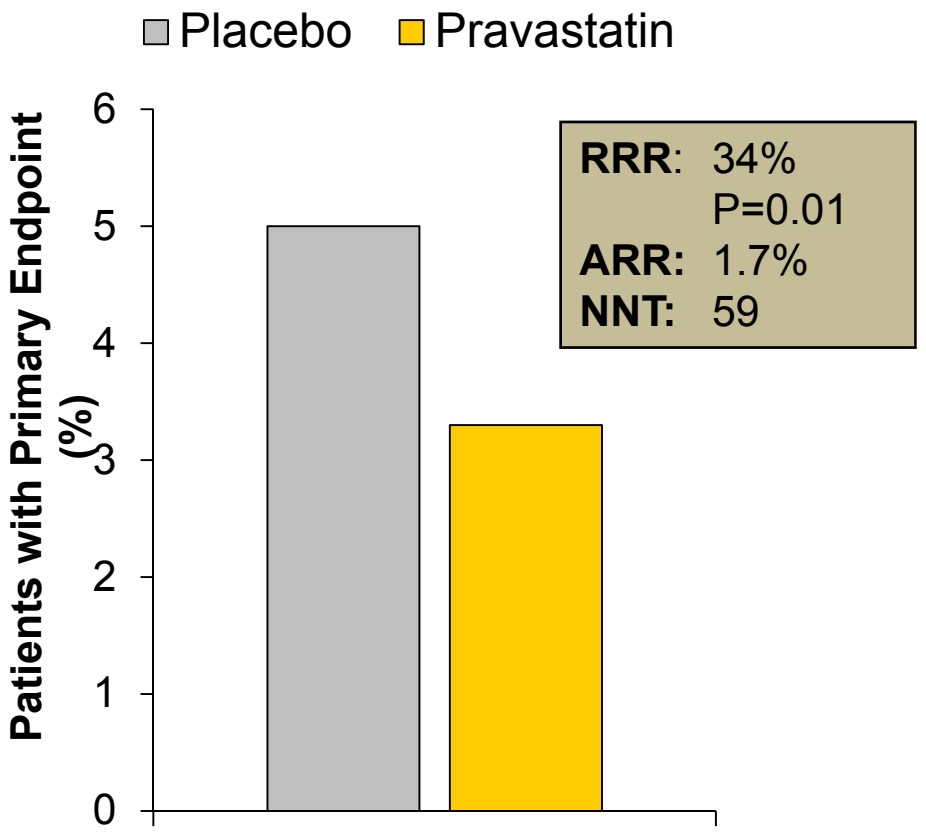
ASCOT-LLA: Primary End Point of Nonfatal MI and Fatal CHD



Sever PS, et al. *Lancet*. 2003;361:1149-1158.

Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA)

- Randomized, open-label trial in primary patients age 40-70 years and TC 220-270 mg/dL
- Randomized to pravastatin 10-20 mg daily or placebo
- Mean follow-up 5.3 years
- Primary endpoint: Coronary heart disease



Nakamura H, et al. *Lancet 2006*;368:1155–63.

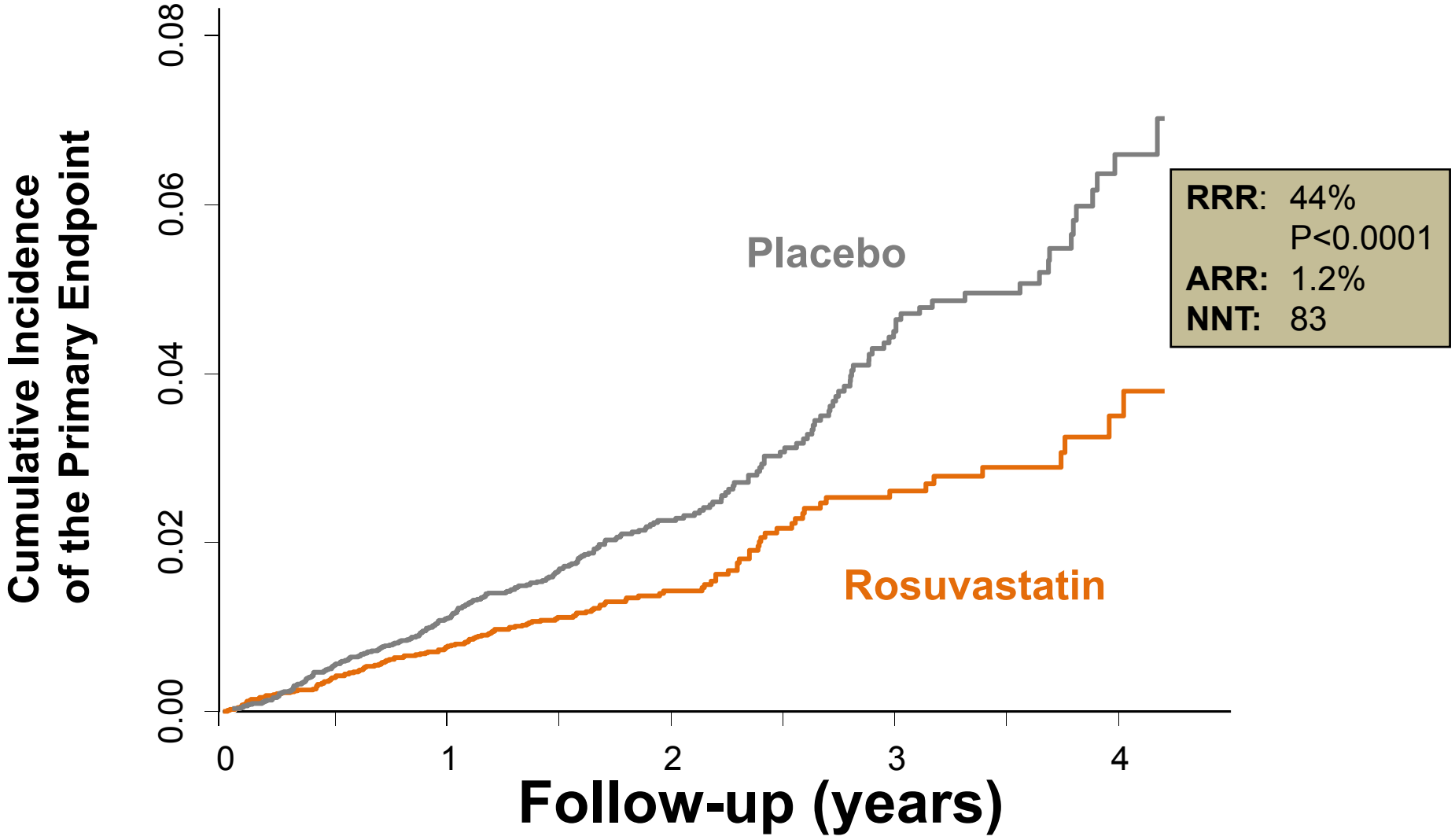
Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (JUPITER)

- Double-blind trial in 17,802 primary prevention men and women with LDL-C <130 mg/dL and hs-CRP ≥2 mg/L
- Randomized to rosuvastatin 20 mg or placebo

- Primary endpoint: Composite of CV death, MI, cerebrovascular event, arterial revascularization, or hospitalization for unstable angina
- Study halted after 1.9 years (maximum of 5 years)
- Rosuvastatin reduced LDL-C by 50% (hs-CRP by 37%)

Ridker PM, et al. *N Engl J Med*. 2008;359:2195-2207.

JUPITER: Results



Ridker PM, et al. *NEJM.* 2008;359:2195-2207.

ACC/AHA 2013 Blood Cholesterol Guideline: Nonstatin Drugs

The panel could find no data supporting the routine use of nonstatin drugs combined with statin therapy to reduce further ASCVD events

- In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.

Stone NJ, et al. Circulation. 2013: published online before print November 12, 2013.

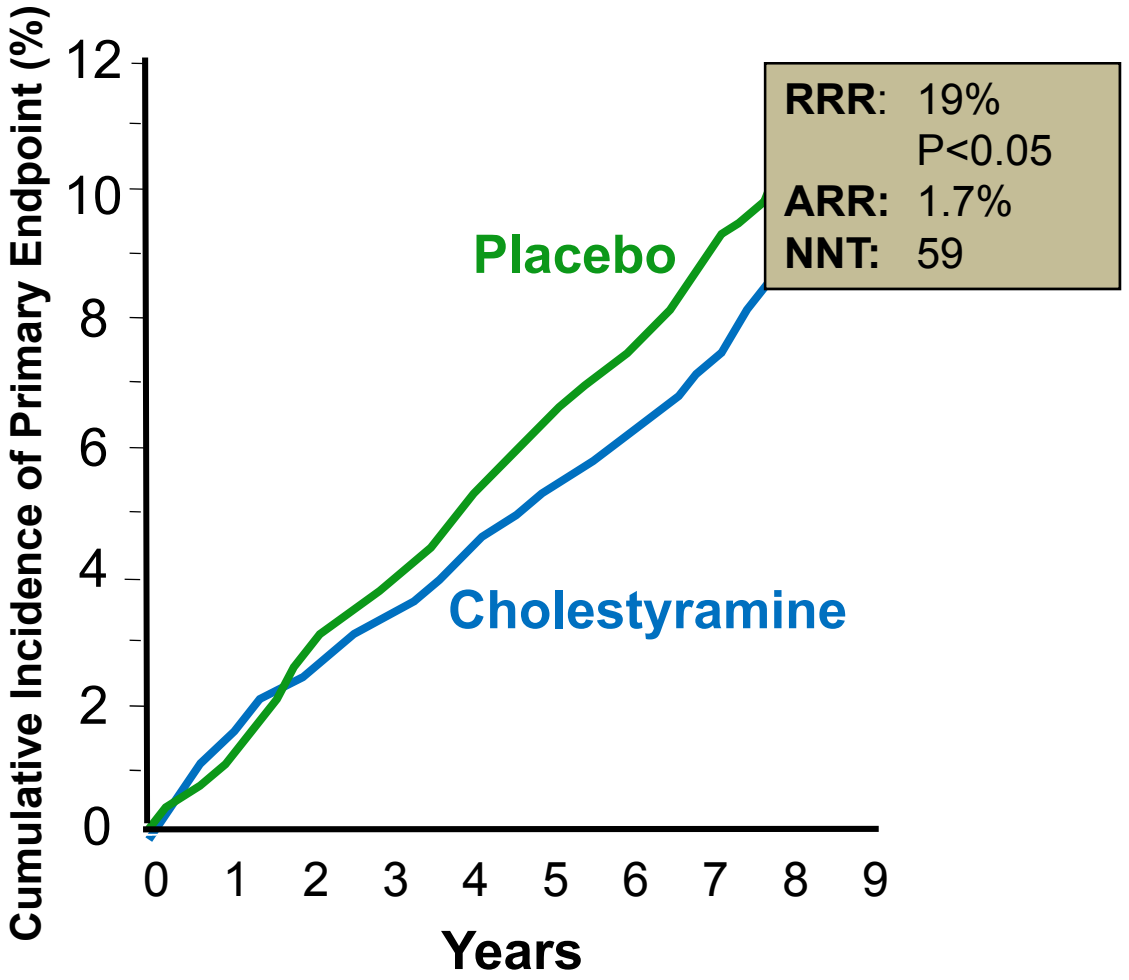
LDL-C Focused
Nonstatin Drug Therapies Clinical Trials

- Bile Acid Sequestrants (i.e., colesevelam, colestipol, cholestyramine)
  - LRC-CPPT

- Cholesterol Absorption Inhibitor (ezetimibe)
  - ENHANCE
  - SEAS
  - ARBITER-6
  - SHARP

Lipid Research Clinics Coronary Primary Prevention Trial

- 3806 primary prevention men, <60 years old with TC ≥ 265 mg/dL, randomized, double-blind to cholestyramine 24 g/day or placebo
- Mean duration was 7.4 years
- Mean LDL-C was 216 mg/dL; reduced 20.3% with cholestyramine
- Primary Endpoint: CHD death + nonfatal MI



The Lipid Research Clinics Coronary Primary Prevention Trial results. *JAMA.* 1984;251:351-364.

Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE)

- 720 patients with familial hypercholesterolemia
- Most (81%) previously treated with statins
- Randomized, double-blind to simvastatin 80 mg vs. ezetimibe/simvastatin 10/80 mg for 2 years

- Results: Primary Endpoint
  - No significant difference in mean carotid intimal medial thickness (CIMT) (P=0.64)

Kastelein JP, et al. *N Engl J Med*. 2008;358:1431-1443.

Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis (SEAS)

- 1873 patients with mild/moderate aortic stenosis randomized to ezetimibe/simvastatin 10/40 mg daily or placebo for 52.2 months
- Primary endpoint: Composite of major CV events

- Results – ezetimibe/simvastatin vs. placebo:
  - Primary outcome: 35.3% vs. 38.2% (P=0.59)
  - Aortic valve events: 32.6% vs. 35.1% (P=0.73)
  - Ischemic CV events: 15.7% vs. 20.1% (P=0.02)

Rossebø AB, et al. *N Engl J Med.* 2008;359:1343-1356.

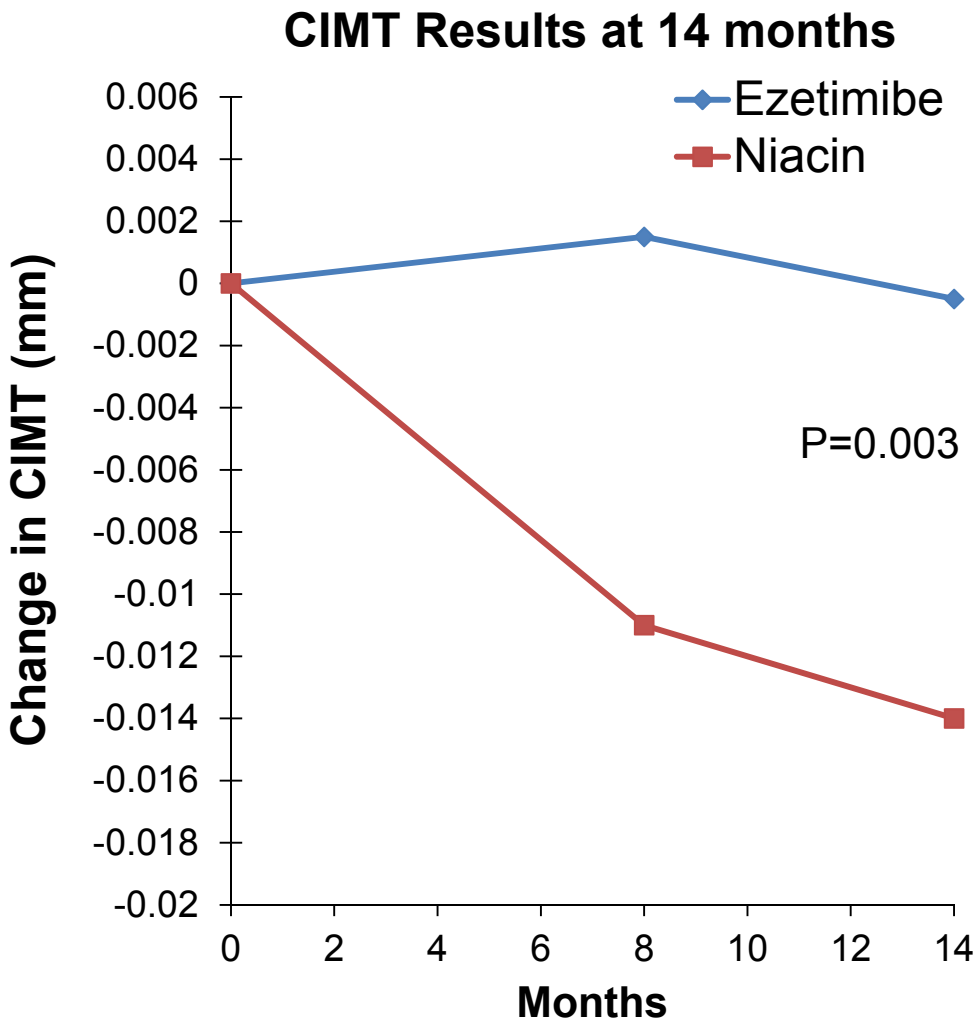
Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol–6 HDL and LDL Treatment Strategies (ARBITER 6–HALTS)

- 208 patients with CHD or CHD risk equivalents on long-term statin therapy with LDL-C <100 mg/dL and HDL-C <50 mg/dL (men) or <55 mg/dL (women)
- Randomized to add either extended-release niacin (goal 2000 mg daily) or ezetimibe (10 mg daily)
- Primary Endpoint: Between-group difference in the change in CIMT at 14 months from baseline

Taylor AJ, et al. *N Engl J Med*. 2009;361:2113-2122.

ARBITER 6–HALTS - Results

- HDL-C:
  - Niacin increased by 7.5 mg/dL
  - Ezetimibe had no significant change
- LDL-C:
  - Ezetimibe had a greater lowering than niacin (17.6 vs 10.0 mg/dL)



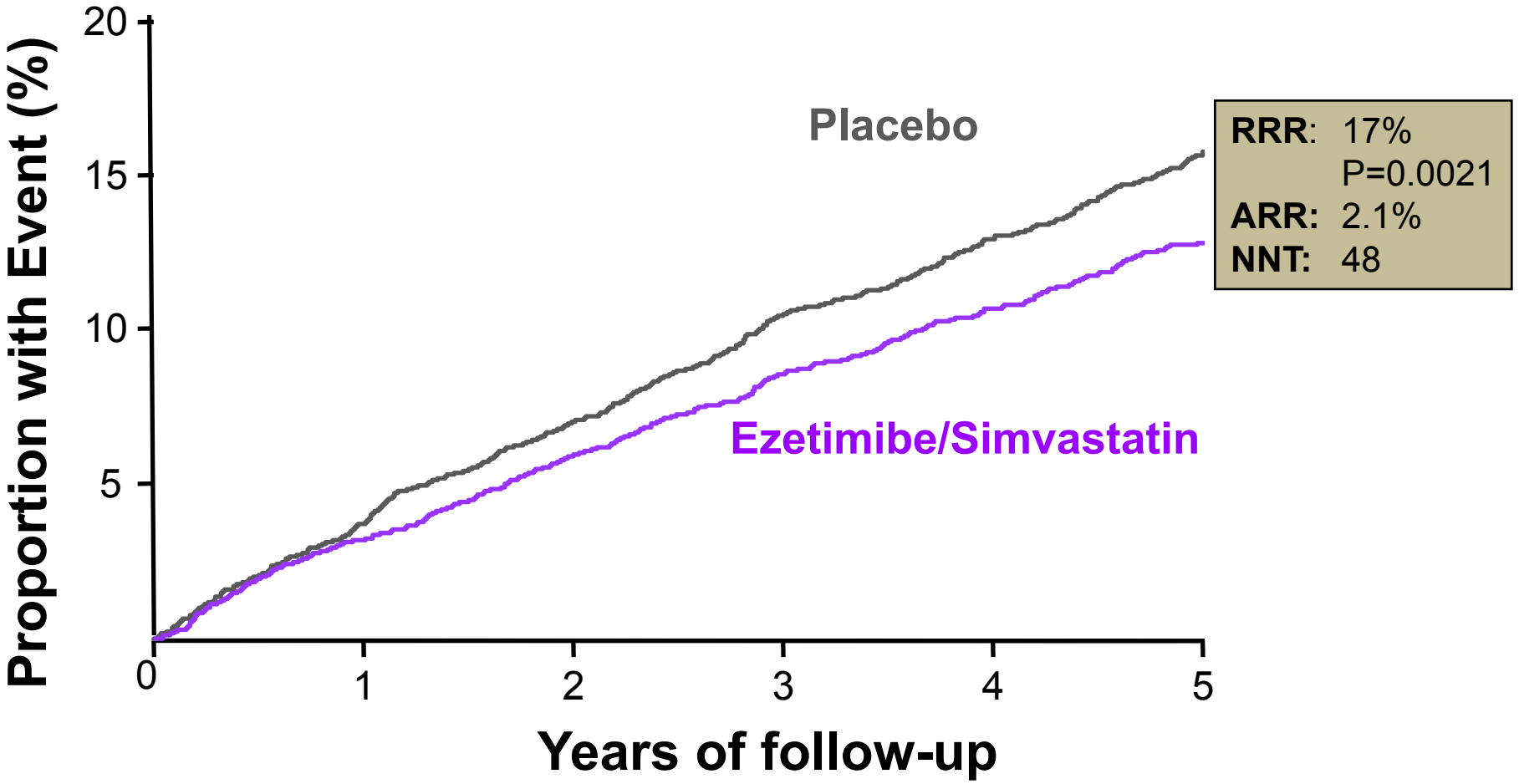
Taylor AJ, et al. *N Engl J Med*. 2009;361:2113-2122.

The Study of Heart and Renal Protection (SHARP)

- 9438 patients with chronic kidney disease
  - Not on dialysis: elevated creatinine on 2 occasions ≥1.7 mg/dL (men) or ≥1.5 mg/dL (women)
  - On dialysis: hemodialysis or peritoneal dialysis
- Age ≥40 years with no history of MI or coronary revascularization
- Randomized to ezetimibe/simvastatin10/20 mg daily, simvastatin 20 mg daily, or placebo for 1 year to assess safety; after 1 year, simvastatin monotherapy group randomized to one of the other two groups
- Total median follow-up was 4.9 years

Baigent C, et al. *Lancet* 2011; 377: 2181–92

SHARP - Primary Endpoint Results: Major Atherosclerotic Events



Baigent C, et al. *Lancet* 2011; 377: 2181–92

Mixed Lipid Modification Focused Nonstatin Drug Therapies Clinical Trials

- Niacin
  - Coronary Drug Project
  - FATS
  - HATS
  - AIM-HIGH
  - HPS2-THRIVE

Coronary Drug Project

- Randomized, double-blind, placebo-controlled trial in 8341 men with prior MI and hypercholesterolemia
- Tested 5 lipid-modifying agents: Low-dose estrogen, High-dose estrogen, Dextrothyroxine, Clofibrate, Niacin
- 2789 patients in the placebo group and 1119 patients in the niacin group followed for 5 to 8.5 yrs (mean 6.2 yrs)
- Results at follow-up:
  - Primary endpoint: Total mortality
    - 24.4% with niacin, 25.4% with placebo; P=ns
  - Secondary endpoint: Recurrent nonfatal MI
    - 10.2% with niacin, 13.8% with placebo; P<0.05

Coronary Drug Project. *JAMA*. 1975;231:360-381.

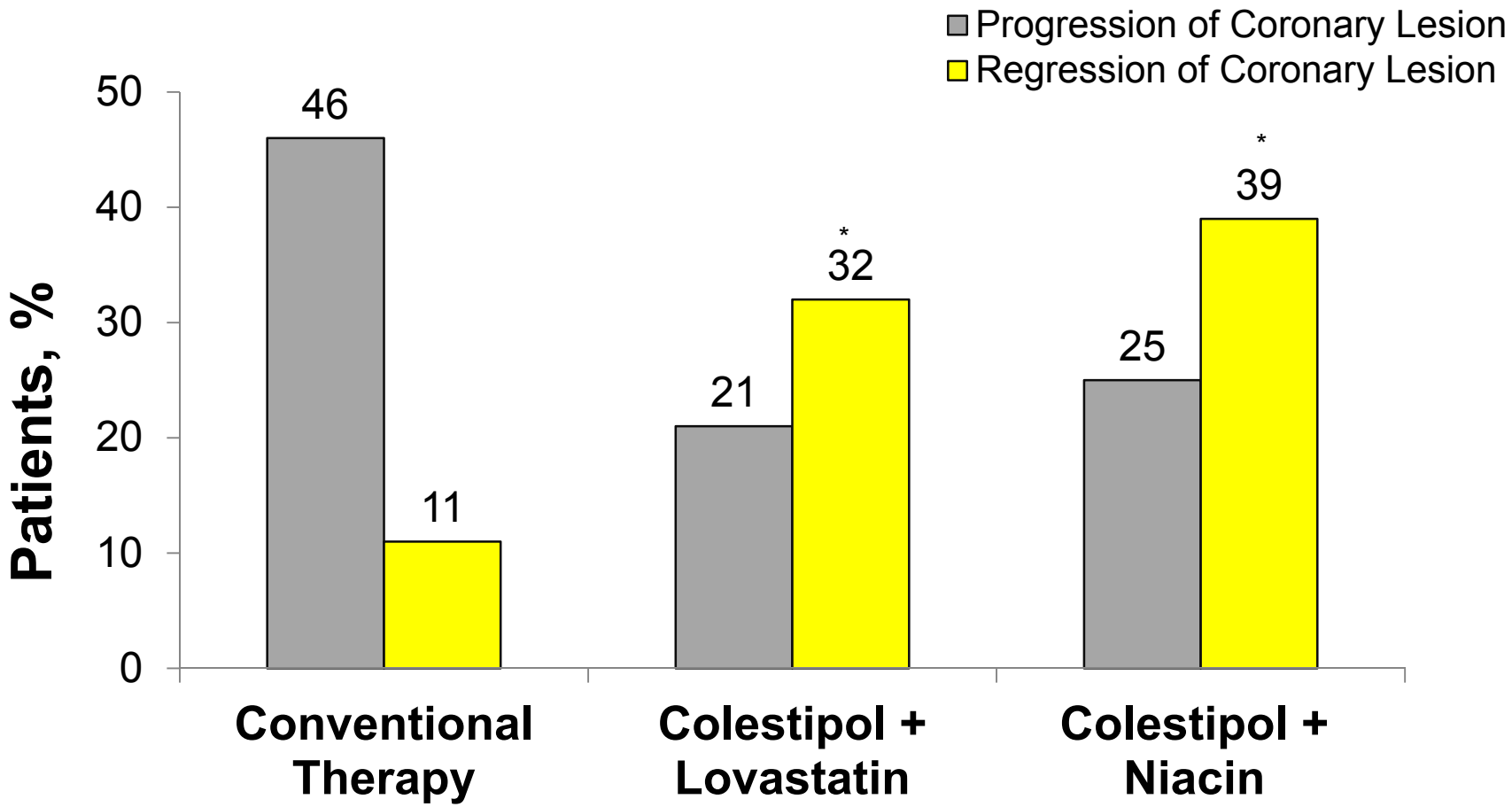
Familial Atherosclerosis Treatment Study (FATS)

- 146 secondary prevention men aged ≤ 62 years with average stenosis of 34% and Apo B >125 mg/dL
- Treatment Groups
  - Lovastatin 20 mg BID + colestipol 10 g TID
  - Niacin 1 g QID + colestipol 10 g TID
  - Conventional therapy

- Primary endpoint: Arteriographic change in coronary stenosis

Brown G, et al. *N Engl J Med*. 1990;323:1289-1298.

FATS: Angiographic Results at 2.5 years



N = 120 men with coronary artery disease
*P<0.005 vs conventional therapy

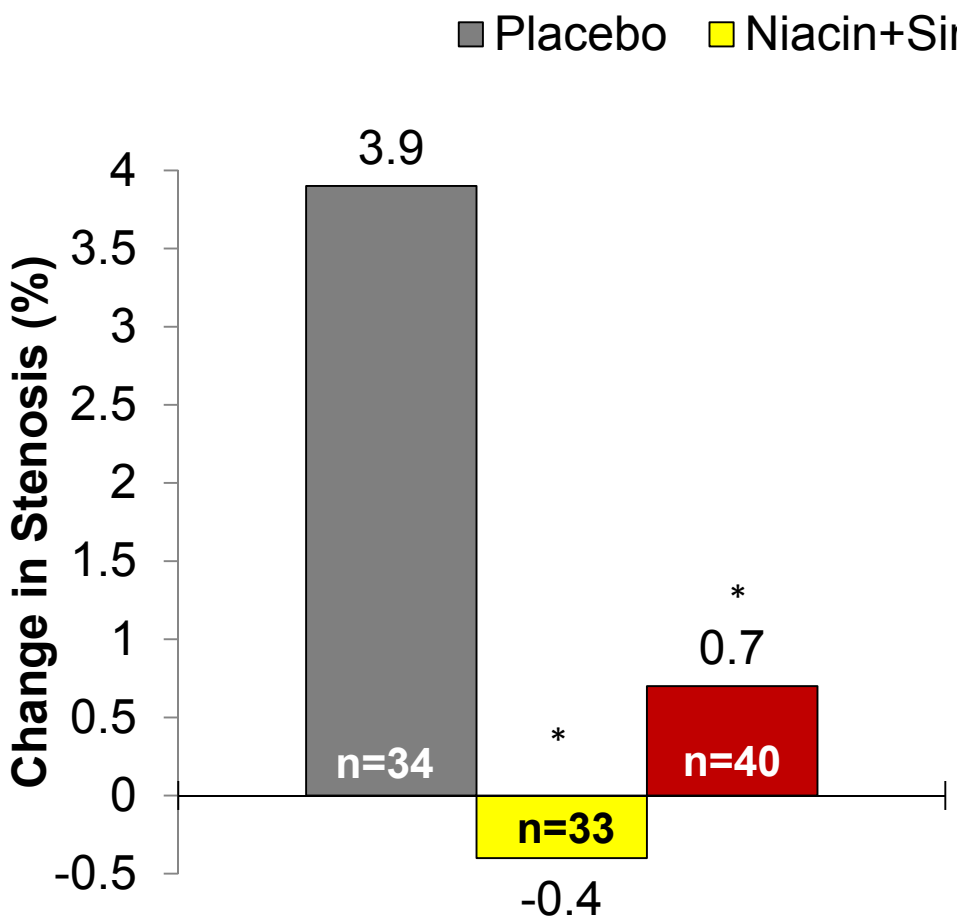
Brown G, et al. *N Engl J Med.* 1990;323:1289-1298.

HDL-Atherosclerosis Treatment Study (HATS)

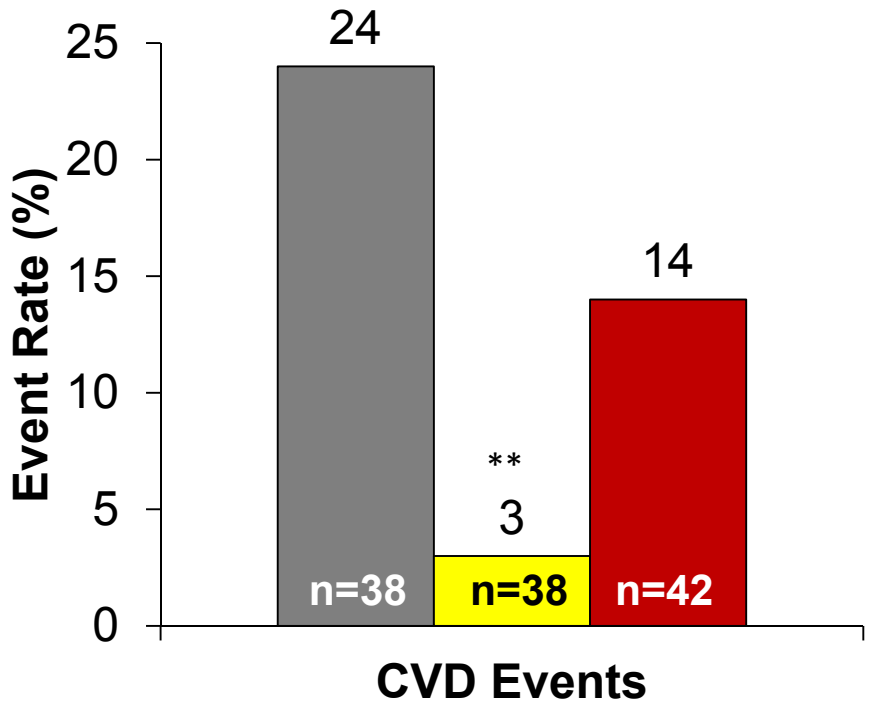
- 160 patients with measurable CAD by angiography
  - HDL-C ≤ 35 mg/dL and LDL-C ≤ 145 mg/dL
- Patients randomized to:
  - Placebo
  - Antioxidant vitamins (E/C/ß-carotene/selenium) [VIT]
  - Simvastatin 10-20 mg + niacin 2-4 g
  - Simvastatin 10-20 mg + niacin 2-4 g + VIT
- Primary Endpoints: Arteriographic change in coronary stenosis and the occurrence of a first CV event
- Repeat quantitative angiography after 3 years

Brown BG, et al. *N Engl J Med*. 2001;345:1583-1592.

HATS: Primary End Points



Quantitative Coronary Angiography



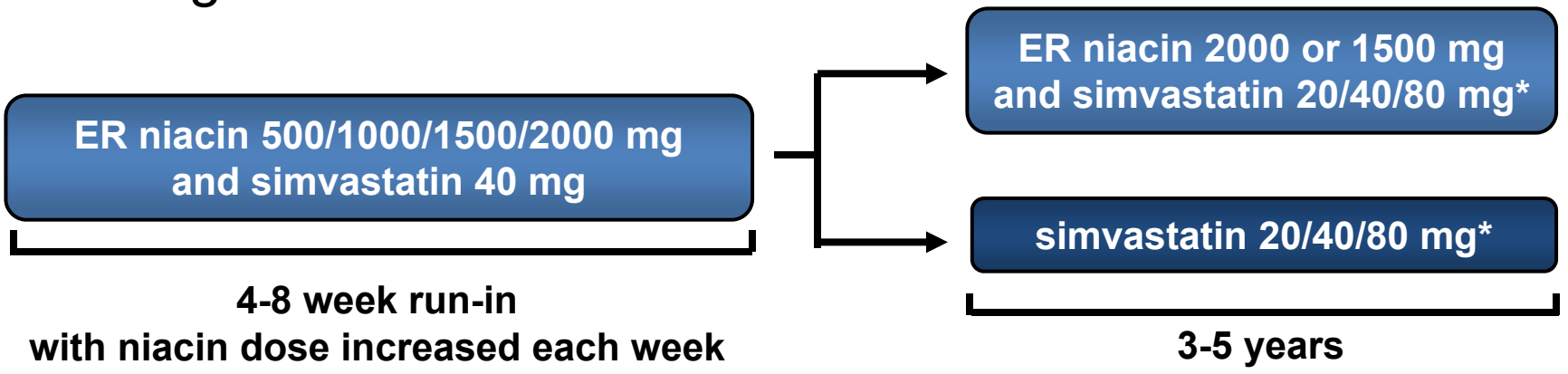
CVD Events

*P≤0.005 vs. placebo; ** P=0.03 vs. placebo
Mean dose of simvastatin was 13 mg/day
Mean dose of niacin was 2400 mg/day

Brown BG, et al. *N Engl J Med.* 2001;345:1583-1592.

Niacin Plus Statin to Prevent Vascular Events (AIM-HIGH)

- 3414 patients age ≥ 45 years with ASCVD and dyslipidemia (low HDL-C, triglycerides 150-400 mg/dL, LDL-C < 180 mg/dL)
- Primary Endpoint: Composite of CV events
- Drug allocation:



*** dependent on LDL-C levels, ezetimibe 10 mg may be added as well**

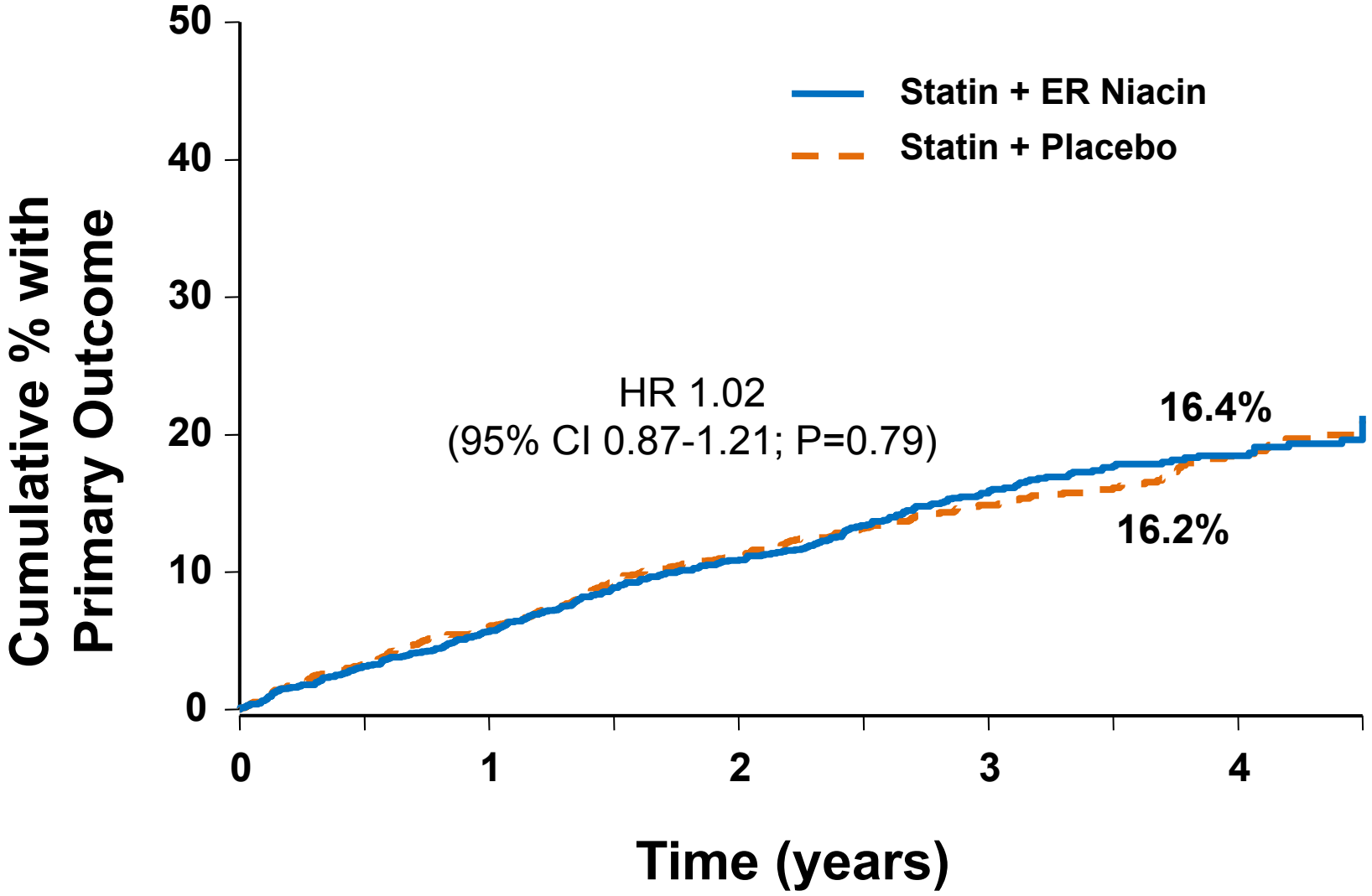
Boden WE, et al. *N Engl J Med* 2011;365:2255-67.

AIM-HIGH: Results

	Placebo + Statin (N = 1696)		ER Niacin + Statin (N = 1718)	
mean/median values (mg/dL)	**Baseline (N = 1696)**	**Year 1 (N = 1554)**	**Baseline (N = 1718)**	**Year 1 (N = 1561)**
LDL-C	76	70	76	66
Triglycerides	162	155	164	121
HDL-C	35	38	34	43
Apolipoprotein AI	123	127	122	132

Boden WE, et al. *N Engl J Med* 2011;365:2255-67.

AIM-HIGH: Primary Endpoint Results



Boden WE, et al. *N Engl J Med* 2011;365:2255-67.

ER Niacin with Laropiprant in High-Risk Patients: HPS2-THRIVE

- 25,673 patients with vascular disease randomized to extended-release niacin/laropiprant 2000/40 mg daily or placebo for a median of 3.9 years
- All patients treated with a standardize background of statin-based LDL-C lowering therapy
- Primary Endpoint: major vascular events
  - Niacin/laropiprant 13.2%
  - Placebo 13.7% (P = 0.29).
- Niacin–laropiprant associated with more serious adverse effects (glycemic control, gastrointestinal system, musculoskeletal system, skin, infection, and bleeding

The HPS2-THRIVE Collaborative Group. N Engl J Med 2014;371:203-12.

Triglyceride/HDL-C Focused Nonstatin Drug Therapies Clinical Trials

- Fibric Acid Derivatives
  - Helsinki Heart Study
  - VA-HIT
  - FIELD
  - ACCORD

Helsinki Heart Study

- 4081 primary prevention men age 40-55 years with non-HDL-C ≥200 mg/dL
- Randomized, double-blind to gemfibrozil 600 mg twice daily or placebo for 5 years
- Results:
  - 34% reduction in the primary endpoint of CHD events (MI and CV death)
    - Gemfibrozil 27.3 per 1000
    - Placebo 41.4 per 1000
  - LDL-C reduced 11%, HDL-C increased 11%
  - Greatest benefits when triglyceride high or HDL-C low

RRR:	34%
	P<0.02
RR:	1.4%
NNT:	71

Frick MH, et al. *N Engl J Med*. 1987;317:1237-1245.

Veterans Affairs HDL Intervention Trial (VA-HIT)

- Double-blind trial in 2531 men with coronary heart disease (CHD), age < 74 years, HDL-C ≤40 mg/dL, LDL-C ≤140 mg/dL years and triglycerides ≤300 mg/dL
- Randomized to gemfibrozil 1200 mg/day or placebo
- Mean lipid values were: LDL-C 111 mg/dL, HDL-C 32 mg/dL and triglycerides 161 mg/dL
- 25% had diabetes, 57% had hypertension, average body mass index was 29 kg/m^2
- Median follow-up was 5.1 years

- Primary endpoint: nonfatal MI or fatal CHD

Rubins HB, et al. *N Engl J Med*. 1999;341:410-418.

VA-HIT: Results

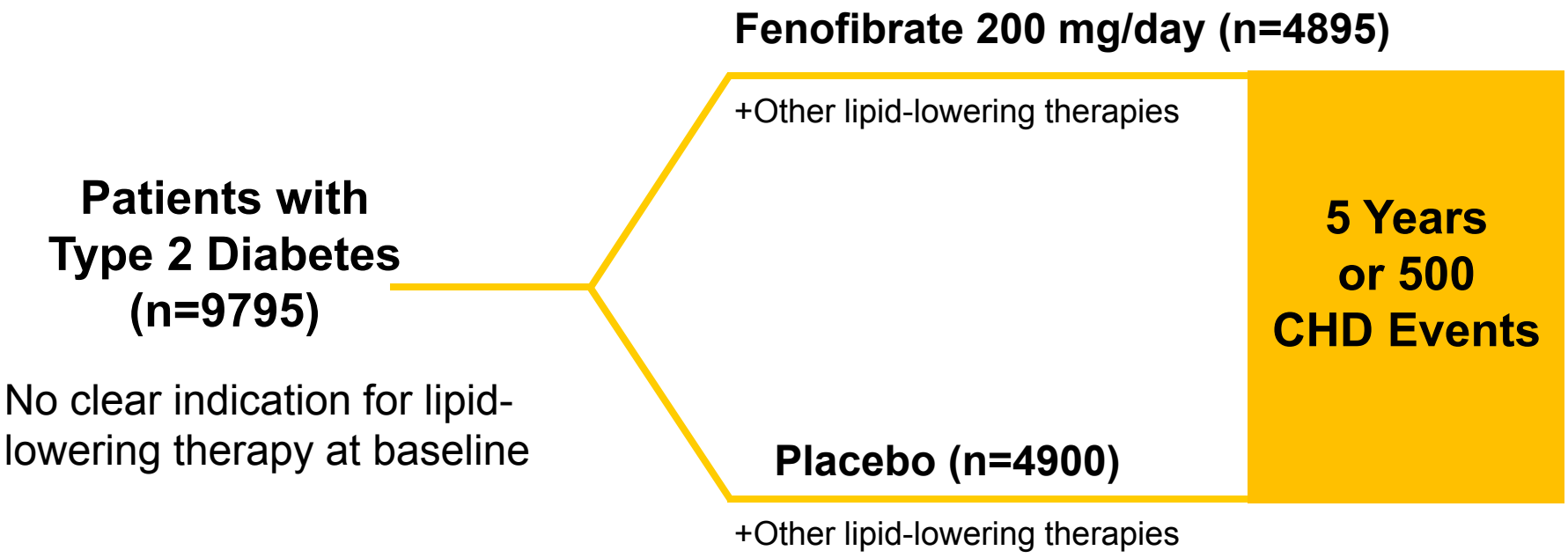
- Percentage of patients with primary endpoint:
  - Gemfibrozil 17.3%
  - Placebo 21.7%

RRR: 20%
P=0.0006
ARR: 4.4%
NNT: 23

- Mean/median lipid values with gemfibrozil vs placebo
  - LDL-C 113 vs 113 mg/dL (P=ns)
  - HDL-C 34 vs 32 mg/dL (P<0.001)
  - Triglycerides 113 vs 161 mg/dL (P<0.001)

Rubins HB, et al. *N Engl J Med*. 1999;341:410-418.

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)



- Primary endpoint: CHD event

FIELD Study Investigators. *Cardiovasc Diabetol*. 2004;3:9-24.

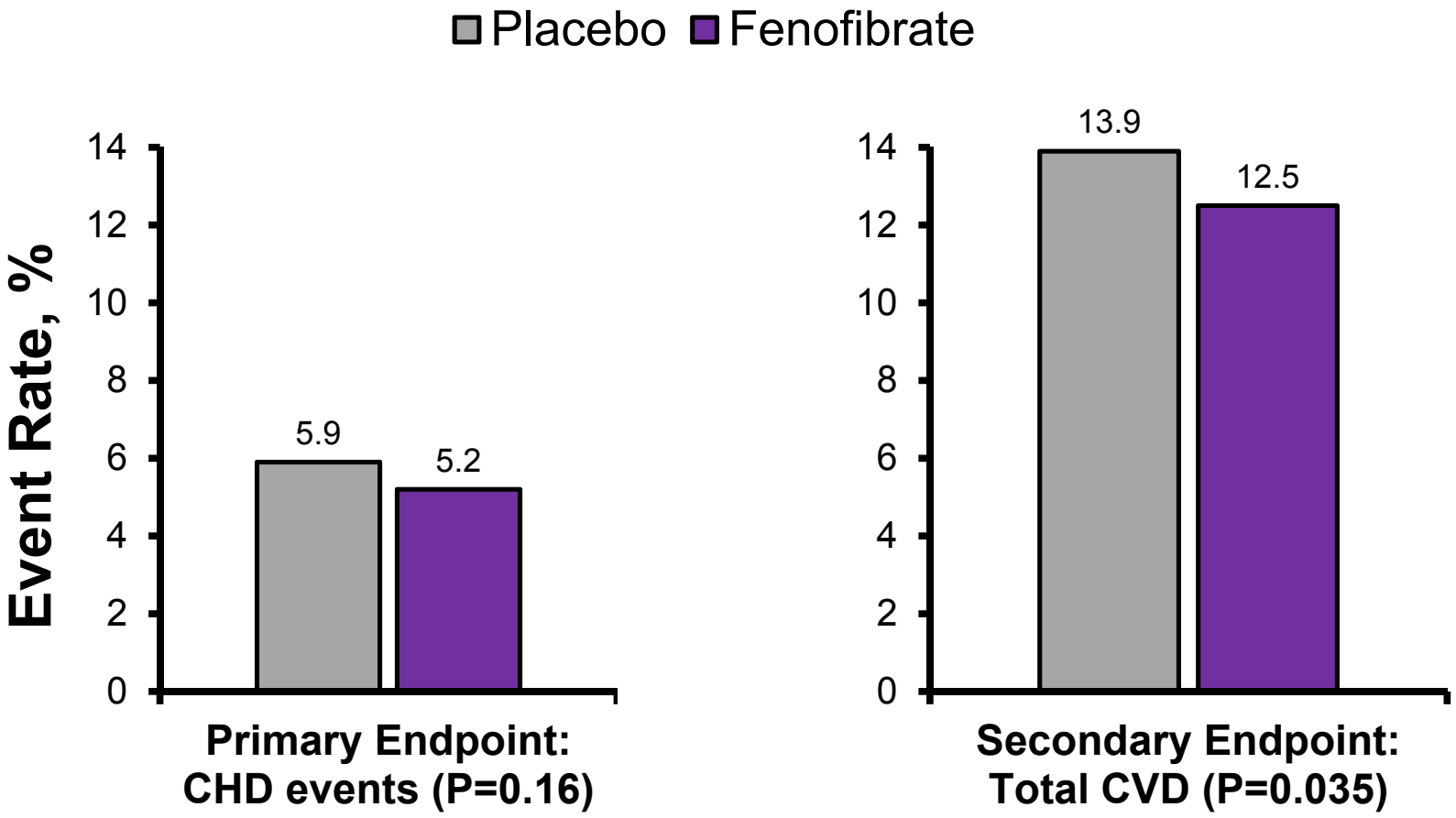
FIELD: Baseline Characteristics

Characteristic	Placebo (n=4900)	Fenofibrate (n=4895)
Male, %	63	63
No Prior CVD, %	78	78
Lipid parameters, mg/dL		
TC	195	195
LDL-C	119	119
HDL-C	43	43
TG	153	154
Dyslipidemic*, %	37	39

*TG >150 mg/dL and HDL-C <40 mg/dL for men or <50 mg/dL for women

Keech A, et al. *Lancet*. 2005;366:1849-1861.

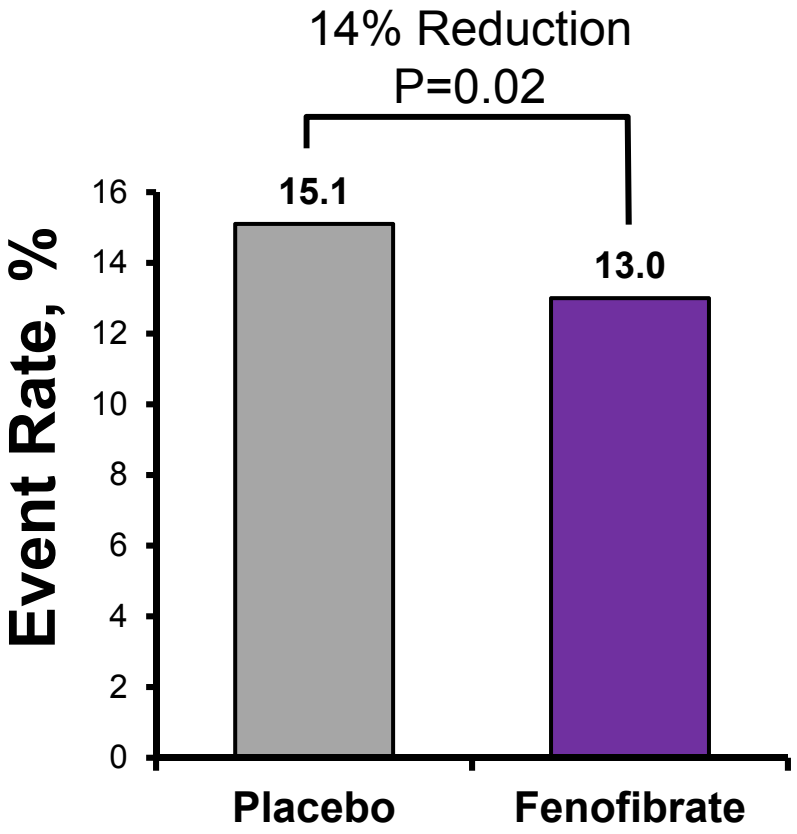
FIELD: Results



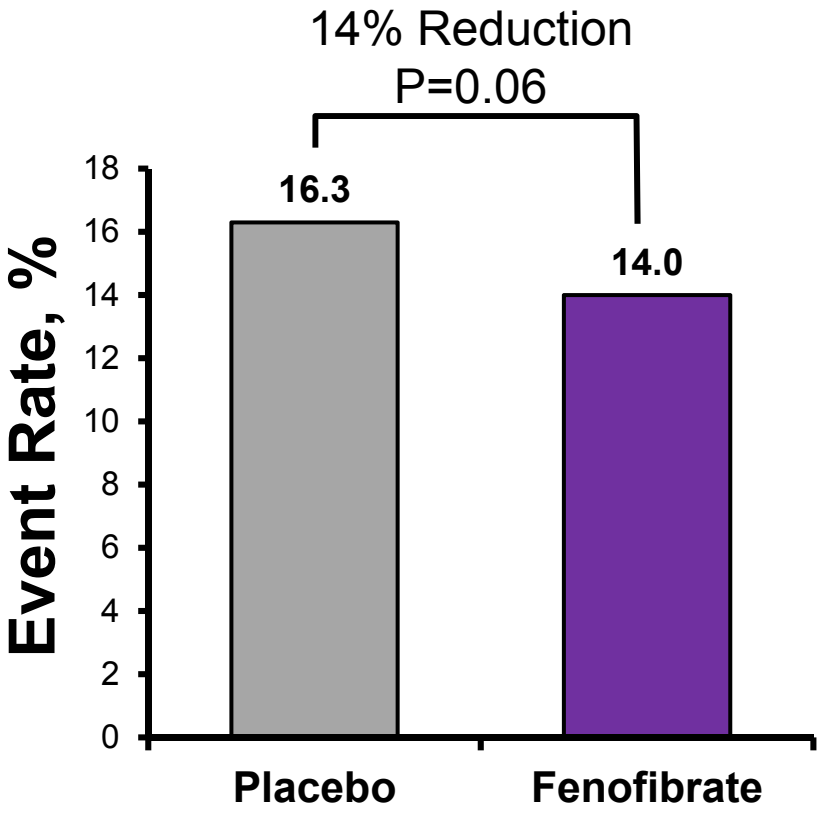
Keech A, et al. *Lancet*. 2005;366:1849-1861.

FIELD: Subgroup Analyses

Patients With Low HDL-C*



Patients With Dyslipidemia†



*<40 mg/dL (men) and <50 mg/dL (women) at baseline
†Triglycerides ≥150 mg/dL and low HDL-C at baseline

Keech A, et al. *Lancet*. 2005;366:1849-1861.

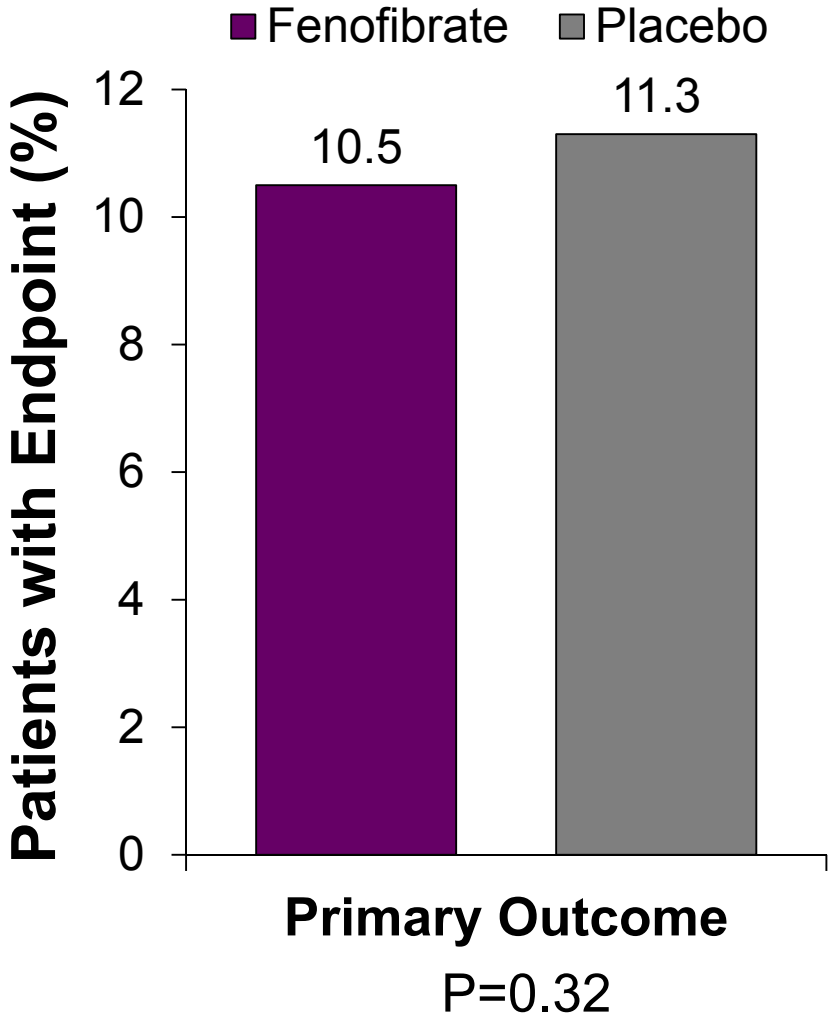
Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study

- 5518 patients with type 2 diabetes treated with open label simvastatin randomized, double blind, to fenofibrate 160 mg daily (with renal adjustment) or placebo
- Primary outcome: nonfatal MI, nonfatal stroke, CV death
- Mean follow-up was 4.7 years

	Baseline	End of Study	
		Fenofibrate	Placebo
LDL-C (mg/dL)	100.6	81.1	80.0
HDL-C (mg/dL)	38.1	41.2	40.5
Triglycerides (mg/dL)	162	122	144

ACCORD Study Group. *N Engl J Med*. 2010;362:1563-1574.

ACCORD: Results



- Subgroup analyses:
  - Possible heterogeneity in treatment according to sex, with benefit for men and harm for women (P= 0.01)
  - Possible benefit in patients with both high baseline triglycerides (≥204 mg/dL) and a low baseline HDL-C (≤34 mg/dL) (P=0.057)

ACCORD Study Group. *N Engl J Med*. 2010;362:1563-1574.

ACC/AHA 2013 Blood Cholesterol Guideline: Additional Recommendations

- The panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA Class II-IV ischemic systolic heart failure or in patients on maintenance hemodialysis

Stone NJ, et al. Circulation. 2013: published online before print November 12, 2013.

Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

- 5011 patients ≥ 60 years of age with NYHA class II, III, or IV ischemic, systolic heart failure (mean EF 31%)
- Randomized, double-blind to rosuvastatin 10 mg daily or placebo for a median follow up of 32.8 months
- Results:
  - Primary endpoint of CV death or nonfatal MI or stroke
    - Rosuvastatin 27.5%
    - Placebo 29.3% (P=0.12)

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

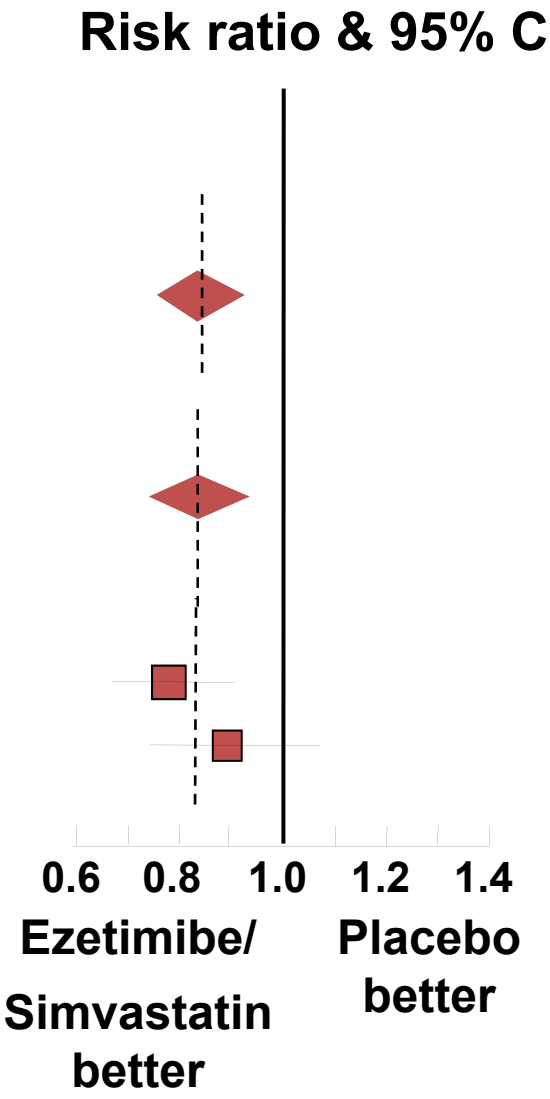
Lipid-Lowering Therapy in Patients with End-Stage Renal Disease (ESRD) Requiring Hemodialysis

Trial	Population	Primary Endpoint	Relative Risk (95% CI)
4D: • Atorvastatin 20 mg daily vs placebo for 4 years	Type 2 diabetes plus long-term hemodialysis (n=1255)	CV death, nonfatal MI, fatal/nonfatal stroke	0.92 (0.77–1.10)
AURORA: • Rosuvastatin 10 mg daily vs placebo for 3.8 years	Long-term hemodialysis (n=2776)	CV death, nonfatal MI, nonfatal stroke	0.96 (0.84–1.11)

Wanner C et al. N Engl J Med. 2005; 353:238-48.
Fellström BC et al. N Engl J Med. 2009; 360:1395-407.

SHARP: Major Vascular Events

Event	Ezetimibe/ Simvastatin (n=4650)	Placebo (n=4620)
Major vascular event	**701 (15.1%)**	**814 (17.6%)**
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**
Non-dialysis (n=6247)	**296 (9.5%)**	**373 (11.9%)**
Dialysis (n=3023)	**230 (15.0%)**	**246 (16.5%)**



Note: No significant heterogeneity between non-dialysis and dialysis patients (P=0.25)

Baigent C, et al. *Lancet* 2011; 377: 2181–92

Schizophrenic Life of Ezetimibe

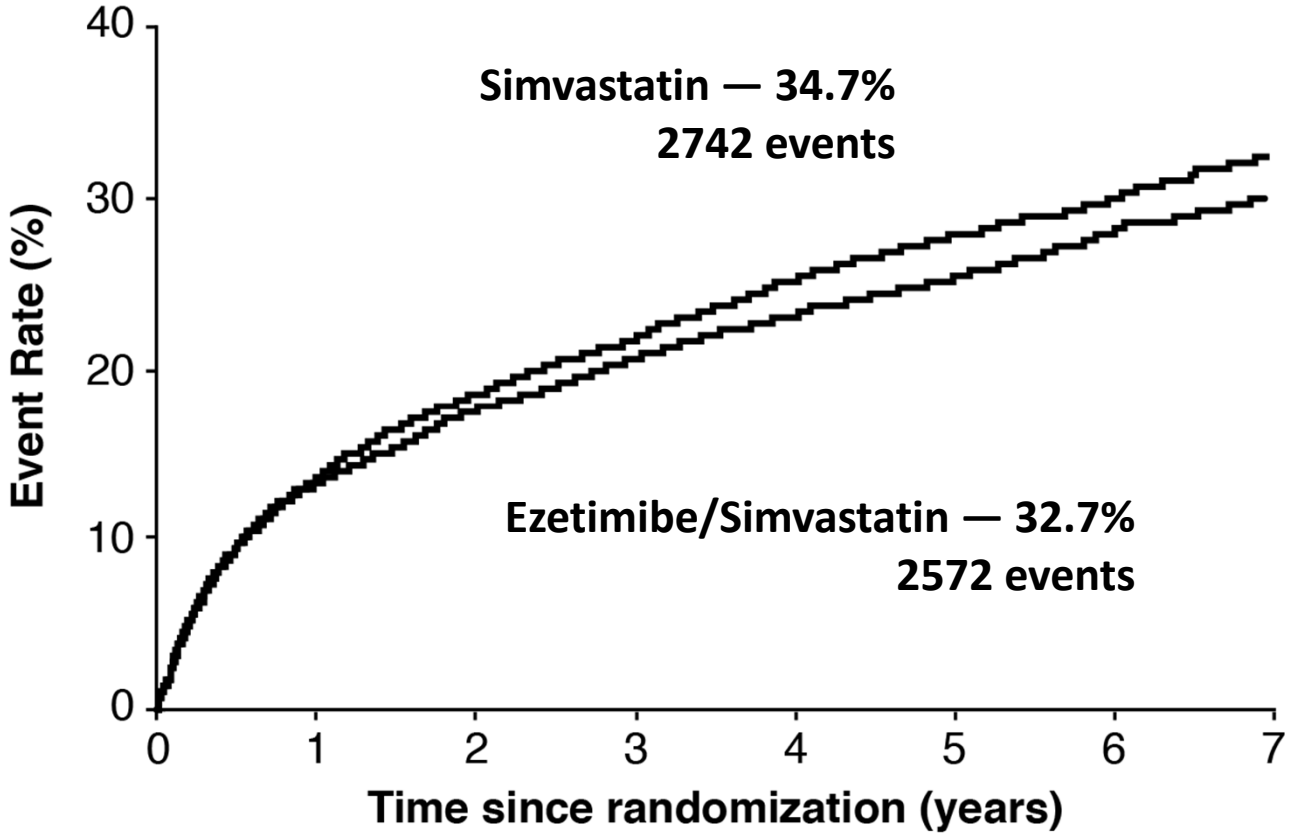
- 2002 – Approval of ezetimibe
- 2004 – Approval of ezetimibe/simvastatin combination
- 2005 – IMPROVE-IT study starts targeting 12,500 patients
- 2006 – ENHANCE published after 18 month delay
- 2008 – Excess cancer cases in the SEAS trial
- 2008 – IMPROVE-IT changes target enrollment to 18,000; completion delayed until 2012
- 2009 – FDA investigation concludes cancer risk unlikely
- 2010 – IMPROVE-IT completion delayed until 2013
- 2011 – SHARP Trial
- 2015 – Release of IMPROVE-IT results

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

- Double-blind trial in 18,144 patients with an acute coronary syndrome, age ≥50 years with a high CV risk feature, and LDL-C 50-125 mg/dL (50-100 if on lipid-lowering therapy)
- Randomized to simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg for 4.9 years
- Primary endpoint: CV death, MI, hospital admission for unstable angina, coronary revascularization, or stroke
- Mean LDL-C values
  - Simvastatin alone 69.9 mg/dL
  - Ezetimibe /simvastatin 53.2 mg/dL

Cannon CP et al. N Engl J Med 2015;372:2387-97.

IMPROVE-IT: Results



RRR: 20%
P=0.016
ARR: 2%
NNT: 50

RRR: 5.8%

Cannon CP et al. N Engl J Med 2015;372:2387-97.

7-year event rates

Key Take-Away Messages: Landmark Clinical Trials

- Applying basic principles of clinical trials and statistics is needed when interpreting landmark clinical trials and applying findings to patient care
- Multiple landmark clinical trials have had a major influence on recommendations for treatment of dyslipidemia
- Statin-based landmark trials have consistently demonstrated reduced risk of CV events
- Nonstatin have been evaluated in landmark clinical trials with mixed results and various interpretations