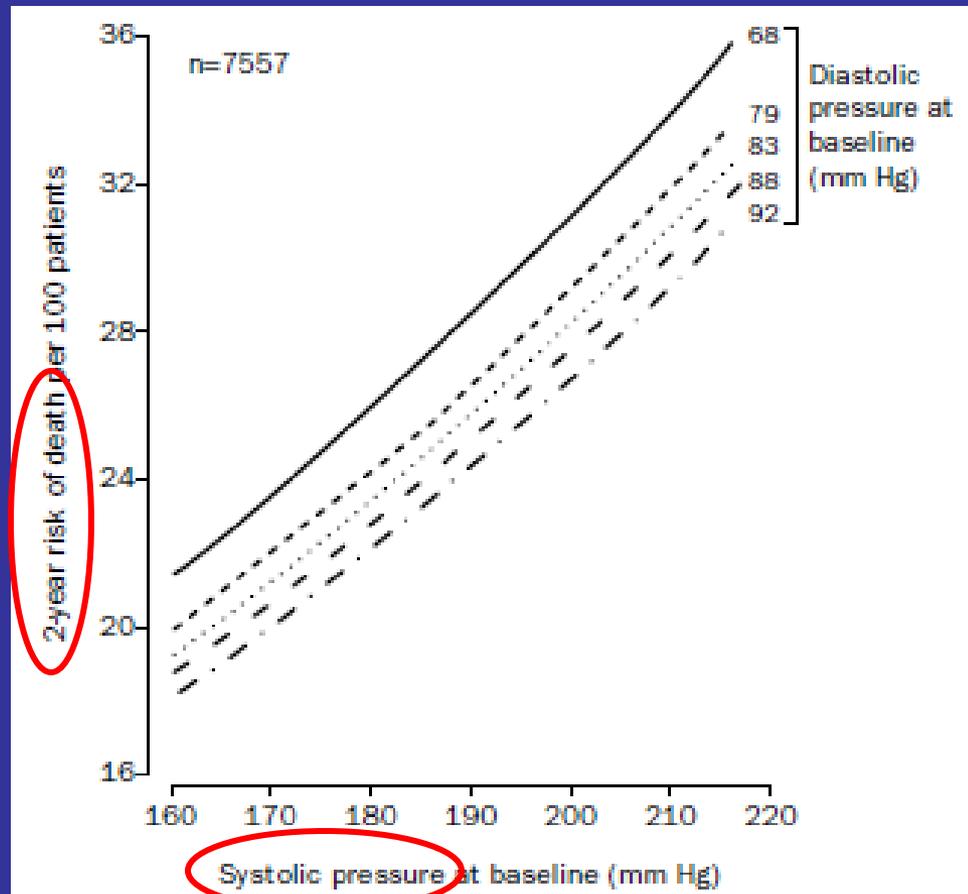


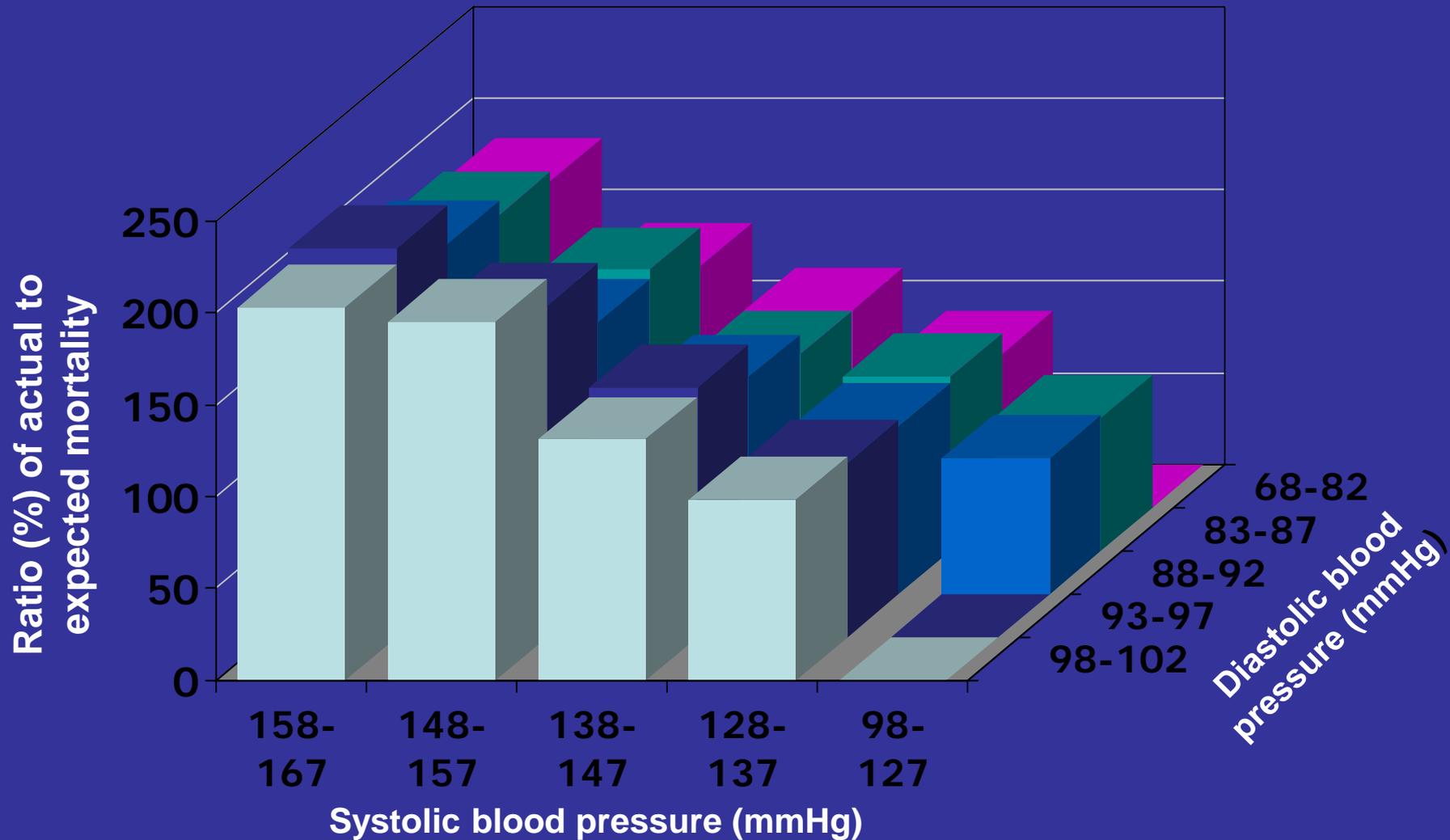
# Prevention of Cardiovascular Disease

- Screen for CV risk factors
- Achieve a healthy lifestyle
  - Diet, Body Weight, Exercise,
  - *Smoke cessation*
- ***Control blood pressure***
- ***Optimize lipid levels***
- Avoid/treat diabetes
- ***Aspirin based upon risk/benefit***

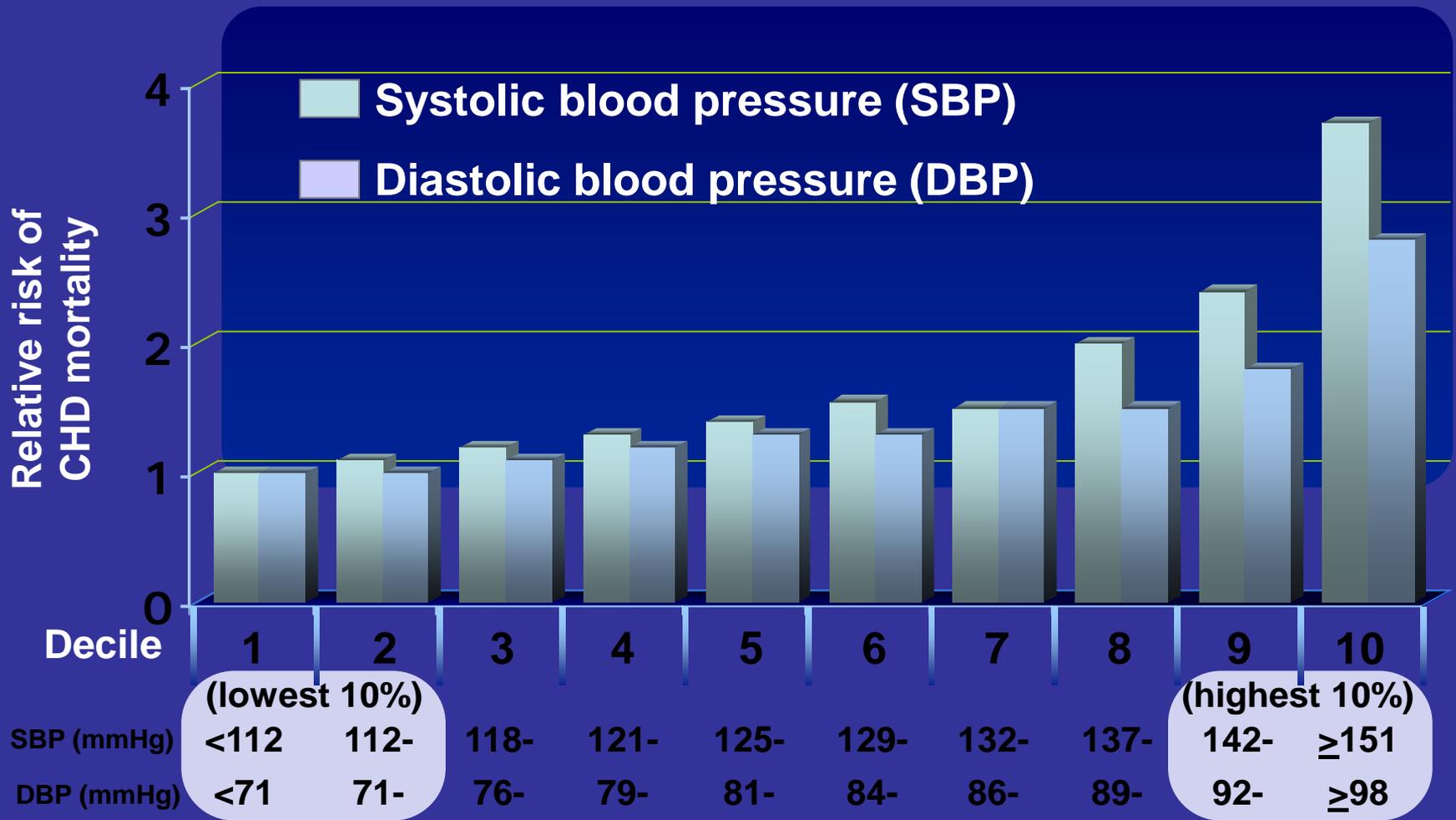
# Mortality Risk with Systolic Pressure at Fixed Diastolic Pressure



# Mortality According to Blood Pressure in Men Age 50 to 69



# Risk of CHD Death According to SBP and DBP in MRFIT



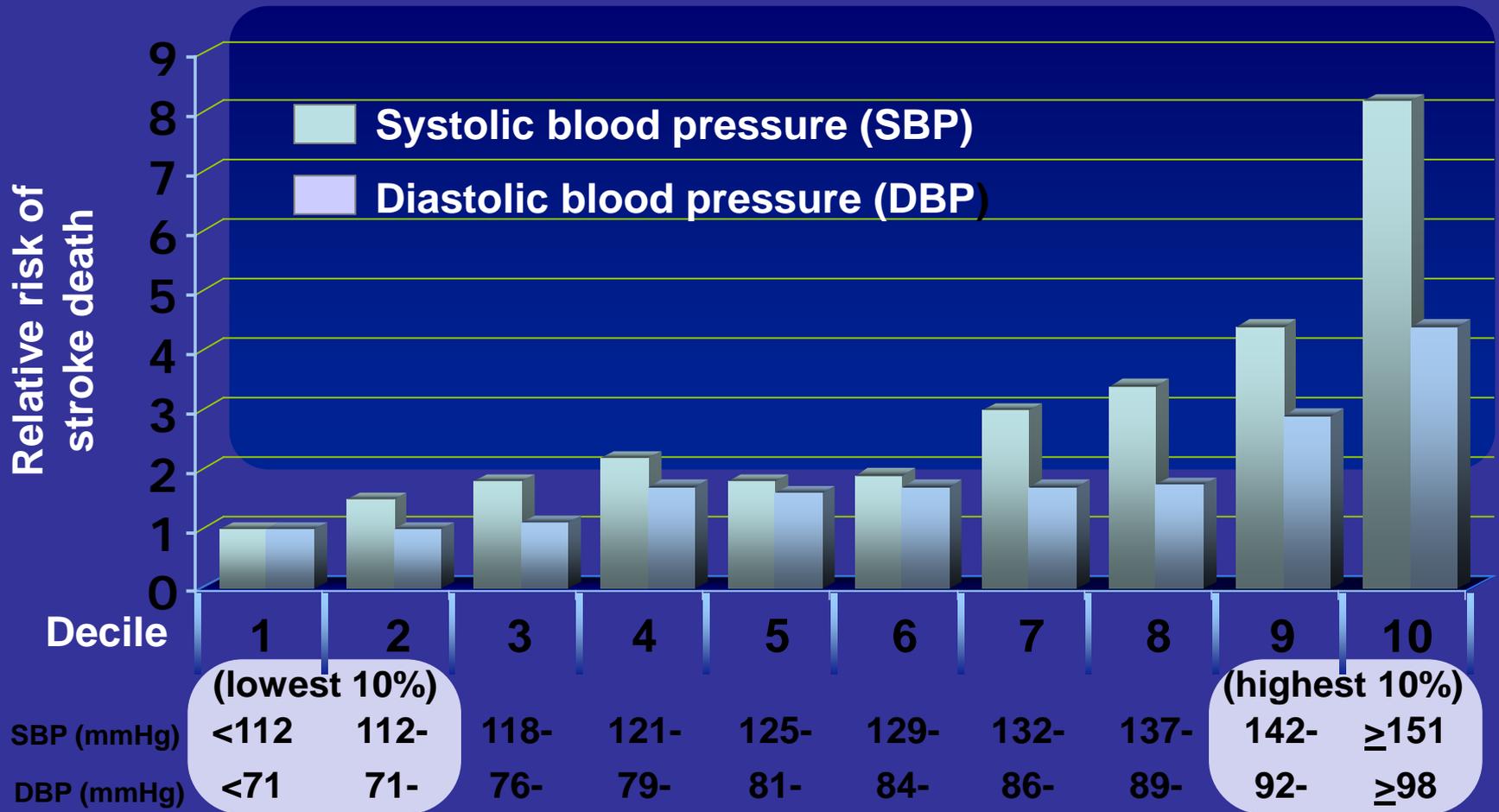
CHD=coronary heart disease

He J, et al. Am Heart J. 1999;138:211-219.

Copyright 1999, Mosby Inc.

[www.hypertensiononline.org](http://www.hypertensiononline.org)

# Risk of Stroke Death According to SBP and DBP in MRFIT

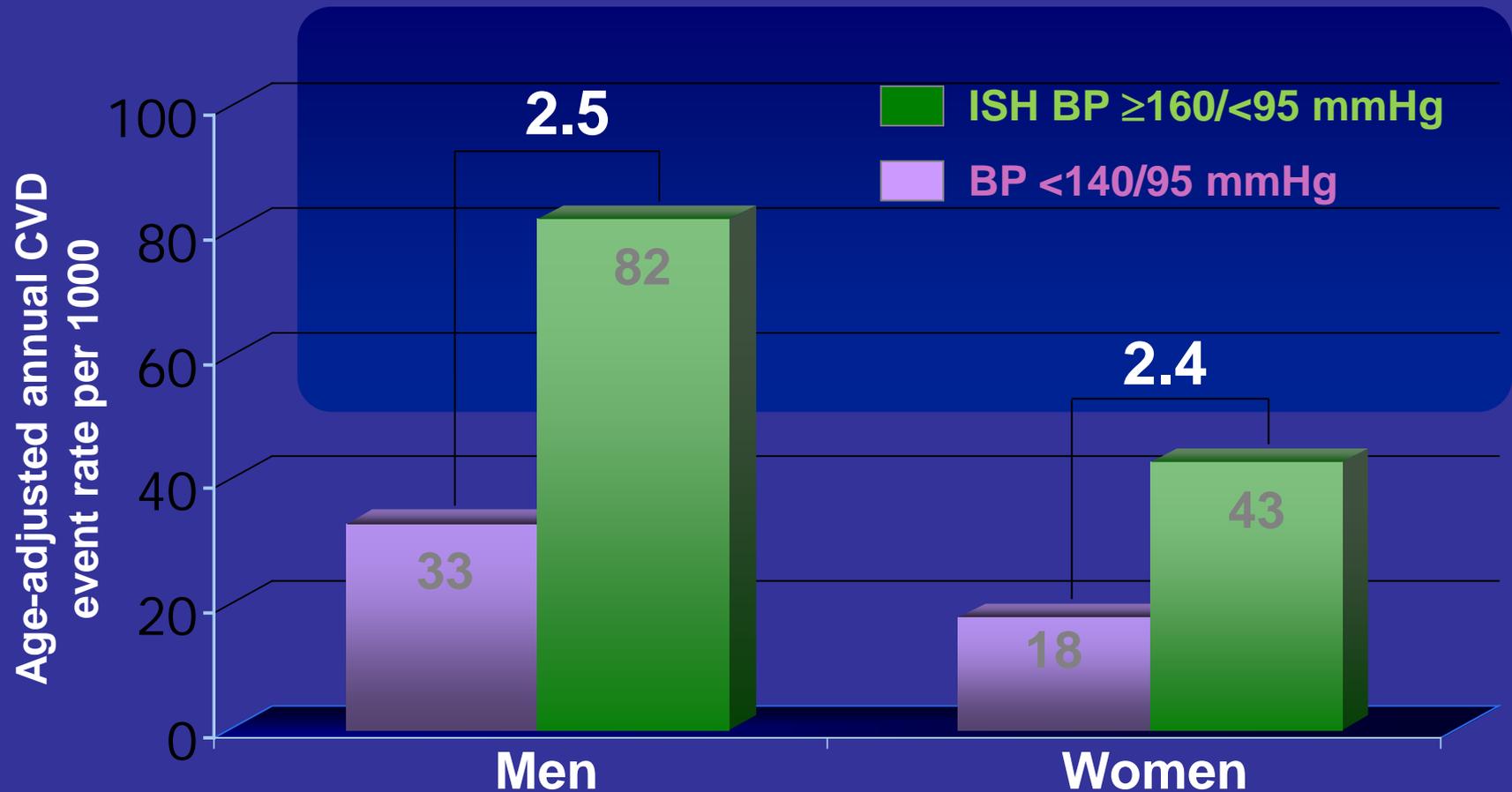


He J, et al. Am Heart J. 1999;138:211-219.

Copyright 1999, Mosby Inc.

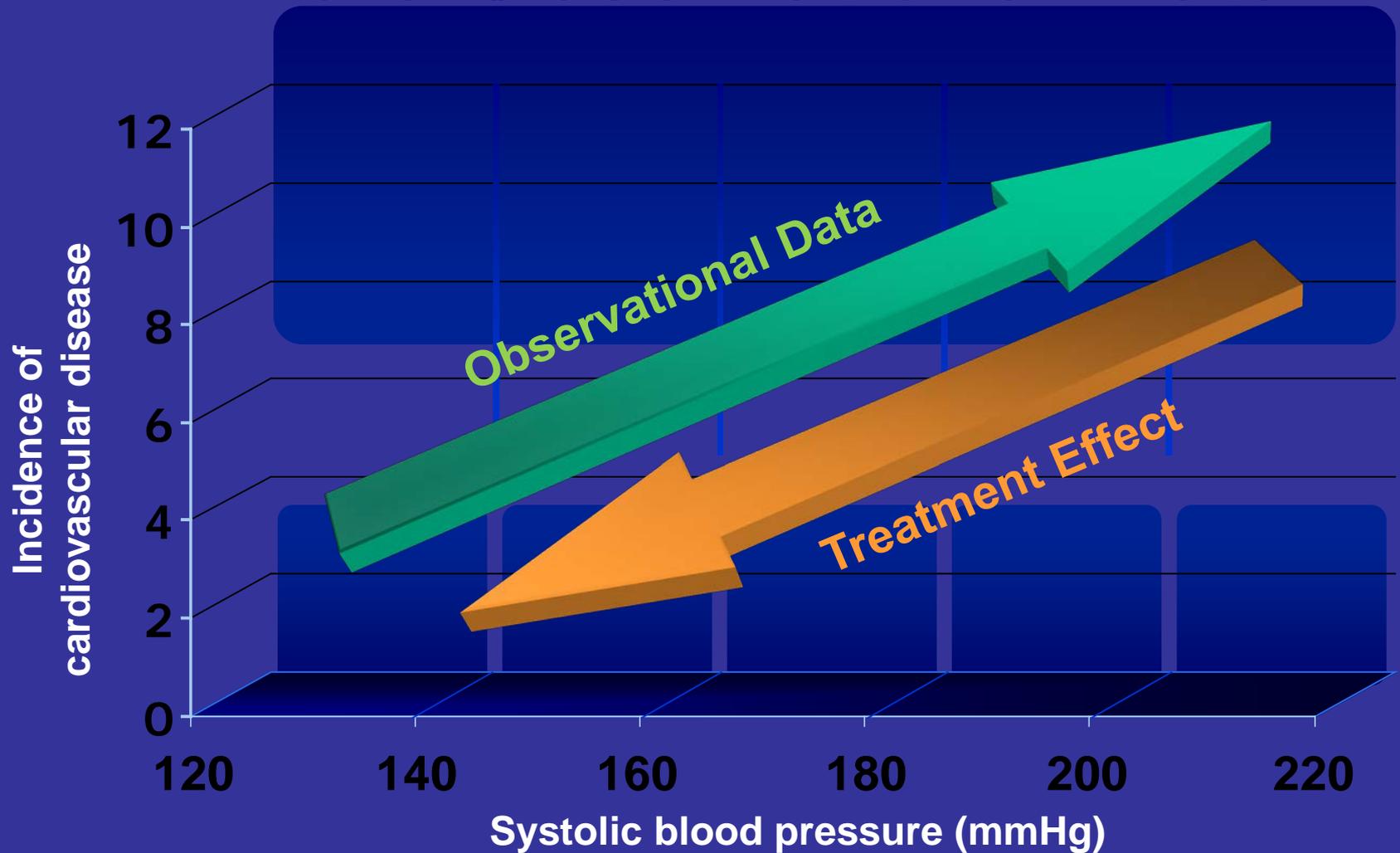
[www.hypertensiononline.org](http://www.hypertensiononline.org)

# Isolated Systolic Hypertension and CVD Risk in Framingham

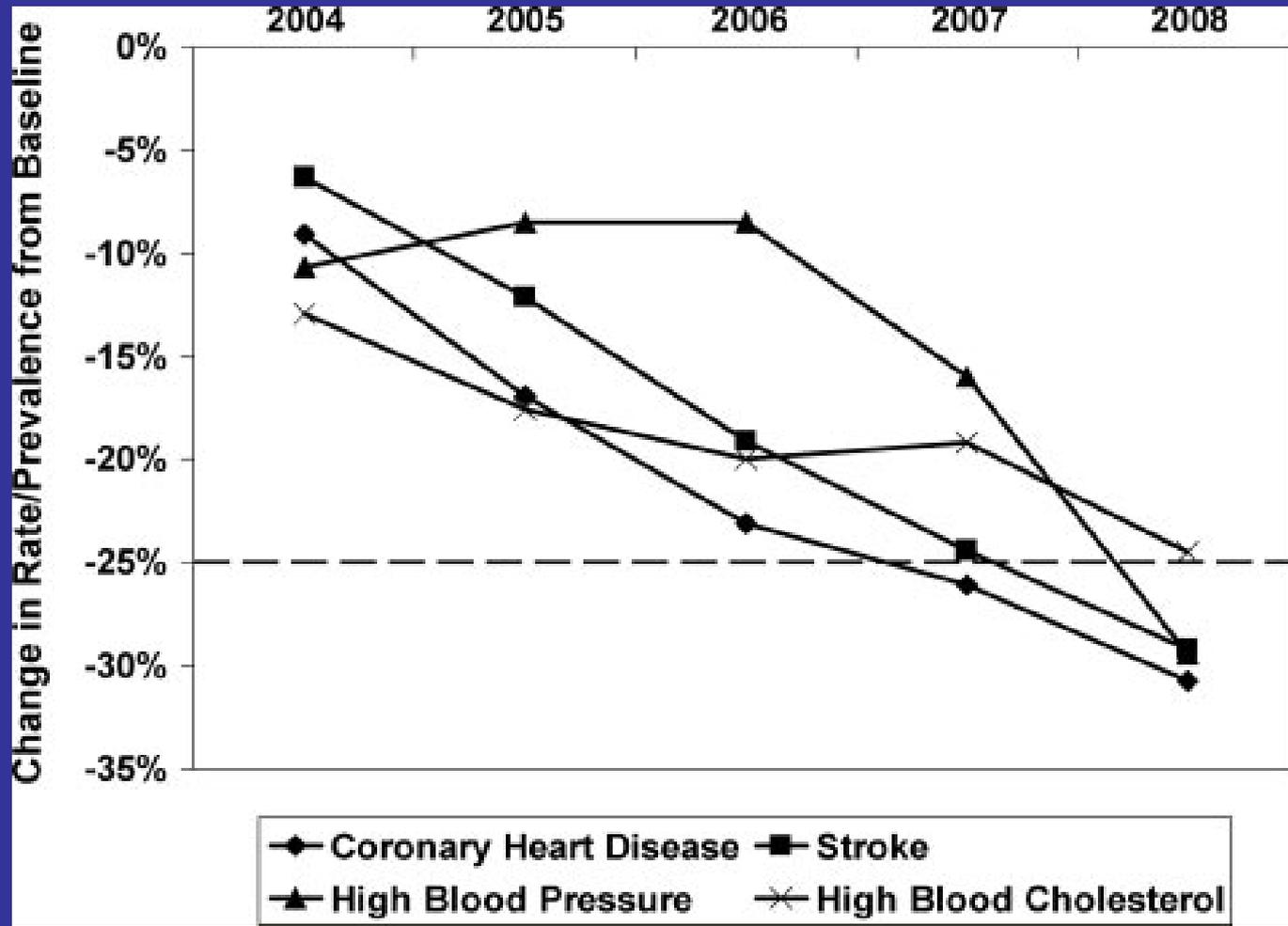


CVD=cardiovascular disease ISH=isolated systolic hypertension  
P<0.001 for difference between both men and women with ISH and  
blood pressure (BP) <140/95 mmHg

# Hypertension Treatment Effect Mirrors Observational Data



# CV Events and BP and Cholesterol Change



# Landmark Clinical Trials

## Hypertension Treatment and Cardiovascular Disease Outcomes

**1967** – VA Cooperative Study on DBP 115-129

**1970** – VA Cooperative Study on DBP 90-114

**1979** – HDFP

**1980** – Australian Trial, Oslo Trial

**1985** – MRC I, EWPHE

**1991** – SHEP, STOP-Hypertension

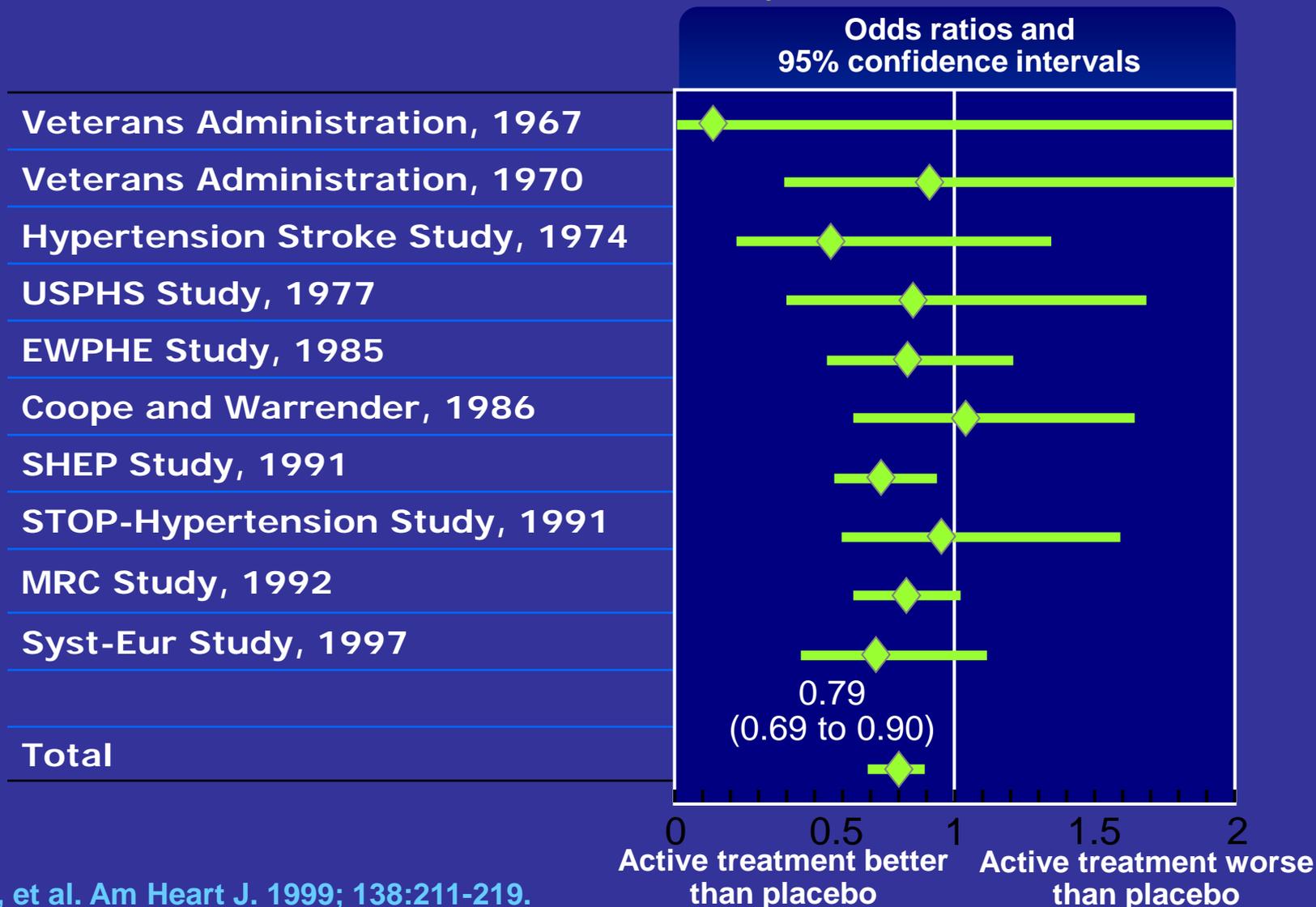
**1992** – MRC II in the elderly

**1997** – Syst-Eur

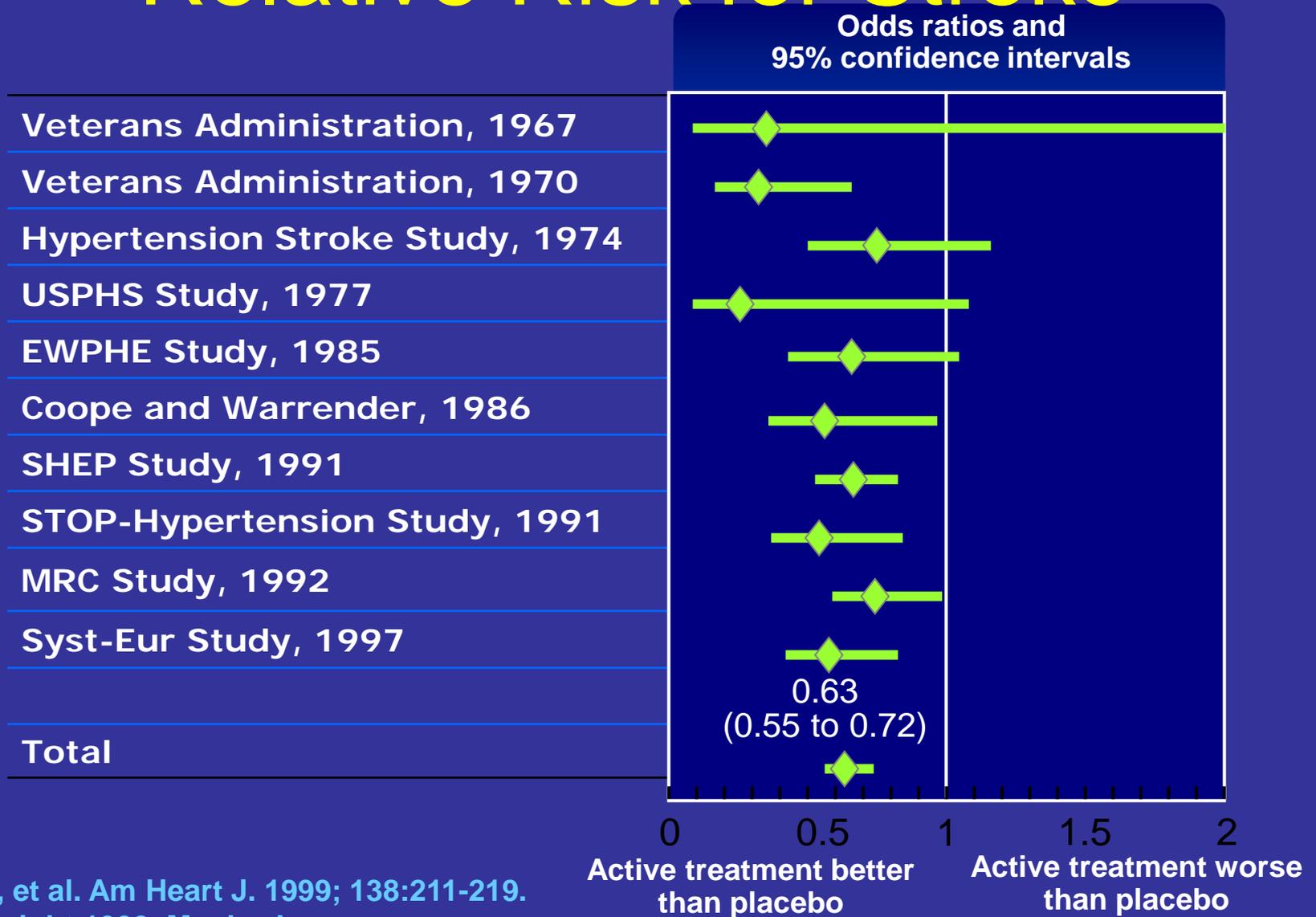
**2002** – LIFE

**2002** – ALLHAT

# Relative Risk for Coronary Heart Disease



# Relative Risk for Stroke



He J, et al. Am Heart J. 1999; 138:211-219.  
Copyright 1999, Mosby, Inc.

# Population-Based Strategy

## SBP Distributions

After Intervention → ← Before Intervention

← Reduction in BP →

Reduction in SBP  
mmHg

% Reduction in Mortality  
Stroke CHD Total

2

-6

-4

-3

3

-8

-5

-4

5

-14

-9

-7

# JNC 7: Treatment Overview

Table 1. Classification and management of blood pressure for adults\*

BP CLASSIFICATION	SBP* MMHG	DBP* MMHG	LIFESTYLE MODIFICATION	INITIAL DRUG THERAPY	
				WITHOUT COMPELLING INDICATION	WITH COMPELLING INDICATIONS (SEE TABLE 8)
NORMAL	<120	and <80	Encourage		
PREHYPERTENSION	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
STAGE 1 HYPERTENSION	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
STAGE 2 HYPERTENSION	≥160	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

\* Treatment determined by highest BP category.

† Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

‡ Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

# Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials

Jan A Staessen, Jerzy Gasowski, Ji G Wang, Lutgarde Thijs, Elly Den Hond, Jean-Pierre Boissel, John Coope, Tork Ekbom, François Gueyffier, Lisheng Liu, Karla Kerlikowske, Stuart Pocock, Robert H Fagard

## Summary

**Background** Previous meta-analysis of outcome trials in hypertension have not specifically focused on isolated systolic hypertension or they have explained treatment benefit mainly in function of the achieved diastolic blood

pressure was 100 mm Hg or greater and diastolic blood pressure was less than 95 mm Hg. We used non-parametric methods and Cox regression to model the risks associated with blood pressure and to correct for regression dilution bias. We calculated pooled effects of treatment from stratified 2 × 2 contingency tables after application of Zelen's test of heterogeneity.

2–22,  $p=0.02$ ), cardiovascular mortality by 18%, all cardiovascular complications by 26%, stroke by 30%, and coronary events by 23%. The number of patients to treat for 5 years to prevent one major cardiovascular event was lower in men (18 vs 38), at or above age 70 (19 vs 39), and in patients with previous cardiovascular complications (16 vs

Treatment reduced mortality by 13%, cardiovascular mortality by 18%, stroke by 30%, and coronary events by 23%.

pressure was 100 mm Hg or greater and diastolic blood pressure was less than 95 mm Hg. We used non-parametric methods and Cox regression to model the risks associated with blood pressure and to correct for regression dilution bias. We calculated pooled effects of treatment from stratified 2 × 2 contingency tables after application of Zelen's test of heterogeneity.

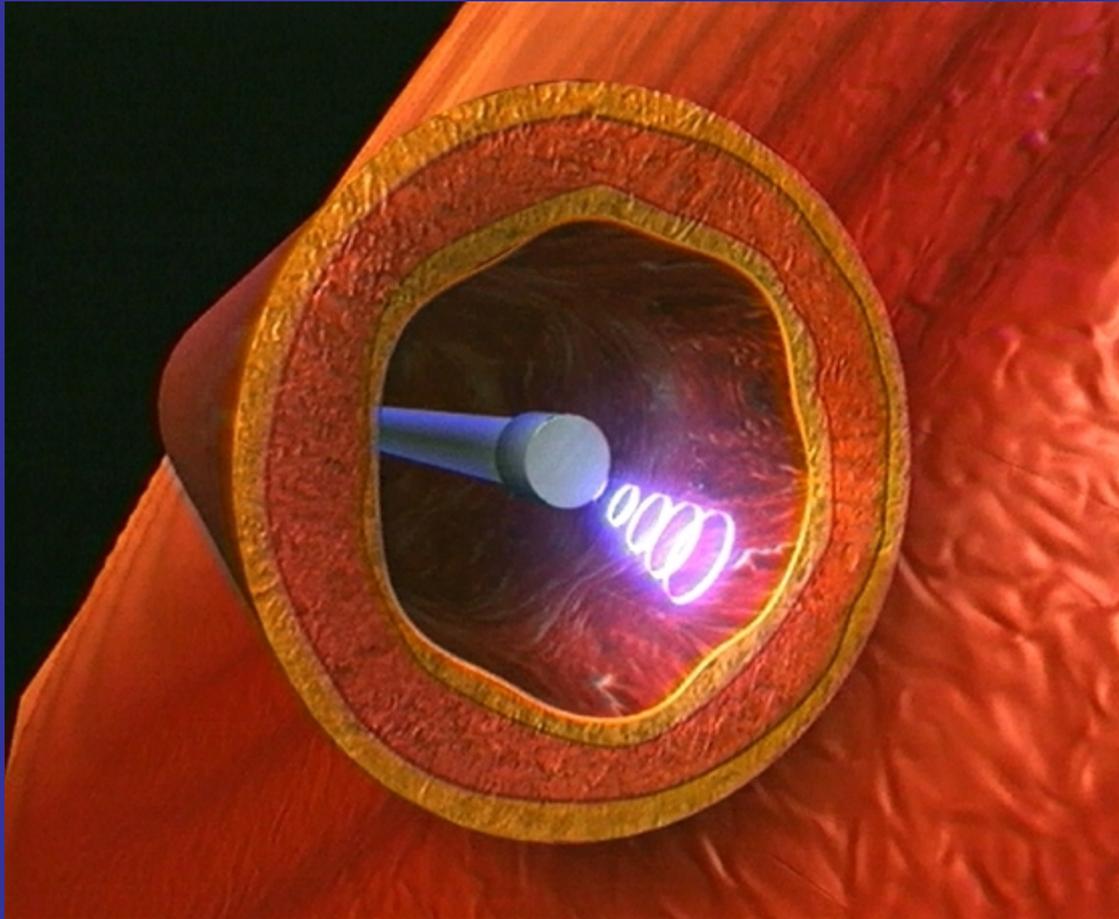
**Findings** In eight trials 15 693 patients with isolated systolic hypertension were followed up for 3.8 years (median). After correction for regression dilution bias, sex, age, and diastolic blood pressure, the relative hazard rates associated with a 10 mm Hg higher initial systolic blood pressure were 1.26 ( $p=0.0001$ ) for total mortality, 1.22 ( $p=0.02$ ) for stroke, but only 1.07 ( $p=0.37$ ) for coronary events. Independent of systolic blood pressure, diastolic blood pressure was inversely correlated with total mortality, highlighting the role of pulse pressure as risk factor.

previous cardiovascular complications or wider pulse pressure. Treatment prevented stroke more effectively than coronary events. However, the absence of a relation between coronary events and systolic blood pressure in untreated patients suggests that the coronary protection may have been underestimated.

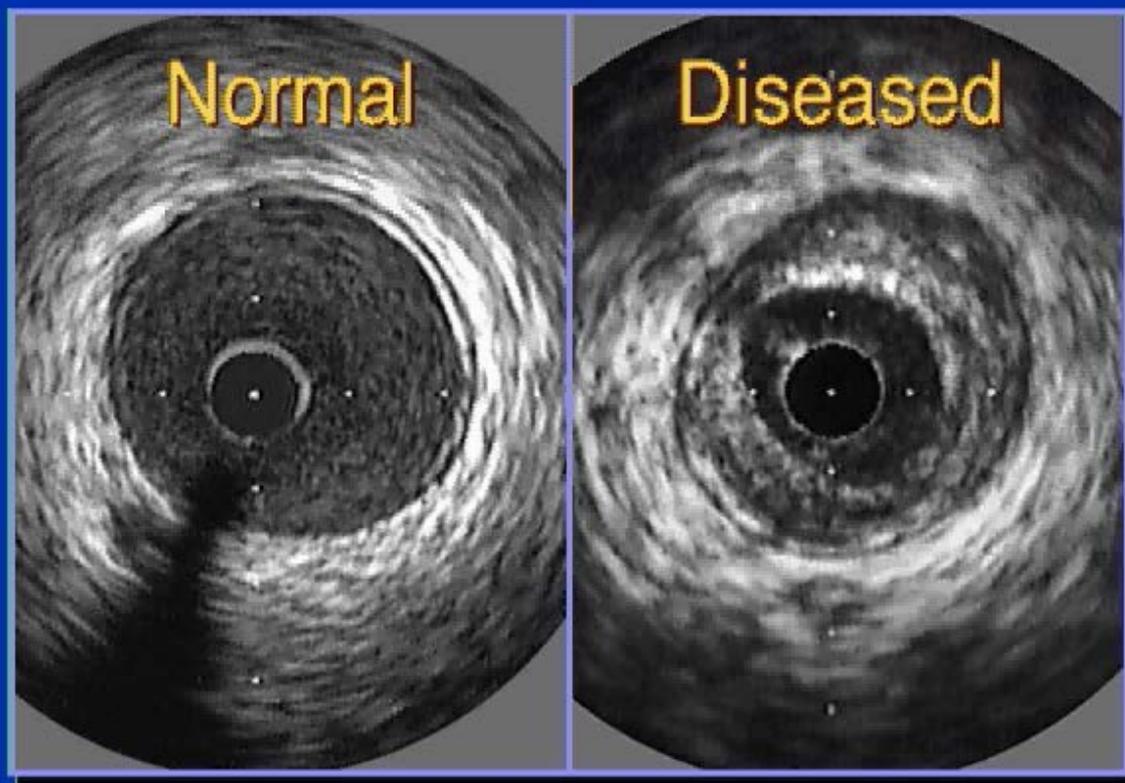
*Lancet* 2000; **355**: 865–872

Active treatment reduced total mortality by 13% (95% CI

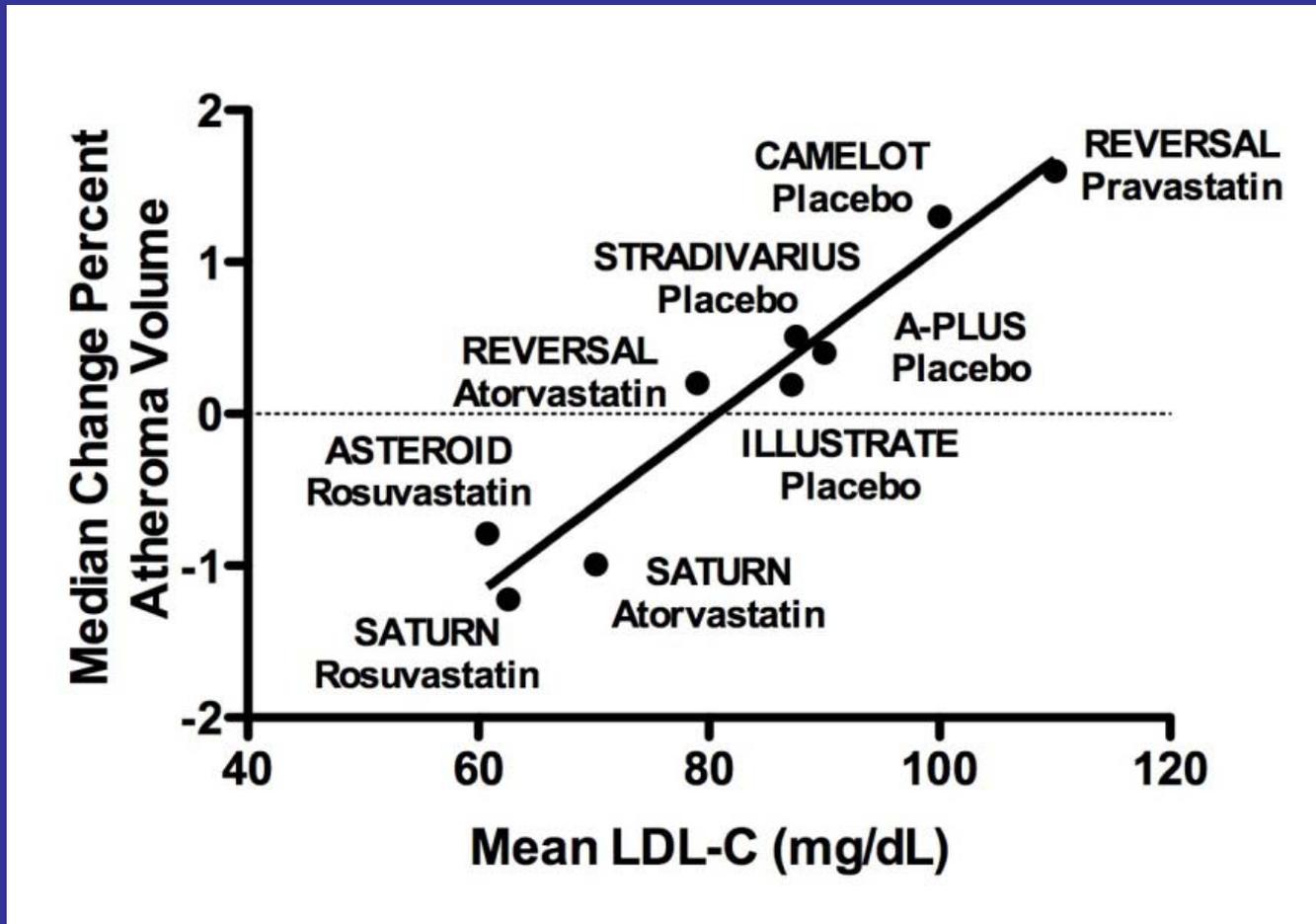
# Intravascular Ultrasound



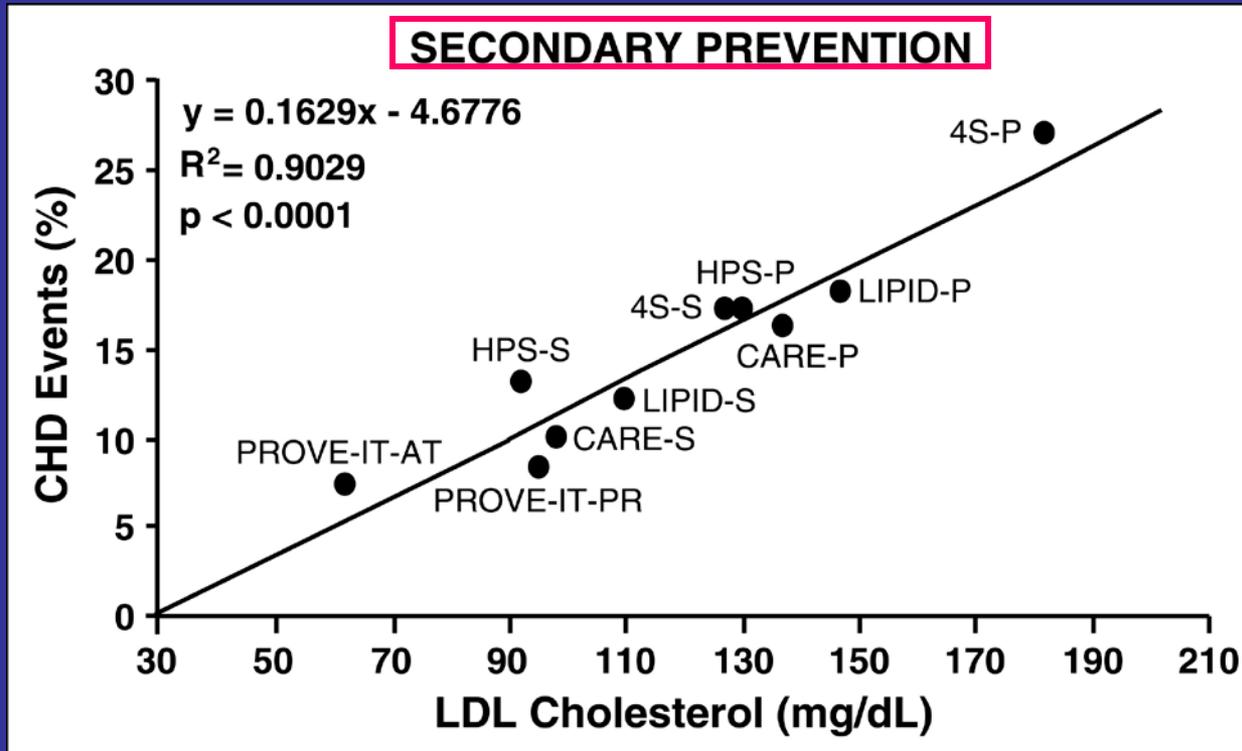
# CAD by IVUS



# LDL and Atheroma Volume

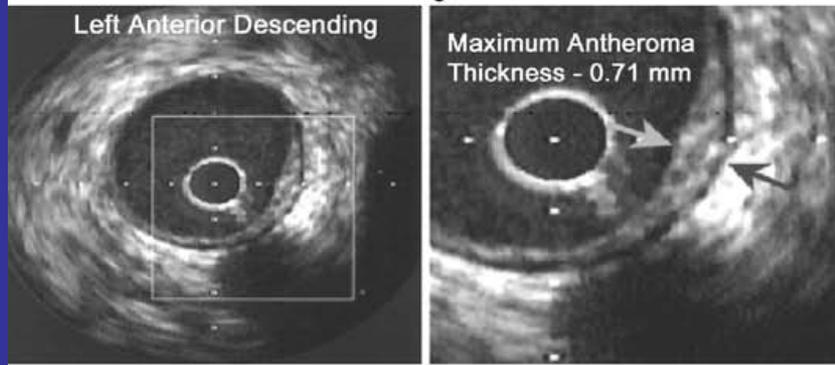


# Relation of LDL to Event Rate

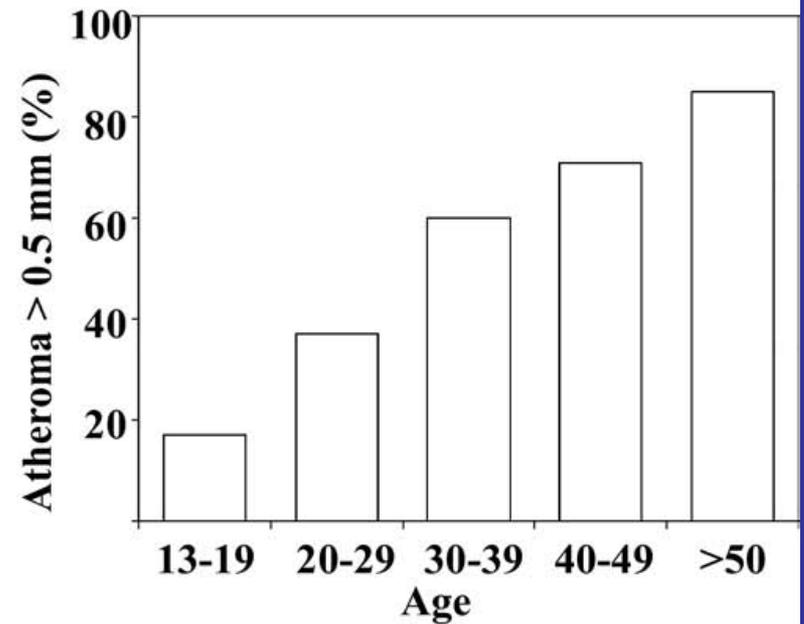
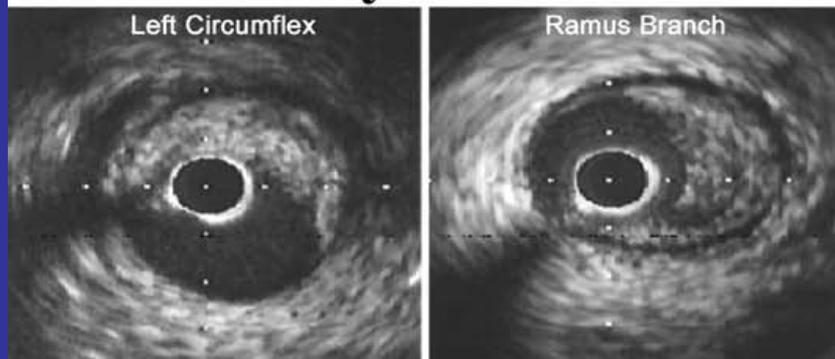


O'Keefe et al; JACC, 2004

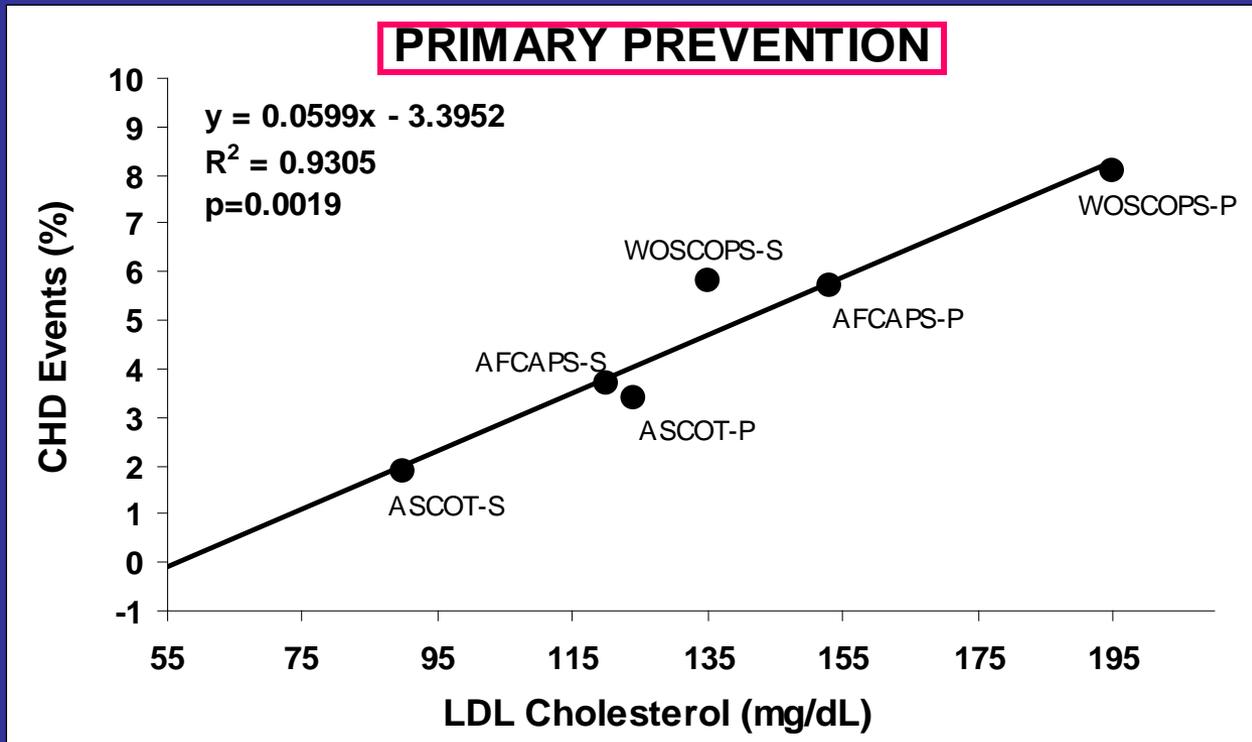
# CAD in Young Adults



**33 y.o. woman**

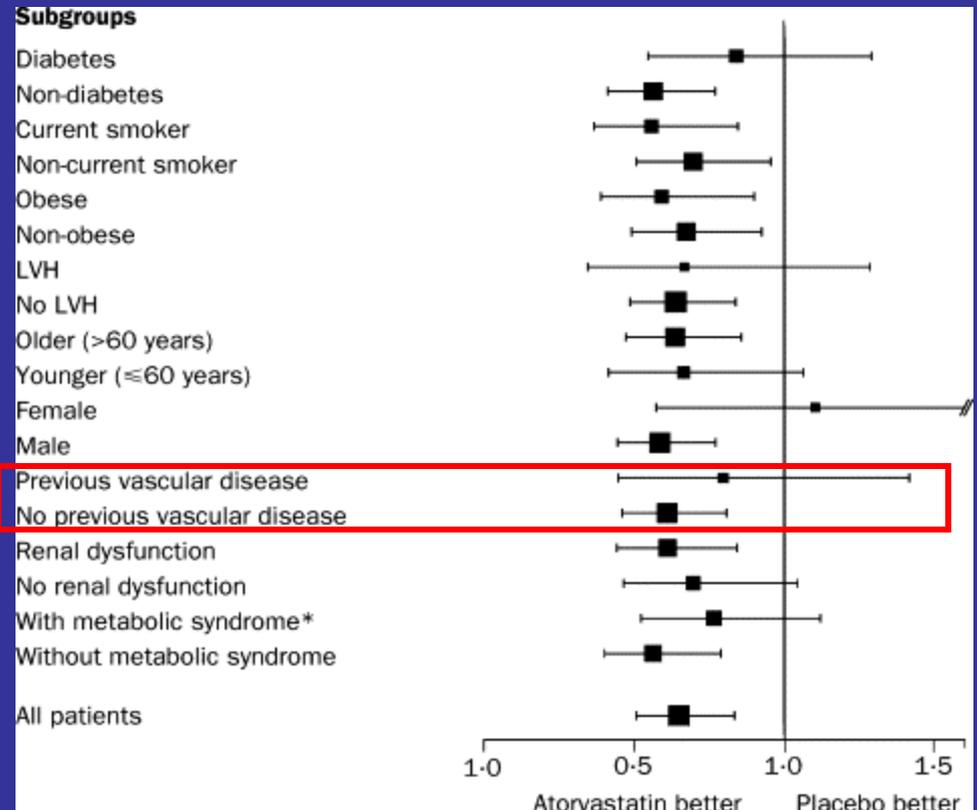
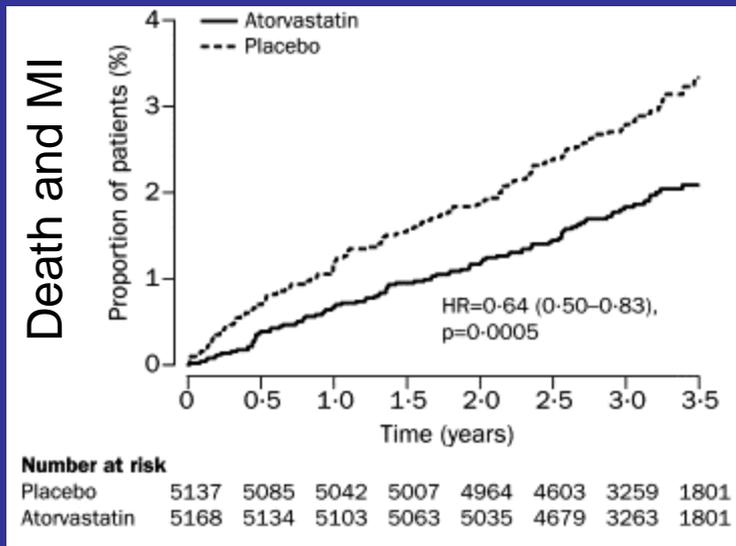


# Relation of LDL to Event Rate



O'Keefe et al; JACC, 2004

# Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm



Original Article

# Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., Robert J. Glynn, Sc.D., for the JUPITER Study Group

N Engl J Med  
Volume 359(21):2195-2207  
November 20, 2008



The NEW ENGLAND  
JOURNAL of MEDICINE

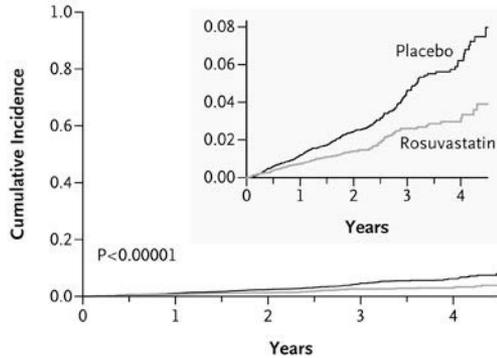
# Study Overview

- In this trial, 17,802 healthy men and women with low-density lipoprotein cholesterol levels of less than 130 mg per deciliter and high-sensitivity C-reactive protein levels of 2.0 mg per liter or more were randomly assigned to rosuvastatin or placebo
- At a median of 1.9 years, the incidence of major cardiovascular events was significantly lower in the rosuvastatin group



# Cumulative Incidence of CV Events in JUPITER

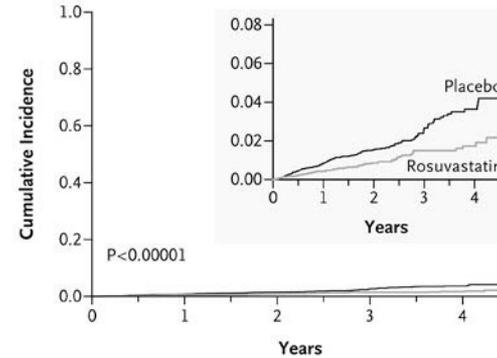
**A Primary End Point**



**No. at Risk**

Rosuvastatin	8901	8631	8412	6540	3893	1958	1353	983	538	157
Placebo	8901	8621	8353	6508	3872	1963	1333	955	531	174

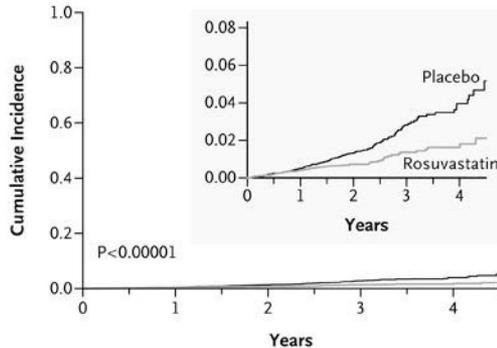
**B Myocardial Infarction, Stroke, or Death from Cardiovascular Causes**



**No. at Risk**

Rosuvastatin	8901	8643	8437	6571	3921	1979	1370	998	545	159
Placebo	8901	8633	8381	6542	3918	1992	1365	979	547	181

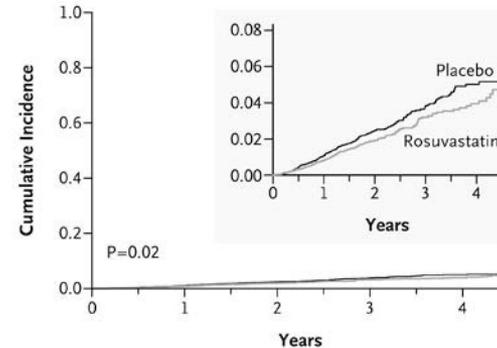
**C Revascularization or Hospitalization for Unstable Angina**



**No. at Risk**

Rosuvastatin	8901	8640	8426	6550	3905	1966	1359	989	541	158
Placebo	8901	8641	8390	6542	3895	1977	1346	963	535	176

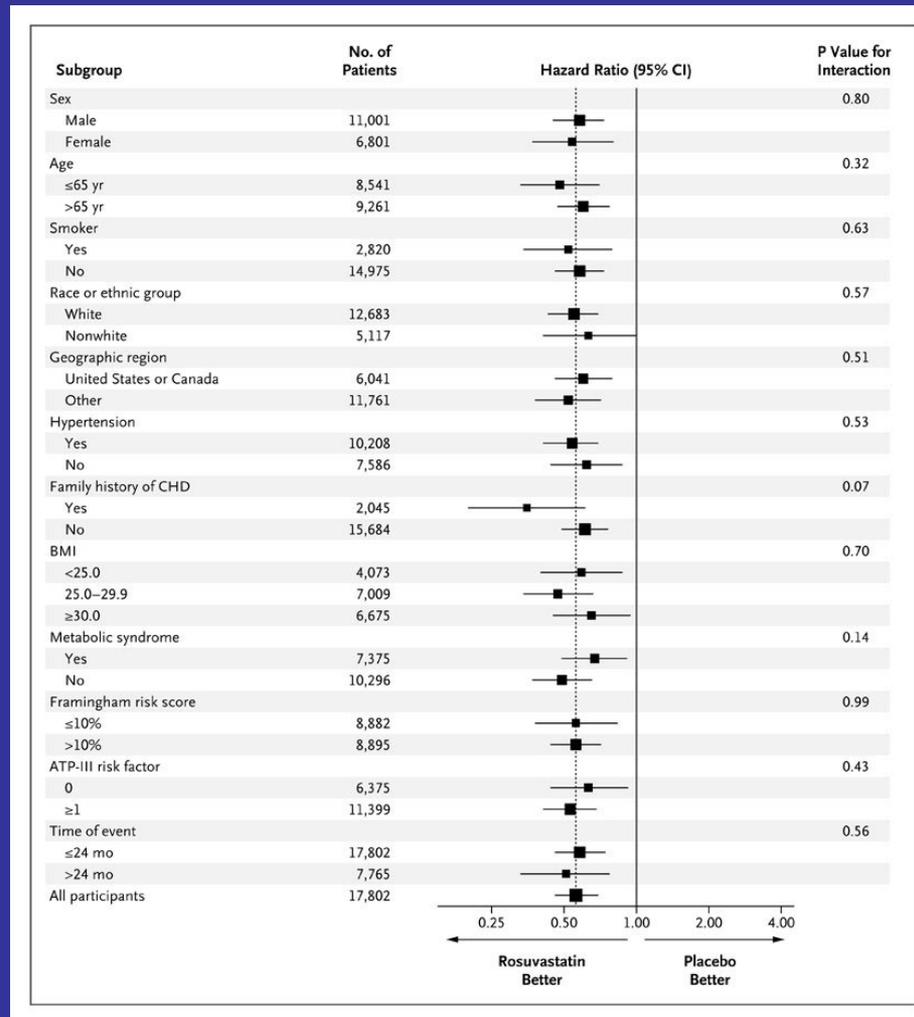
**D Death from Any Cause**



**No. at Risk**

Rosuvastatin	8901	8847	8787	6999	4312	2268	1602	1192	676	227
Placebo	8901	8852	8775	6987	4319	2295	1614	1196	681	246

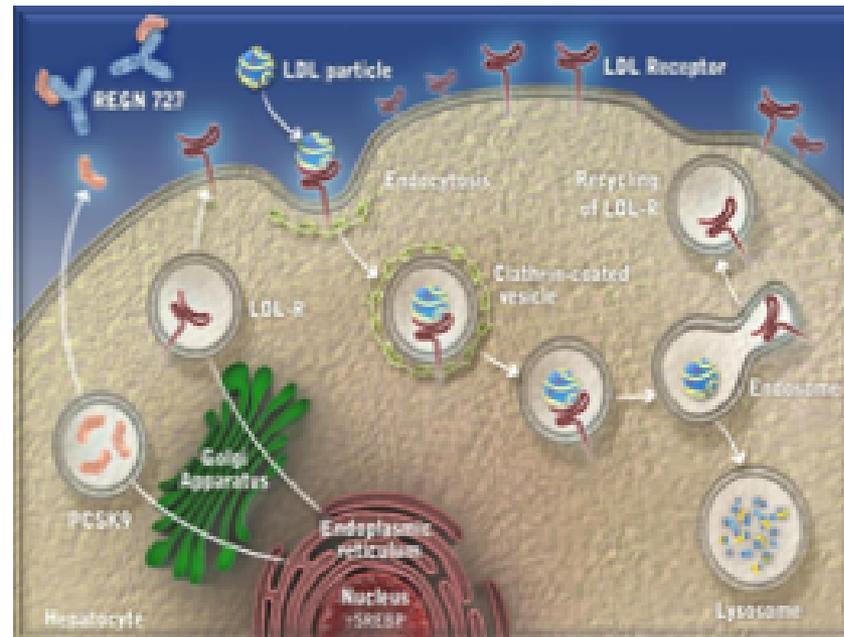
# Effects of Rosuvastatin on the Primary End Point, According to Baseline Characteristics



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

# PCSK9 Monoclonal Antibody for Hypercholesterolemia

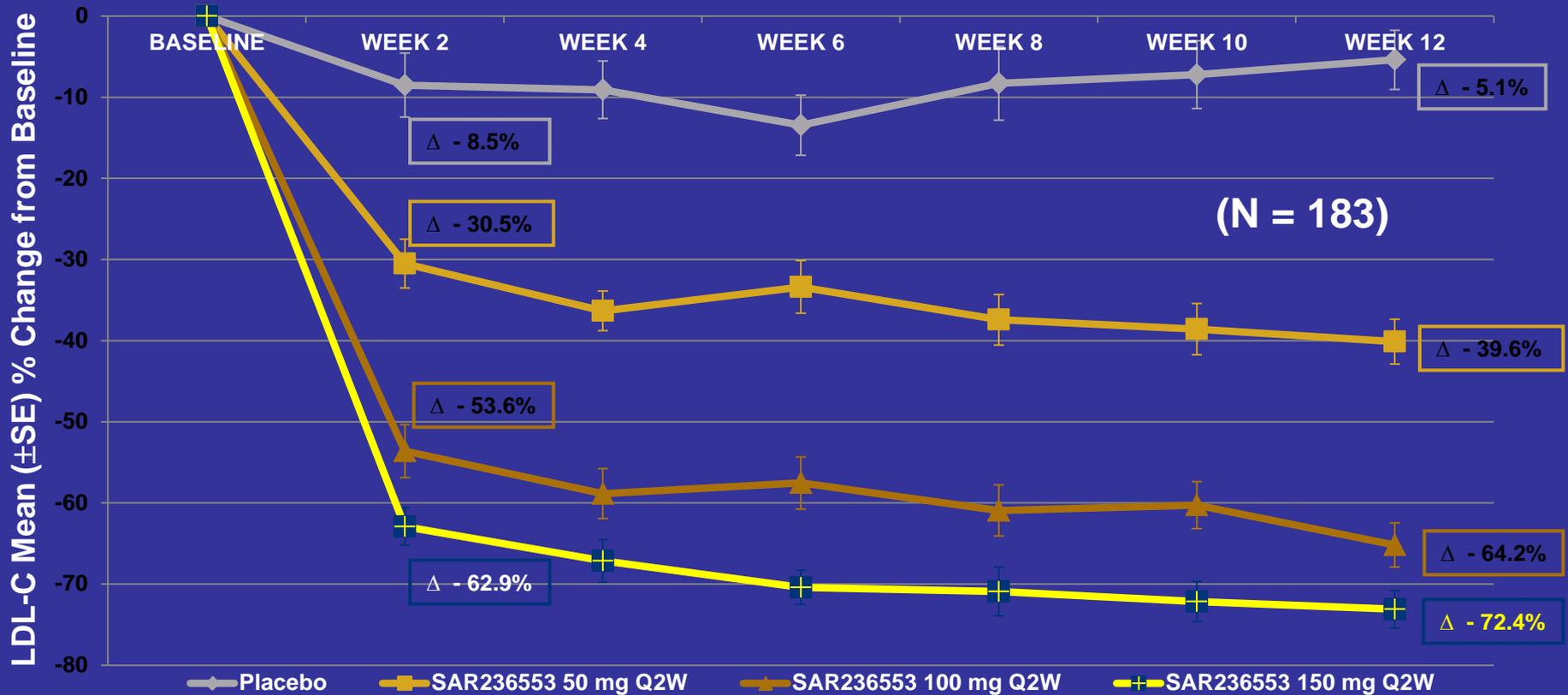
- Gain-of-function mutations of PCSK9 → hypercholesterolemia
- SAR236553/REGN727 highly specific, fully human monoclonal antibody (mAb) to PCSK9
- Phase 1 trial<sup>1</sup>
  - Dose dependently reduced LDL-C by 36-58% with/without atorvastatin
  - Safe and well-tolerated



Impact of PC SK9 mAb on LDL Receptor Expression

<sup>1</sup>Stein EA et al. N Engl J Med 2012;366:11 08-18.

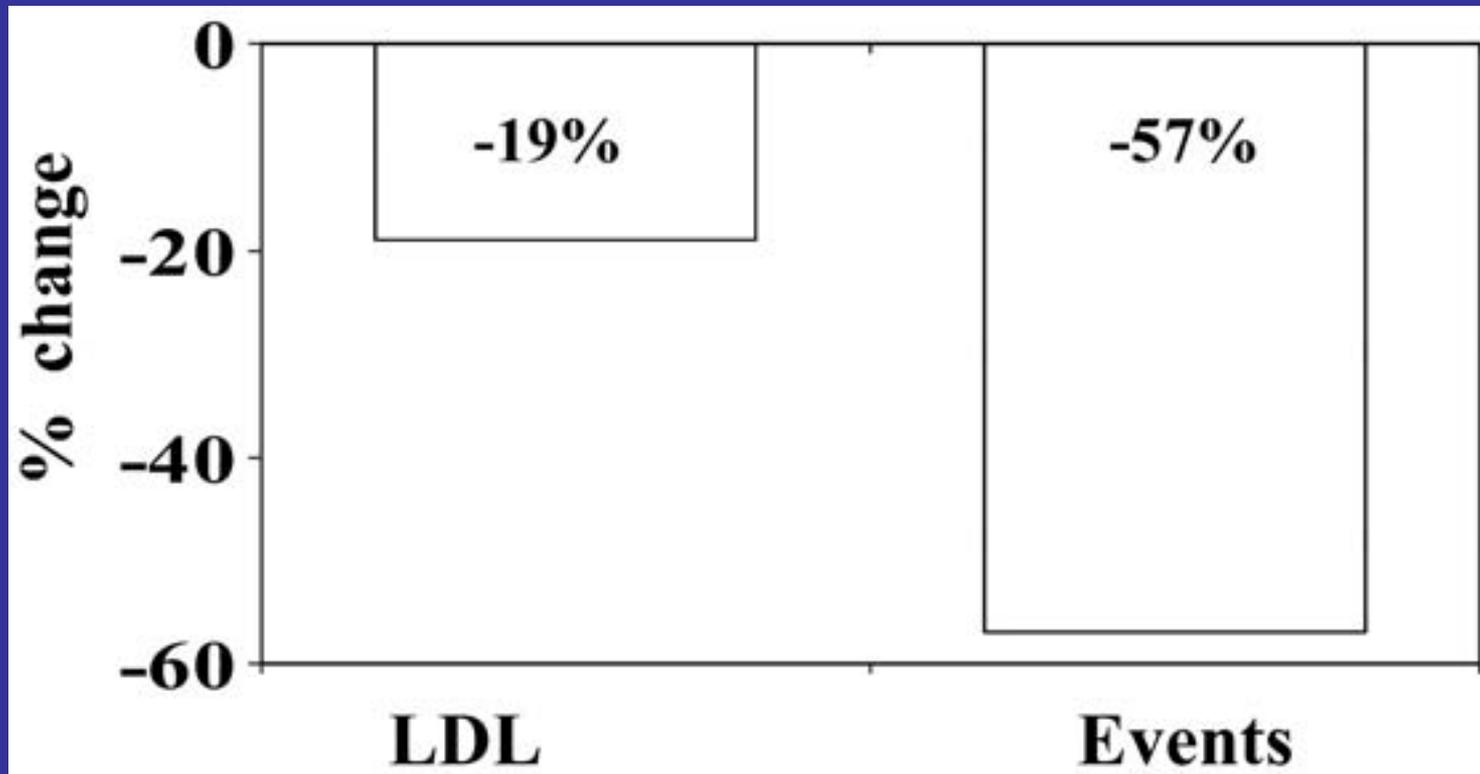
# Phase II Trial REGN727/SAR236553 in Hypercholesterolemia



- Patients with primary hypercholesterolemia received SQ placebo or range of SAR236553 doses every 2 or 4 weeks for 12 weeks as adjunct to statins
- More sustained efficacy with Q2W vs. Q4W regimen

J Am Coll Cardiol 2012;Mar 26:[Epub ahead of print].

# Lifetime Risk Reduction in ARIC



Cohen et al; NEJM, 2006

# Early LDL Reduction

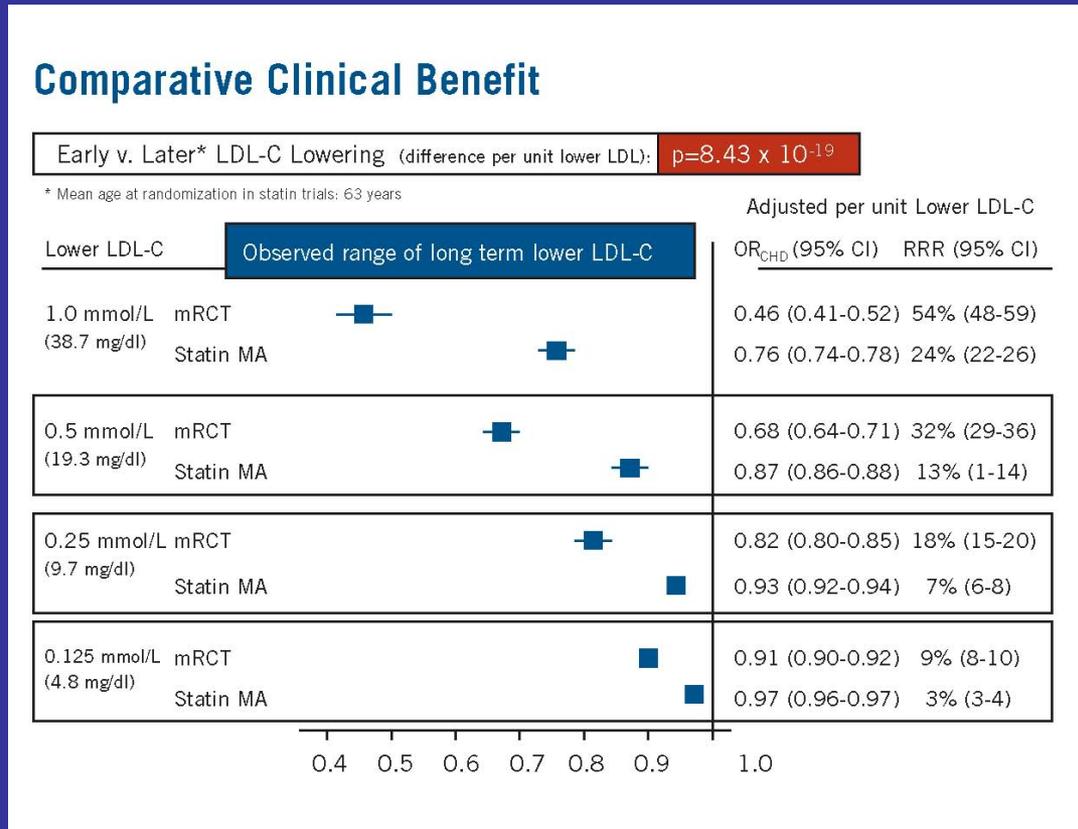
Brian A. Ference, MD, MPhil, MSc

- Objective

- Mendelian randomized controlled trial of long term reduction in low-density lipoprotein cholesterol (LDL-C) beginning early in life
- Use allele associated with lower LDL-C as proxy for treatment that lowers LDL-C beginning at birth, to estimate clinical benefit of lowering LDL-C beginning early in life

- Methods

- Studies involving 9 SNPs from 6 different genes
- Randomization to allele associated with lower LDL-C (treatment arm) or other allele (usual care arm)
- Primary analysis: Association between exposure allele and CHD
- Primary endpoint: CHD (CV death, MI, coronary revascularization)



# Early LDL Reduction

- Results

- Prolonged exposure to lower LDL-C beginning early in life associated with 3-fold greater clinical benefit for each unit lower LDL-C than treatment with a statin started later in life

- Conclusions

- Clinical benefit of lowering LDL-C depends on both timing and magnitude of LDL-C reduction
- Prolonged exposure to lower LDL-C beginning early in life (before development of atherosclerosis) substantially more effective at reducing CHD risk than current practice of lower LDL-C beginning later in life (after development of atherosclerosis).
- This increased clinical benefit appears to be independent of the mechanism of LDL-C lowering

## Comparative Clinical Benefit

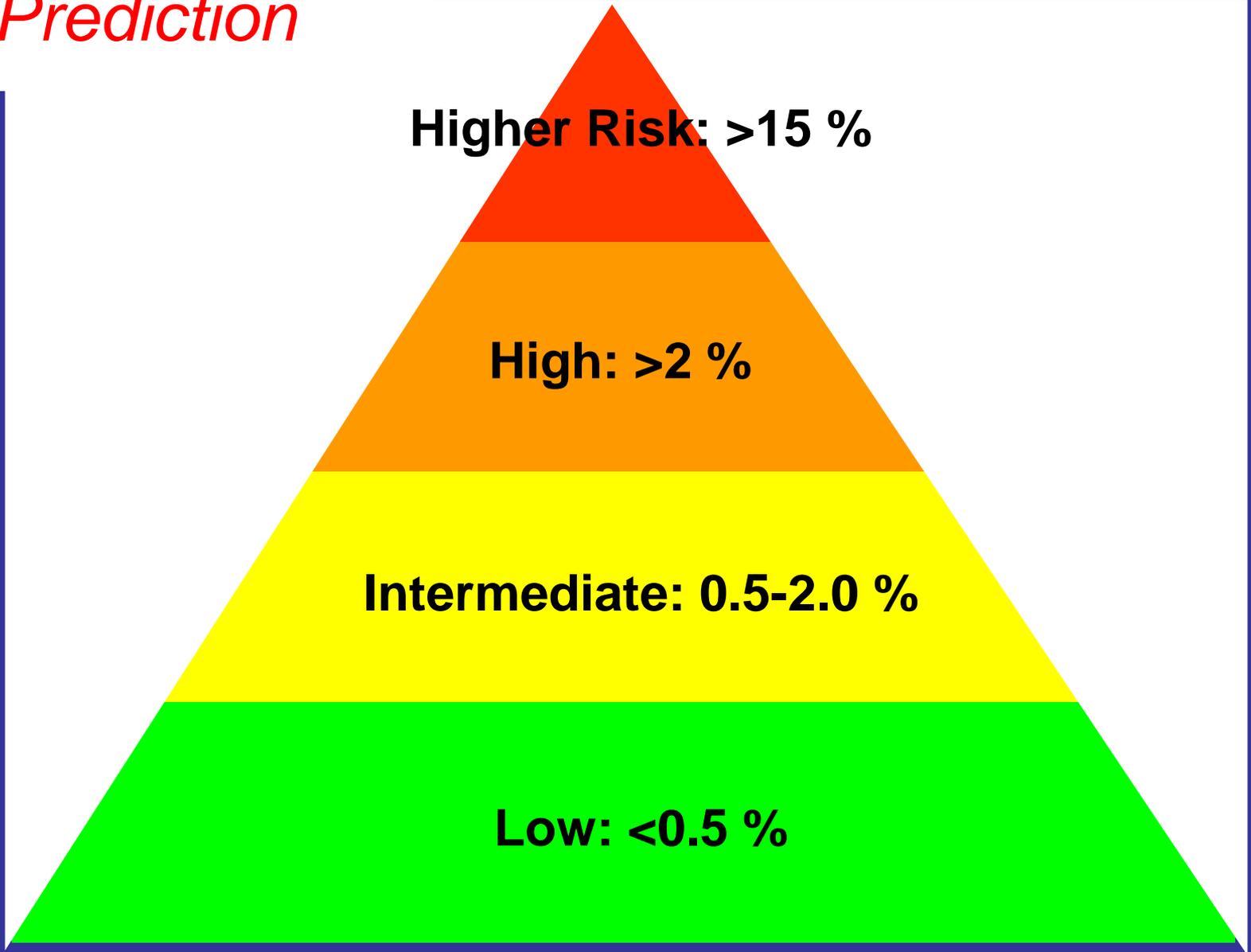
Timing of LDL-C Lowering	Source of	Size (N)	Adjusted per 38.7 mg/dl (1 mmol/L) Lower LDL-C		
			OR <sub>CHD</sub> (95% CI)	RRR (95% CI)	p (difference)
Early in life	mRCT	326,443	0.46 (0.41-0.52)	54% (48-59)	p=8.4x10 <sup>-19</sup>
Later in life	Meta-Analysis of Statin trials	169,138	0.76 (0.74-0.78)	24% (22-26)	

Early in life:	38.7 mg/dl (1 mmol/L)	lower LDL-C	→	~ 55% RRR	(OR: 0.46)
Later in life:	116 mg/dl (3 mmol/L)	lower LDL-C	→	~ 55% RRR	(OR: 0.44=0.76*0.76*0.76)

- Prolonged exposure to lower LDL-C beginning early in life is associated with 3-fold greater clinical benefit for each unit lower LDL than treatment with a statin started later in life
  - May explain much of residual risk of coronary events experienced by persons being treated with a statin started later in life

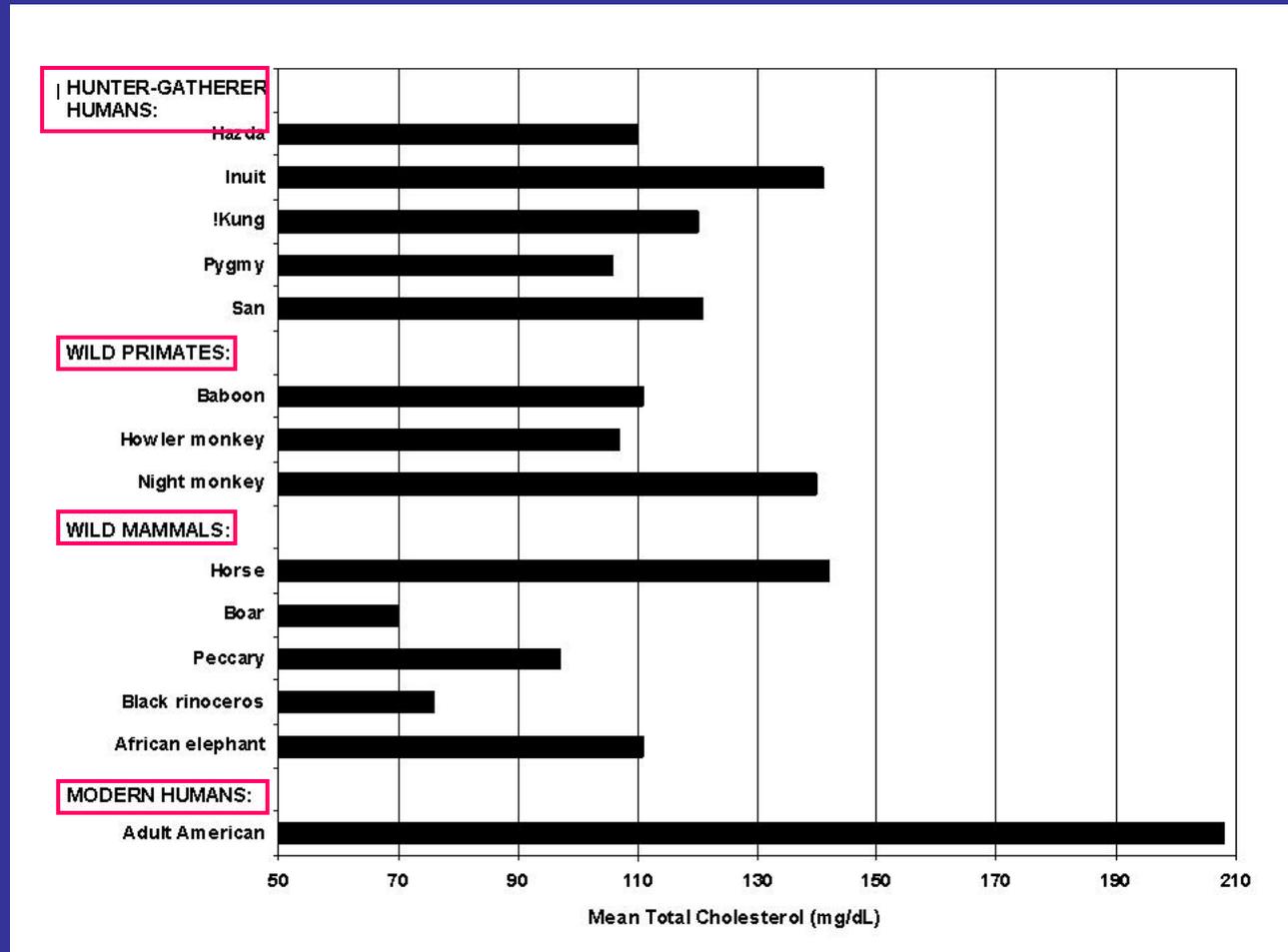
# *Risk Prediction*



# What is Normal LDL?

- Umbilical blood in range of 50 mg/dl
- Hypobetalipoproteinemia can have normal survival
- LDL receptors 50% saturated at 10 mg/dl
- Most mammals have LDL of 50-70 mg/dl

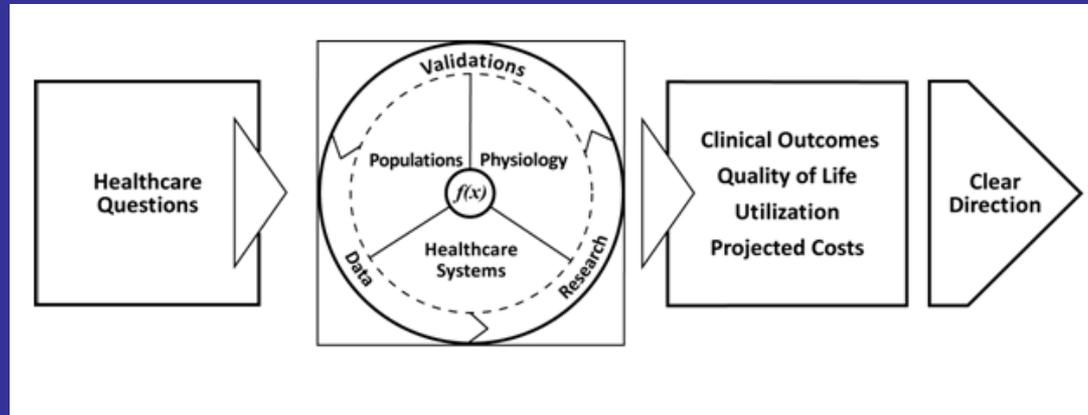
# Comparative Cholesterol Levels



# Objective

Use a well validated large-scale computer simulation model to compare the clinical and cost effectiveness of several screening strategies to universal treatment and to no treatment at all.

# The Archimedes Model



- The Archimedes Model is a clinically detailed simulation of human physiology, disease progression and healthcare delivery.
- The core of the model is a set of algebraic and differential equations representing the physiological pathways pertinent to diseases and their complications.
- Use of a single model enables Archimedes to address co-morbidities, multiple organ syndromes, drugs with multiple effects, and combinations of treatments.
- The use of differential equations preserves the continuous nature of biological variables and time, as well as the interactions between them.
- Diseases and outcomes are defined in terms of underlying variables, enabling diseases to occur and progress in the same continuous fashion as reality. Interventions to both prevent and manage diseases are modeled at the level of the underlying biology.
- The model accuracy has been validated against over 50 major clinical trials, including several statin trials relevant to this study such as HPS, 4S, IDEAL, and TNT.

# Simulation: Multi-arm trial

Compare current standard of care with leading candidates representing alternate approaches

Perform a multi-arm trial comparing

- “*Standard care*” via ATP-III guidelines
- *Unconditional treatment*: aspirin + statin for all
- *Imaging modalities* via SHAPE guideline (2 variations)
  - Using coronary artery calcium (CACs)
  - Using carotid intima-media thickness (CIMT)
- ***Also compare to “do nothing” arm, where aspirin + statin not prescribed***

# Simulation Specs

## *Population*

- Approx 50,000-person sample
- Representative cross-section of US primary-prevention population, aged 40-75
- Simulated individuals derived from people in NHANES, 1999-2004, to capture correct correlations & distributions of risk factors, histories

## *Duration*

- Track for 35 years – until youngest members turn 75 – reporting results annually

## *Outcomes*

- Primary health outcome: composite of MI, stroke, and CV death
- Benefit, via quality-adjusted life-years (QALYs)
- Cost-effectiveness, via  $\Delta\text{cost} / \Delta\text{QALY}$   
[Costs and QALYs discounted 3% per year]

# Standard Care

- Subjects receive standard care as provided in the Archimedes Model
  - Cholesterol management as specified in ATP-III guidelines
    - Low risk: 0-1 risk factor                      LDL target: 160 mg/dl
    - Moderate risk: 2+ risk factors                      LDL target: 130 mg/dl
    - High risk: established CHD or equiv                      LDL target: 100 mg/dl
    - Very high risk: establ CHD + add'l risk                      LDL target: 70 mg/dl
  - Management of hypertension, diabetes, etc. consistent with JNC-7, ADA guidelines, ...
  - Regular screening and care visits

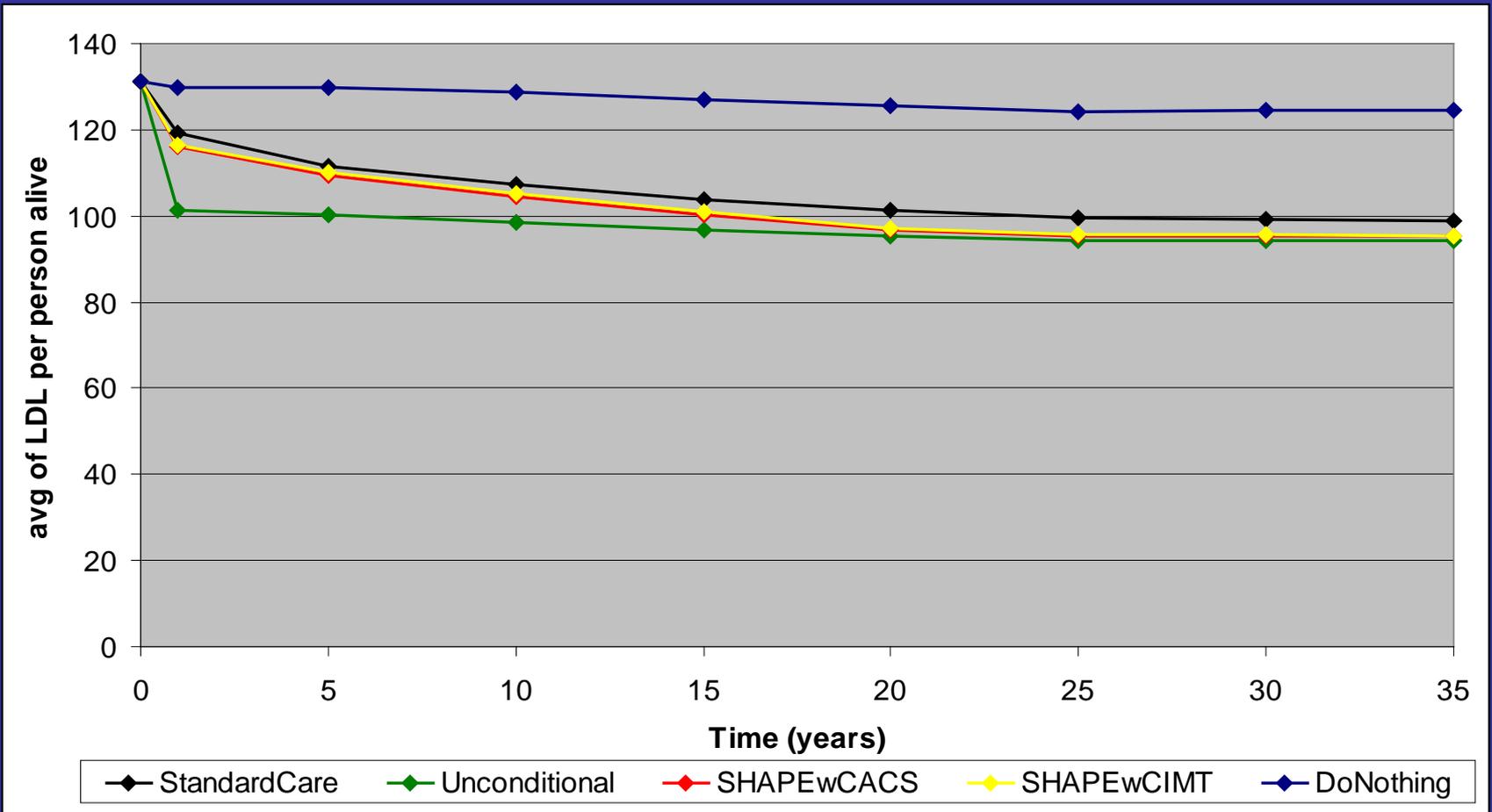
# Unconditional Treatment Arm

- All subjects receive statin therapy (simva 20mg) and low-dose aspirin (81mg)
- No screening process to initiate treatment; no titration of treatment for primary prevention
- Following CHD (or equivalent) events, change to “standard care” for secondary prevention
- No explicit modeling of side effects nor discontinuation of treatment. Side effects of treatment were modeled indirectly through their influence on long-term adherence.

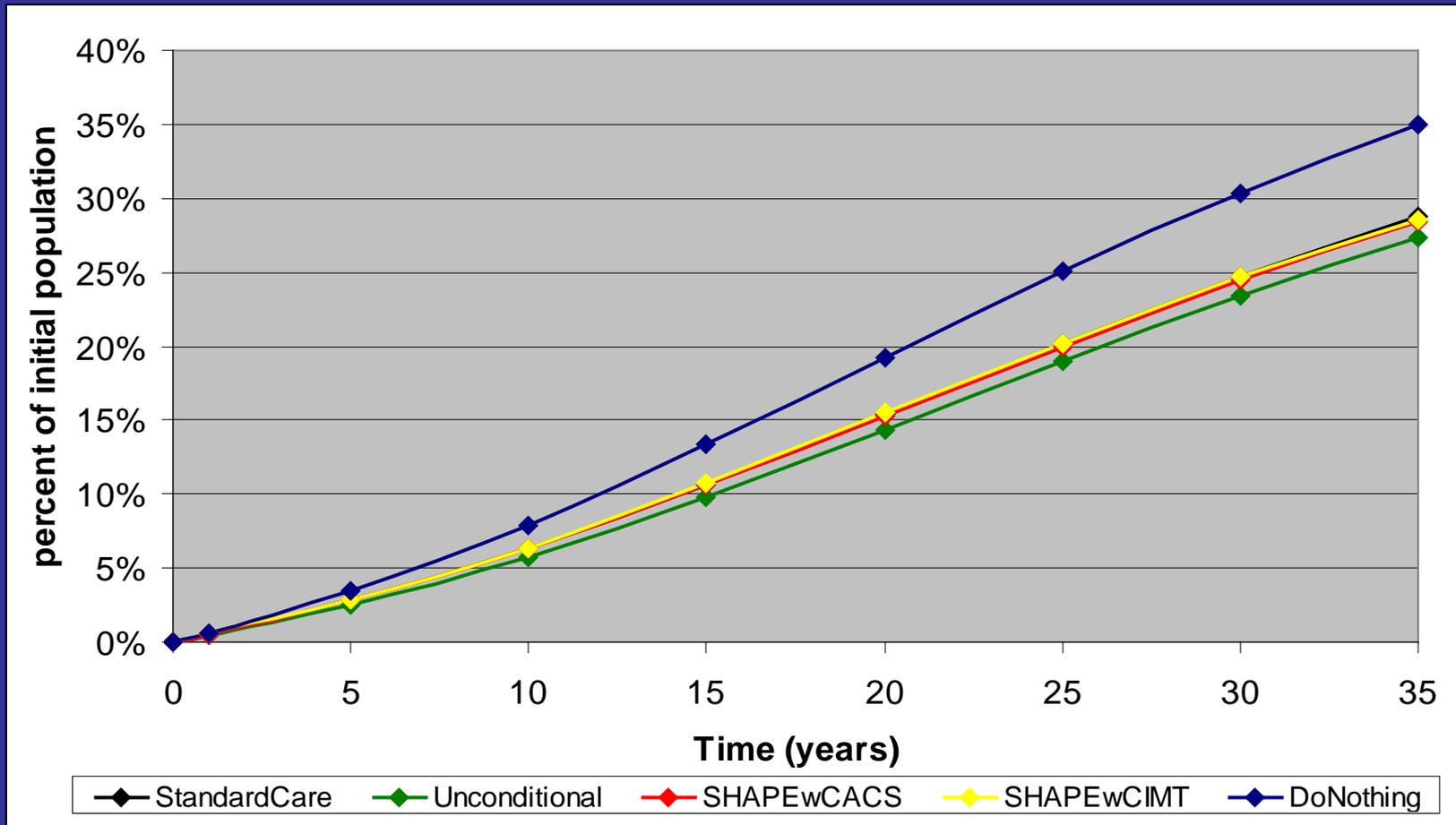
# Intervention Details

- Statin usage
  - Titration of dosage to reach LDL goal  
[except “unconditional” where simva 20 for all]
- Aspirin usage
  - Subjects begin taking low-dose aspirin when they reach the “intermediate” risk level  
[except in “unconditional”]
- Adherence rate: assumed 50%; can be varied

# Average LDL Cholesterol at 50% Adherence



# Cumulative Probability of a first hard CVD event at 50% Adherence



# Clinical Effectiveness and Cost Effectiveness

	DO NOTHING	STANDARD CARE	SHAPE (CIMT)	SHAPE (CACS)	UNCONDITIONAL
<i>35-yr probability of first hard CVD event</i>	35% <sup>+</sup>	28.8% <sup>•</sup>	28.6% <sup>•</sup>	28.4% <sup>•</sup> ‡	27.4% <sup>•</sup> <sup>+</sup>
<i>total cost</i>	\$49,479	\$49,505	\$50,022	\$50,238	\$49,343
<i>total QALYs</i>	16.62	16.95	16.95	16.97	17.02
<i>Δcost/ΔQALY vs DO NOTHING</i>	---	\$80	\$1,649	\$2,206	cost saving
<i>Δcost/ΔQALY vs STANDARD CARE</i>	Reduces QALYs	---	no benefit	\$58,164	cost saving

Costs and QALYs per initial person in the population.

Figures based on a primary-prevention population, age 40-75, followed 35 yrs.

Adherence rates of 50% for all four screening and prevention scenarios.

• P < 0.0001 vs DO NOTHING; + P < 0.0001 vs STANDARD CARE; ‡ P = 0.06 vs STANDARD CARE

# Conclusions

- The Archimedes Model provides a powerful tool for simulation and exploration of alternative treatment scenarios
- Screening with standard care (ATP-III), CACS and CIMT as per SHAPE, and Unconditional treatment strategies all reduce hard CV events at low cost/QALY compared to doing nothing
- Unconditional treatment with statin and ASA is cost saving and is the only strategy that is significantly superior to ATP-III

# How It All Started

- **Coordinated effort to improve quality**

- State Department of Managed Health Care 
- Medical groups beyond managed care organizations
- UC Berkeley School of Public Health
- Rand Health (GO Grant)

- **Goal: Achieve national HEDIS 90% percentile targets**

- Blood pressure, lipids, blood sugar

- **University of Best Practices meetings**

- Monthly meetings
- Physicians, nurses, administrators, pharmacist
- Discuss successful strategies
- Now sharing data among group participants

HEDIS, Healthcare Effectiveness Data and Information Set

# Be There Campaign

- **Concept: “Heart Attack and Stroke-free Zone”**
  - Audacious goal to capture attention
  - Extends the risk reduction efforts to all citizens
  - Actively engages persons in their own health (care)
  - Conveys ownership to population
  - Taps in to community pride
- **Aim: Achieve both screening for risk factors and compliance with interventions**
- **Funding: \$650,000; philanthropy**
- **Steering Committee: Private-public partnership**

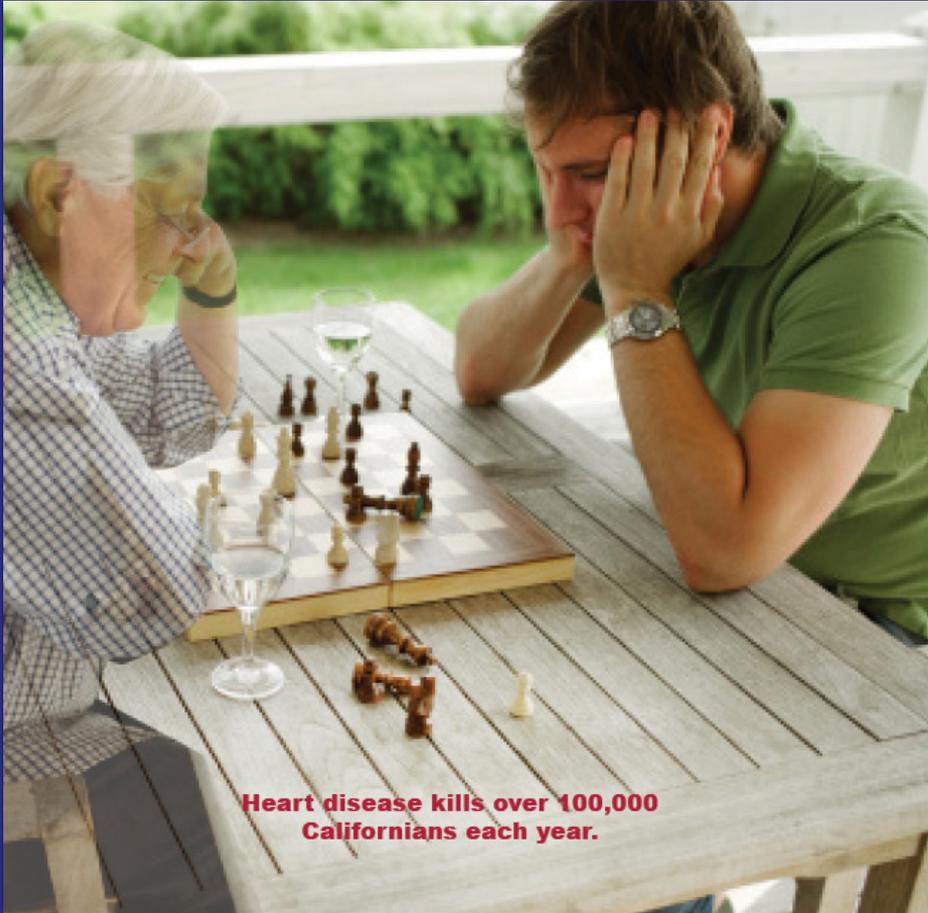
# San Diego Demonstration Project Going Emotional!

- ❑ Emotional “tug” is critical for commitment to change one’s behavior
- ❑ Benefit to those we love can be a bigger driver than benefit to oneself
- ❑ Caring for one’s own health makes it possible to “be there” for those we love!

*“When something is missing in your life,  
it usually turns out to be someone.”*  
Robert Brault



# Be There Campaign



**Heart disease kills over 100,000 Californians each year.**

DAD, YOU NEVER LET ME WIN.  
NOW, I WOULD DO ANYTHING TO  
HAVE YOU BEAT ME ONE MORE TIME.

Heart Attack and Stroke are preventable. See your doctor today to find out your risk for heart disease and stroke and to get on the right treatments to reduce your risk for premature death.

**Take charge of your health today and visit:  
[www.betheresandiego.org](http://www.betheresandiego.org)**

The campaign to make San Diego a heart attack and stroke-free zone.



**be there.**  
*san diego*

# Be There Campaign



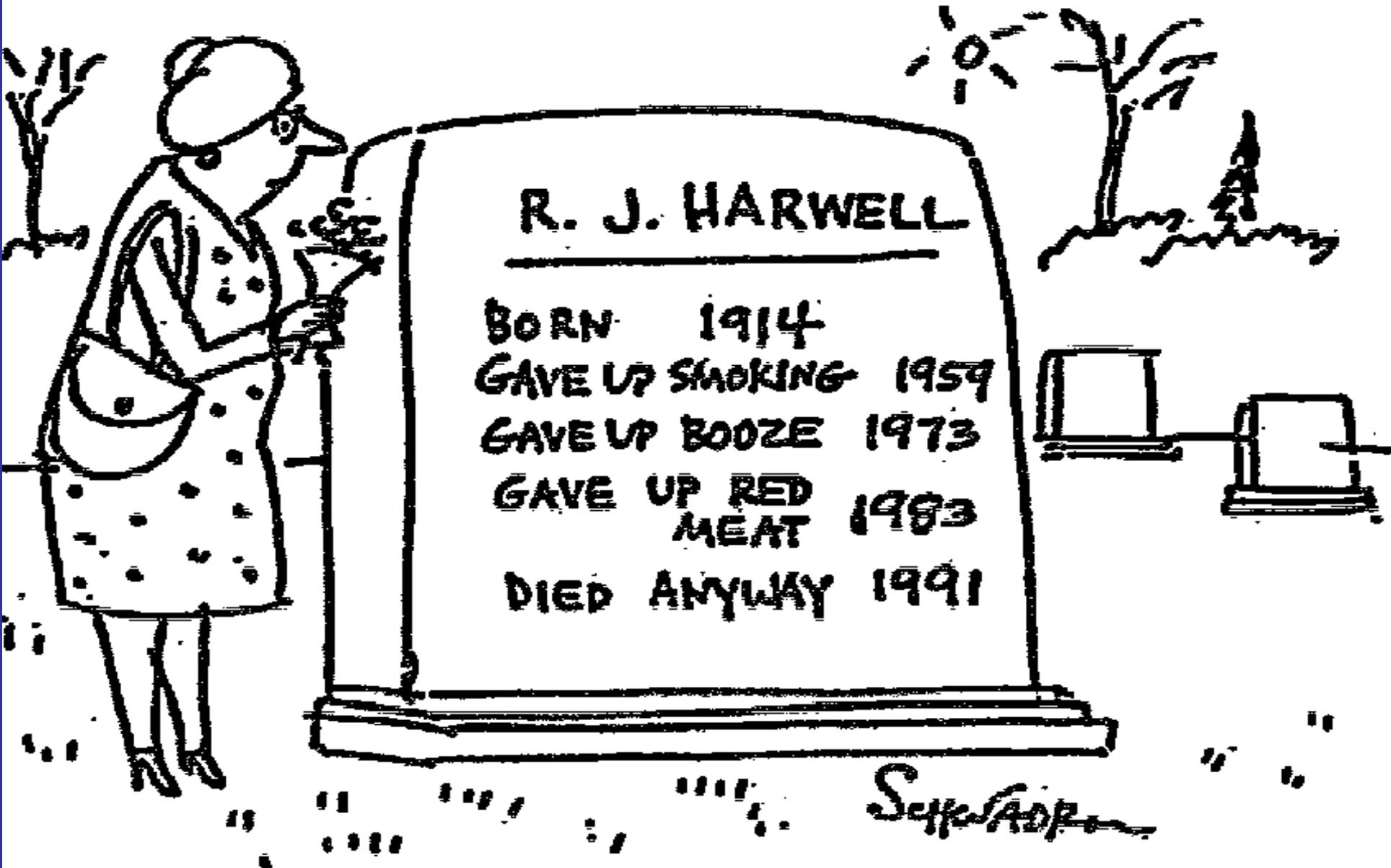
BE THERE FOR YOURSELF,  
YOUR LOVED ONES, AND  
OUR COMMUNITY

Heart Attack and Stroke are preventable. See your doctor today to find out your risk for heart disease and stroke and to get on the right treatments to reduce your risk for premature death.

**Take charge of your health today and visit:**  
[www.betheresandiego.org](http://www.betheresandiego.org)

The campaign to make San Diego a heart attack and stroke-free zone.





# Statins for Secondary Prevention in Elderly Patients

## A Hierarchical Bayesian Meta-Analysis

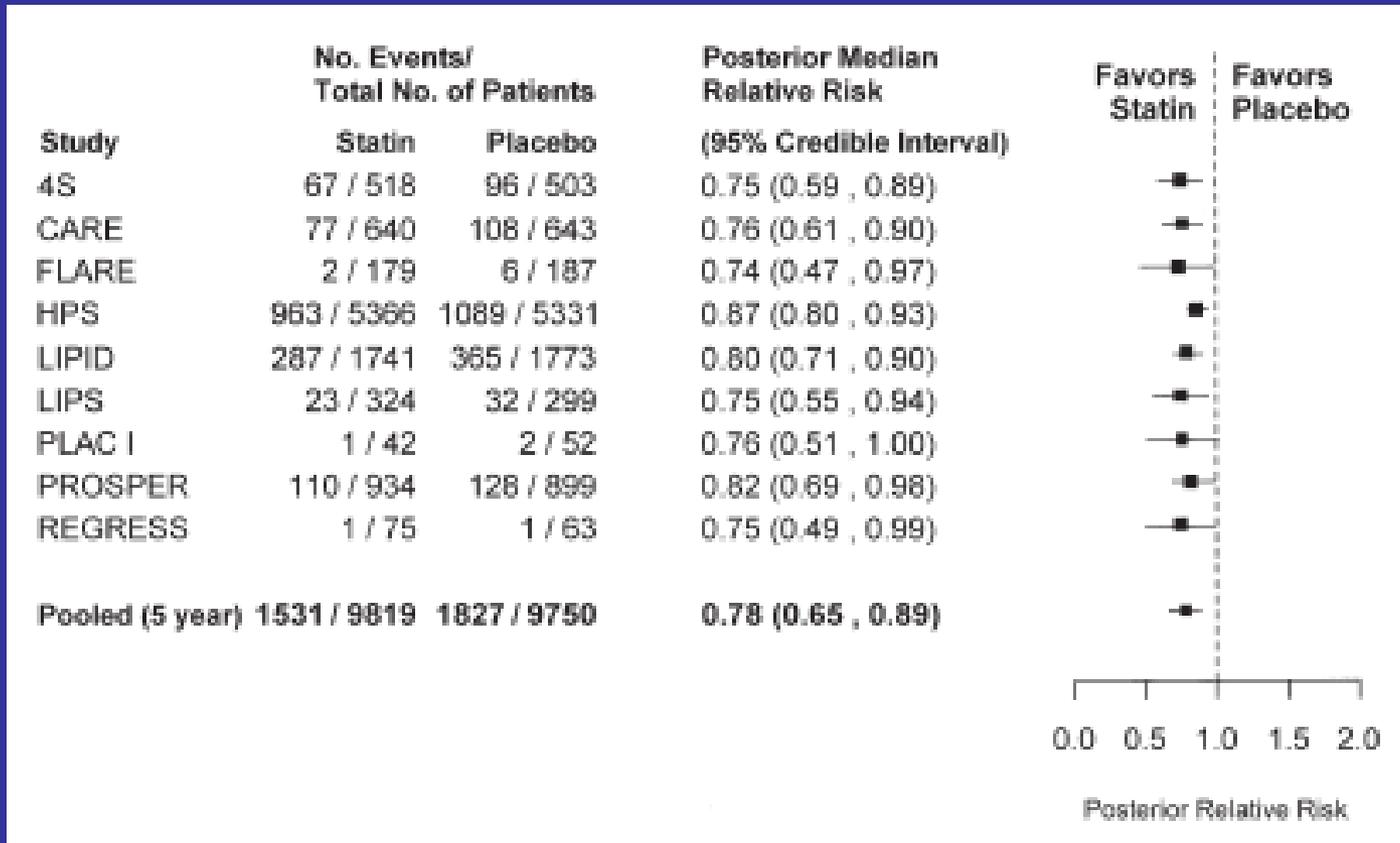
Jonathan Afilalo, MD,\* Gustavo Duque, MD, PHD,\*† Russell Steele, PHD,‡

J. Wouter Jukema, MD, PHD,§ Anton J. M. de Craen, PHD,|| Mark J. Eisenberg, MD, MPH\*¶

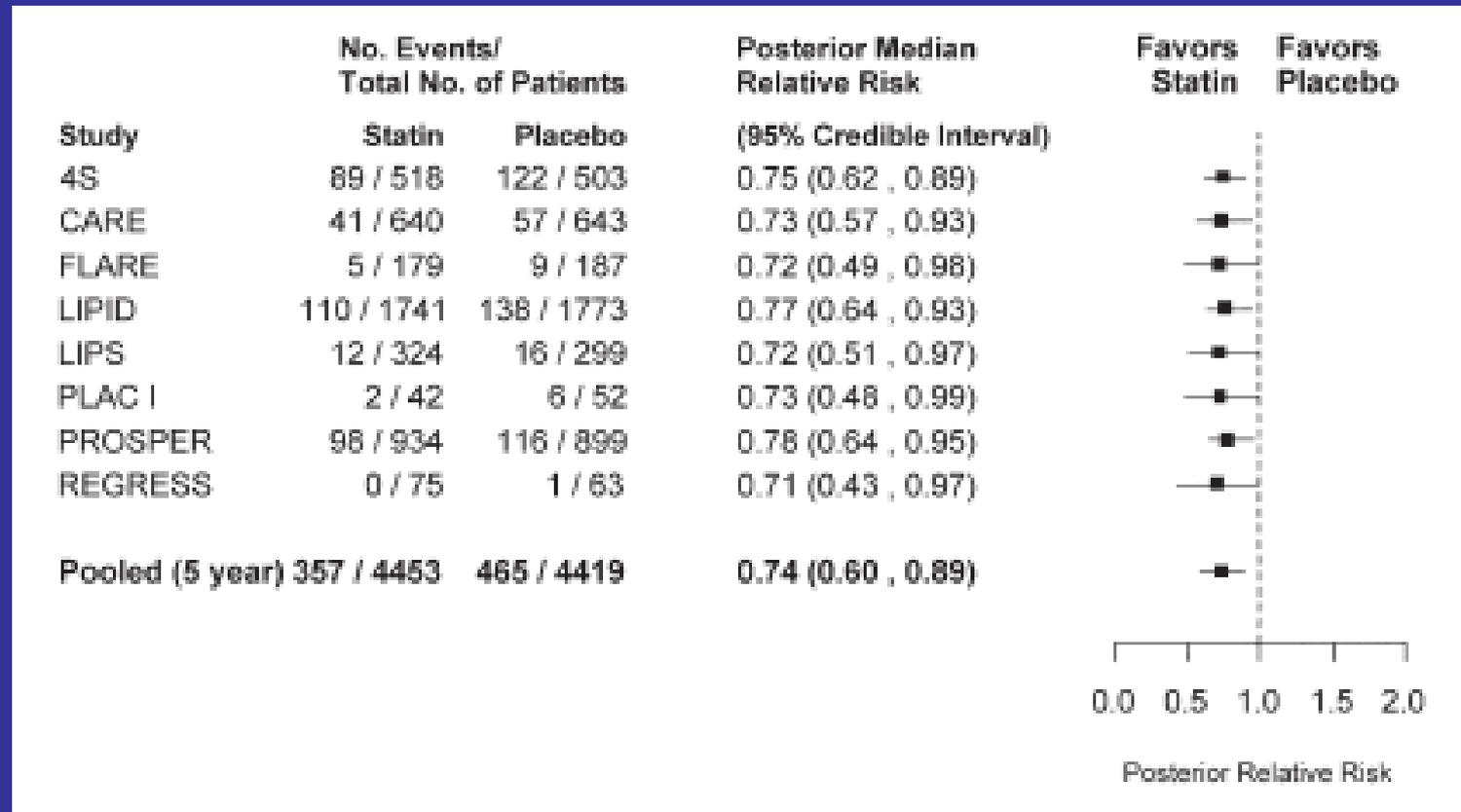
*Montreal, Canada; and Leiden, the Netherlands*

- Objectives** This study was designed to determine whether statins reduce all-cause mortality in elderly patients with coronary heart disease.
- Background** Statins continue to be underutilized in elderly patients because evidence has not consistently shown that they reduce mortality.
- Methods** We searched 5 electronic databases, the Internet, and conference proceedings to identify relevant trials. In addition, we obtained unpublished data for the elderly patient subgroups from 4 trials and for the secondary prevention subgroup from the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial. Inclusion criteria were randomized allocation to statin or placebo, documented coronary heart disease,  $\geq 50$  elderly patients (defined as age  $\geq 65$  years), and  $\geq 6$  months of follow-up. Data were analyzed with hierarchical Bayesian modeling.
- Results** We included 9 trials encompassing 19,569 patients with an age range of 65 to 82 years. Pooled rates of all-cause mortality were 15.6% with statins and 18.7% with placebo. We estimated a relative risk reduction of 22% over 5 years (relative risk [RR] 0.78; 95% credible interval [CI] 0.65 to 0.89). Furthermore, statins reduced coronary heart disease mortality by 30% (RR 0.70; 95% CI 0.53 to 0.83), nonfatal myocardial infarction by 26% (RR 0.74; 95% CI 0.60 to 0.89), need for revascularization by 30% (RR 0.70; 95% CI 0.53 to 0.83), and stroke by 25% (RR 0.75; 95% CI 0.56 to 0.94). The posterior median estimate of the number needed to treat to save 1 life was 28 (95% CI 15 to 56).
- Conclusions** Statins reduce all-cause mortality in elderly patients and the magnitude of this effect is substantially larger than had been previously estimated. (J Am Coll Cardiol 2008;51:37-45) © 2008 by the American College of Cardiology Foundation

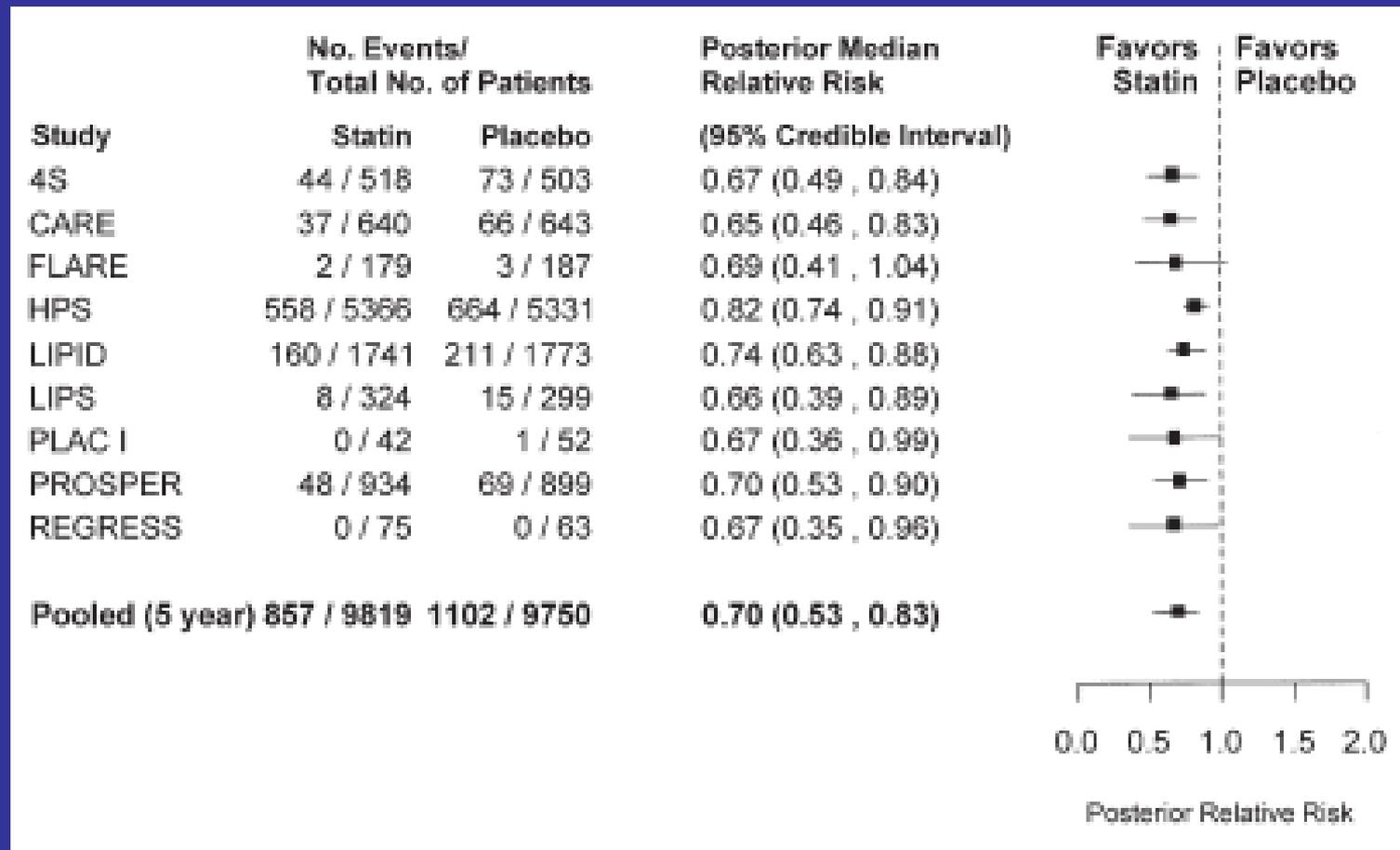
# Statins in Elderly *CHD*: All Cause Mortality



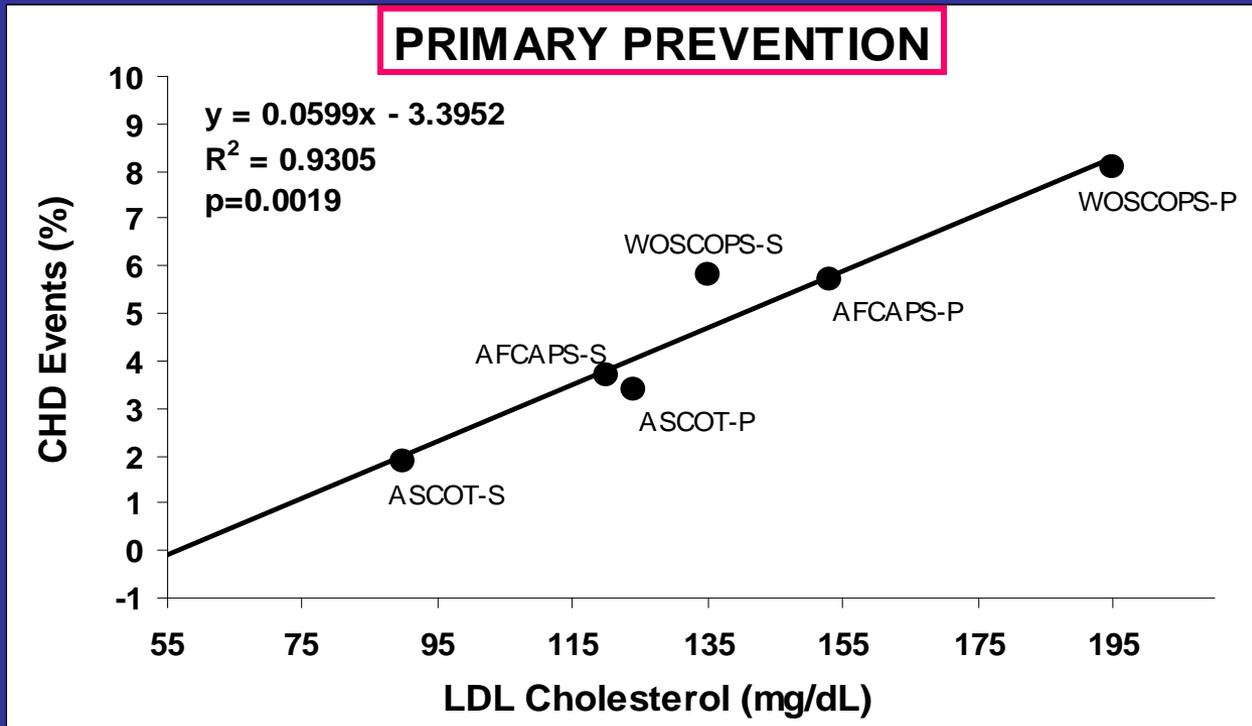
# Statins in Elderly *CHD*: Nonfatal MI



# Statins in Elderly *CHD*: CHD Mortality

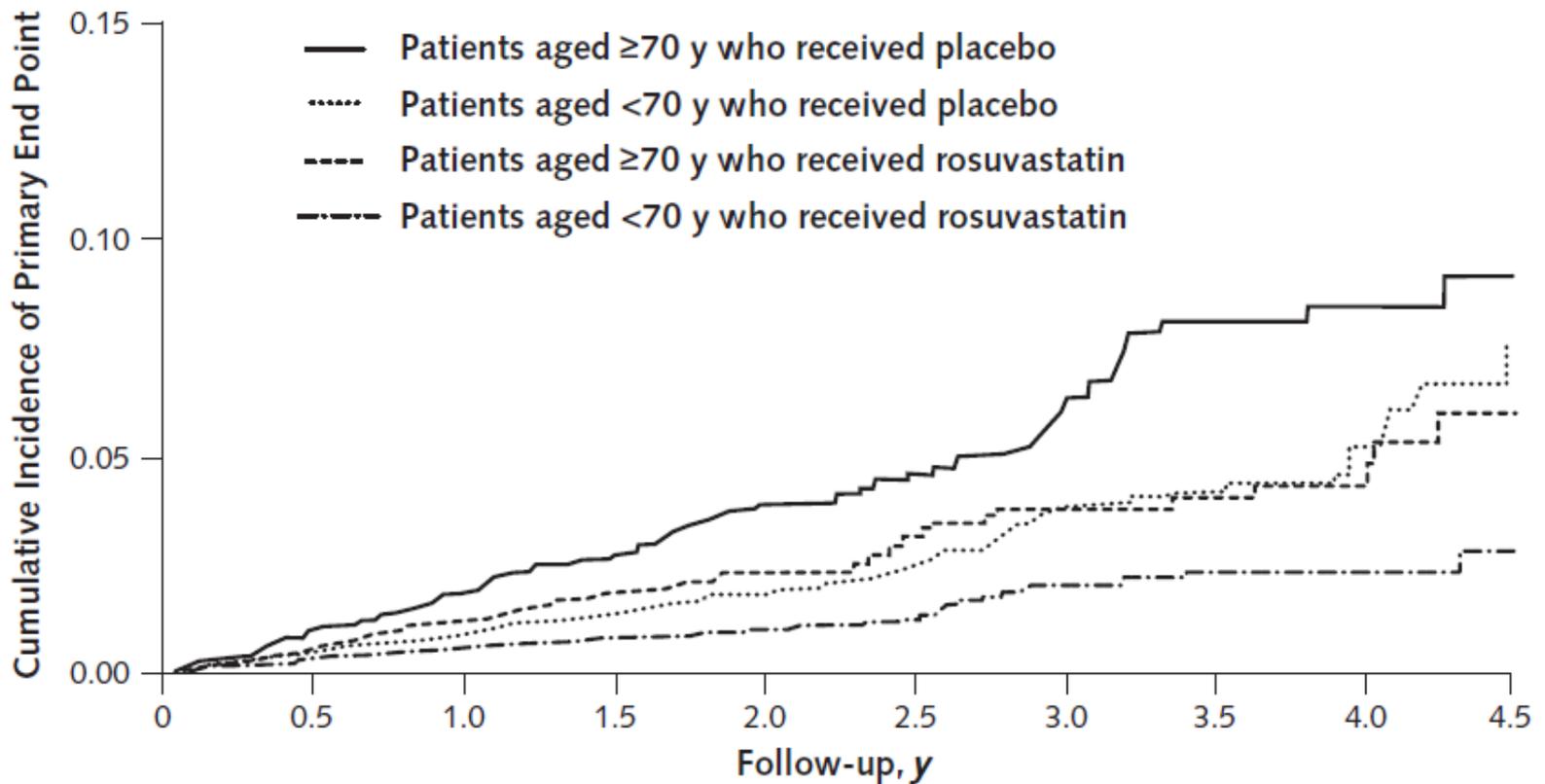


# Relation of LDL to Event Rate



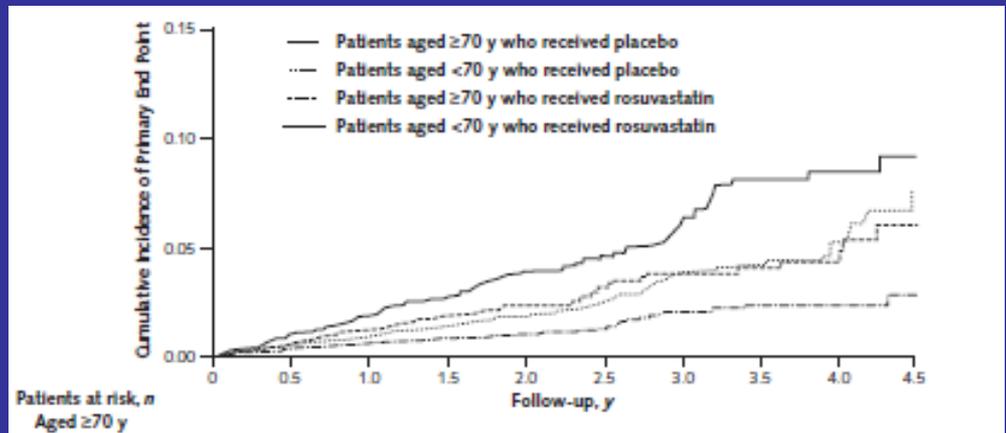
O'Keefe et al; JACC, 2004

# JUPITER Results in Elderly: Primary Endpoint (1<sup>st</sup> CV Event)

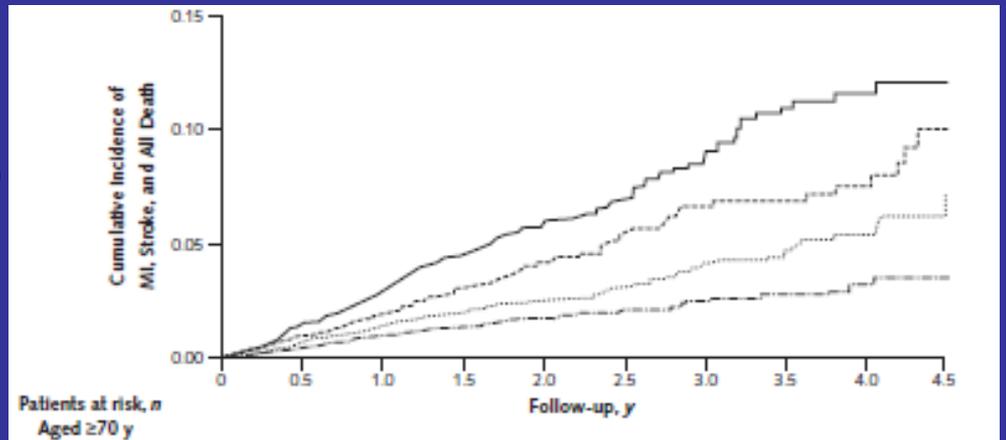


# JUPITER: Results in Elderly

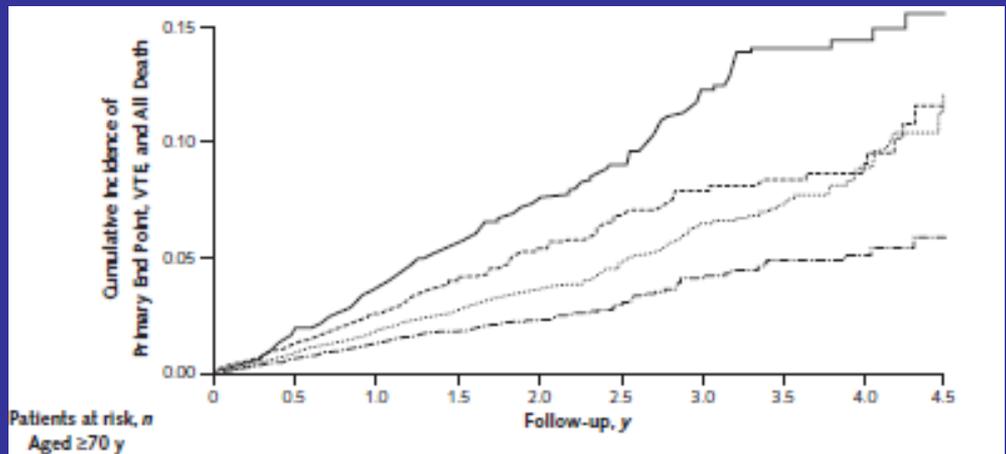
1<sup>st</sup> CV  
Event



MI, Stroke,  
Death



First CV Event  
And Death



# Is aspirin indicated in this patient?

- Yes, if he becomes diabetic.
- Yes, because of the added benefit to reduce stroke.
- No, 325 mg ASA increases risk of GI bleed.
- No, because he is hypertensive.
- It all depends on the relation between the risk for CV events versus GI bleed.

## Clinical Guidelines

# Aspirin for the Prevention of Cardiovascular Disease: U.S. Preventive Services Task Force Recommendation Statement

U.S. Preventive Services Task Force\*

+ Author Affiliations

### Abstract

**Description:** Update of the 2002 U.S. Preventive Services Task Force (USPSTF) recommendation about the use of aspirin for the prevention of coronary heart disease.

**Methods:** Review of the literature since 2002, focusing on new evidence on the benefits and harms of aspirin for the primary prevention of cardiovascular disease, including myocardial infarction and stroke. The new evidence was reviewed and synthesized according to sex.

**Recommendations:** Encourage men age 45 to 79 years to use aspirin when the potential benefit of a reduction in myocardial infarctions outweighs the potential harm of an increase in gastrointestinal hemorrhage. (A recommendation)

Encourage women age 55 to 79 years to use aspirin when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage. (A recommendation)

Evidence is insufficient to assess the balance of benefits and harms of aspirin for cardiovascular disease prevention in men and women 80 years or older. (I statement)

# Estimated MIs prevented and estimated harms of using aspirin for 10 years in a hypothetical cohort of 1000 men. Estimates are based on age and 10-year CHD risk.

## U.S. Preventive Services Task Force

Ann Intern Med 2009;150:396-404

As indicated, the estimated number of MIs prevented varies with 10-year CHD risk. The estimated harms of using aspirin vary with age. Therefore, both 10-year CHD risk and age must be considered when determining whether the potential harms of aspirin use outweigh the potential benefit in terms of MIs prevented. The shaded areas indicate the combinations of 10-year CHD risk and age for which the number of harms (GI bleeding and hemorrhagic stroke) are greater than or approximately equal to the number of MIs prevented.\*

Variable	Estimated MIs Prevented (per 1000 Men), <i>n</i>		
	Age 45–59 Years	Age 60–69 Years	Age 70–79 Years
<b>10-year CHD risk</b>			
1%	3.2	3.2	3.2
2%	6.4	6.4	6.4
3%	9.6	9.6	9.6
4%	12.8	12.8	12.8
5%	16	16	16
6%	19.2	19.2	19.2
7%	22.4	22.4	22.4
8%	25.6	25.6	25.6
9%	28.8	28.8	28.8
10%	32	32	32
11%	35.2	35.2	35.2
12%	38.4	38.4	38.4
13%	41.6	41.6	41.6
14%	44.8	44.8	44.8
15%	48	48	48
16%	51.2	51.2	51.2
17%	54.4	54.4	54.4
18%	57.6	57.6	57.6
19%	60.8	60.8	60.8
20%	64	64	64
	<b>Estimated Harms, <i>n</i></b>		
<b>Type of event</b>			
GI bleeding	8	24	36
Hemorrhagic stroke	1	1	1

\* Calculations of estimated benefits and harms rely on assumptions and are by nature somewhat imprecise. Estimates of benefits and harms, especially at the borders of the shaded and unshaded areas, should be considered in the full context of clinical decision making and used to stimulate shared decision making. The calculations in the table are based on the following assumptions: that there is a 32% risk reduction of MIs with regular aspirin use (3) and that gastrointestinal bleeding includes serious hemorrhage, perforation, or other complications leading to hospitalization or death. The harm of GI bleeding in the table assumes that the risk for GI bleeding increases with age and that the men are not taking nonsteroidal anti-inflammatory drugs, do not have upper GI pain, or do not have a history of GI ulcer (2).

# MI and Stroke Prevented by ASA

## MI

Variable	Estimated MIs Prevented (per 1000 Men), n		
	Age 45-59 Years	Age 60-69 Years	Age 70-79 Years
<b>10-year CHD risk</b>			
1%	3.2	3.2	3.2
2%	6.4	6.4	6.4
3%	9.6	9.6	9.6
4%	12.8	12.8	12.8
5%	16	16	16
6%	19.2	19.2	19.2
7%	22.4	22.4	22.4
8%	25.6	25.6	25.6
9%	28.8	28.8	28.8
10%	32	32	32
11%	35.2	35.2	35.2
12%	38.4	38.4	38.4
13%	41.6	41.6	41.6
14%	44.8	44.8	44.8
15%	48	48	48
16%	51.2	51.2	51.2
17%	54.4	54.4	54.4
18%	57.6	57.6	57.6
19%	60.8	60.8	60.8
20%	64	64	64
	<b>Estimated Harms, n</b>		
<b>Type of event</b>			
GI bleeding	8	24	36
Hemorrhagic stroke	1	1	1

## Stroke

Variable	Estimated Strokes Prevented (per 1000 Women), n		
	Age 55-59 Years	Age 60-69 Years	Age 70-79 Years
<b>10-year stroke risk</b>			
1%	1.7	1.7	1.7
2%	3.4	3.4	3.4
3%	5.1	5.1	5.1
4%	6.8	6.8	6.8
5%	8.5	8.5	8.5
6%	10.2	10.2	10.2
7%	11.9	11.9	11.9
8%	13.6	13.6	13.6
9%	15.3	15.3	15.3
10%	17	17	17
11%	18.7	18.7	18.7
12%	20.4	20.4	20.4
13%	22.1	22.1	22.1
14%	23.8	23.8	23.8
15%	25.5	25.5	25.5
16%	27.2	27.2	27.2
17%	28.9	28.9	28.9
18%	30.6	30.6	30.6
19%	32.3	32.3	32.3
20%	34	34	34
	<b>Estimated Harm, n</b>		
<b>Type of event</b>			
GI bleeding	4	12	18

# CV Prevention in Elderly: Summary

- Recommend Mediterranean type diet, optimal weight, daily exercise, no smoking
- Keep BP <140 mm/Hg systolic and LDL cholesterol <130 mg/dl.
- If 10 yr risk  $\geq$  20%; ASA 75 mg and statin to reduce LDL to 100 mg/dl
- Reduce BP < 130 in diabetics or renal disease
- Start low dose and monitor closely

# Cardiovascular Risk Factors

## Non-modifiable

- History of CV Disease
- Age
- Sex
- Family history

## Modifiable

- Blood pressure
- Smoking
- High LDL, low HDL
- Diet
- Weight
- Physical conditioning
- Thrombogenic factors

Hypertension in Elderly

AND

# Hypertension in Elderly

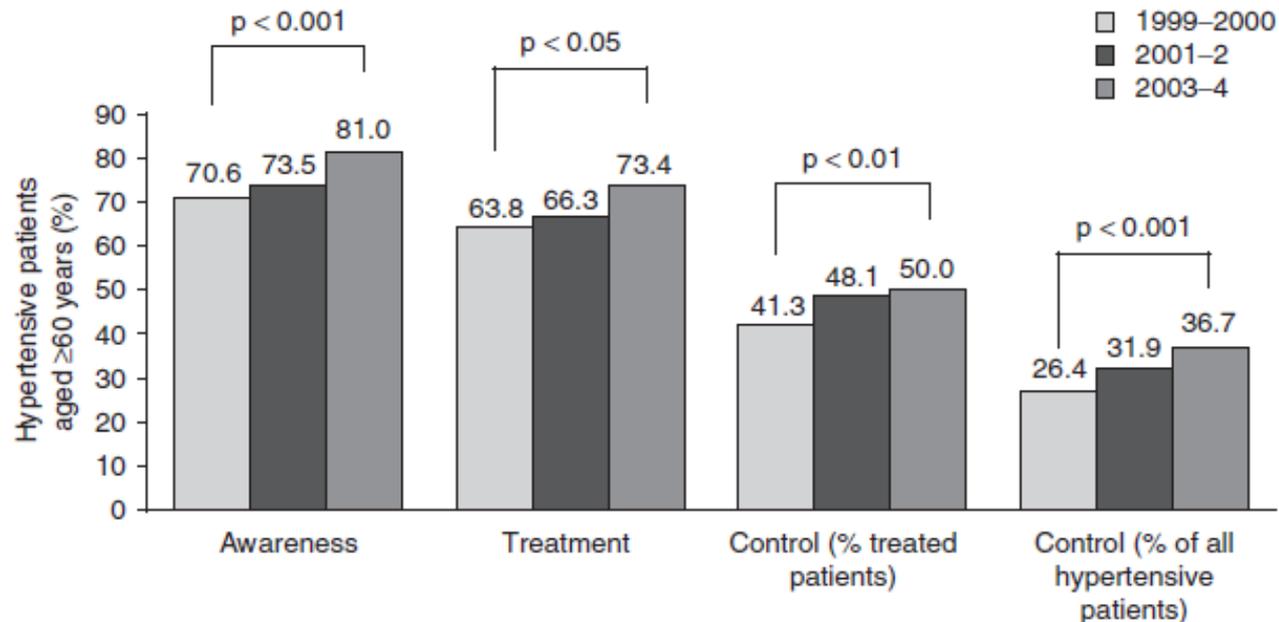


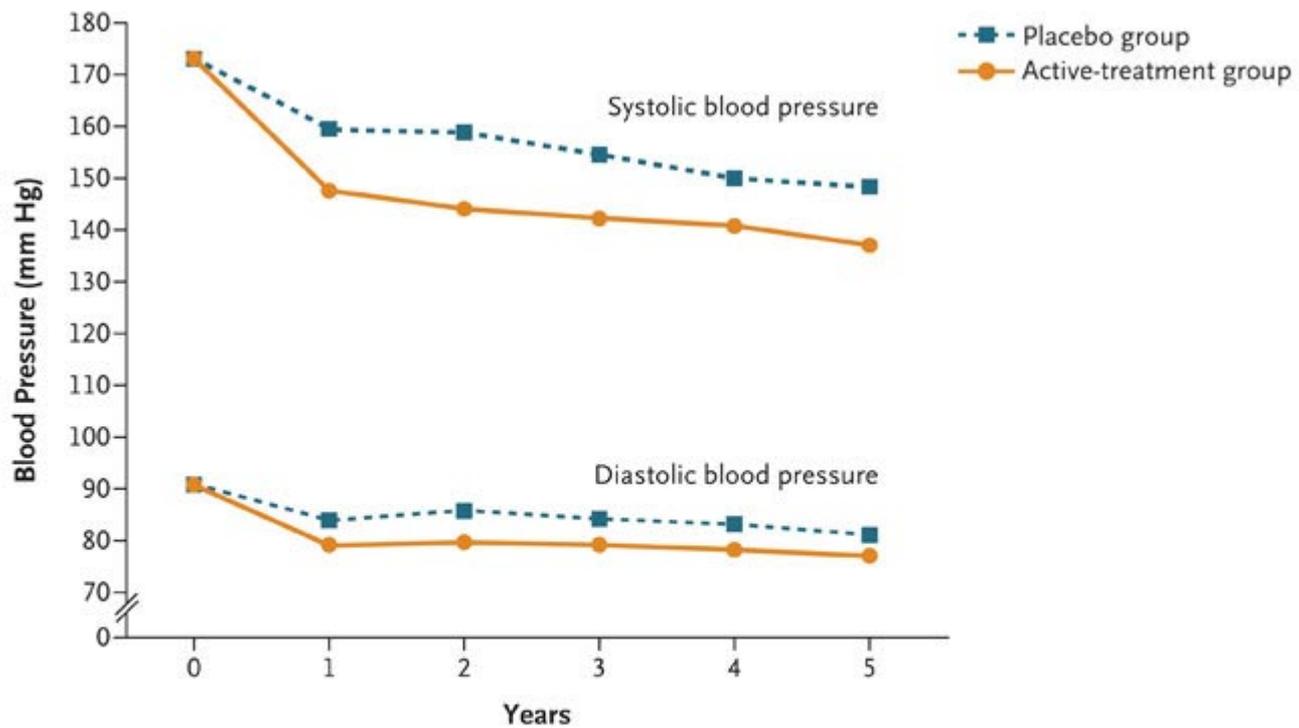
Fig. 2. Rates of blood pressure awareness, treatment and control among hypertensive patients aged ≥60 years in progressive National Health and Nutrition Examination Survey (NHANES) surveys between 1999 and 2004 (data from Ong et al.<sup>[3]</sup>).

# Compelling Indications for Antihypertensive Therapies

Compelling indication	Recommended drug classes						Clinical trial basis
	diuretics	$\beta$ -adrenoceptor antagonists	ACE inhibitors	ARBs	CCBs	aldosterone antagonists	
Heart failure	✓	✓	✓	✓		✓	ACC/AHA Heart Failure guideline, <sup>[45]</sup> MERIT-HF, <sup>[46]</sup> COPERNICUS, <sup>[47]</sup> CIBIS, <sup>[48]</sup> SOLVD, <sup>[49]</sup> AIRE, <sup>[50]</sup> TRACE, <sup>[51]</sup> ValHEFT, <sup>[52]</sup> RALES, <sup>[53]</sup> CHARM <sup>[54]</sup>
Post-MI		✓	✓	✓ <sup>a</sup>		✓	ACC/AHA post-MI guidelines, <sup>[55]</sup> BHAT, <sup>[56]</sup> SAVE, <sup>[57]</sup> CAPRICORN, <sup>[58]</sup> EPHEBUS, <sup>[59]</sup> VALIANT <sup>[60]</sup> <sup>a</sup>
High coronary disease risk	✓	✓	✓		✓		ALLHAT, <sup>[34]</sup> HOPE, <sup>[61]</sup> ANBP2, <sup>[62]</sup> LIFE, <sup>[39]</sup> CONVINCe, <sup>[63]</sup> EUROPA, <sup>[64]</sup> INVEST <sup>[65]</sup>
Diabetes	✓	✓	✓	✓	✓		NKF-ADA guidelines, <sup>[66,67]</sup> UKPDS, <sup>[68]</sup> ALLHAT <sup>[34]</sup>
Chronic kidney disease			✓	✓			NKF guideline, <sup>[67]</sup> captopril trial, <sup>[69]</sup> RENAAL, <sup>[70]</sup> IDNT, <sup>[71]</sup> REIN, <sup>[72]</sup> AASK <sup>[73]</sup>
Recurrent stroke prevention	✓		✓	✓ <sup>a</sup>			PROGRESS, <sup>[74]</sup> MOSES <sup>[43]</sup> <sup>a</sup>

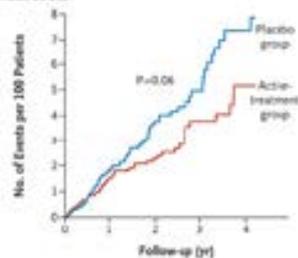
<sup>a</sup> Modified based on data published subsequent to JNC 7 and not appearing in JNC 7 guidelines.

**ACC**=American College of Cardiology; **ADA**=American Diabetes Association; **AHA**=American Heart Association; **CCB**=calcium channel blocker (calcium channel antagonist); **MI**=myocardial infarction; **NKF**=National Kidney Foundation.



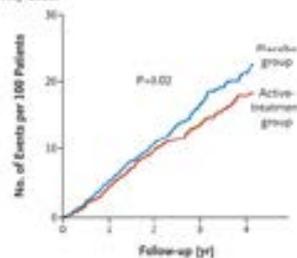
**No. at Risk**

Placebo group	1912	1468	701	330	191	116
Active-treatment group	1933	1540	754	373	207	118

**A Fatal or Nonfatal Stroke**

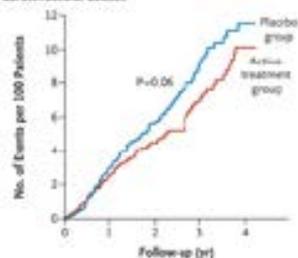
No. at Risk

Placebo group	1912	1484	887	534	194
Active-treatment group	1953	1517	873	417	229

**B Death from Any Cause**

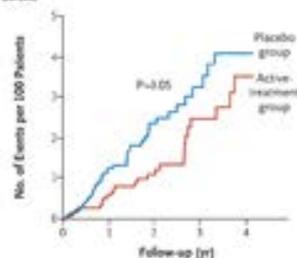
No. at Risk

Placebo group	1912	1482	814	379	202
Active-treatment group	1953	1545	877	420	231

**C Death from Cardiovascular Causes**

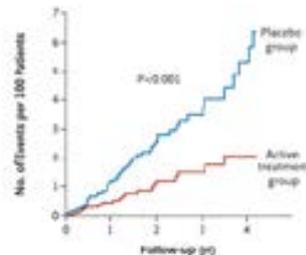
No. at Risk

Placebo group	1912	1492	814	379	202
Active-treatment group	1953	1545	877	420	231

**D Death from Stroke**

No. at Risk

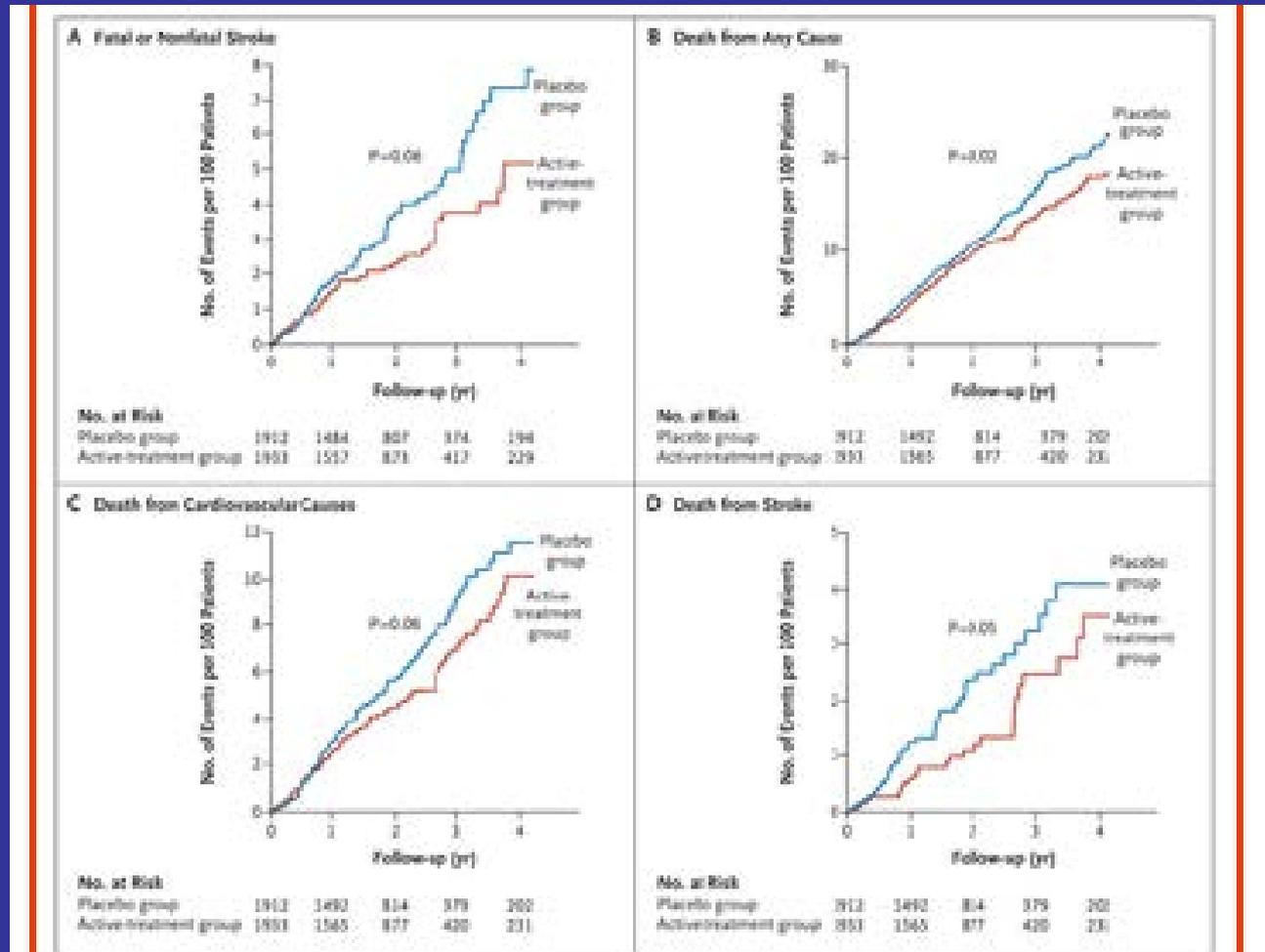
Placebo group	1912	1492	814	379	202
Active-treatment group	1953	1545	877	420	231

**E Heart Failure**

No. at Risk

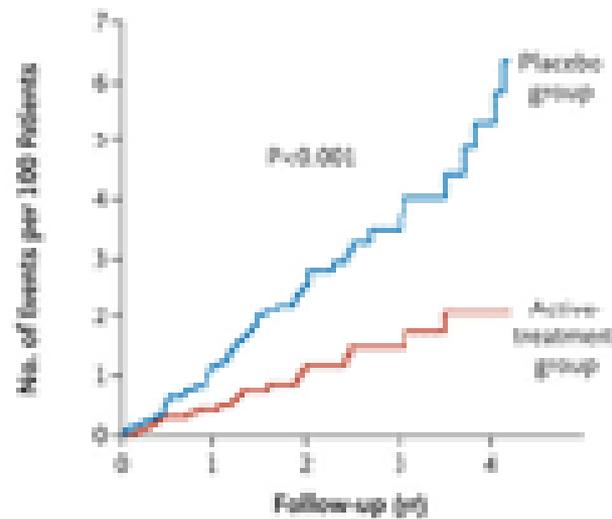
Placebo group	1912	1480	794	347	188
Active-treatment group	1953	1159	872	416	228

# Death and Stroke in HYVET



# Heart Failure in HYVET

## E Heart Failure



### No. at Risk

Placebo group	1912	1480	794	347	168
Active-treatment group	1933	1159	872	404	228