Importance of Evidence-Based Treatment for Cardiovascular Diseases

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What is Evidence-Based Medicine (EBM) ?

- Definition: the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient (David Sackett, 1996)
- the integration of clinical expertise, patient values, and the best evidence into the decision making process for patient care.
- requires new skills of the clinician, including efficient literature-searching, and the application of formal rules of evidence in evaluating the clinical literature.

Two types of EBM

- Evidence-based guidelines (EBG)
  - the practice of evidence-based medicine at the organizational or institutional level
  - includes the production of guidelines, policy, and regulations
  - evidence based healthcare ; evidence based treatment
- Evidence-based individual decision (EBID) making
  - evidence-based medicine as practiced by the individual health care provider
  - There is concern that current evidence-based medicine focuses excessively on EBID.

Steps in the EBM Process

The patient	1. Start with the patient -- a clinical problem or question arises out of the care of the patient
The question	2. Construct a well built clinical question derived from the case
The resource	3. Select the appropriate resource(s) and conduct a search
The evaluation	4. Appraise that evidence for its validity (closeness to the truth) and applicability (usefulness in clinical practice)
The patient	5. Return to the patient -- integrate that evidence with clinical expertise, patient preferences and apply it to practice
Self-evaluation	6. Evaluate your performance with this patient

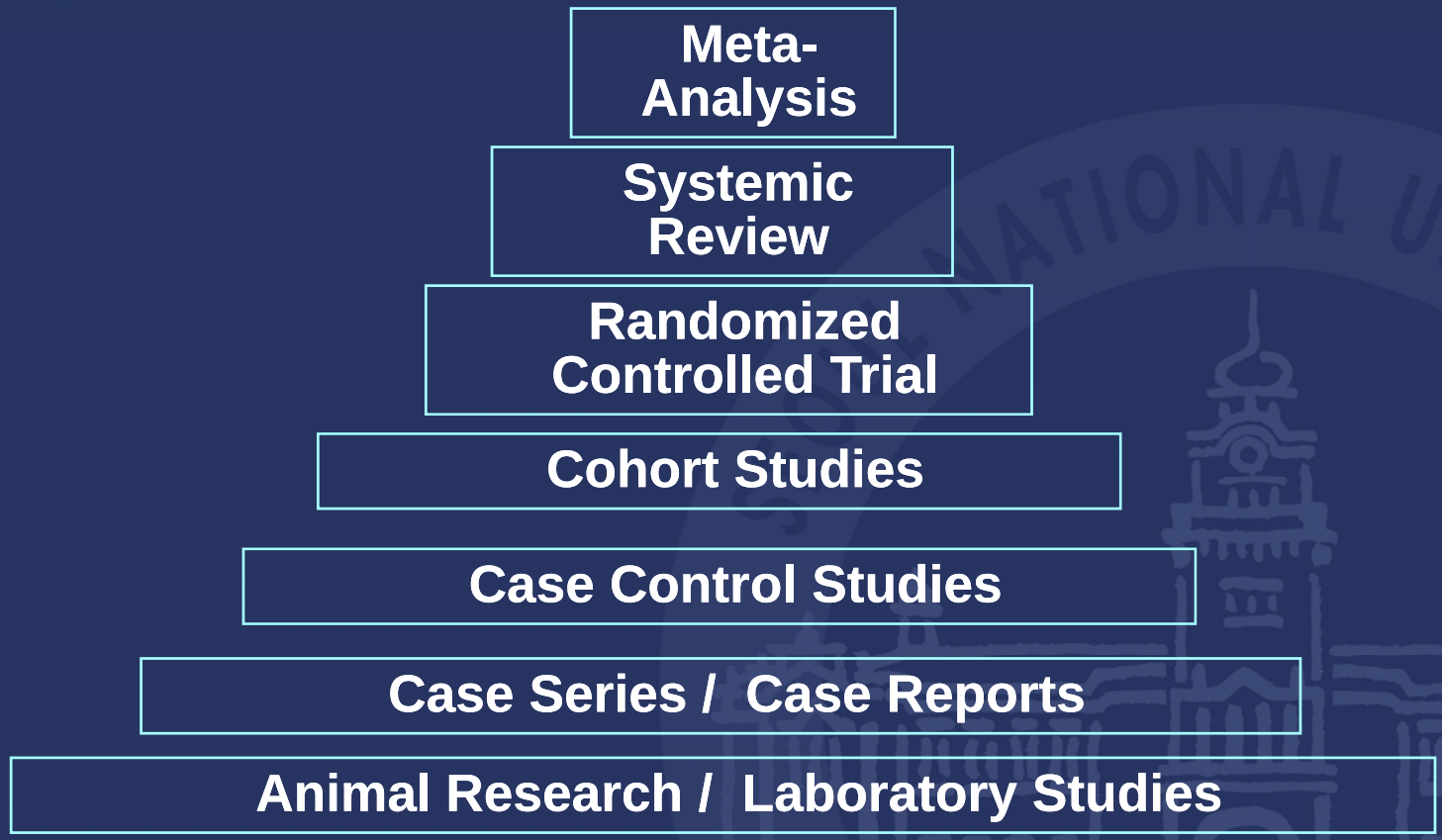
EBM Issues

Opponents	Proponents
“Old hat". Using the literature to guide their decisions for a long time. The label is new.	The new focus on EBM "formalizes" that "old hat" process and filters the literature
“Cook book medicine". Based solely on the evidence, down playing sound clinical judgment.	Should be one part of the process. must be blended with individual clinical expertise, patient preferences
Mindless application of population studies to the treatment of the individual.	Decide whether or not the information and results are applicable to your patient
Often there is no randomized controlled trial or "gold standard" in the literature	Consider the "evidence pyramid" and look for the next best level of evidence.
Difficulty in getting access to the evidence and in conducting effective searches to identify the best evidence	Librarians can help identify the best resources and teach clinicians effective searching skills

Type of Question in EBM

Diagnosis	how to select and interpret diagnostic tests
Therapy	how to select treatments to offer patients that do more good than harm and that are worth the efforts and costs of using them
Prognosis	how to estimate the patient's likely clinical course over time and anticipate likely complications of disease
Harm/Etiology	how to identify causes for disease (including iatrogenic forms)

Type of Study : Evidence Pyramid



Type of Question & the Best Study Design

Type of Question	Suggested best type of Study
Therapy	RCT>cohort > case control > case series
Diagnosis	prospective, blind comparison to a gold standard
Etiology/Harm	RCT > cohort > case control > case series
Prognosis	cohort study > case control > case series
Prevention	RCT>cohort study > case control > case series
Clinical Exam	prospective, blind comparison to gold standard
Cost	economic analysis

Qualification of evidence

- U.S. Preventive Services Task Force
  - Level I: *Evidence obtained* from at least one properly designed randomized controlled trial.
  - Level II-1: from well-designed controlled trials without randomization.
  - Level II-2: from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
  - Level II-3: from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
  - Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
- UK National Health Service
- Grade Working Group

Applying Classification of Recommendations and Level of Evidence (ACC/AHA Guideline)

Class I	Class IIa	Class IIb	Class III
Benefit >>> Risk Procedure/ Treatment SHOULD be performed/ administered	*Benefit >> Risk* *Additional studies with focused objectives needed* IT IS REASONABLE to perform procedure/administer treatment	*Benefit ≥ Risk* *Additional studies with broad objectives needed; Additional registry data would be helpful* Procedure/Treatment MAY BE CONSIDERED	*Risk ≥ Benefit* *No additional studies needed* Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL

Level A:	Recommendation based on evidence from multiple randomized trials or meta-analyses Multiple (3-5) population risk strata evaluated; General consistency of direction and magnitude of effect
Level B:	Based on evidence from a single randomized trial or non-randomized studies Limited (2-3) population risk strata evaluated
Level C:	Recommendation based on expert opinion, case studies, or standard-of-care Very limited (1-2) population risk strata evaluated

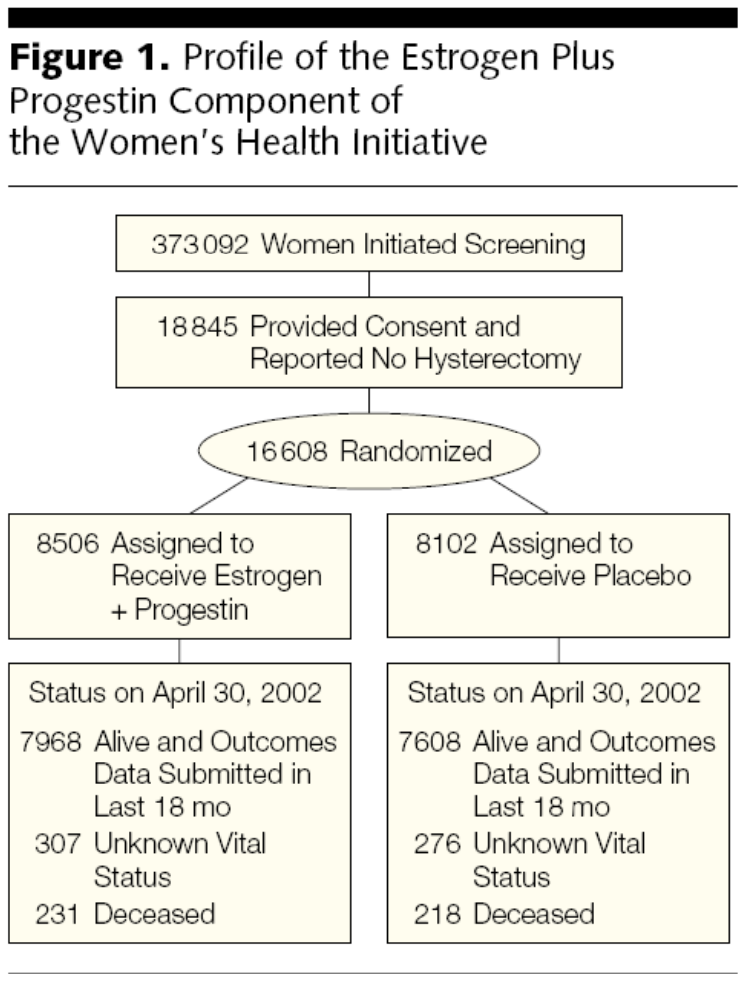
Several Studies Have Failed to Demonstrate Expected Clinical Outcomes

Therapy	Clinical Trials	Results
Hormone therapy	WHI	Harmful
Vitamin E	HOPE, HPS	Neutral
Folate, B6, B12	HOPE2, NORVIT	Negative
Fibrate	FIELD	Negative(↑death)
Muraglitazar	Dual-PPAR agonist	Harmful
Rosiglitazone	Systematic Review	?

Lessons From Several Examples of Outcome Failure

Estrogen plus Progestin Component of WHI Trial:

Risks & Benefits of Hormone Therapy in Healthy Postmenopausal Women



- ***Objective***
  - **To assess the major health benefits and risks of the most commonly used combined hormone preparation in the US (primary prevention)**
- ***Patients***
  - **16,608 postmenopausal women aged 50-79 years with an intact uterus at baseline**
- ***Intervention***
  - **Conjugated equine estrogens/ medroxyprogesterone actate 0.625/2.5 mg/d (n=8,506)**
  - **Placebo (n=8,102)**
- ***Primary end point***
  - **Primary outcome: coronary heart disease**
  - **Primary adverse outcome: invasive breast cancer**

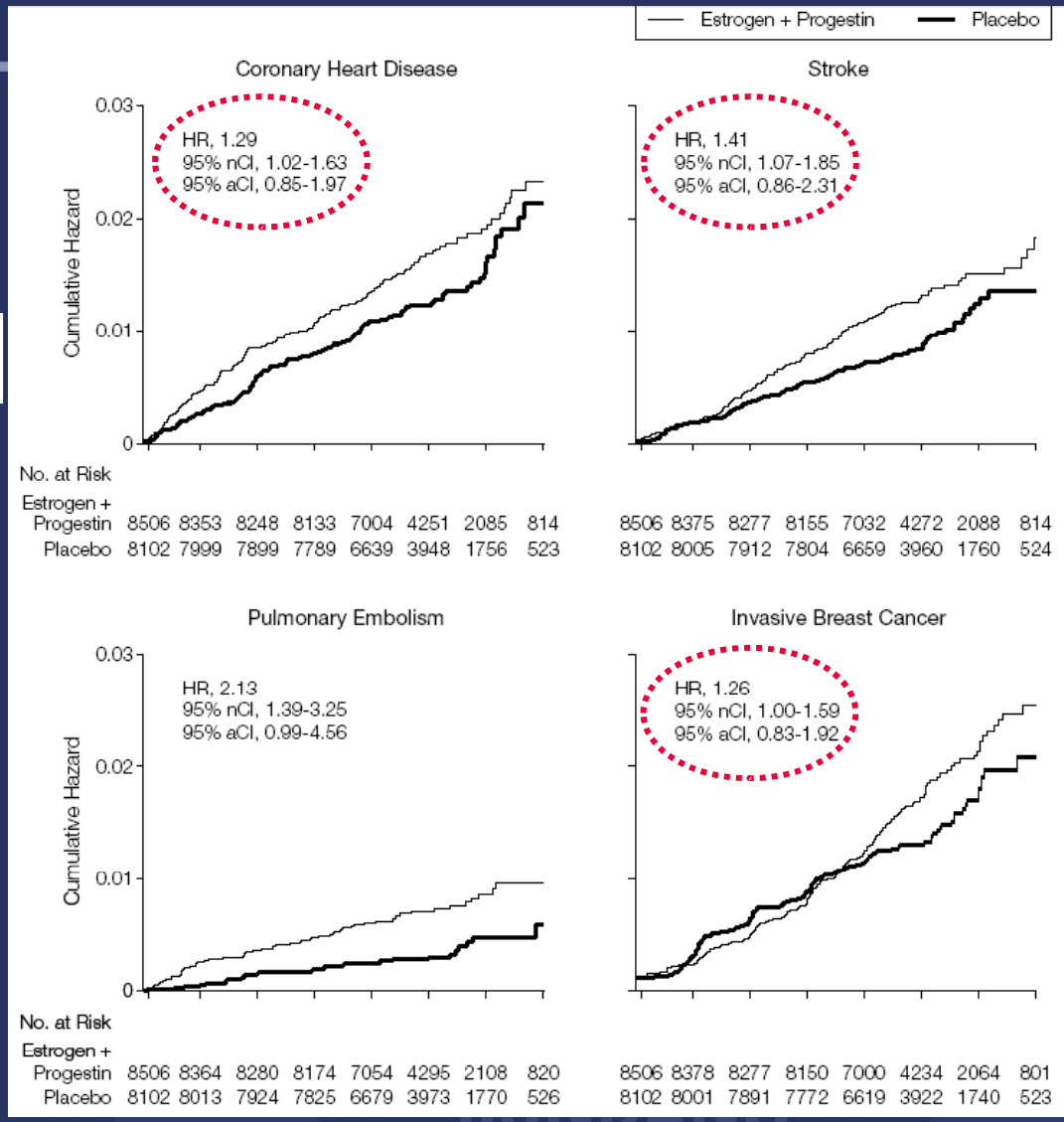
Writing group for the Women's Health Initiative investigators. *JAMA* 2002; 288: 321-333

WHI: Monitoring Board Recommended Stopping the Trial Because of Increased Risks for CVD and Cancer

- Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin:
  - ***7 more CHD events!***
  - ***8 more Strokes!***
  - ***8 more PEs!***
  - ***8 more invasive breast cancers!***

"Results from WHI indicate that the combined postmenopausal hormones CEE plus MPA should not be initiated or continued for the primary prevention of CHD. In addition, the substantial risks for CV disease and breast cancer must be weighted against the benefit for fracture in selecting…."

– WHI study group



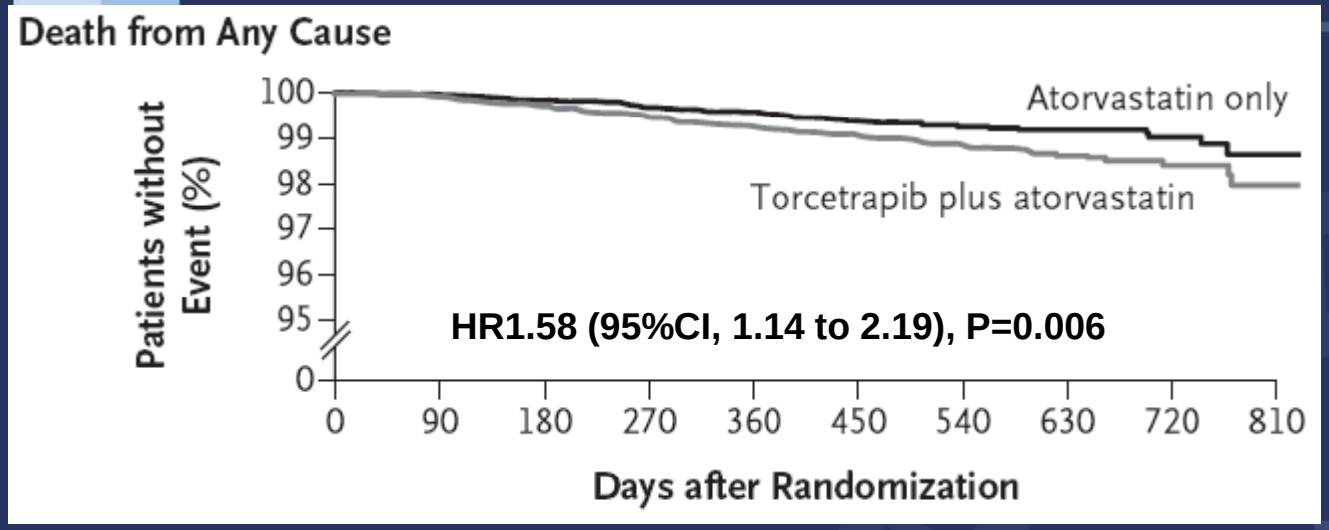
Writing group for the Women's Health Initiative investigators. *JAMA* 2002; 288: 321-333

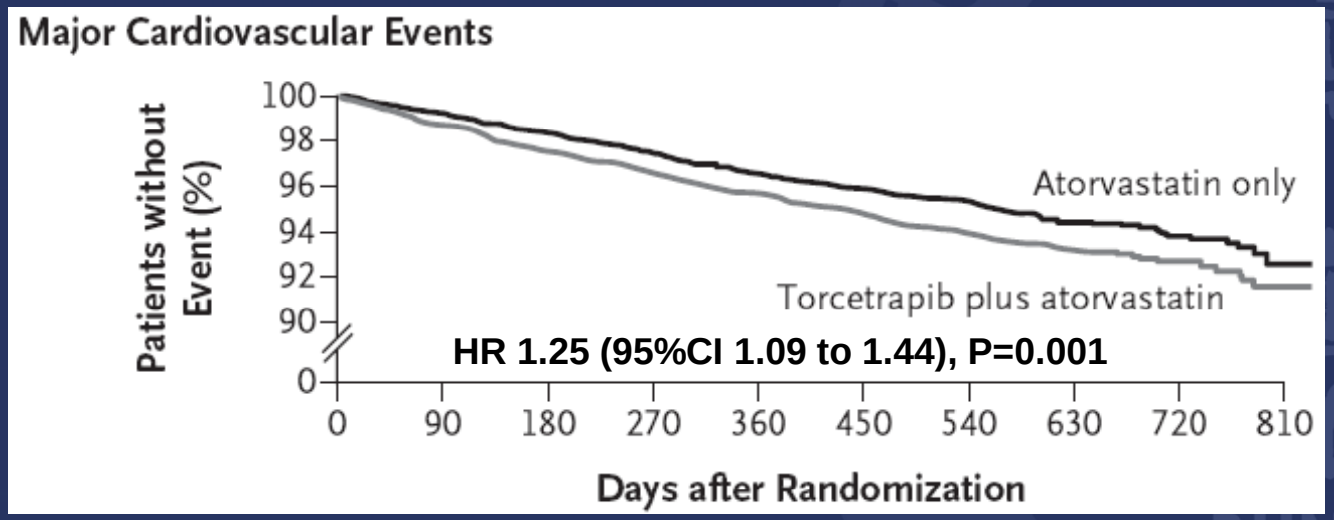
ILLUMINATE: Effects of Torcetrapib in Patients at High Risk for Coronary Events

- ***Objective***
  - To investigate whether torcetrapib, a potent CETP inhibitor, might reduce major CV events
- ***Patients***
  - 15,067 patients at high CV risk
- ***Intervention***
  - Torcetrapib plus atorvastatin *versus* atorvastatin alone
- ***Primary end point***
  - Time to the first major CV event (CHD death, nonfatal MI, stroke, or hospitalization for unstable angina)

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

ILLUMINATE was Terminated Prematurely Because of an Increased Risk of Death and Cardiac Events with Torcetrapib



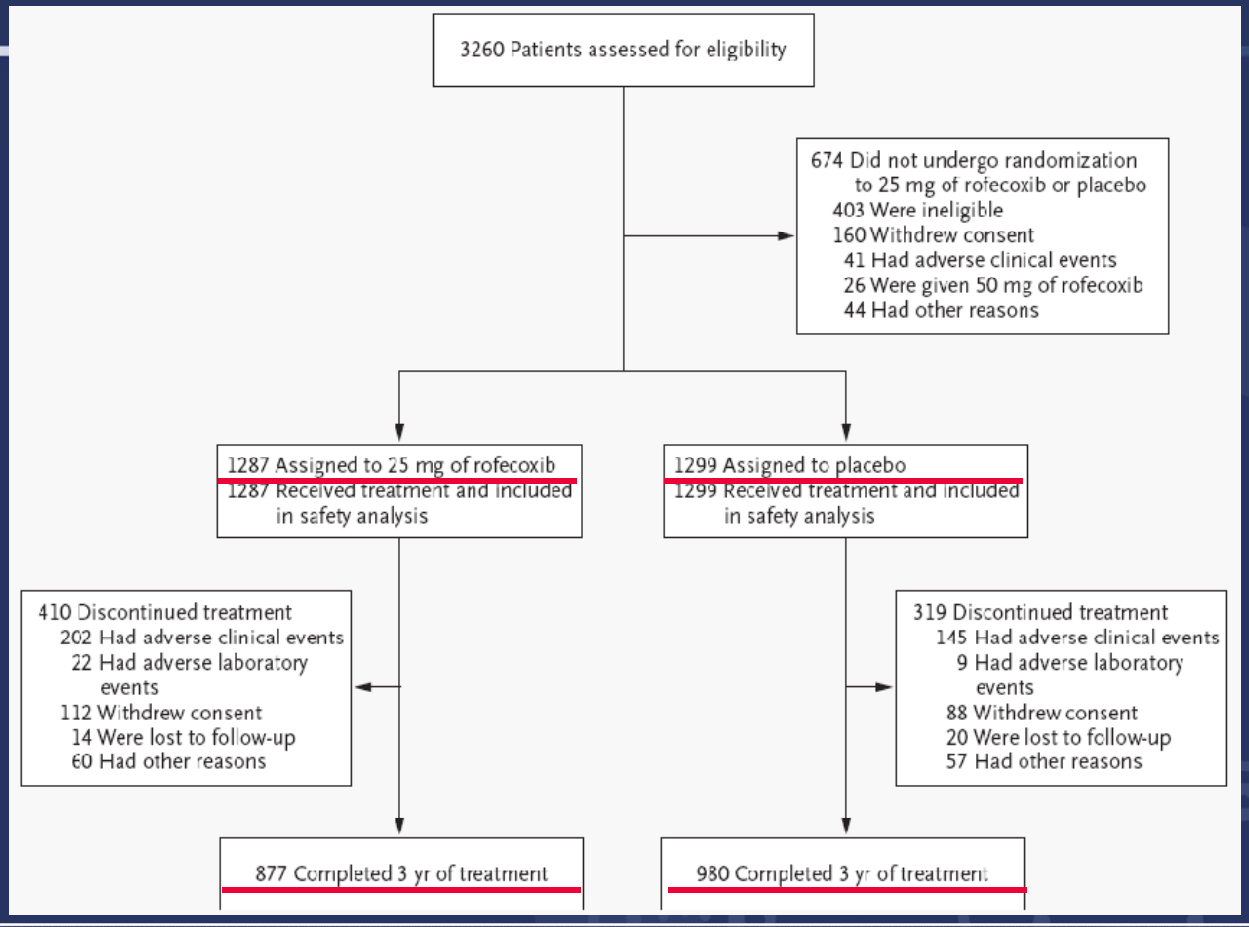


- ***Lipid profiles:***
  HDL (72.1% ↑)
  LDL (24.9% ↓)
  CRP(7% ↓)
- ***Off-target effects:***
  ↑ SBP 5.4 mmHg
  ↓ K+, ↑ Na HCO3
  (↑aldosterone levels)

"Torcetrapib therapy resulted in an increased risk of mortality and morbidity of unknown mechanism."

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

APPROVe Trial: CV Outcomes Associated with the Use of the Selective COX-2 Inhibitor Rofecoxib



Objective:

- To determine the effect of three years of treatment with rofecoxib on the risk of recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas

Bresalier RS et al. *N Engl J Med* 2005; 352: 1092-1102

APPROVe: On September 30 2004, Rofecoxib Voluntarily Withdrawn from Market

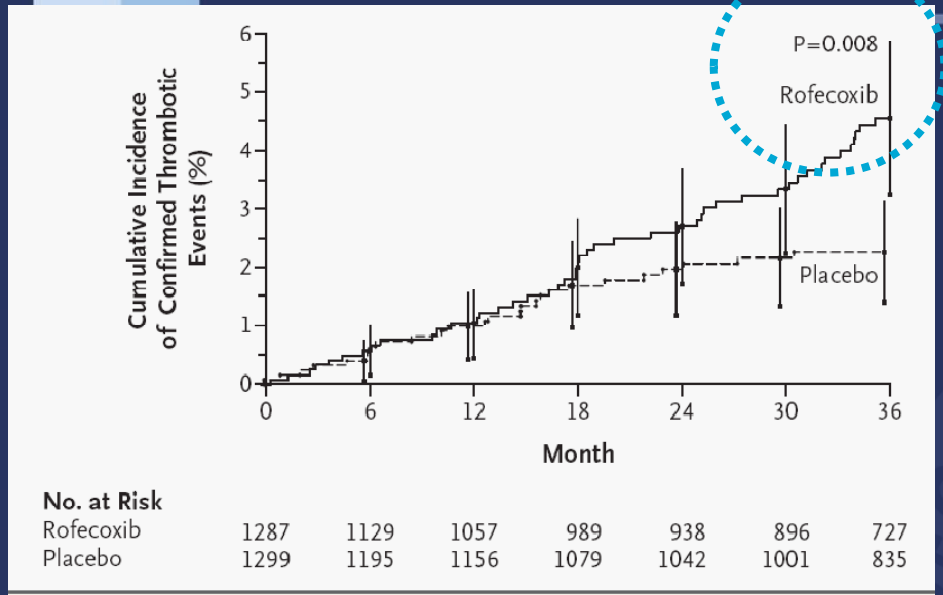


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed Serious Thrombotic Events.

Vertical lines indicate 95 percent confidence intervals.

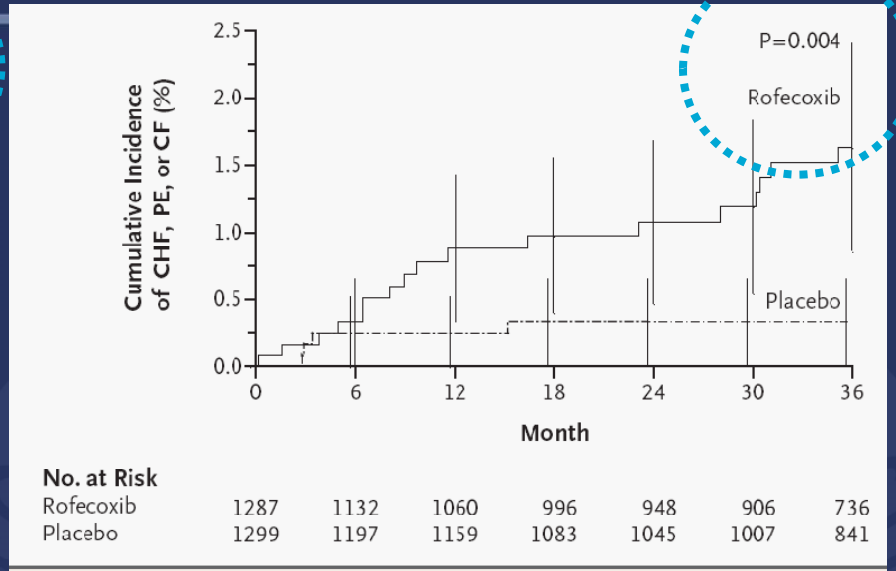


Figure 3. Kaplan–Meier Estimates of the Cumulative Incidence of Investigator-Reported Congestive Heart Failure (CHF), Pulmonary Edema (PE), or Cardiac Failure (CF).

Vertical lines indicate 95 percent confidence intervals.

"We should have started this (RCTs comparing these drugs to a nonselective NSAID, such as ibuprofen) a long time ago. … The fact that so many are prescribed is unfortunate. Doctors should be cautious about any of these drugs."

– Dr. James Wright, professor of pharmacology, University of British Columbia

Bresalier RS et al. *N Engl J Med* 2005; 352: 1092-1102

FIELD: Effects of Long-Term Fenofibrate Therapy on CV Events in Patients with Type II DM

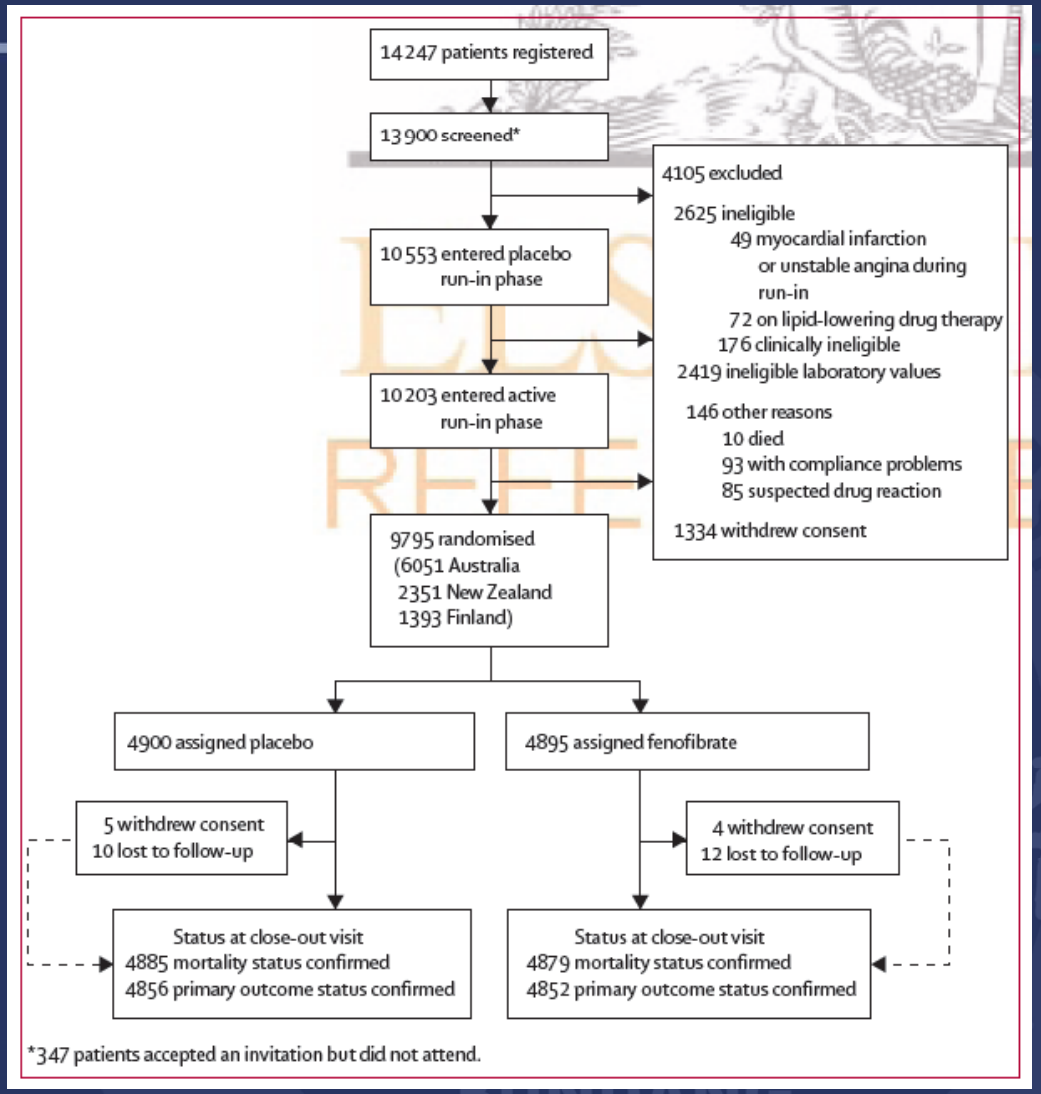
Study Profile

Patients population:

- 9795 patients with type 2 diabetes mellitus diagnosed according to WHO criteria

Efficacy outcomes:

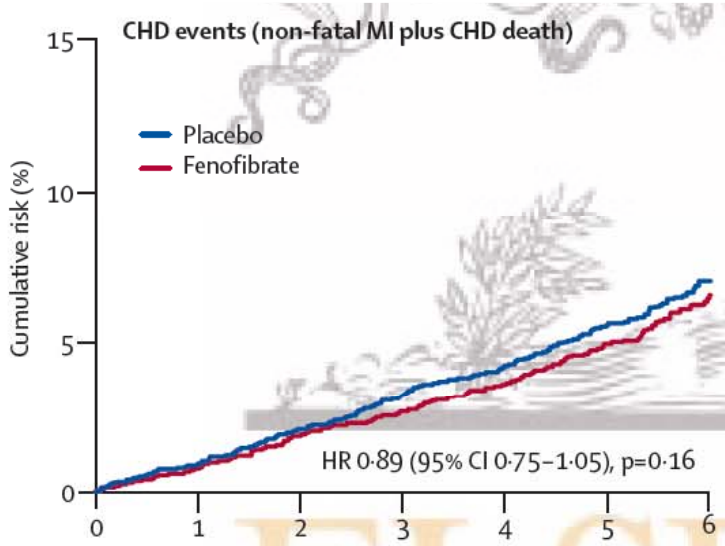
- Primary efficacy end point: Non-fatal MI & death from CHD
- Secondary efficacy outcome: Major CVD events, total CVD events, CHD death, total CVD death, stroke, revascularization, non-CHD mortality, total mortality

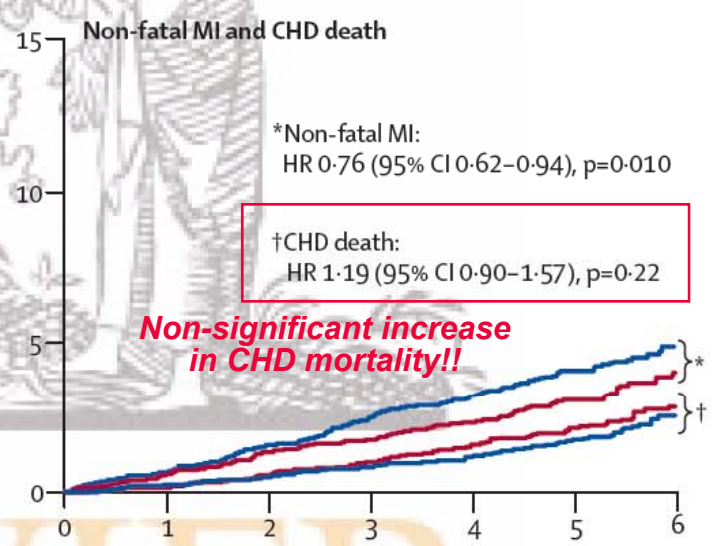


The FIELD investigators. *Lancet* 2005; 366: 1849-1861

FIELD: Fenofibrate Did *Not* Significantly Reduce the Risk of the Primary Outcome of Coronary Events

Negative Findings in FIELD Study





Numbers at risk

Placebo	4900	4835	4741	4646	4547	2541	837
Fenofibrate	4895	4837	4745	4664	4555	2553	850

Numbers at risk: non-fatal MI

Placebo	4900	4835	4741	4646	4547	2541	837
Fenofibrate	4895	4837	4745	4664	4555	2553	850

Numbers at risk: CHD death

Placebo	4900	4866	4815	4759	4689	2651	882
Fenofibrate	4895	4866	4806	4740	4649	2638	889

"Fenofibrate should be considered in the context of the well established benefits of statin therapy, where its main use will probably be in combination therapy. …" *– the FIELD study investigators*

The FIELD investigators. *Lancet* 2005; 366: 1849-1861

Rosiglitazone Obtained Additional Black-Box Warning Due to Increased Risk of Ischemic Events

FDA meta-analysis

Table 1. Results of FDA Meta-Analysis of 42 Randomized Trials Comparing Rosiglitazone with Other Drugs or Placebo.

Adverse Event	Rosiglitazone Group (N=8604)	Control Group (N=5633)	Odds Ratio (95% CI)	P Value
	% of patients			
Any ischemia	2.0	1.5	1.4 (1.1–1.8)	0.02
Serious ischemia	1.0	0.8	1.4 (1.0–2.1)	0.06
Myocardial infarction, cardiovascular death, or stroke	0.73	0.67	1.2 (0.7–1.8)	0.40

"Ultimately, the committee voted to recommend not that Rosiglitazone be removed from the market but rather that label warnings and extensive educational efforts be instituted immediately. …" *– FDA's conclusion*

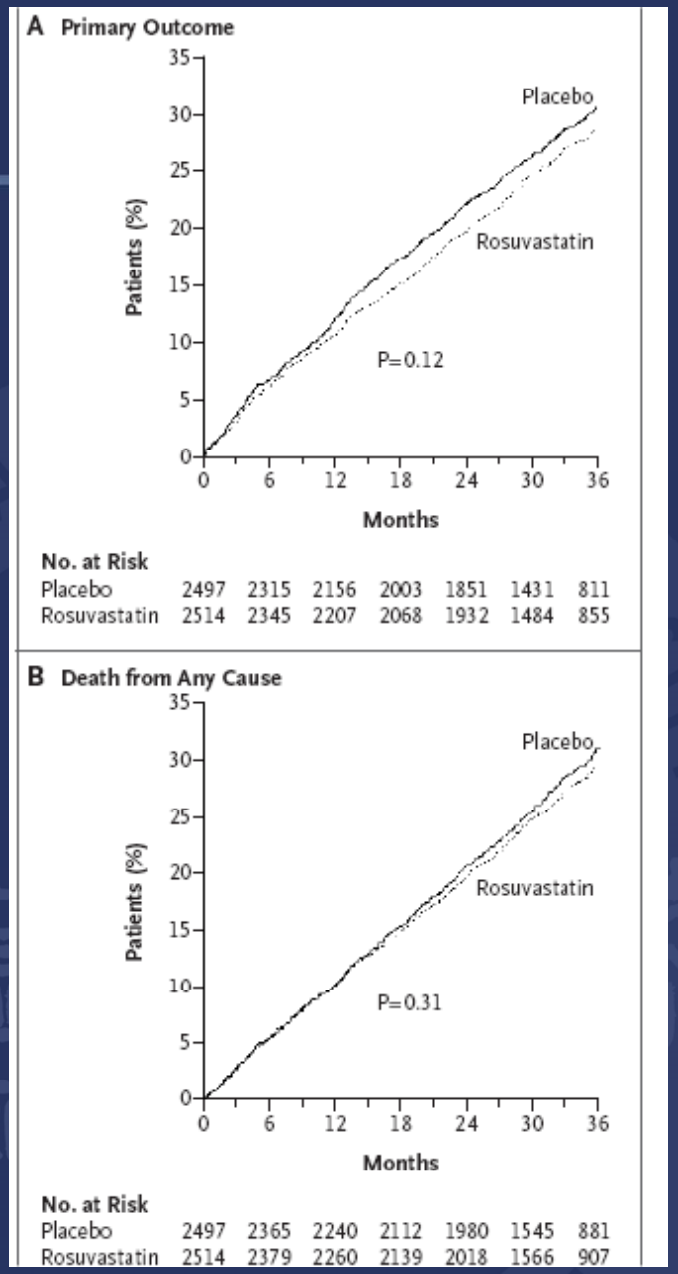
Additional black-box warning:

"Avandia is associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction…"

CORONA: Rosuvastatin Did Not Reduce the Primary Outcome or Death

- A total of 5011 patients at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure were randomly assigned to receive 10 mg of Rosuvastatin or placebo per day.
- The primary composite outcome : death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
- Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations.

N Engl J Med 2007:357;2248-61

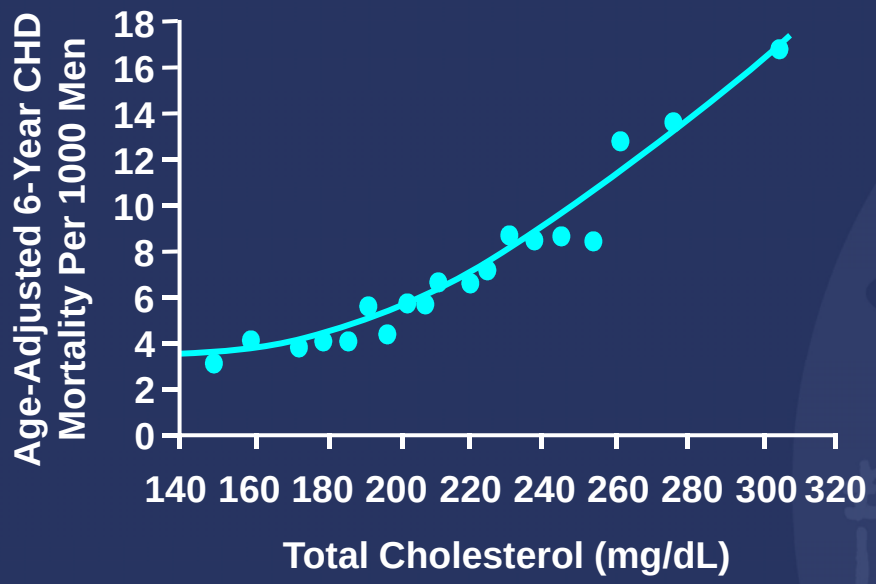


Evidences :

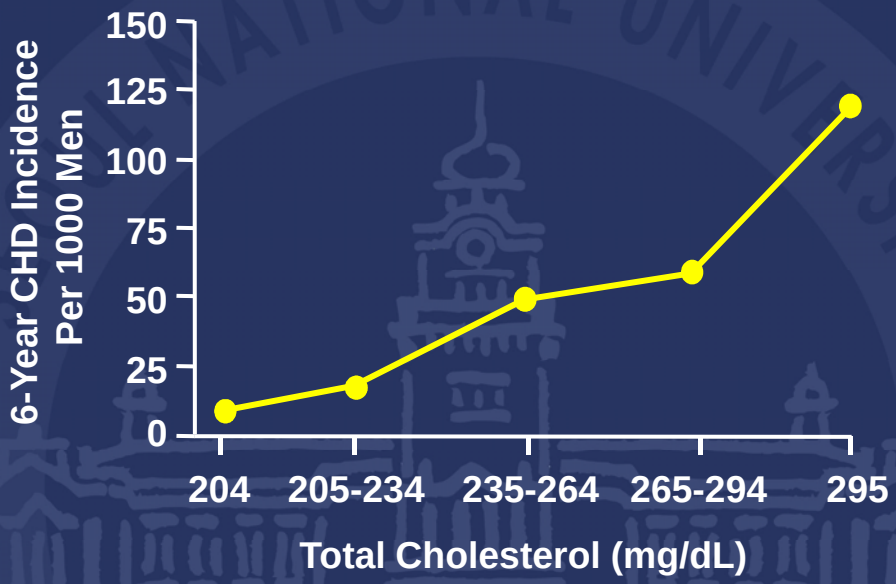
Role of Statin in Prevention and Mortality in High Risk Patients

Elevated Cholesterol Levels Associated With High Risk of CHD

Multiple Risk Factor Intervention Trial (MRFIT) (N=361,662)



Framingham Study (N=5209)



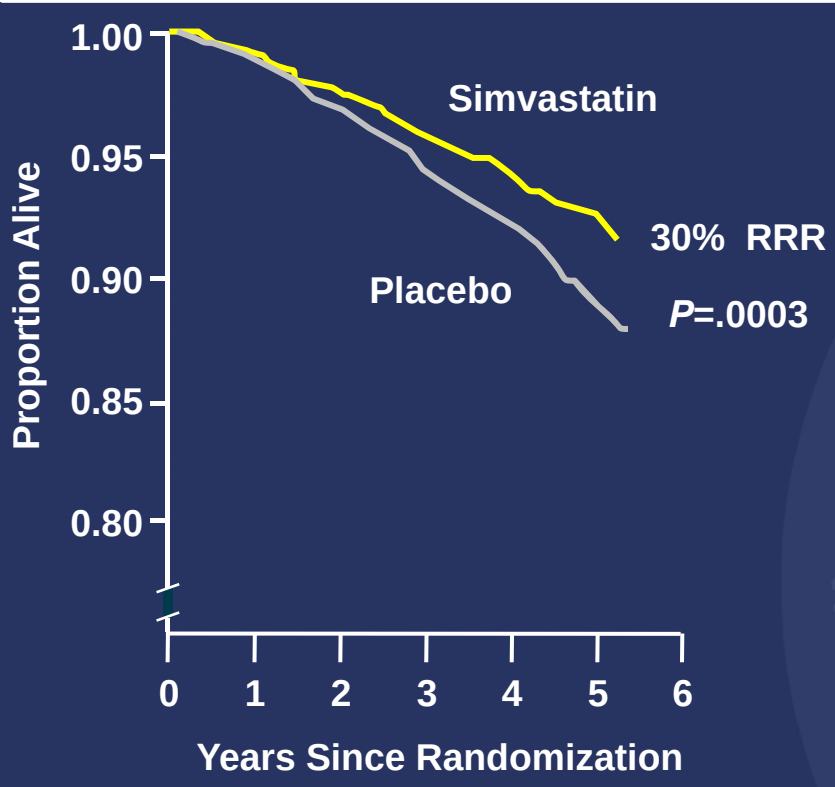
Each 1% Reduction in Total Cholesterol Level Resulted in a 2% Decrease in CHD Risk

Each 1% Increase in Total Cholesterol Level Associated With a 2% Increase in CHD Risk

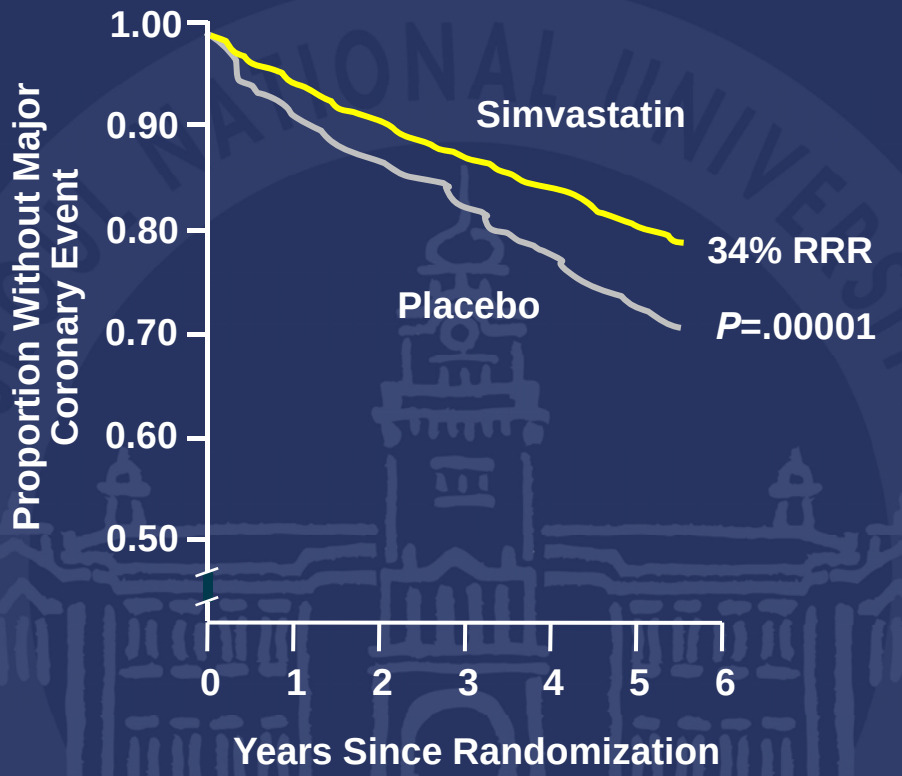
Adapted from Martin MJ et al. *Lancet.* 1986;2:933-936, with permission.
Reproduced from Castelli WP. *Am J Med*. 1984;76:4-12, with permission.

4S Proved 2º Prevention With Statins Could Lower Mortality and CV Events

Primary End Point: Total Mortality



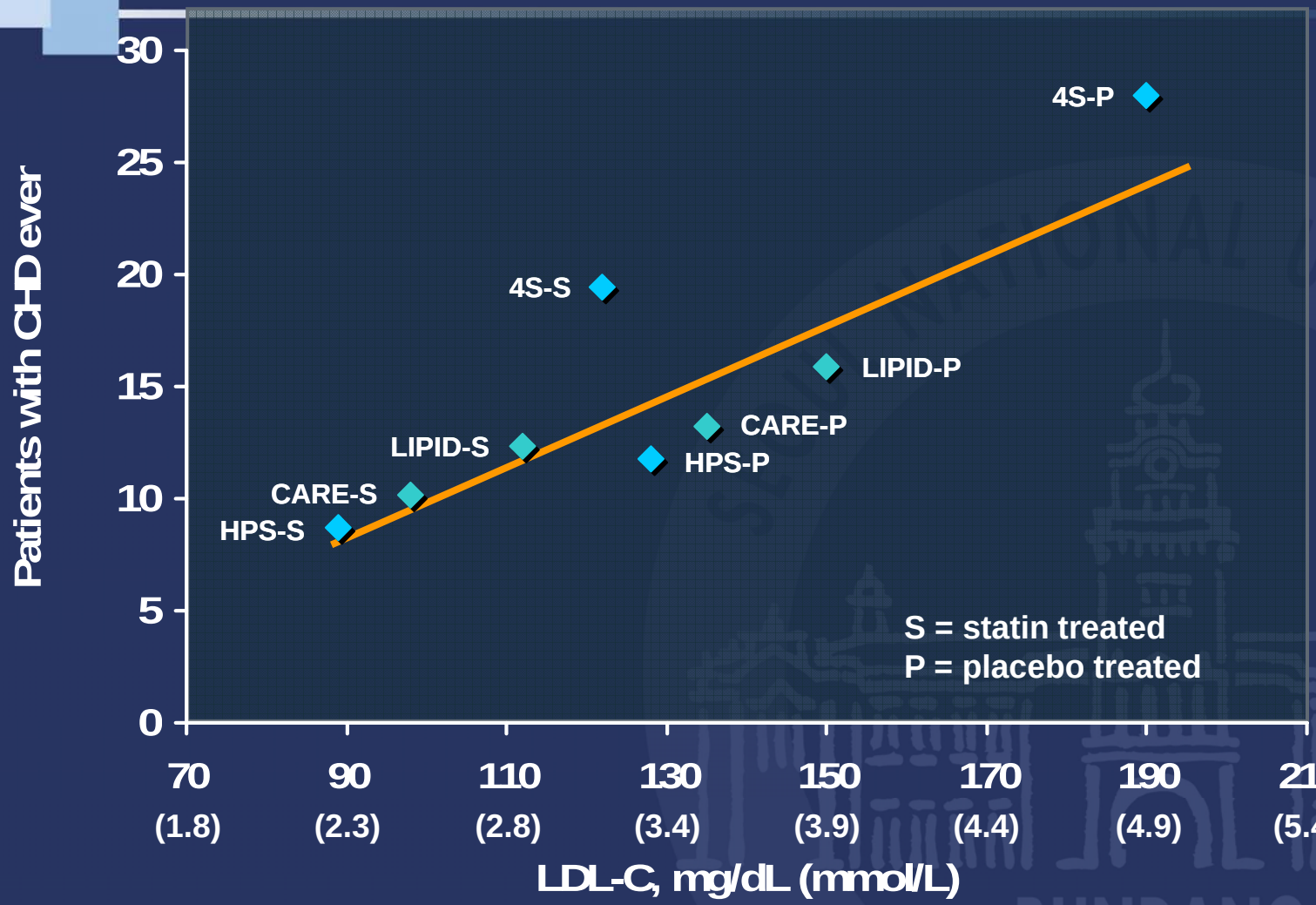
Secondary End Point: Major Coronary Events*



* Defined as coronary death, nonfatal definite or probable MI, silent MI, or resuscitated cardiac arrest.

Reproduced from Scandinavian Simvastatin Survival Study Group. *Lancet.* 1994;344:1383-1389, with permission.

Effects of More Intensive Lipid Lowering in CHD Patients



Modified from Kastelein JJP. *Atherosclerosis.* 1999;143(suppl 1):S17-S21

The majority of patients with CHD are not treated to their target LDL-C goal

Heart Disease and Stroke Statistics—2006 Update[1]

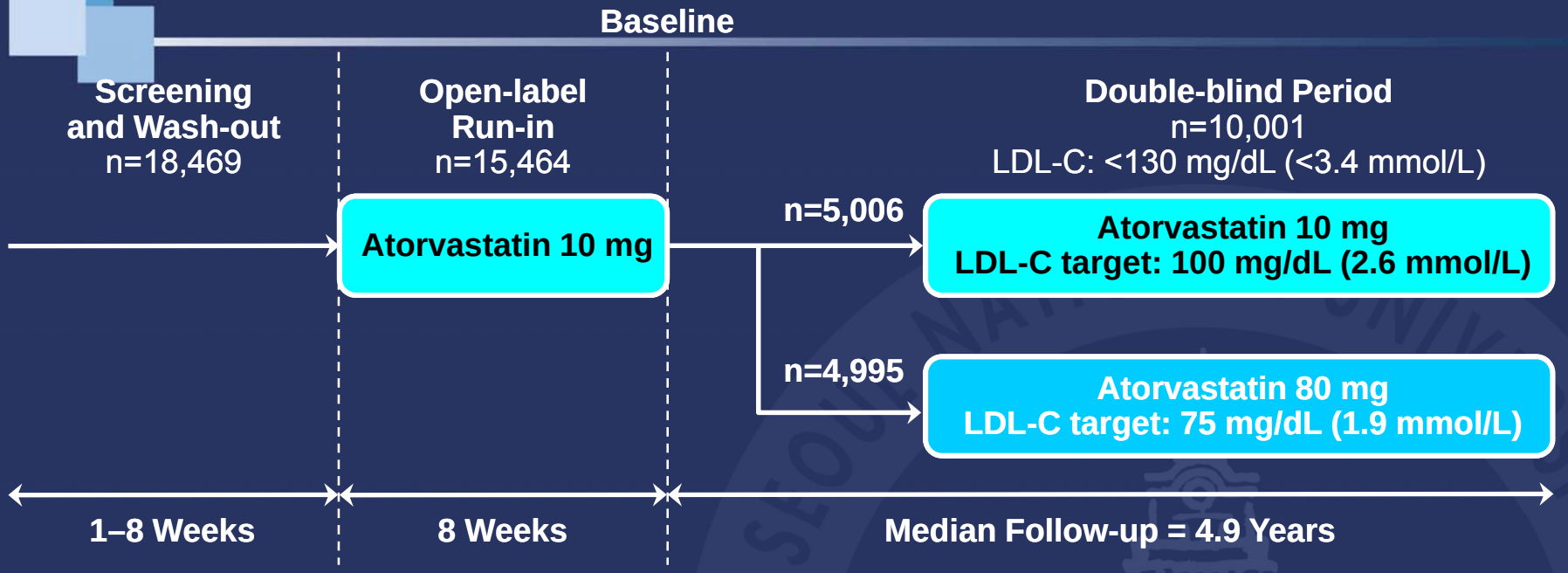
A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee

- "**Less than half of even the highest-risk persons, those who have symptomatic CHD, are receiving lipid-lowering treatment.**"

- "**Only about a third of treated patients are achieving their LDL goal; less than 20% of CHD patients are at their LDL goal.**"

Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* [serial online]. 2006;113:e85-e151. Available at: http://circ.ahajournals.org/cgi/reprint/113/6/e85. Accessed February 16, 2006.

TNT: Study Design



Patient Population

- CHD
- LDL-C: 130-250 mg/dL (3.4-6.5 mmol/L)
- Triglycerides ≤600 mg/dL (≤6.8 mmol/L)

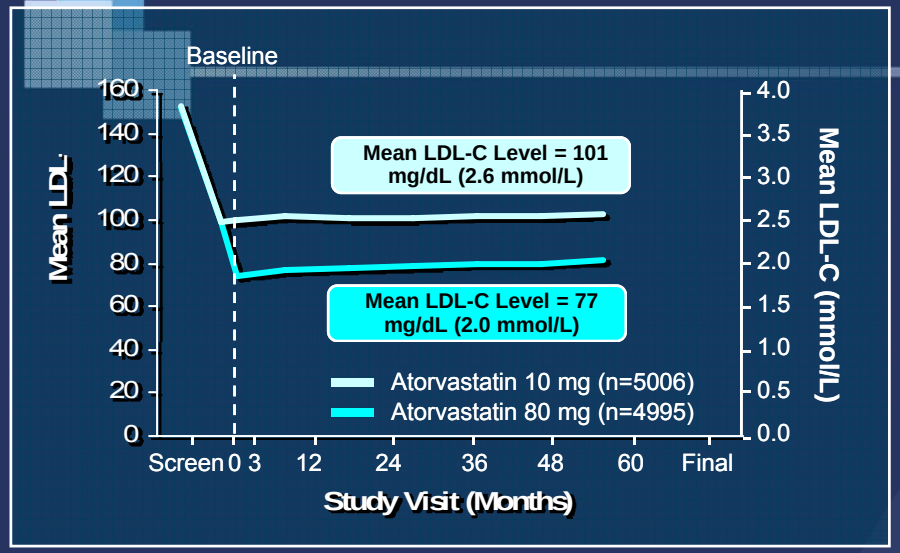
Primary Efficacy Outcome Measure

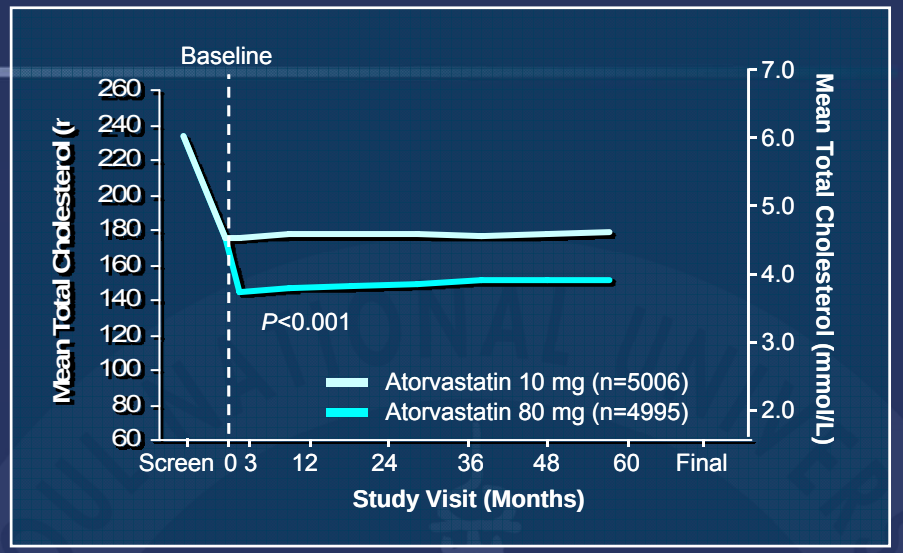
- Time to occurrence of a major CV event:
  - CHD death
  - Nonfatal, non–procedure-related MI
  - Resuscitated cardiac arrest
  - Fatal or nonfatal stroke

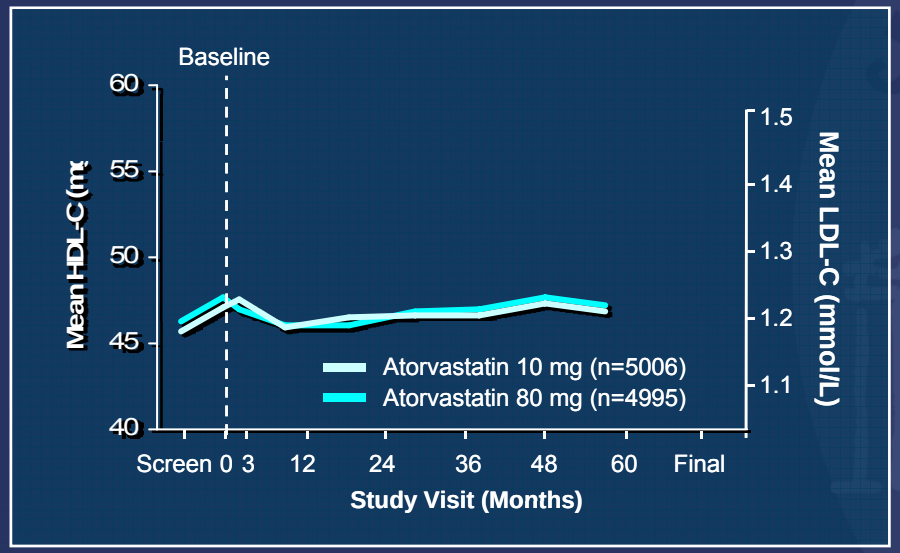
Atorvastatin is not indicated for secondary prevention of CHD in all countries

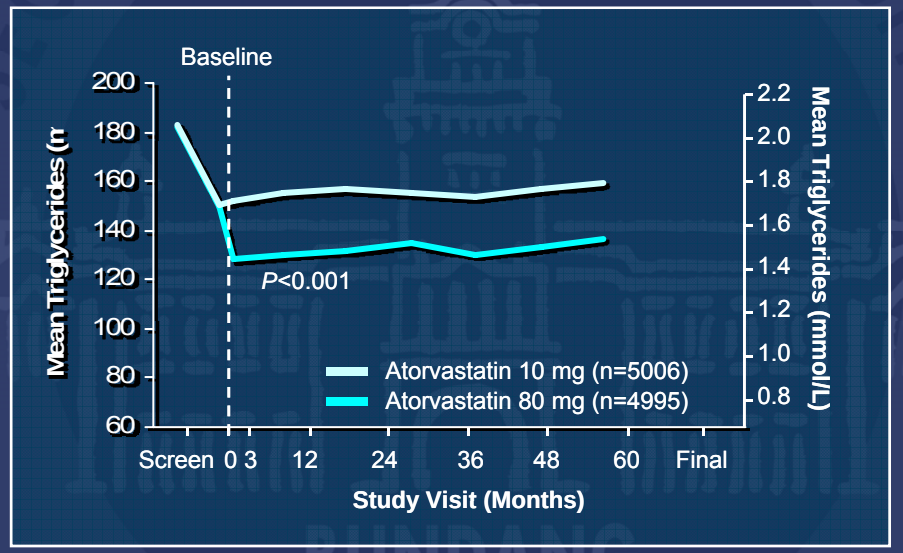
Adapted from LaRosa JC, et al. *N Engl J Med.* 2005;352: 1425-1435

TNT:
Changes in Lipid Levels by Treatment Group





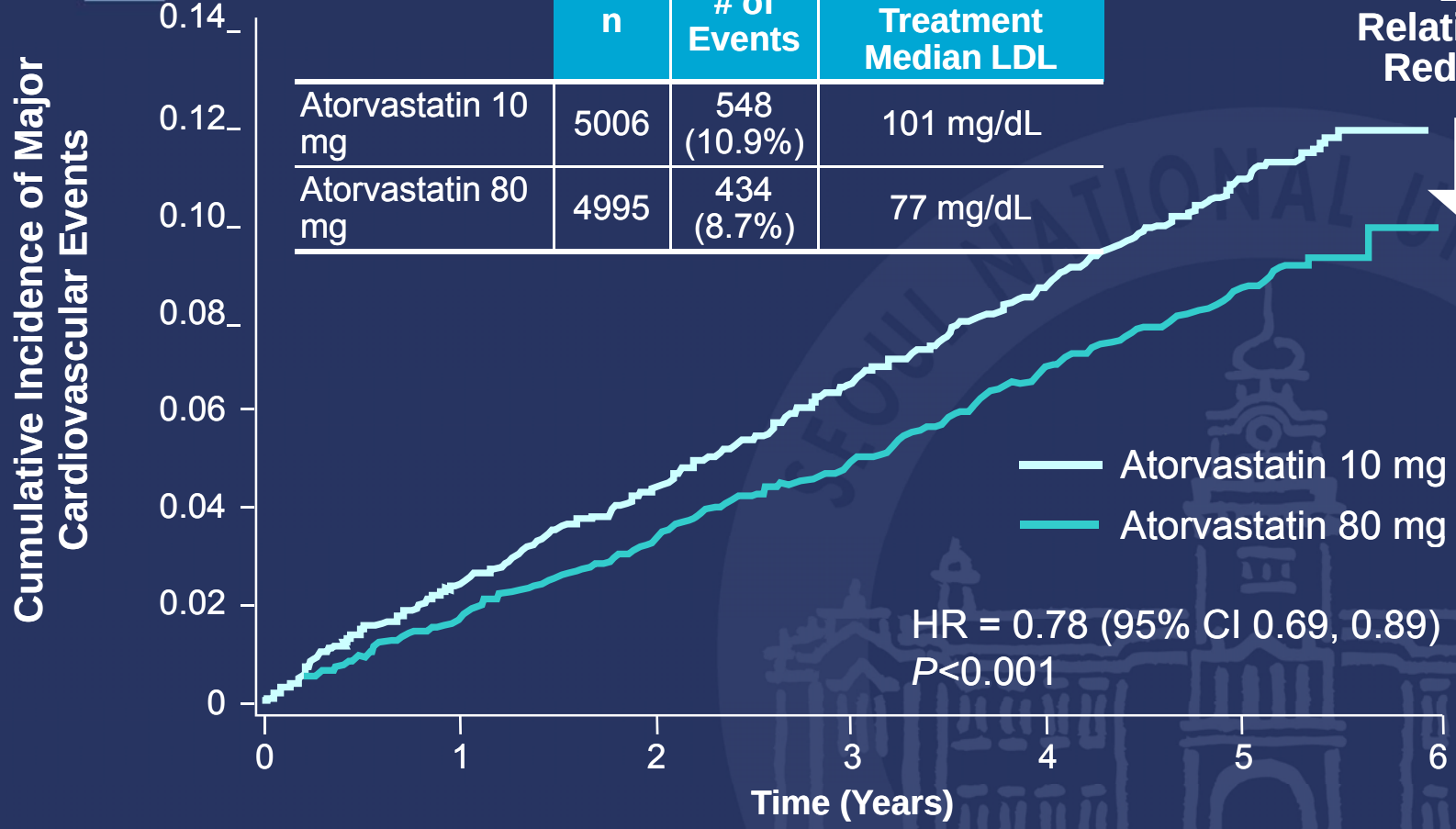




Atorvastatin is not indicated for secondary prevention of CHD in all countries

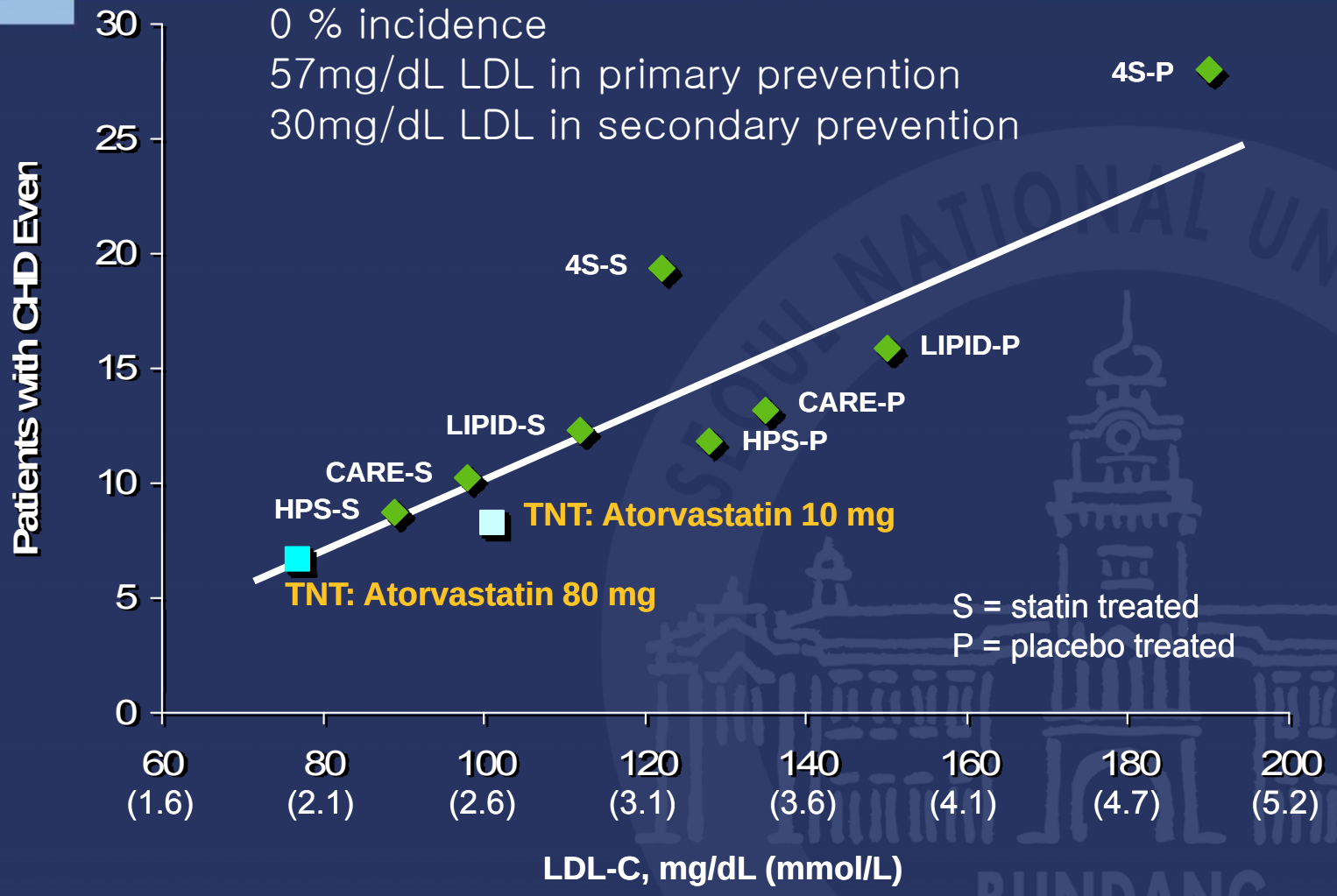
TNT: Primary Efficacy Outcome Measure: Major Cardiovascular Events*

	n	# of Events	End of Treatment Median LDL
Atorvastatin 10 mg	5006	548 (10.9%)	101 mg/dL
Atorvastatin 80 mg	4995	434 (8.7%)	77 mg/dL



*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke.

TNT: Significant Benefit in Lowering LDL-C Well Below 100 mg/dL (2.6 mmol/L) With Atorvastatin 80 mg



Summary: Consistent Clinical Benefit from Atorvastatin 80 mg at LDL-C <100 mg/dL

Study	Patients	Follow-up LDL-C mg/dL(mmol/L)		1° Endpoint RRR*(%)	P-value
		Atorvastatin	Comparator		
TNT (n=10,001)	Stable CHD	77(2.0)	101(2.6) Atorvastatin 10	**22%**	<0.001
IDEAL (n=8888)	Prior MI	81(2.1)	104(2.7) Simvastatin 20-40	**11%**	0.07
MIRACL (n=3,086)	ACS	72(1.9)	135(3.5) Placebo	**16%**	0.048
PROVE-IT (m=4,162)	ACS	62(1.6)	95(2.5) Pravastatin 40	**16%**	0.005

Summary

- Cardiovascular disease is a major global health issue and CHD is associated with high direct and indirect costs
- The evidences of outcome failure
  - WHI showed combined postmenopausal hormones therapy should not be initiated or continued for the primary prevention of CHD.
  - ILLUMINATE proved Torcetrapib therapy resulted in an increased risk of mortality and morbidity of unknown mechanism despite favorable effect on lipid profiles.
- The evidences of outcome success
  - 4S and HPS proved secondary prevention with statins could lower mortality and CV events
  - TNT showed the benefits of more intensive therapy lowering LDL-C well below 100 mg/dL (2.6 mmol/L) in stable CHD patients

Summary of EBM in Cardiovascular Medicine

- EBM is the integration of clinical expertise, patient values, and the best evidence into the decision making process for patient care.
- The evidence, by itself, does not make a decision for you, but it can help support the patient care process.
- The full integration of these three components into clinical decisions enhances the opportunity for optimal clinical outcomes and quality of life.