

Statin and Beyond

The Journey Continue

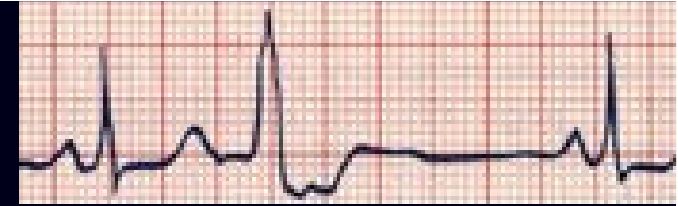


*Overview of The
Current Thinking*

울산의대
서울아산병원
심장내과
이철환

PVC Therapy

Milestone of EBM



Say no, lab markers!

Medical practice is changing!

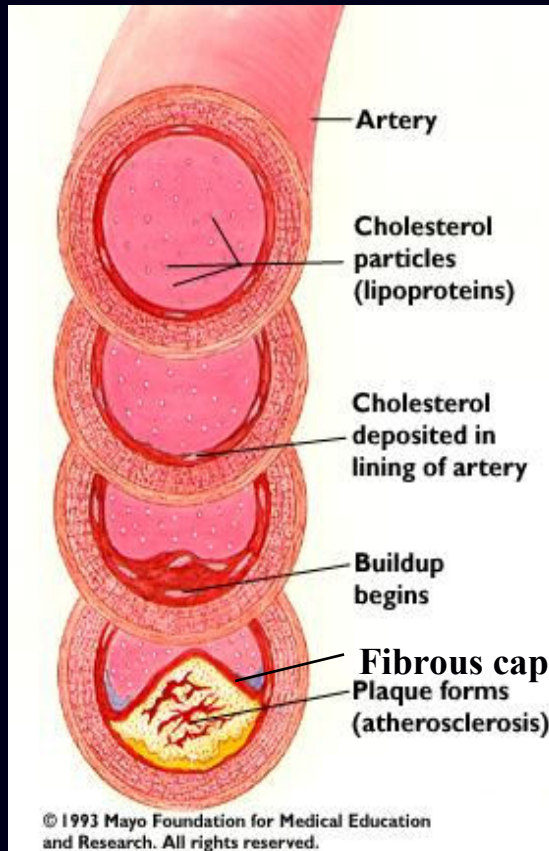
RCT: Foundation for evidence based medicine

In 1960, the **randomized clinical trial (RCT)** was an oddity.

It is now accepted that **virtually no drugs and devices can enter clinical practice without clinical trials.**

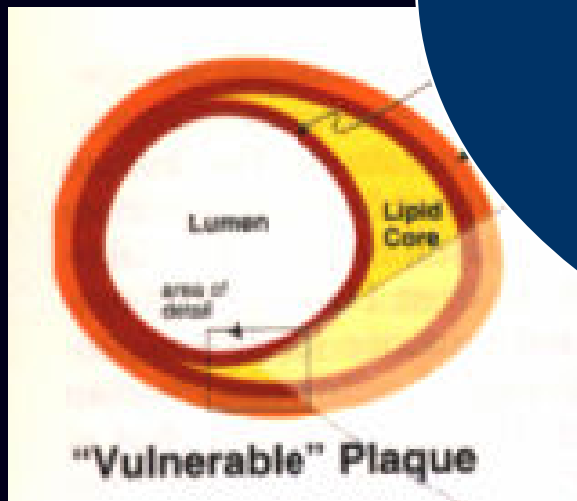
Atherosclerosis

Chronic immuno-inflammatory disease



HYPERLINKED GO CATEGORY	TOTAL GENES	CHANGED GENES	P-Value	FALSE DISCOVERY RATE
GO:0002376_immune_system_process	684	147	5.52E-45	0
GO:0006955_immune_response	530	127	5.97E-44	0
GO:0006952_defense_response	459	93	5.32E-26	0
GO:0050896_response_to_stimulus	1851	219	2.46E-25	0
GO:0009605_response_to_external_stimulus	506	85	2.99E-18	0
GO:0006954_inflammatory_response	255	55	6.42E-17	0
GO:0009611_response_to_wounding	351	64	1.10E-15	0
GO:0006935_chemotaxis	130	36	5.11E-15	0
GO:0042330_taxis	130	36	5.11E-15	0
GO:0007626_locomotory_behavior	161	39	4.62E-14	0
GO:0006968_cellular_defense_response	62	21	3.89E-11	0
GO:0007155_cell_adhesion	611	79	8.80E-11	0
GO:0022610_biological_adhesion	611	79	8.80E-11	0
GO:0002504_antigen_processing_and_presentation_of_pe	13	10	1.61E-10	0
GO:0042221_response_to_chemical_stimulus	386	57	3.15E-10	0
GO:0019882_antigen_processing_and_presentation	42	16	1.15E-09	0
GO:0007610_behavior	259	42	4.57E-09	0
GO:0030595_leukocyte_chemotaxis	18	10	1.86E-08	0
GO:0045321_leukocyte_activation	160	30	2.74E-08	0
GO:0001775_cell_activation	182	32	4.67E-08	0
GO:0001816_cytokine_production	94	21	1.58E-07	0
GO:0002250_adaptive_immune_response	72	18	2.00E-07	0
GO:0002460_adaptive_immune_response_based_on_soma	72	18	2.00E-07	0
GO:0007154_cell_communication	2977	240	2.03E-07	0
GO:0007165_signal_transduction	2678	220	2.06E-07	0
GO:0050900_leukocyte_migration	22	10	2.20E-07	0
GO:0030593_neutrophil_chemotaxis	10	7	3.10E-07	0
GO:0002443_leukocyte_mediated_immunity	71	17	8.46E-07	0
GO:0046649_lymphocyte_activation	139	25	8.94E-07	0
GO:0042108_positive_regulation_of_cytokine_biosynthetic	44	13	1.28E-06	0
GO:0042089_cytokine_biosynthetic_process	69	16	2.80E-06	0
GO:0045727_positive_regulation_of_protein_biosynthetic_	54	14	2.85E-06	0
GO:0042107_cytokine_metabolic_process	70	16	3.43E-06	0

Act Locally, Think Globally !



Once a coronary disease,
Permanent coronary disease!



Secondary prevention

Where Should We Go?

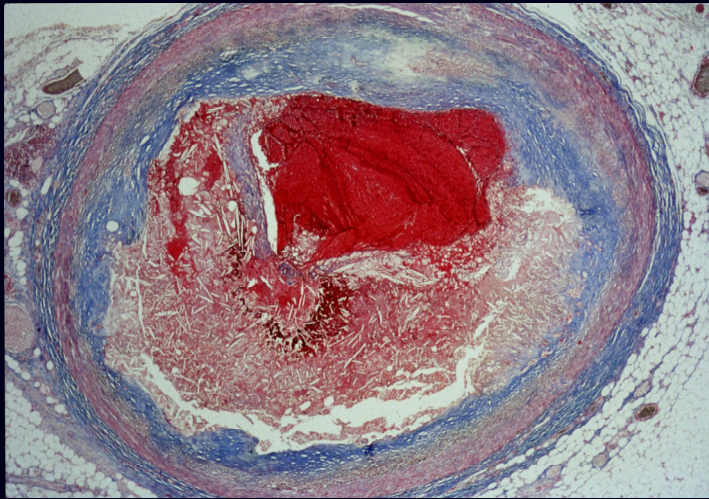
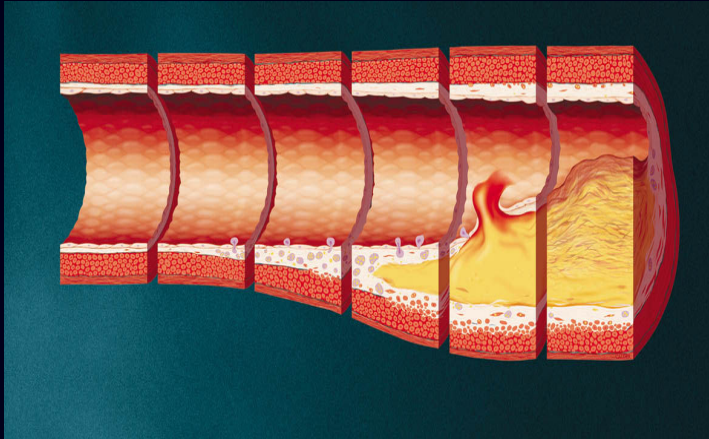
“21st Cardiovascular Health Care”

Prevention of acute coronary events
must be the primary goal.

Eugene Braunwald

You can't find it.
You can treat it.

Beyond the Culprit Lesion



Vulnerable Plaque

- Lack of luminal obstruction does not mean a lack of atherosclerosis.
- Vulnerable plaque: rupture or thrombosis-prone plaque
- It is important to find and treat vulnerable plaque for prevention of heart attack.

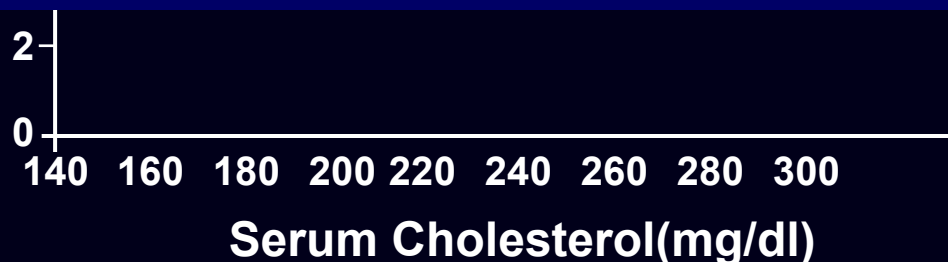
Theoretical promise does not necessary translate into clinical outcome benefits.

Cholesterol as a Disease

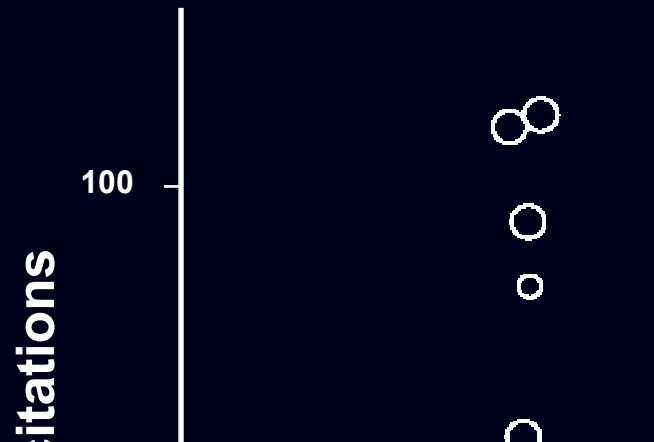


Prove What?

Not lab. endpoints (hypothesis)
But health outcome (confirmation)



The initial road to cholesterol treatments was rather bumpy.



Cholesterol Lowering Trials before Statin Era

Red Flag !

for Cholesterol Hypothesis

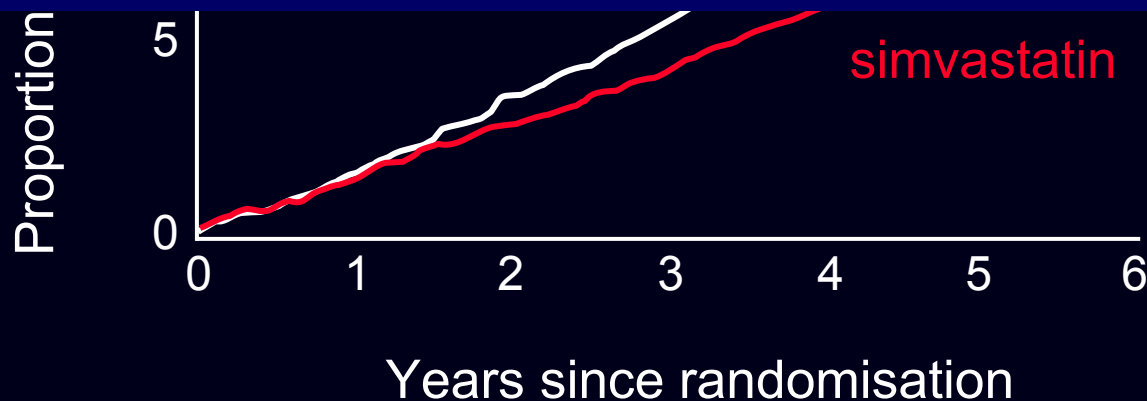
Unsupportive trials Supportive trials

A quantum advance
in atherosclerosis

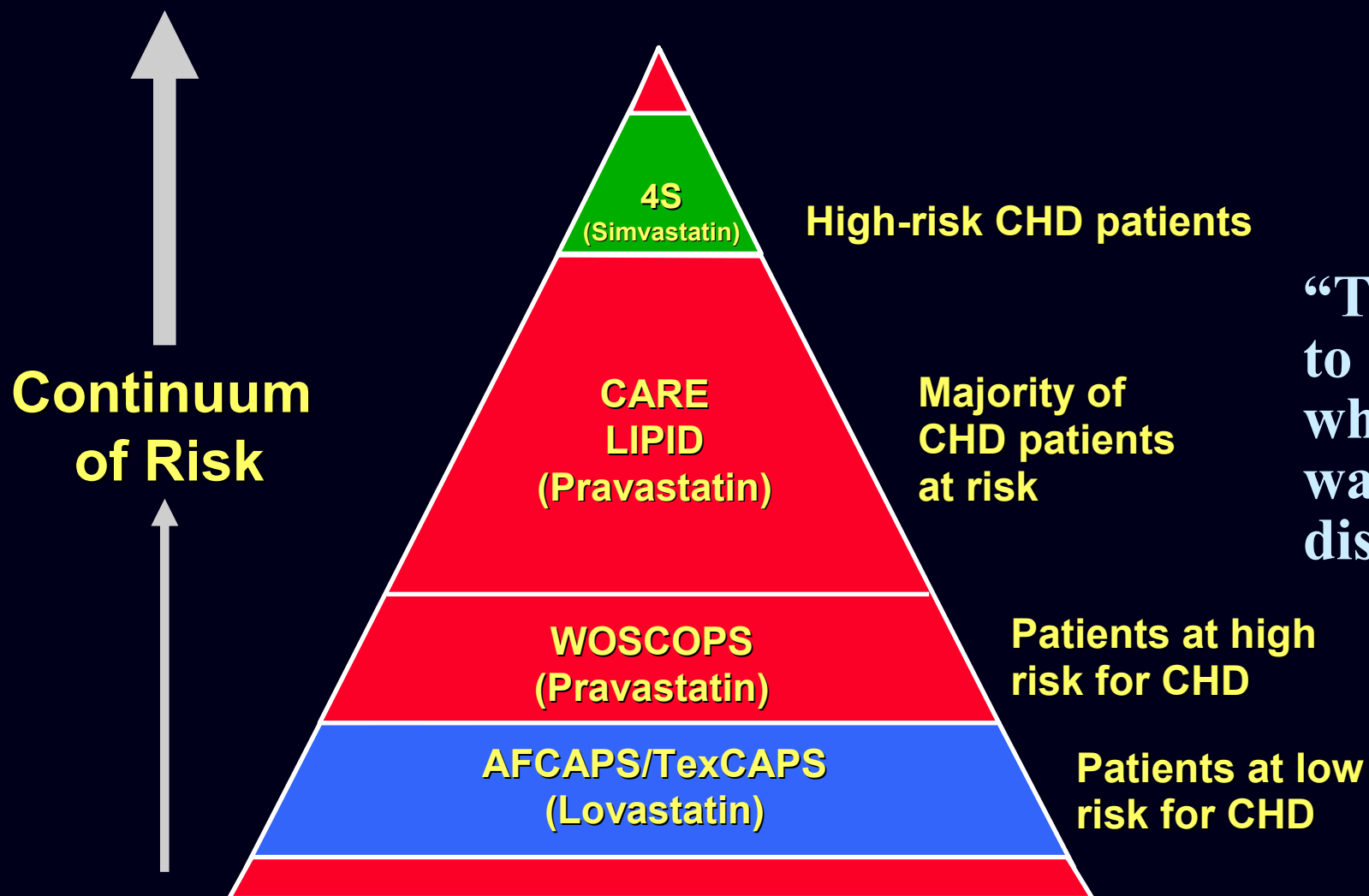
Atherosclerosis Revolution 4S Study

Miracle Drug !

The end of cholesterol controversy



The First Wave of Statin Trials



“The statins are to atherosclerosis what penicillin was to infectious disease”

*A 'yes or no' approach
is not valid in HPS era.*

Heart Protection Study

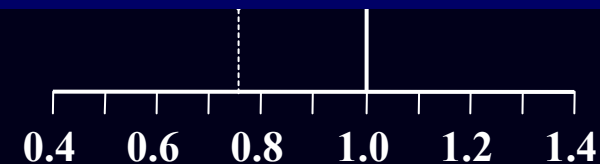
Statins are the new aspirin.

Baseline	STATIN	PLACEBO	Risk ratio and 95% CI	
Feature	(10269)	(10267)	STATIN better	STATIN worse

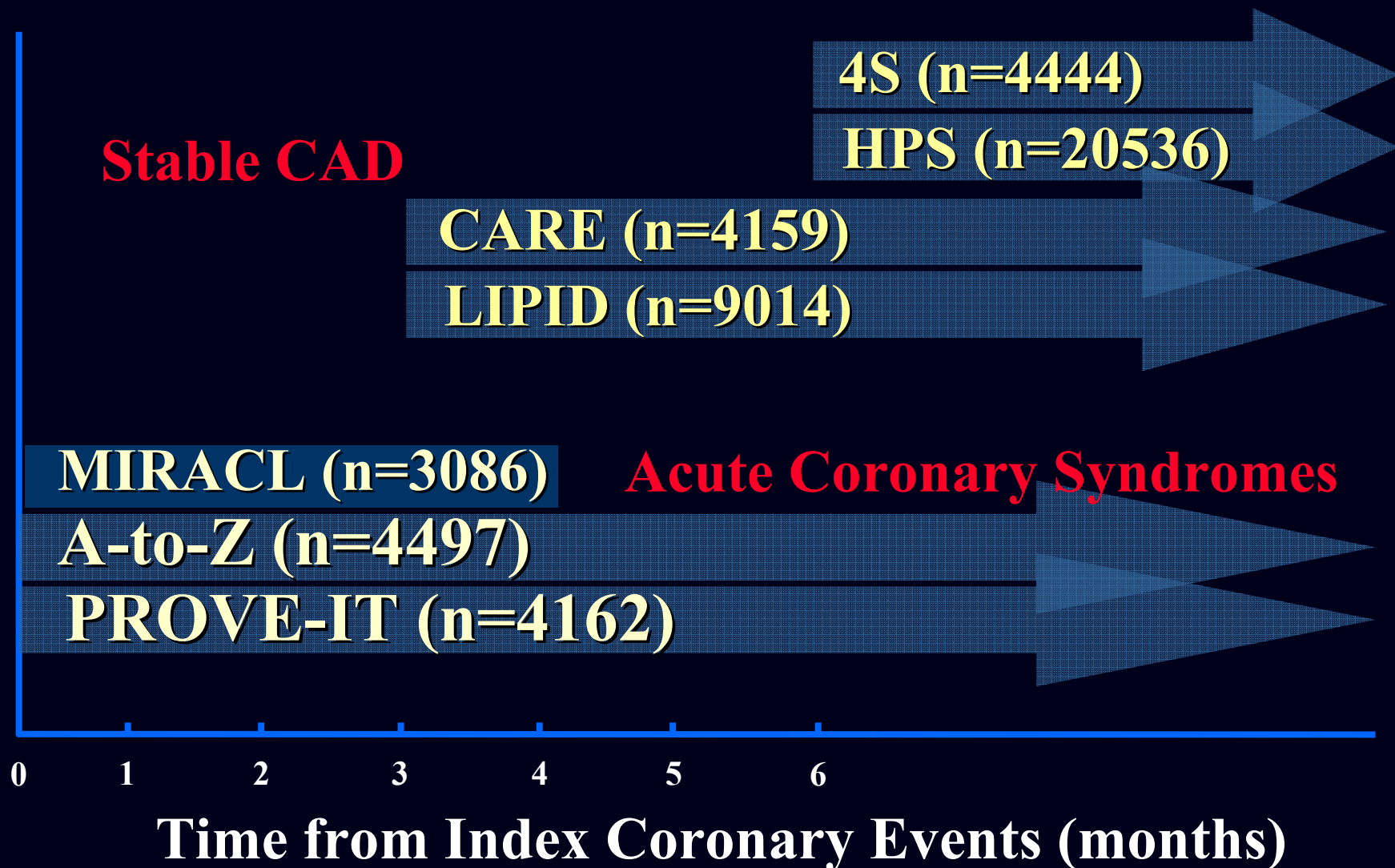
**Every patients with atherosclerosis has
LDL-C that is too high for him or her.**

(19.9%)

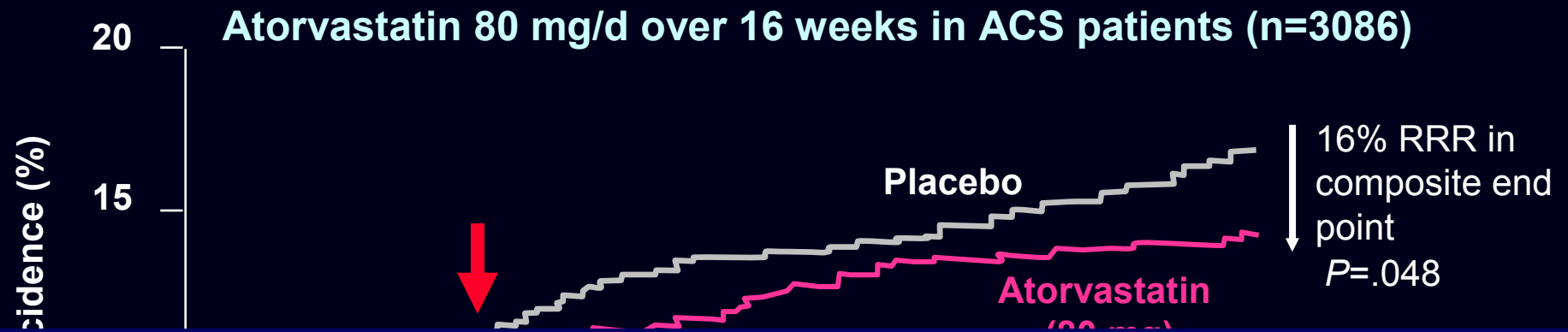
(25.4%)



Statin Trials in CAD



MIRACL in ACS

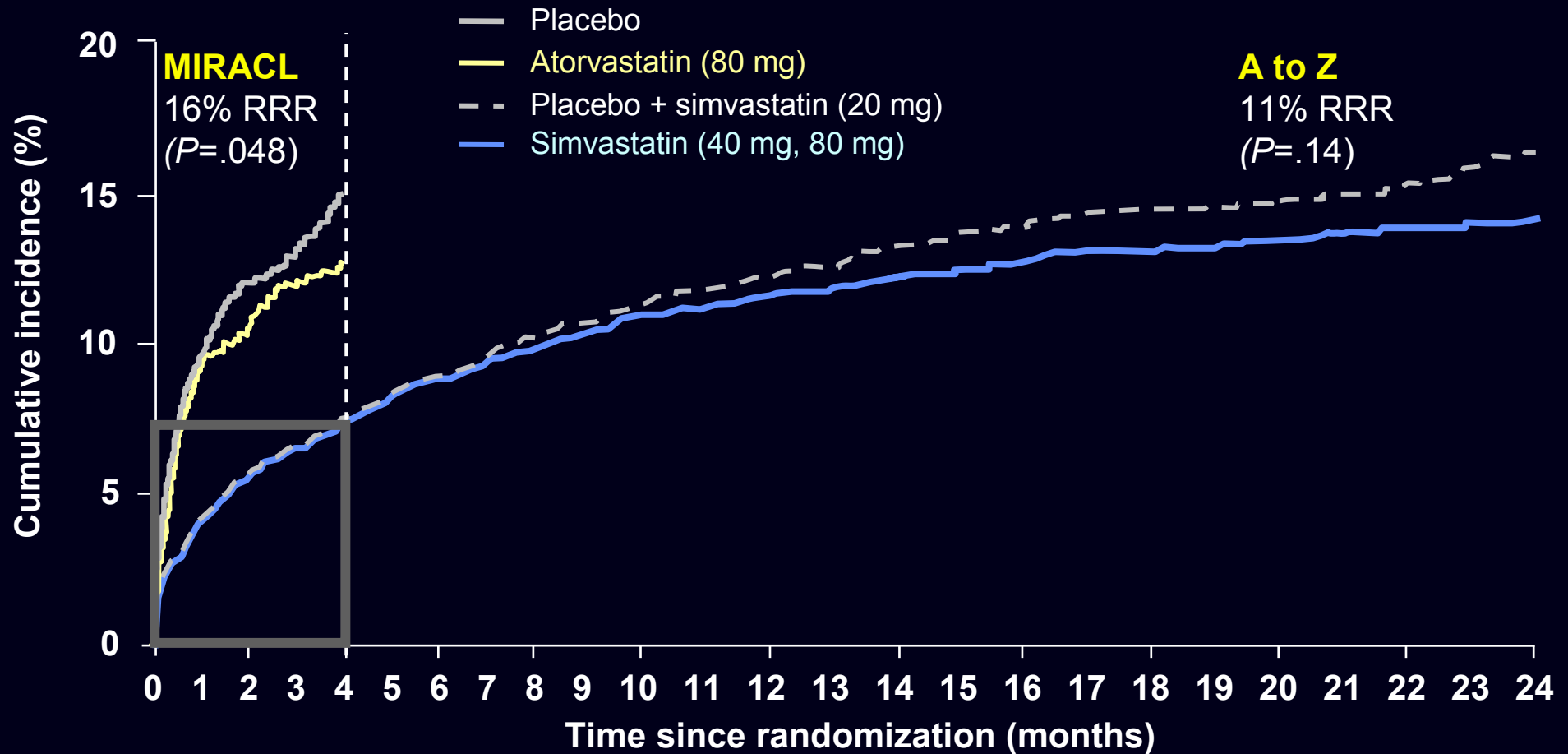


Early inflammatory phase
Statin heals the plaque!

Time since randomization (weeks)

MIRACL vs. A-to-Z in ACS

Occurrence of primary composite end point*



Patient populations differed between studies.

*Primary end point in MIRACL was death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia requiring rehospitalization; primary end point in A to Z was the composite of CV death, nonfatal MI, readmission for ACS, and stroke.

Schwartz GG et al. *JAMA*. 2001;285:1711-1718; de Lemos JA et al. *JAMA*. 2004;292:1307-1316.

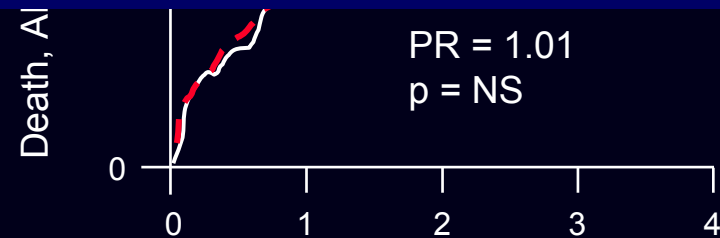
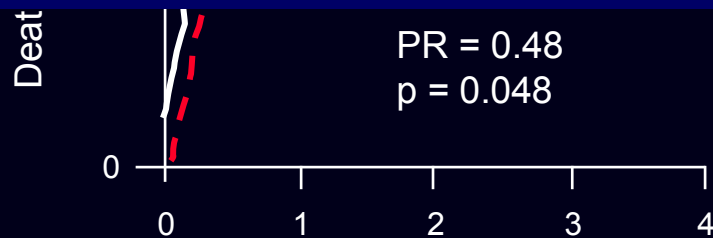
MIRACL vs. A-to-Z in ACS

MIRACL

A-to-Z

Speed of Action!

The early benefits of statin therapy are not working through LDL lowering.

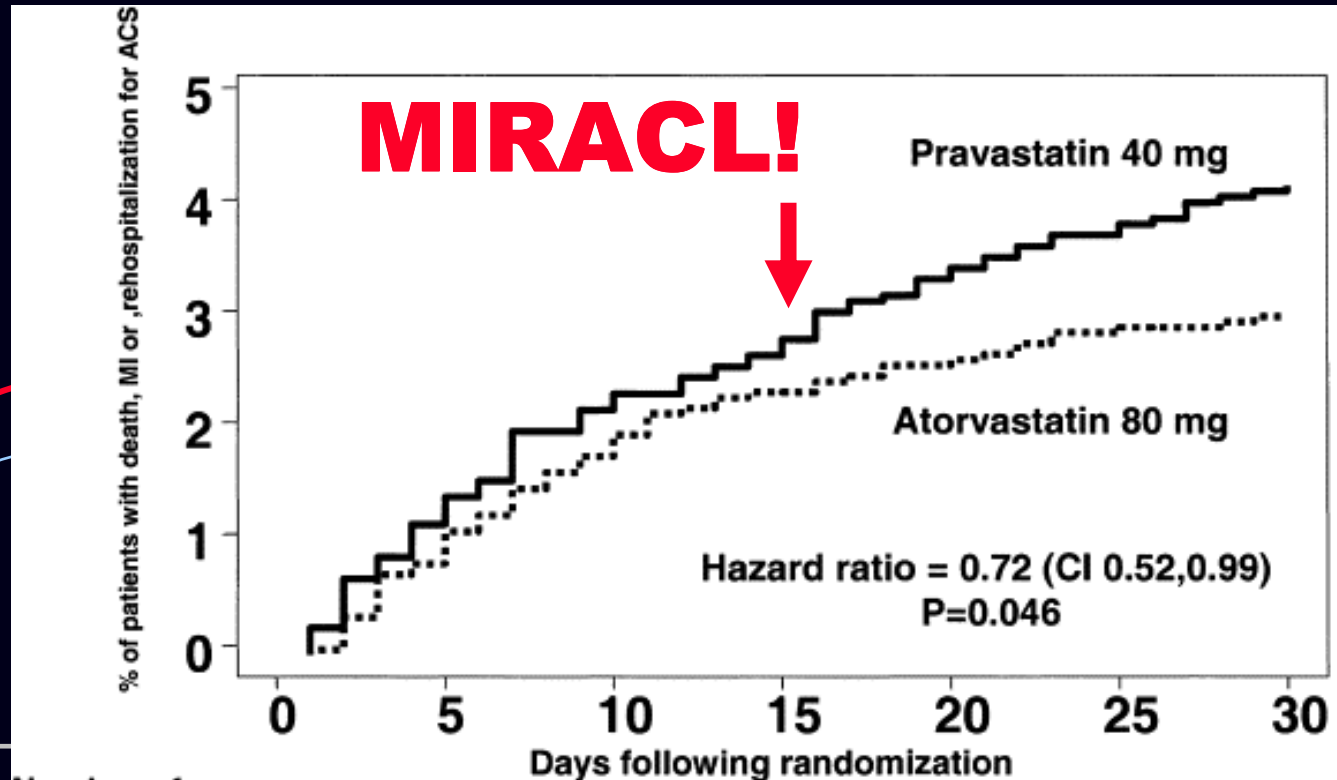
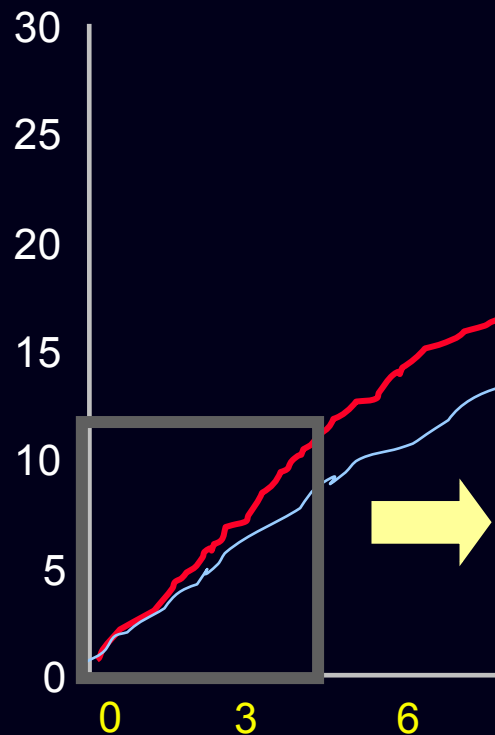


Δ LDL-C, mg/dl	63 vs. 62
Δ CRP, %	34 vs. 17

*The only head-to-head
comparison study*

PROVE-IT

% Patients with Event*



Number of Patients at risk	0	5	10	15	20	25	30	
Pravastatin	2063	2025	2002	1988	1969	1958	1943	Pravastatin
Atorvastatin	2099	2064	2042	2026	2015	2007	1997	Atorvastatin

- N=4,162 ACS (early invasive-3/4; multiple medications)
- Among patients who have recently had an ACS, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen.

Recurrent Events after ACS



Time is life!

**A longer time to benefit results
in a number of days of unprotected risk.**

Days after presentation

Days after presentation

Fields of Statins

A Time for Change in 1° Prevention

ASCOT (Hypertension)

CARDS (Diabetes)

The Dynamics of Statins

not a drug for high cholesterol
but rather **for high risk patients**
(**>age 40 and hypertension or DM**)

A New Weapon **Statin Fever** **for Stroke Prevention**

Evidence over a wide range of population

Primary prevention (atorvastatin 10 mg)


ASCOT (hypertension): 27% reduction

CARDS (diabetes): 48% reduction

Secondary prevention (atorvastatin 80 mg)

SPARCL: 16% reduction on top of standard
treatment (aspirin 94% and anti-HT 69%)

Getting clear...



Landmark Statin Trials

Evidence beyond speculation

Statin, Anti-atherosclerotic Drug!

A statin is recommended for all patients with established atherosclerotic disease, in most people with DM, and others at high risk of developing cardiovascular disease. JBC2 (Heart 2005;91:1-52)

anyone who has a risk of $\geq 15\%$ of developing CVD in 10 years, regardless of their lipid concentrations.

Things May Not Be as They Seem

Here today, gone tomorrow!

A series of preventable drug disasters

Therapy

Clinical Trials

Results

Imagine a world without EBM!

“Wonderful placebo effects based on mysticism”

bruise therapy
needle puncture
herb drugs, ...

**The highest priority must be placed on
improving outcomes rather than lab findings.**

Improves the lab findings,
but harms the patients

The Greater Truth:
Just a hollow weapon

Summary of the Fibrate Trials

	WHO	CDP	HHS	VA-HIT	BIP	LEADER	FIELD
Number	15,745	1,103	4,081	2,560	3,090	1,568	9,775
Population	1°	2°	1°	2°	2°	2°	1°
Drug	C	C	G	G	B	B	F
CHD events	-20	-9	-34	-22	-9	-19	-11
Mortality	30	-4	7	-11	0.5	3	11

B: bezafibrate, C: clofibrate, F: fenofibrate, G: gemfibrozil

We have to think why we treat diabetes patients. It is **not to lower a number for triglyceride in a test tube, but to reduce complications!**

If we don't know the benefits,
any risk is not worthwhile!

Think First, Evidence or Impression!

Level A evidence

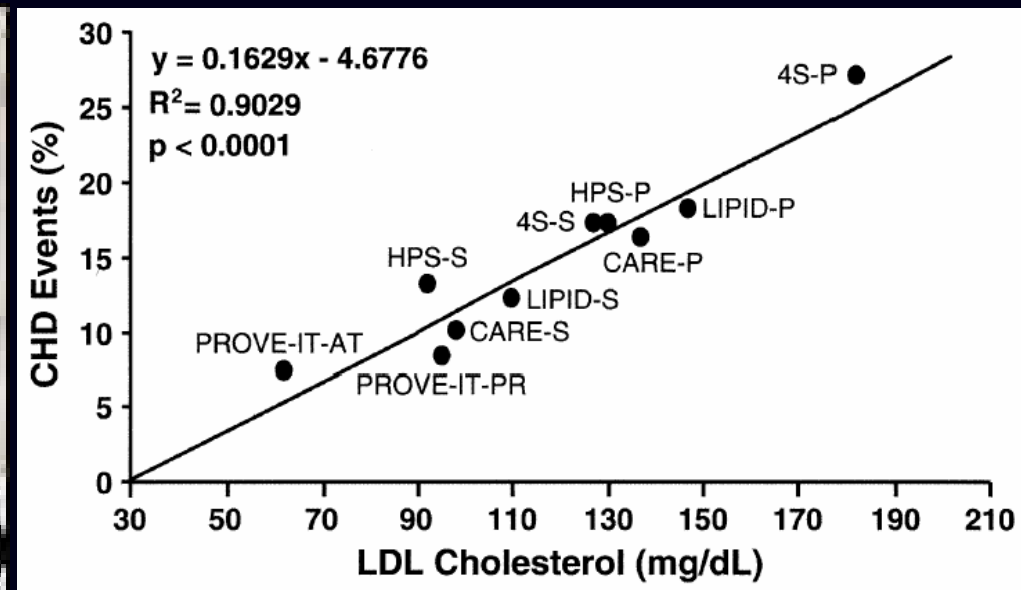
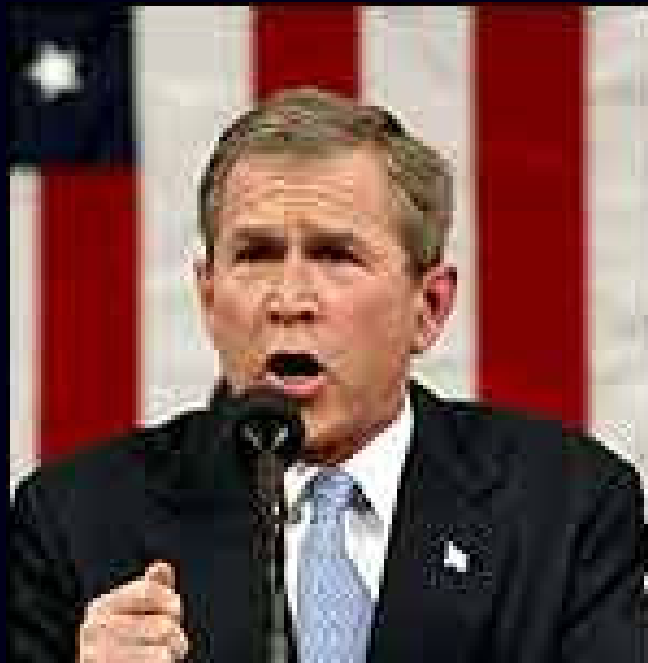
Believe in clinical **outcome data**
rather than surrogate markers!

漢藥, **Show us outcome data!**

Beyond statin euphoria
All thirsty patients' hope

Cholesterol Hypothesis

Axis of Evil, War Against The Cholesterol



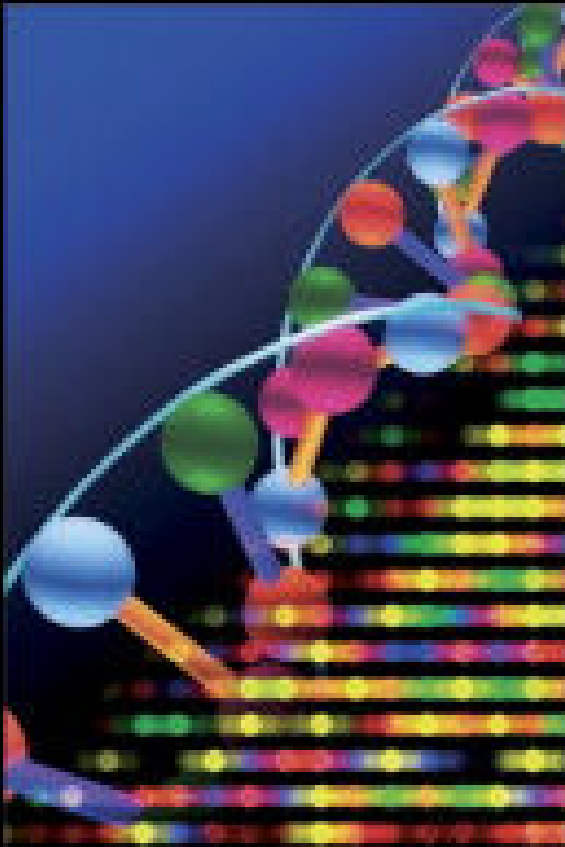
A new wave for therapeutic approaches

Combinations (**statin ⊕ others**) will be the future that may improve on the current standard of care.

Much heat, little light

Big step for science, small step for medicine

Beyond Statin,
The journey continue...



HGP completed, 2003

HDL-targeted therapy
Anti-inflammation
Immune modulation
New targets, etc

Torcetrapib lost a light just before illumination

Lessons from the tocetrapib's failure
『declare a moratorium until evidence!』

The bar to jump over now has gotten a lot higher.

Surrogate outcomes allow smaller, shorter & cheaper trials, but the apparent benefits may be a mirage!

New drugs won't get approval from the FDA unless they show cardiac-event reduction.

Industry Paradox

Sources of Funding

Academics may be losing control of the research agenda and of clinical research at large.

Industry funds an increasing proportion of medical research, especially randomised controlled trials.

*Less used than we believed.
Statin in everyday practice!*

감사합니다.

**From heart attack to stroke
Prevention is better than cure!**

Primary Prevention Era

여러분의 심장병
지킴이가 되겠습니다.

Stop and think about evidence!

앞선 의술, 더 큰 사랑



서울아산병원
Asan Medical Center