Jupiter

Gateway to Vascular Health

Insights

Challenging
The Dogma

울산의대
서울아산병원
심장병원
심장내과
이철환

[100세 쇼크 축복인가 재앙인가] '현대판 불로초(장수약물)' 실마리는 잡았다

박상철·서울대 노화고령사회연구소장·생화학교실 교수

항생제 '댑슨' 장기복용 한센병 남자 환자들, 평균보다 7~8세 장수
장수 효과 검증과정 필요… 5~6년 후 결론 나올 듯

필자가 이 약물의 효과를 발견한 것은 우연한 계기였다. 몇년 전 한센병 환자들이 모여 사는 전남 소록도를 방문했다가 머리를 때리는 듯한 발견을 하게 됐다. 70~80세 되는 한센병 환자들이 이상하다 싶을 정도로 젊게 보이는 것이었다. 기력들도 좋았다.

'장수 약물' 후보들

레스베라트롤(식물이 해충에 저항하는 성분)	탈락	효과가 일관되게 나오지 않음
심바스타틴(콜레스테롤 강하제)	탈락 임박	효과 불확실
라파마이신(면역억제제·항암제 성분)	실험 진행 중	동물실험에서 수명 최대 38% 연장
댑슨(한센병 치료 항생제)	실험 진행 중	동물실험에서 수명 30% 연장

Causes of Death Worldwide, 2007

2007년
한국인 5대 사망원인

Chart (bar graph):
- y-axis: 0, 5, 10, 15, 20, 25, 30
- x-axis categories: 암, 뇌혈관, 심장질환, 당뇨, 교통사고
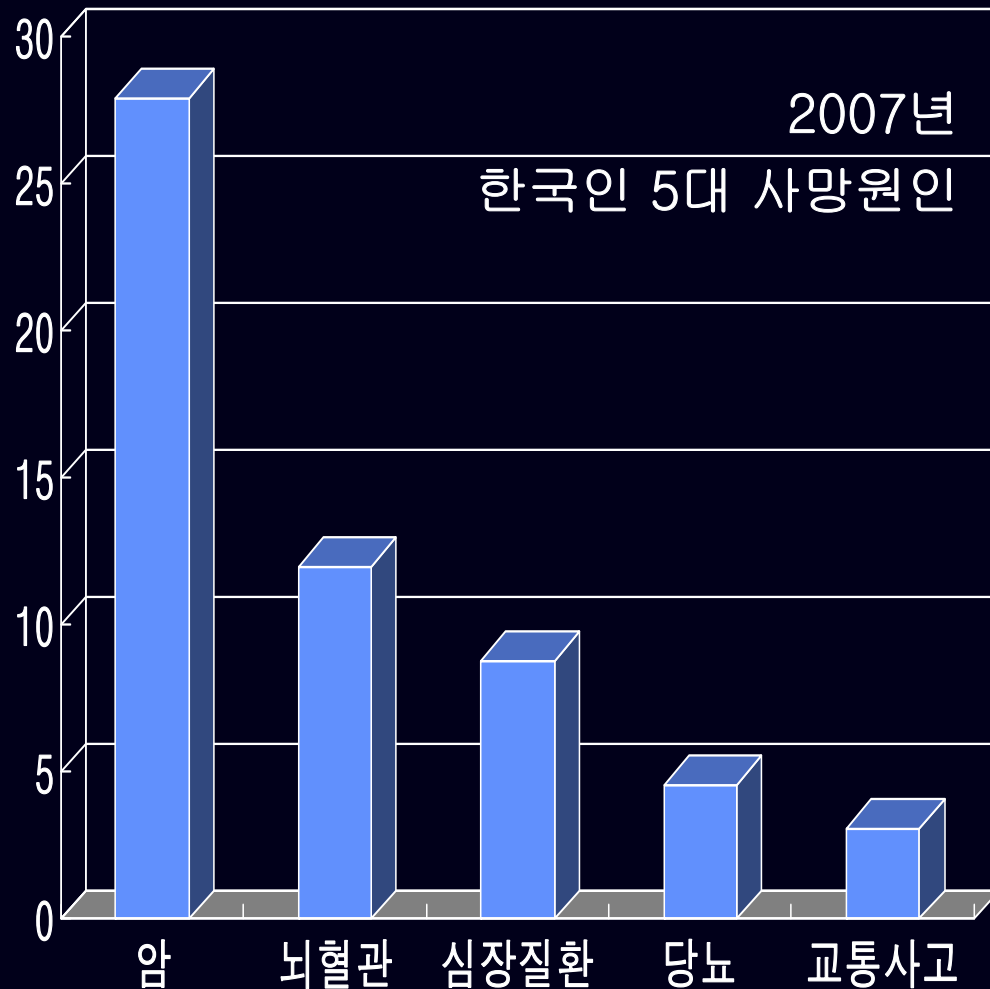
Top 10 Causes of Death - US

1. Diseases of Heart 28.5%
2. Malignant Neoplasms (cancer) 22.8%
3. Cerebrovascular Diseases (stroke) 6.7%
4. Chronic Lower Respiratory Diseases 5.1%
5. Accidents 4.4%
   - Motor Vehicle Traffic Accidents (41% of all accidents)
   - Poisoning (16% of all accidents)
   - Fall (15% of all accidents)
6. Diabetes Mellitus 3.0%
7. Influenza and Pneumonia 2.7%
8. Alzheimer's Disease 2.4%
9. Nephritis, Nephrotic Syndrome and Nephrosis (kidney diseases) 1.7%
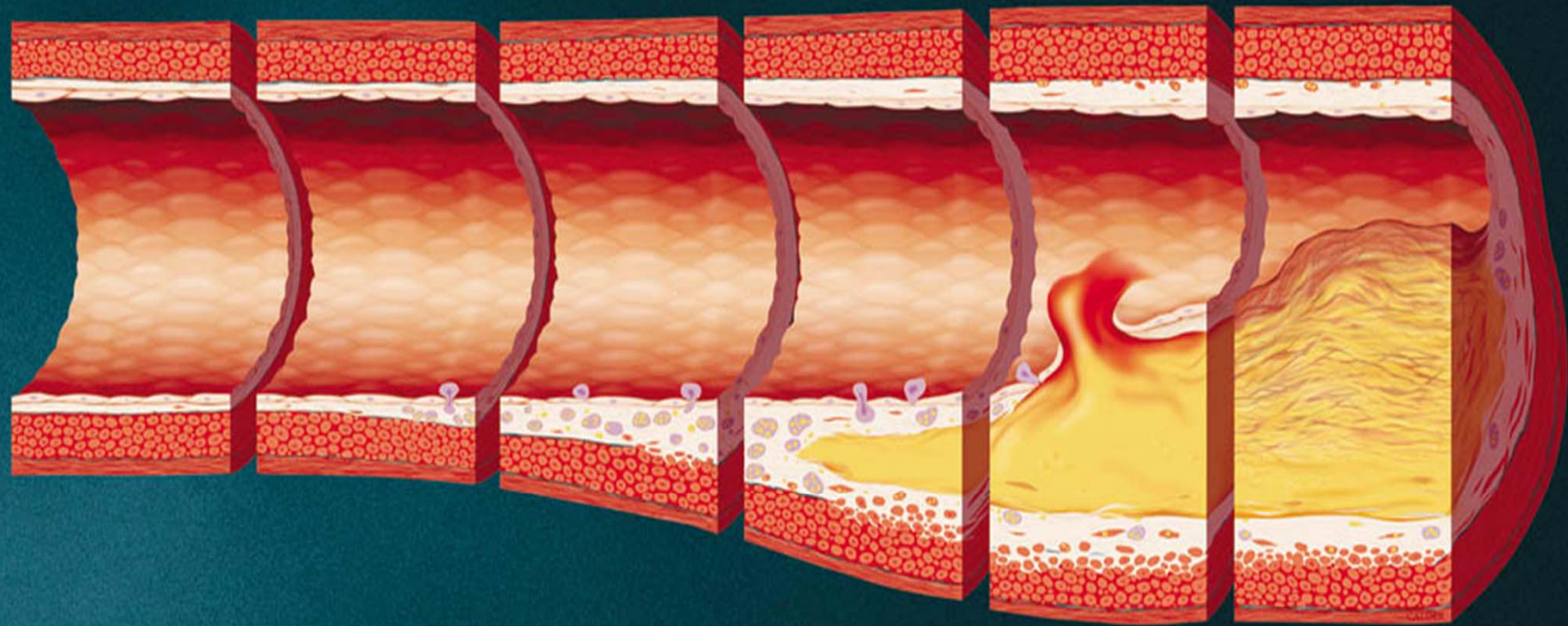10. Septicemia (blood poisoning) 1.4%

All Others 21.4%

Not just a condition found in modern humans

RESEARCH LETTER

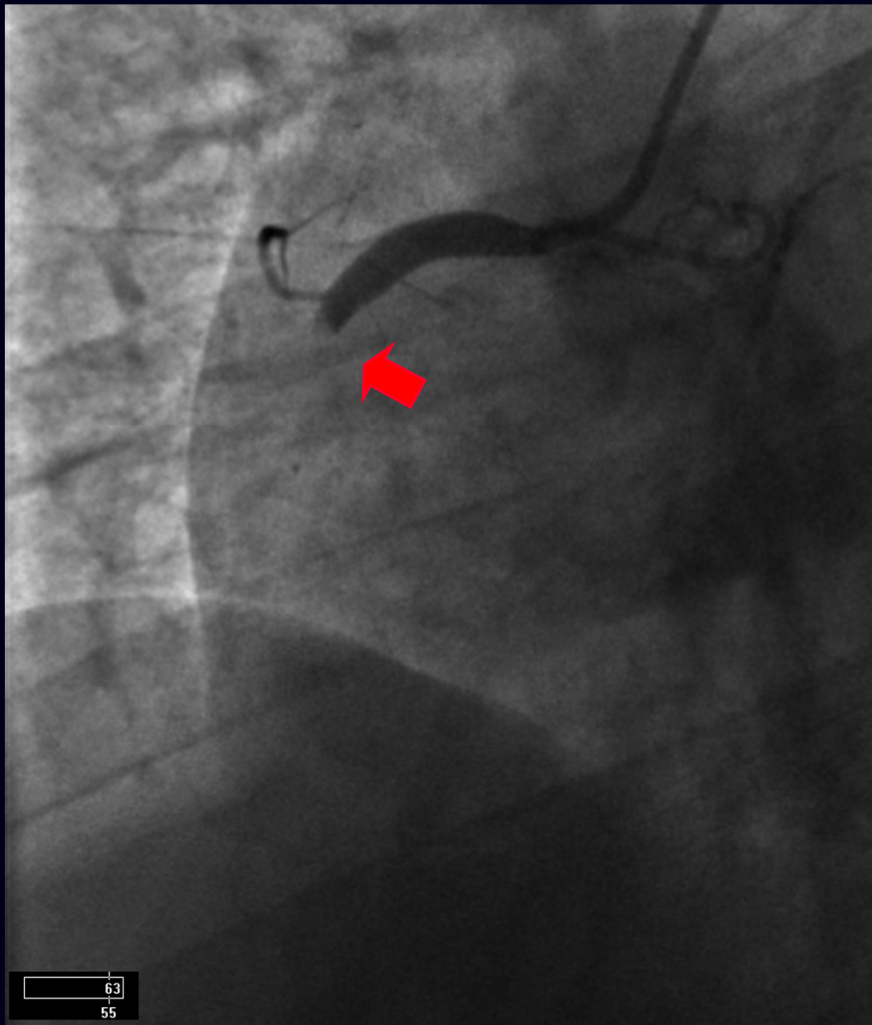**Computed Tomographic Assessment of Atherosclerosis in Ancient Egyptian Mummies**

JAMA®

Abscess rupture: natural drainage?

26/M
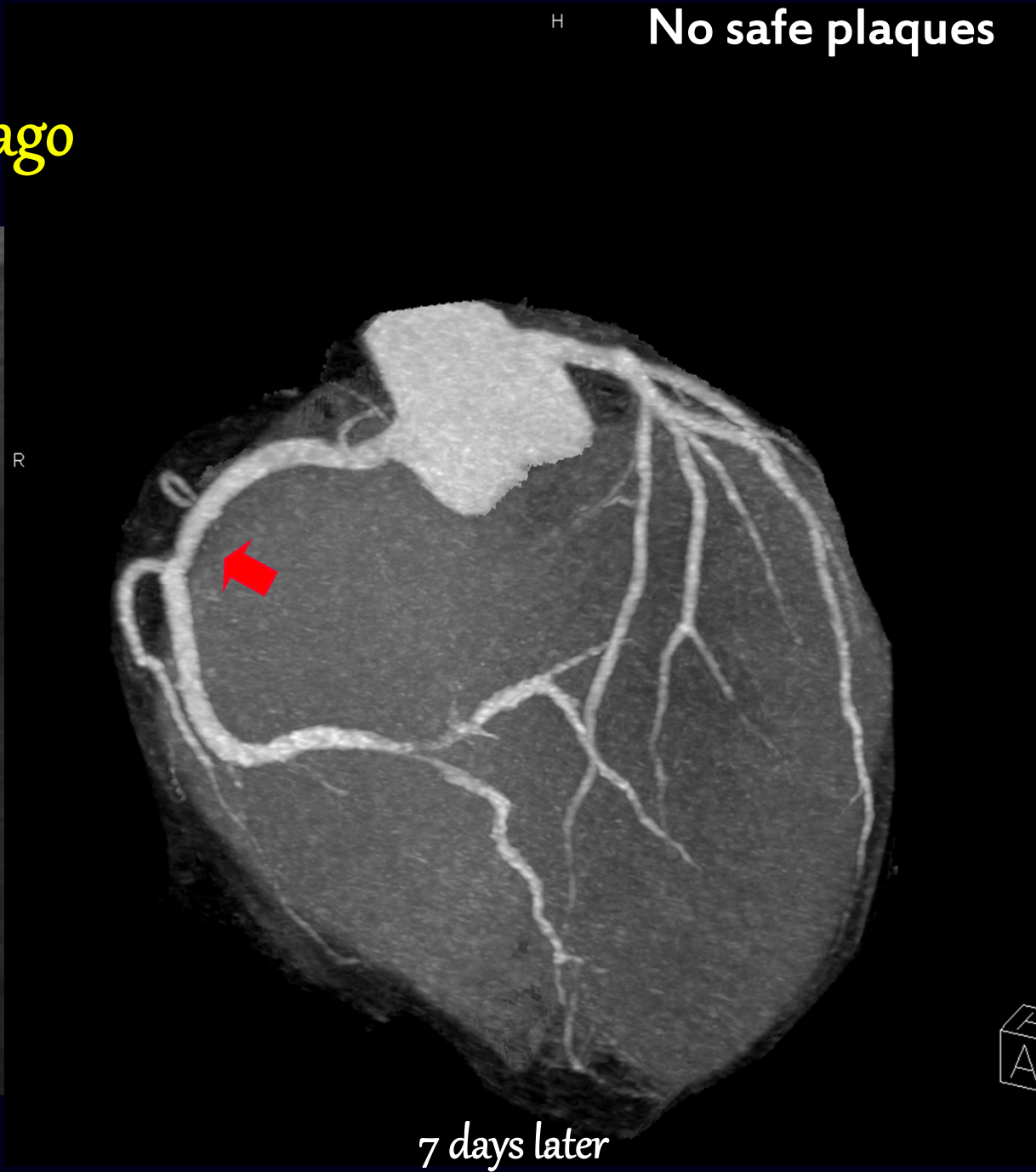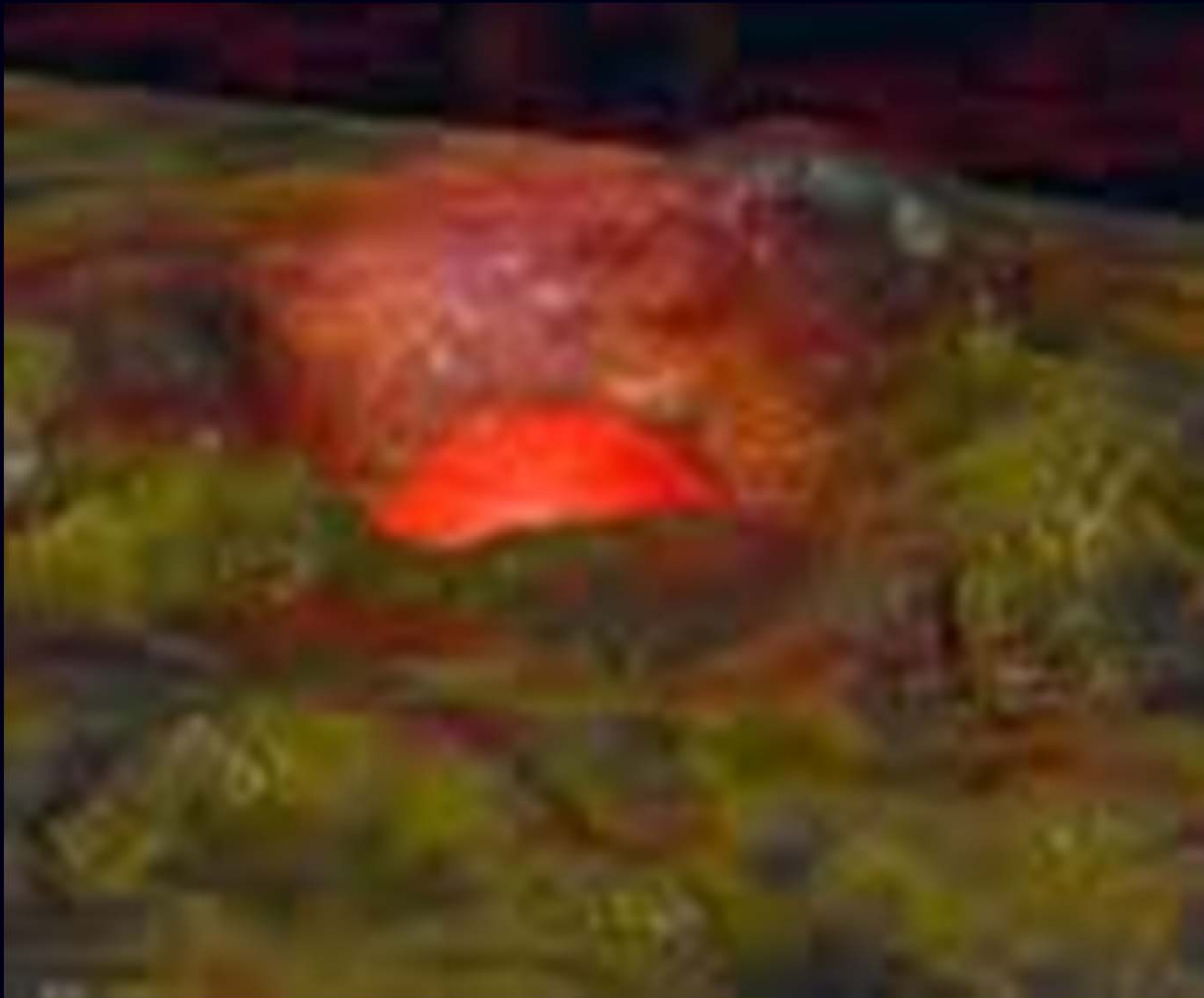Prolonged chest chain, 7 days ago

No safe plaques

3 day later

7 days later

Look at Yellow Stone

If VP can be detected accurately and effective therapeutic intervention initiated, many CV events can be prevented.

Vulnerable plaques
- uncertain future events
- silent plaque rupture
- not interchangeable among vascular beds
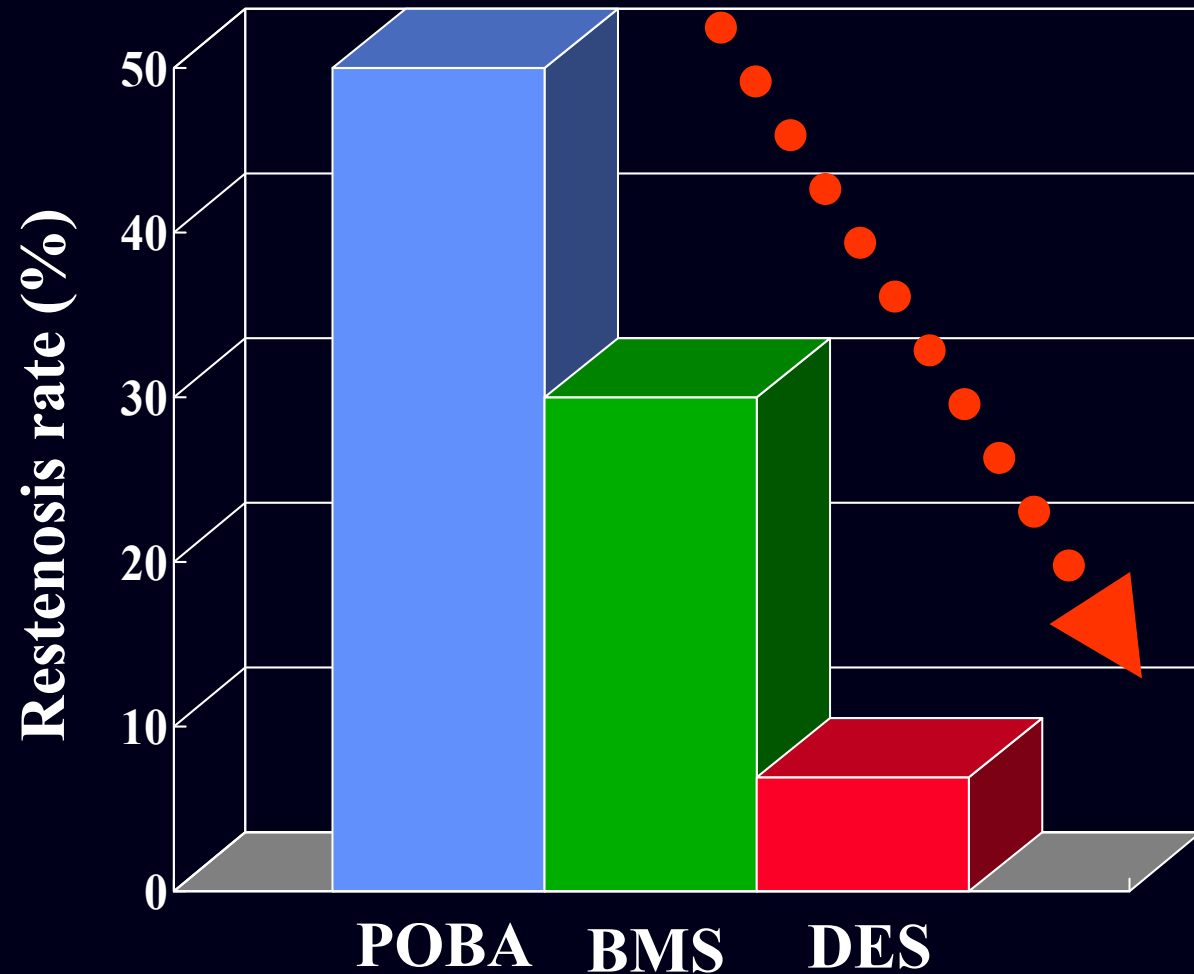**- no safe plaque!**

將欲弱之 必姑強之
將欲去之 必姑與之

Today: 22 CE-certified DES

CE 0086

Cypher™

TAXUS

ENDEAVOR

Endeavor Resolute Stent

Xience™ V

Promus™

AXXION™ DES

translumina®
YUKON™ Choice^DES
Drug Eluting Stent

PICO^Elite
Paclitaxel-Eluting Coronary Stent

amg International

JANUS
Tacrolimus eluting Carbostent™

Eurocor®
TAXCOR®
Paclitaxel-Eluting
Coronary Stent System

Coroflex PLEASE

Infinnium™
PACLITAXEL - ELUTING STENT

Dexamet

APOLLO
Paclitaxel Eluting
Coronary Stent

euca TAX
Paclitaxel Eluting Coronary
Stentsystem

Firebird冠脉涂膜支架
MicroPort

NOBORI™

BioMatrix®
DRUG ELUTING CORONARY STENT SYSTEM
Uncompromised Patient Benefit
through the Combination of Safety and Efficacy

Heart Attack and Brain Attack

Fatal thrombus

Plaque rupture site

Collagenous fibrous cap

Thrombogenic lipid core

"Axis of Evil"

- Arterial wall side
  - LDL cholesterol
  - inflammation

- Arterial lumen side
  - platelet
  - coagulation

Aspirin in Primary Prevention
Individualised Approach

Aspirin's Myth Bleeding Tax !

Antithrombotic Trialists' Collaboration
Lancet 2009;373:1849

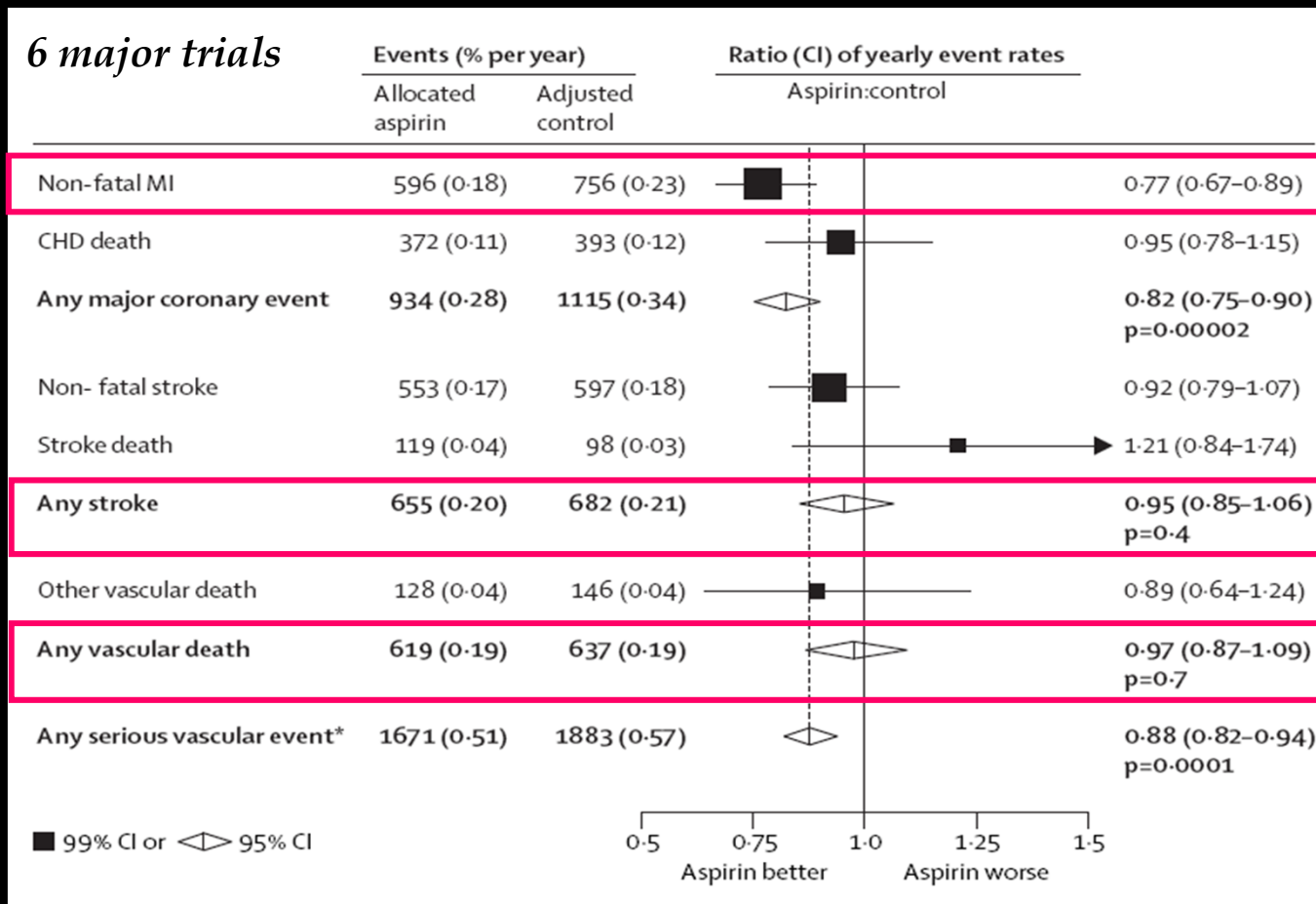| 6 major trials	Events (% per year)		Ratio (CI) of yearly event rates Aspirin:control	
	Allocated aspirin	Adjusted control		
Non-fatal MI	596 (0·18)	756 (0·23)		0·77 (0·67–0·89)
CHD death	372 (0·11)	393 (0·12)		0·95 (0·78–1·15)
Any major coronary event	934 (0·28)	1115 (0·34)		0·82 (0·75–0·90) p=0·00002
Non-fatal stroke	553 (0·17)	597 (0·18)		0·92 (0·79–1·07)
Stroke death	119 (0·04)	98 (0·03)		1·21 (0·84–1·74)
Any stroke	655 (0·20)	682 (0·21)		0·95 (0·85–1·06) p=0·4
Other vascular death	128 (0·04)	146 (0·04)		0·89 (0·64–1·24)
Any vascular death	619 (0·19)	637 (0·19)		0·97 (0·87–1·09) p=0·7
Any serious vascular event*	1671 (0·51)	1883 (0·57)		0·88 (0·82–0·94) p=0·0001

■ 99% CI or ◇ 95% CI

0·5 0·75 1·0 1·25 1·5
Aspirin better   Aspirin worse

- **Primary endpoints - all negative**
- **ICH 32%↑ (1.0-1.75)**
- **Major extracranial bleeding 54%↑ (1.3-1.82)**

0.06% /y ↓CV outcome
0.03% /y ↑major bleed

NICE guideline: Aspirin is not licensed for the primary prevention of vascular events. If aspirin is used in primary prevention, the balance of benefits & risks should be considered for each individual.
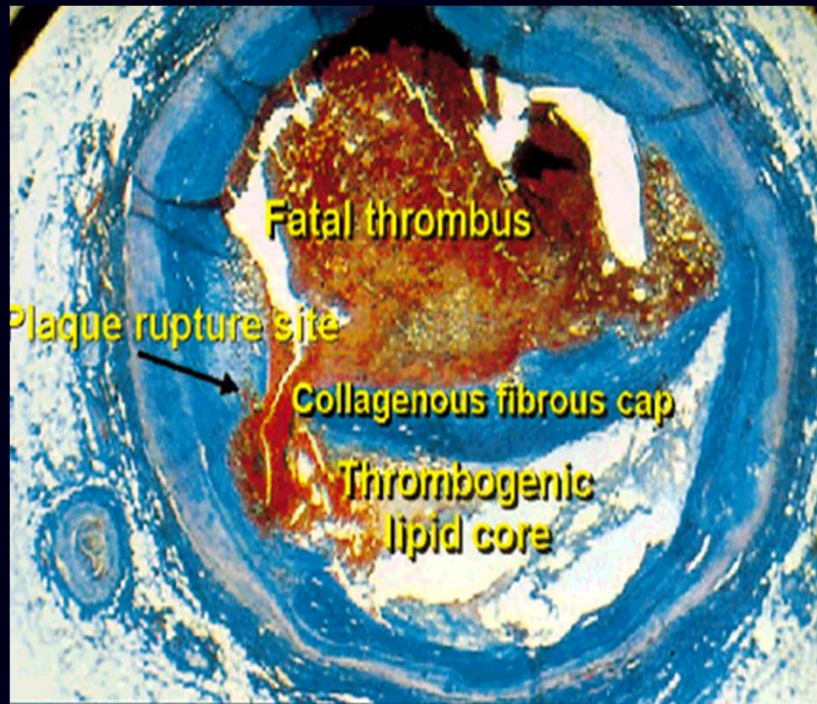
Aspirin ad Infinitum
for Prevention: Really Works?

FDA has not approved aspirin for use   in primary prevention.

International guidelines have started   to recommend withdrawal of aspirin.
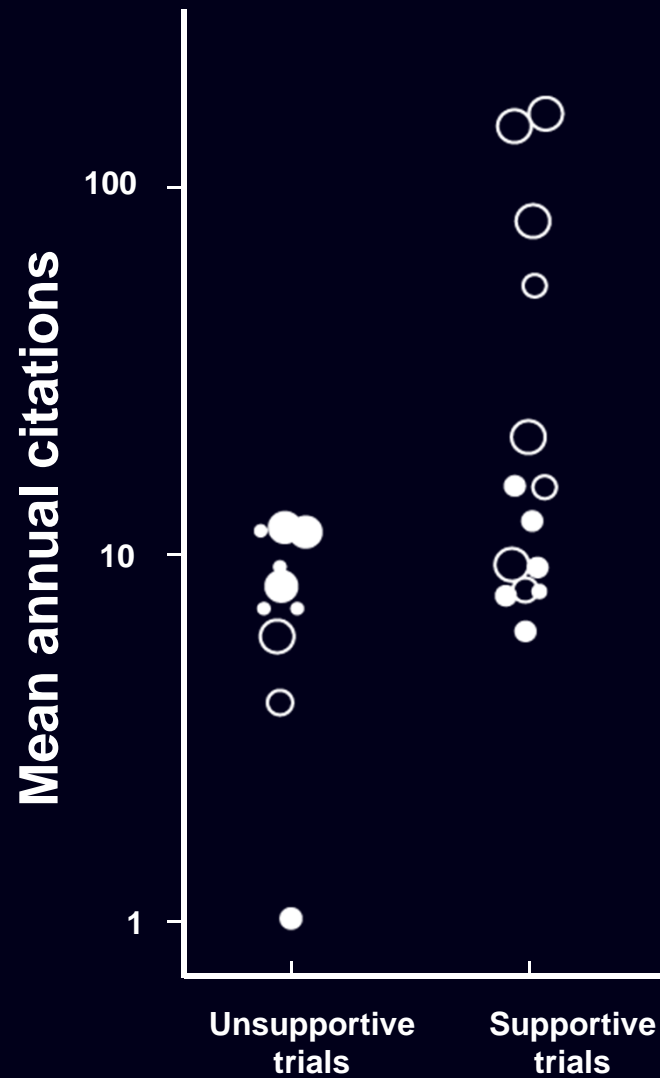
Heart Attack and Brain Attack

Fatal thrombus

Plaque rupture site

Collagenous fibrous cap

Thrombogenic lipid core

"Axis of Evil"

- Arterial wall side
  - LDL cholesterol
  - inflammation

- Arterial lumen side
  - platelet
  - coagulation

The initial road to cholesterol treatments was rather bumpy.
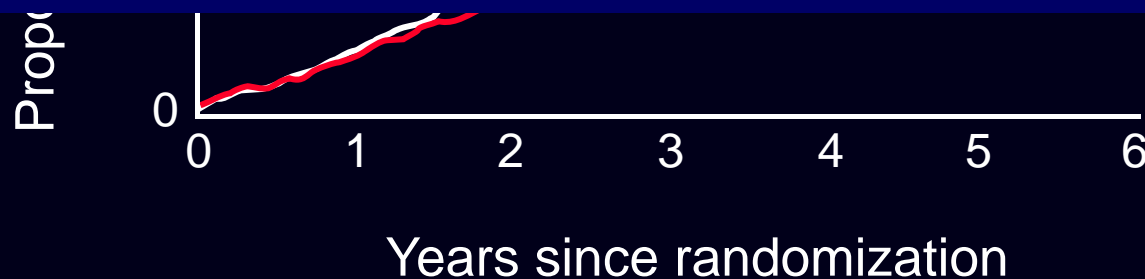
Cholesterol Lowering Trials before Statin Era

Lowering serum cholesterol concentrations does not reduce mortality and is unlikely to prevent coronary heart disease.
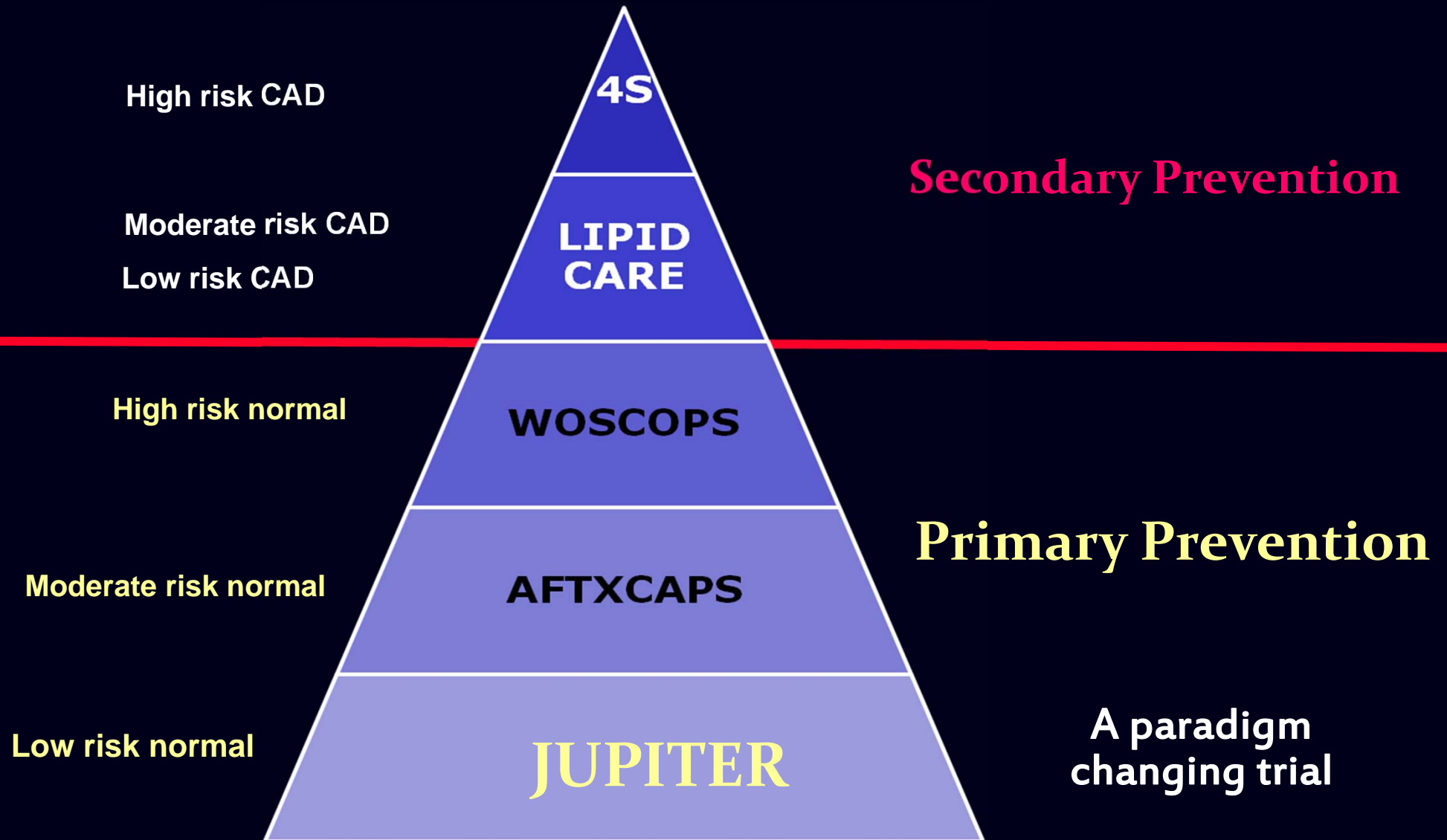
Revolution
Pre-S & S Era 4S

Statins

Miracle drug!
Best selling product

Years since randomization

0 1 2 3 4 5 6

Prop

0

Landmark Statin Trials

Anti-atherosclerosis Drug

High risk CAD

Moderate risk CAD

Low risk CAD

High risk normal

Moderate risk normal

Low risk normal

4S

LIPID CARE

WOSCOPS

AFTXCAPS

JUPITER

Secondary Prevention

Primary Prevention

A paradigm changing trial

Inside

JUPITER

STUDY POPULATION

As described in detail elsewhere,[17,18] men 50 years of age or older and women 60 years of age or older were eligible for the trial if they did not have a history of cardiovascular disease and if, at the initial screening visit, they had an LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) and a high-sensitivity C-reactive protein level of 2.0 mg per liter or more. Other require-

N=17,802
1.9 years follow-up

Rosuvastatin 20mg/d
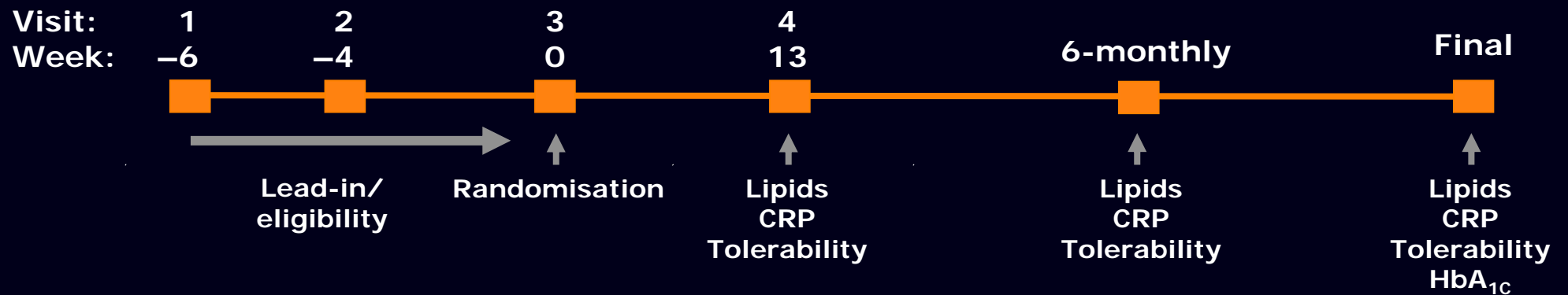Vs. Placebo

"seemingly healthy people"
normal LDL-C & high CRP

Baseline Characteristics*

	Rosuvastatin n=8901	Placebo n=8901
Age (years)	66 (60-71)	66 (60-71)
Male sex (%)	61.5	62.1
Race (%)		
White	71.4	71.1
Black	12.4	12.6
Hispanic	12.6	12.8
Other	3.6	3.5
BMI (kg/m^2)	28.3 (25.3-32.0)	28.4 (25.3-32.0)
Systolic BP (mmHg)	134 (124-145)	134 (124-145)
Diastolic BP (mmHg)	80 (75-87)	80 (75-87)

*All values are median (interquartile range) or N (%).

Baseline Laboratory Parameters [*]

	Rosuvastatin n=8901	Placebo n=8901
Total cholesterol (mg/dL)	186 (168-200)	185 (169-199)
LDL cholesterol (mg/dL)	108 (94-119)	108 (94-119)
HDL cholesterol (mg/dL)	49 (40-60)	49 (40-60)
Triglycerides (mg/dL)	118 (85-169)	118 (86-169)
hsCRP (mg/L)	4.2 (2.8-7.1)	4.3 (2.8-7.2)
Glucose (mg/dL)	94 (87-102)	94 (88-102)
HbA_{1c}(%)	5.7 (5.4-5.9)	5.7 (5.5-5.9)
Glomerular filtration rate, (ml/min/1.73m^2)	73.3 (64.6-83.7)	73.6 (64.6-84.1)

For hsCRP, values are the average of the values obtained at two screening and visits

*All values are median (interquartile range) or N (%).

Ridker P *et al. N Eng J Med* 2008; **359**: 2195-2207

Medical History

Medical History	Rosuvastatin n=8901	Placebo n=8901
Current smoker (%)	15.7	16.0
Family history CHD[†] (%)	11.2	11.8
Metabolic syndrome[‡] (%)	41.0	41.8
Aspirin use (%)	16.6	16.6

[†]Family history of premature CHD defined as first degree relative with CHD at age < 55 yrs (male), < 65 yrs (female); [‡] Metabolic syndrome defined according to consensus criteria of AHA/NHLBI

Ridker P *et al. N Eng J Med* 2008; **359**: 2195-2207

JUPITER Population Compared With Previous Trials

	AFCAPS	WOSCOPS	JUPITER
Patients, n	6,605	6,595	17,802
% male, n	85	100	62
Duration, years	5.2	4.9	1.9
Diabetes, %	6	1	0
Baseline lipids, mg/dL*			
total cholesterol	221	272	183
LDL-C	150	192	104
HDL-C	36–40	44	51
triglycerides	158	164	138
hsCRP, mg/L	0.2	NA	4.3
Statin	Lovastatin 20–40 mg	Pravastatin 40 mg	Rosuvastatin 20 mg

CVD=cardiovascular disease; CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; *Baseline lipid levels are mean values.

Ridker PM *et al. Am J Cardiol* 2007; **100**: 1659–1664

Ridker PM *et al. N Engl J Med*. 2001 **344**: 1959-65

Flying to
JUPITER

A home run
for the public health?

LDL 50%↓
CRP 37%↓

No doubt, it is definitively positive!

Dramatic reductions in odds ratio for acute vascular events
were seen across all subgroups of patients in the JUPITER trial.

A degree of efficacy rarely have been seen
for any particular therapy in medicine history.
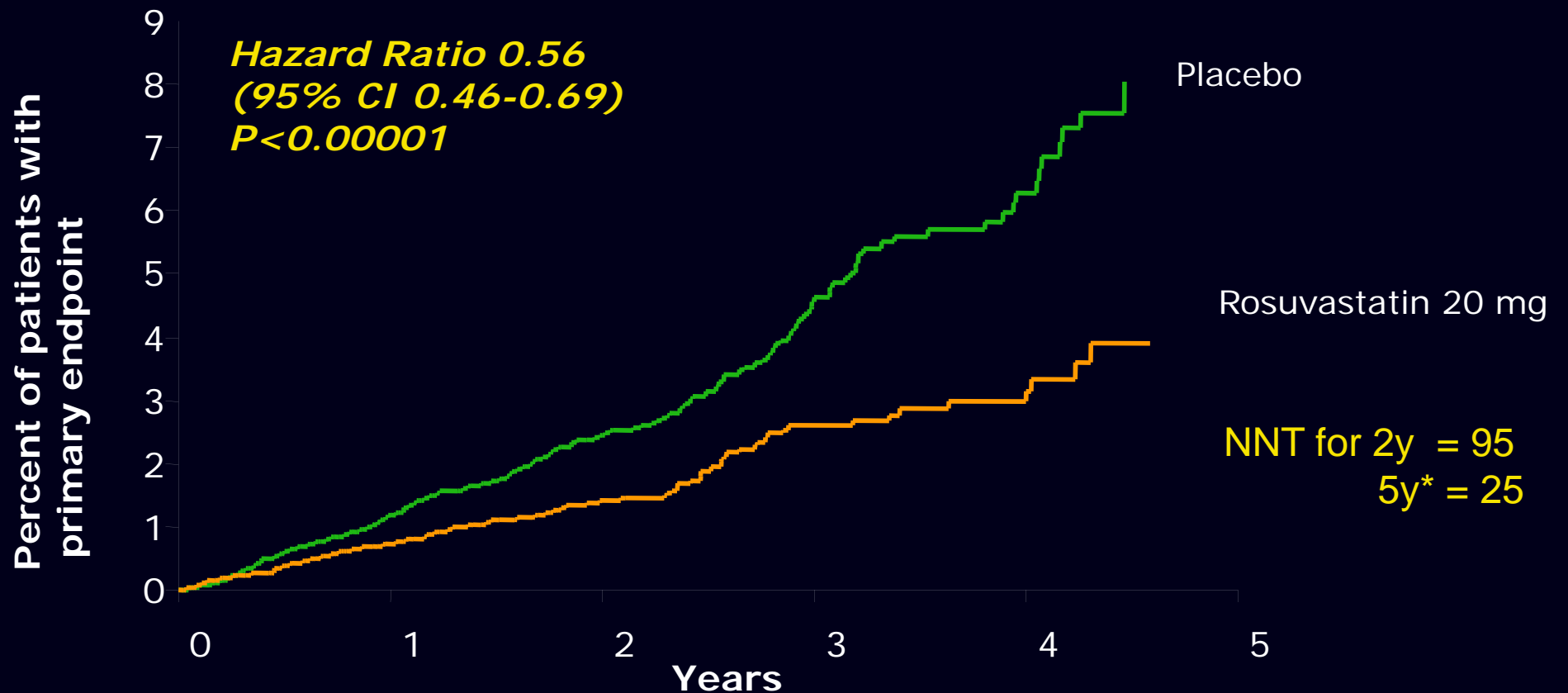
Steven E. Nissen

Effects on LDL-C, HDL-C, TG and hsCRP at 12 months;
Percentage Change Between Rosuvastatin & Placebo
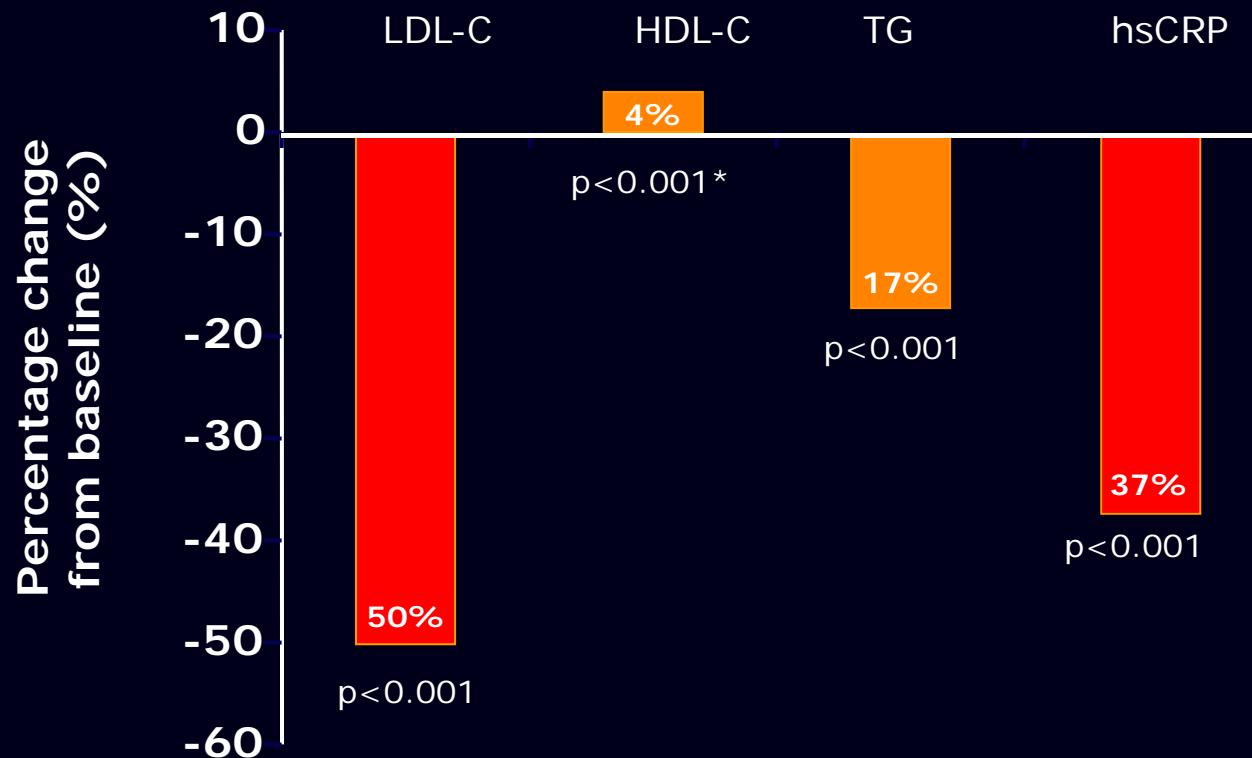
*P-value at study completion (48 months) = 0.34

Ridker P *et al*. *N Eng J Med* 2008; **359**: 2195-2207

Primary Endpoint
Time to first occurrence of CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization

Hazard Ratio 0.56
(95% CI 0.46-0.69)
P<0.00001

Placebo

Rosuvastatin 20 mg

NNT for 2y = 95
5y* = 25

Percent of patients with primary endpoint

Years

Number at risk

RSV	8901	8412	3893	1353	538	157
Placebo	8901	8353	3872	1333	531	174

*Extrapolated figure based on Altman and Andersen method

Ridker P *et al. N Eng J Med* 2008; **359**: 2195-2207

Primary Endpoint Components

	Placebo [n=8901] n (rate**)	Rosuvastatin [n=8901] n (rate**)	HR	95% CI	p-value
Primary Endpoint	**251** (1.36)	**142** (0.77)	**0.56**	0.46-0.69	**<0.001***
(Time to first occurrence of *CV death, MI, stroke, unstable angina, arterial revascularisation*)					
Non-fatal MI	**62** (0.33)	**22** (0.12)	**0.35**	0.22-0.58	**<0.001***
Fatal or non-fatal MI	**68** (0.37)	**31** (0.17)	**0.46**	0.30-0.70	**0.0002**
Non-fatal stroke	**58** (0.31)	**30** (0.16)	**0.52**	0.33-0.80	**0.003**
Fatal or non-fatal stroke	**64** (0.34)	**33** (0.18)	**0.52**	0.34-0.79	**0.002**
Arterial Revascularization	**131** (0.71)	**71** (0.38)	**0.54**	0.41-0.72	**<0.0001**
Unstable angina†	**27** (0.14)	**16** (0.09)	**0.59**	0.32-1.10	**0.09**
CV death, stroke, MI	**157** (0.85)	**83** (0.45)	**0.53**	0.40-0.69	**<0.001***
Revascularization or unstable angina	**143** (0.77)	**76** (0.41)	**0.53**	0.40-0.70	**<0.001***

** Rates are per 100 person years; † Hospitalisation due to unstable angina; *Actual p-value was < 0.00001

HR – Hazard Ratio; CI – Confidence Limit

Total Mortality
Death from any cause

Hazard Ratio 0.80
(95% CI 0.67-0.97)
p=0.02

Placebo

Rosuvastatin 20mg

Percent total mortality
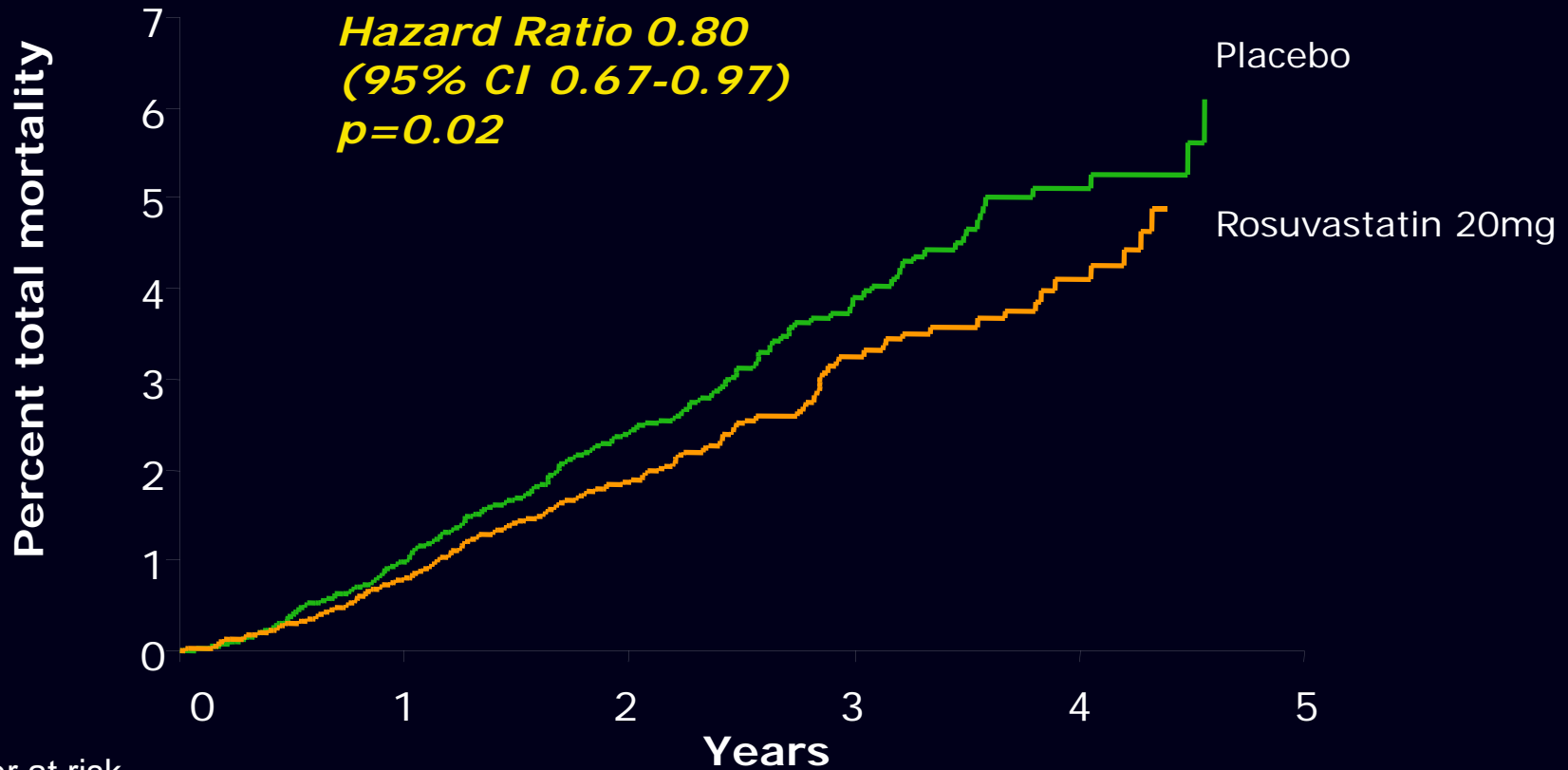
Years

Number at risk

RSV	8901	8787	4312	1602	676	227
Placebo	8901	8775	4319	1614	681	246

Ridker P *et al. N Eng J Med* 2008; **359**: 2195-2207

Stroke Cumulative Incidence of All Stroke

Any Stroke	0.52	0.34-0.79	0.002
Non-fatal stroke	0.52	0.33-0.80	0.003
Ischemic stroke	0.49	0.30-0.81	0.004
Hemorrhagic	0.67	0.24-1.88	0.44
TIA	0.93	0.56-1.56	0.79

Everett BM, *et al. Circulation* 2010; **121**:143-150.
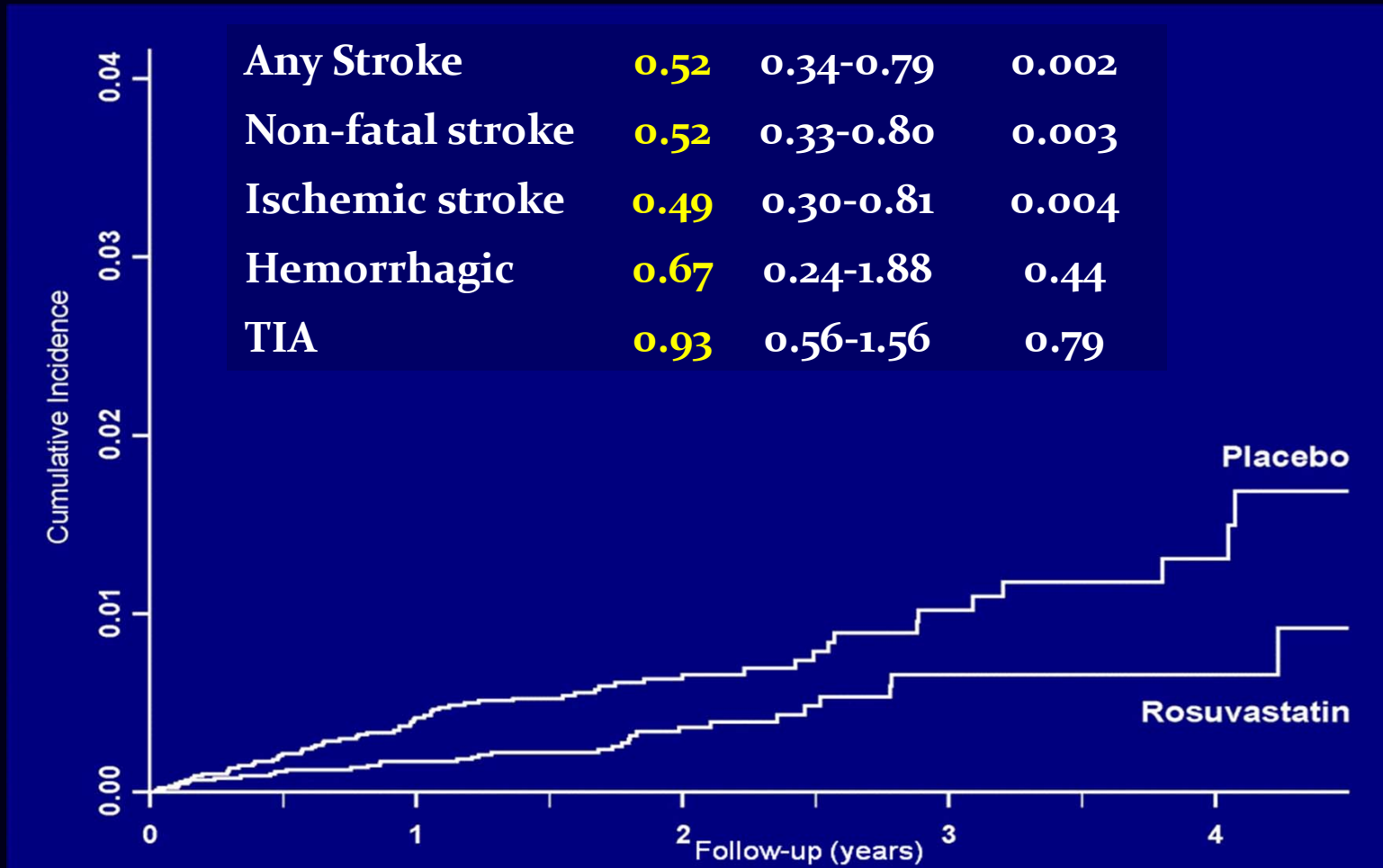
Subgroup Analysis

	N	P- value*
Age		0.32
≤ 65 years	8,541	
>65 yrs	9,261	
Gender		0.80
Males	11,001	
Females	6,801	
Race		0.57
White	12,683	
Non-white	5,117	
Hypertension		0.53
Yes	10,208	
No	7,586	
Region		0.51
US or Canada	6,041	
Other	11,761	
Metabolic syndrome		0.14
Yes	7,375	
No	10,296	
Family history of CHD		0.07
Yes	2,045	
No	15,684	
Framingham risk score		0.99
≤10%	8,882	
>10%	8,895	

Rosuvastatin better   Placebo better

Hazard ratio (95% CI)

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207
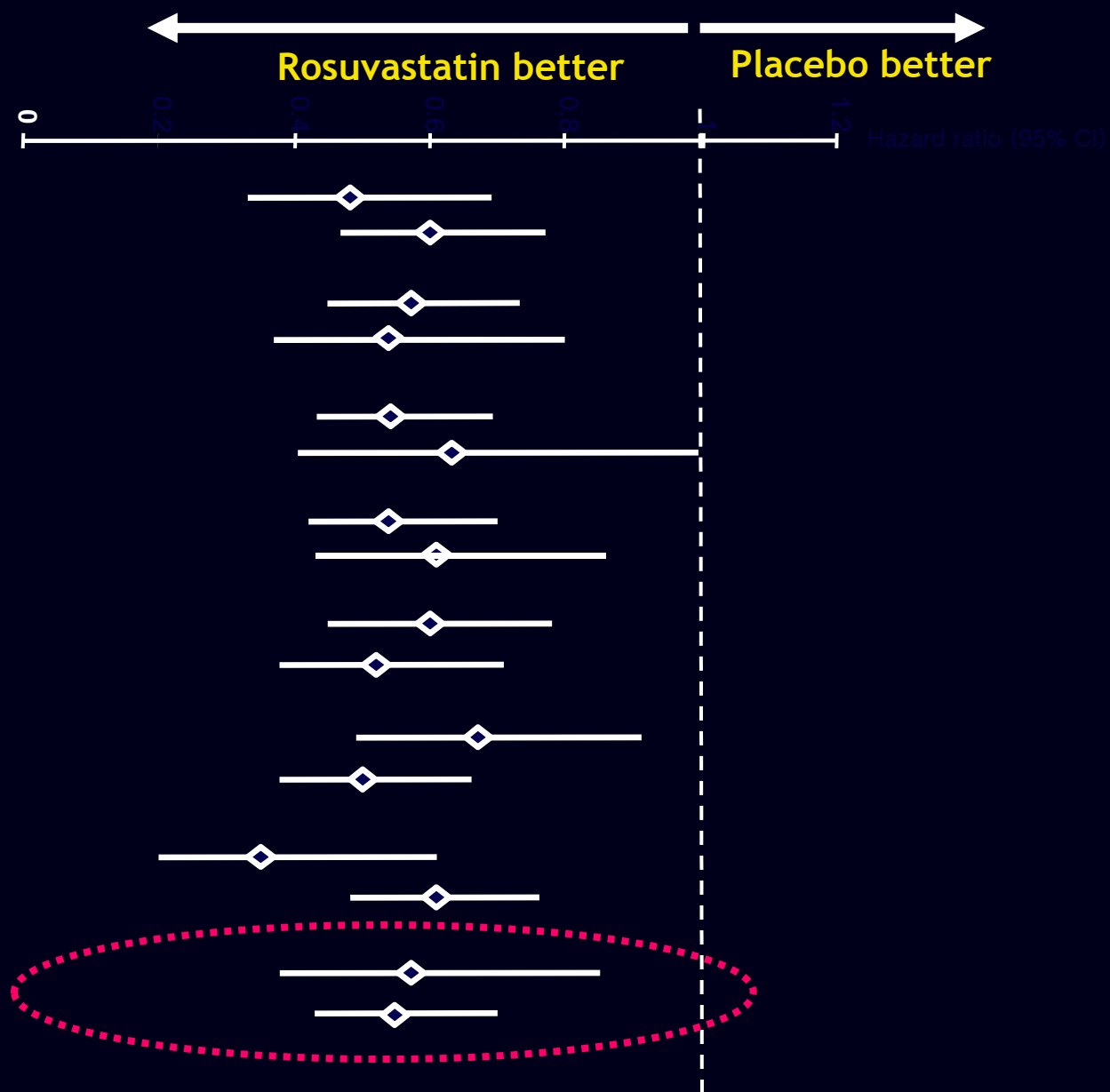
Women Subgroup Data

Primary Endpoint: Time to first occurrence of a CV death, non fatal stroke, non-fatal MI, unstable angina or arterial revascularization

	Rosuva No. (Rate)*	Placebo No. (Rate)*	HR	95% CI	P Value
Women	39 (0.57)	70 (1.04)	0.54	0.37-0.80	P=0.002
Men	103 (0.88)	181 (1.54)	0.58	0.45-0.73	P<0.0001

* Rates are per 100 person-years
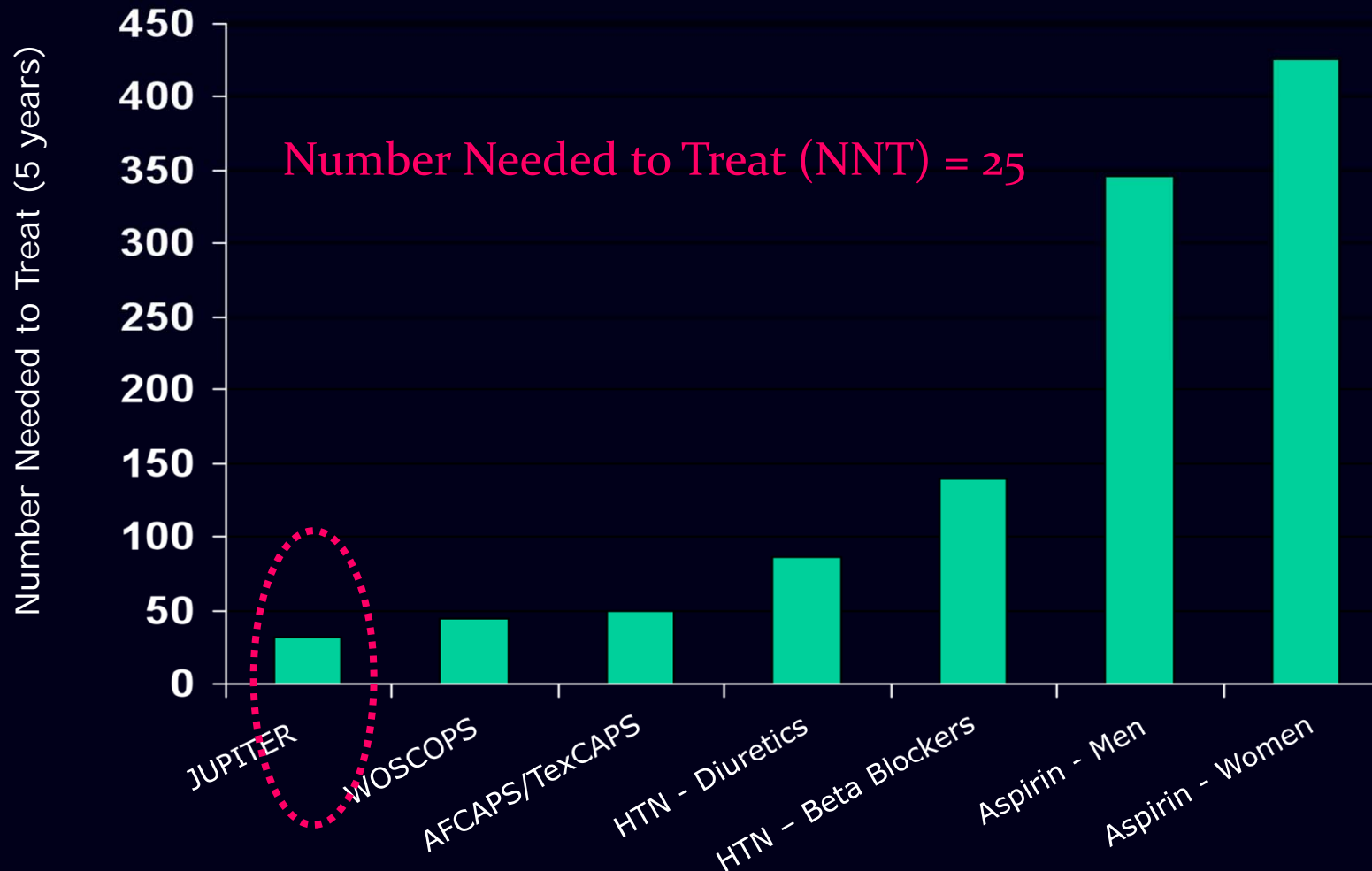
Elderly Subgroup Data

Endpoint	Age	Events	Placebo rate*	HR	95% CI	P-value
Primary endpoint**	≥ 70	194	1.99	0.61	0.46-0.82	<0.001
	< 70	199	1.06	0.51	0.38-0.69	<0.001
Any MI	≥ 70	47	0.50	0.55	0.31-1.00	0.046
	< 70	52	0.30	0.37	0.21-0.69	<0.001
Any stroke	≥ 70	61	0.64	0.55	0.33-0.93	0.023
	< 70	36	0.20	0.45	0.22-0.91	0.020
Revascularisation or Unstable Angina	≥ 70	87	0.95	0.51	0.33-0.80	0.003
	< 70	132	0.69	0.54	0.38-0.77	<0.001
MI/Stroke/CV Death	≥ 70	133	1.36	0.61	0.43-0.86	0.004
	< 70	107	0.60	0.43	0.29-0.65	<0.001
Secondary endpoints:						
Any Death	≥ 70	241	2.04	0.80	0.62-1.04	0.090
	< 70	204	0.86	0.80	0.60-1.05	0.10
VTE	≥ 70	40	0.41	0.59	0.31-1.11	0.096
	< 70	54	0.28	0.55	0.31-0.96	0.031

* Incidence rates are per 100 person years; **Nonfatal MI, nonfatal stroke, revascularisation, unstable angina, CV death

HR – Hazard Ratio; CI – Confidence Interval

Glynn RJ, Ridker PM. http://www.escardio.org/congresses/esc-2009/congress-reports/Documents/710007-Glynn-slides.pdf

JUPITER: 5-Year NNT Values for Primary Prevention of CVD

Ridker et al, NEJM 2008; 359: 2195-207

J-message 1

Prevention is better than cure
The earlier, the better

2007: The tragic failure of CORONA

Ischemic Cardiomyopathy

2008: The great success of JUPITER
"Return of the CRESTOR"

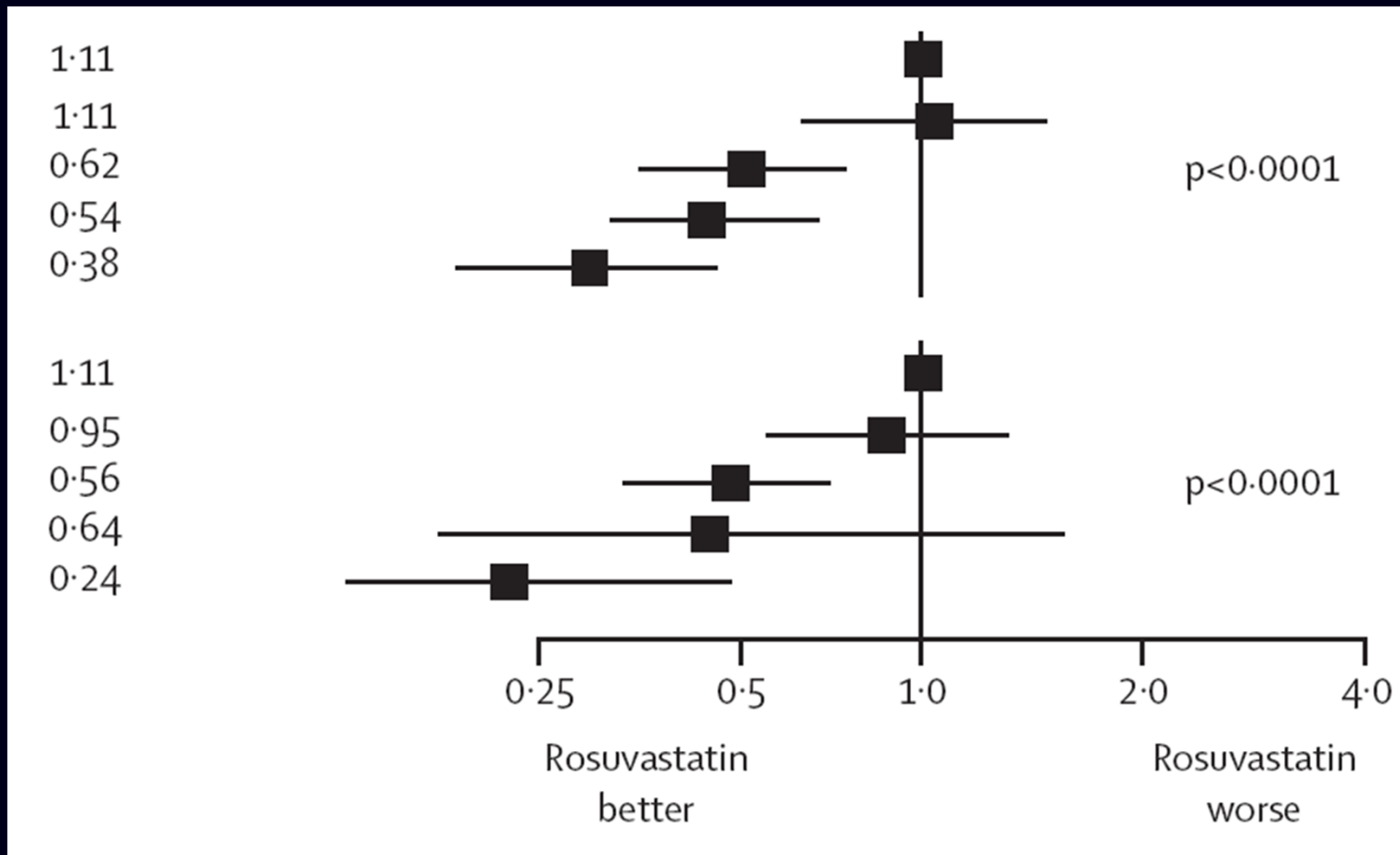## J-message 2
Who gets the benefit?
The lower, the better

Placebo
LDL≥1.8, hsCRP≥2
LDL<1.8, hsCRP≥2
LDL≥1.8, hsCRP<2
LDL<1.8, hsCRP<2

Placebo
LDL≥1.8, hsCRP≥1
LDL<1.8, hsCRP≥1
LDL≥1.8, hsCRP<1
LDL<1.8, hsCRP<1

1·11
1·11
0·62
0·54
0·38

p<0·0001

1·11
0·95
0·56
0·64
0·24

p<0·0001

0·25 0·5 1·0 2·0 4·0

Rosuvastatin better

Rosuvastatin worse

J-message 3
Statins are anti-atherosclerotic drug!
The stronger, the better

From: Gashi, Tracey A
Sent: Thursday, August 12, 2010 11:46 PM
To: Sohn, Hyung Woon
Subject: RE: Question about JUPITER result (from Korean KOL)

Hi Sohn,

Attached is the data from JUPITER which you requested. This is unpublished data so please quote as data on file.

	RSV N=8901	Placebp=8901	HR (95% CI)	P for interaction
	Number of primary endpoint events			

I hope this answers your KOL query

With best wishes

Tracey

demia.[40] The use of certain cardioprotective medications (e.g., ███████████) has increased over time, and these agents may have beneficial effects beyond their effect on risk factors and may contribute to a lower severity of subsequent cardiac events.[36] Although each of

Statin Message

Atherosclerosis will become history!

Interventionists/surgeons, get a new day job!

My Personal Note

... born to love statin

People start life with clean arteries, live with atherosclerosis and die of acute vascular events.

감사합니다.