Evolving Mission of CVD Prevention:

Future Direction of Dyslipidemia and Hypertension management

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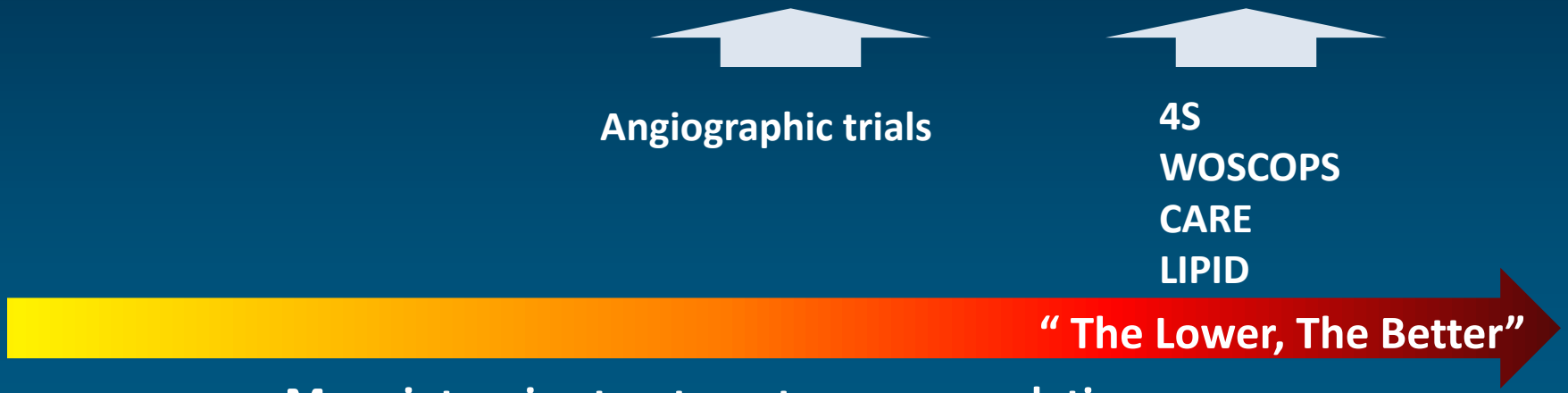
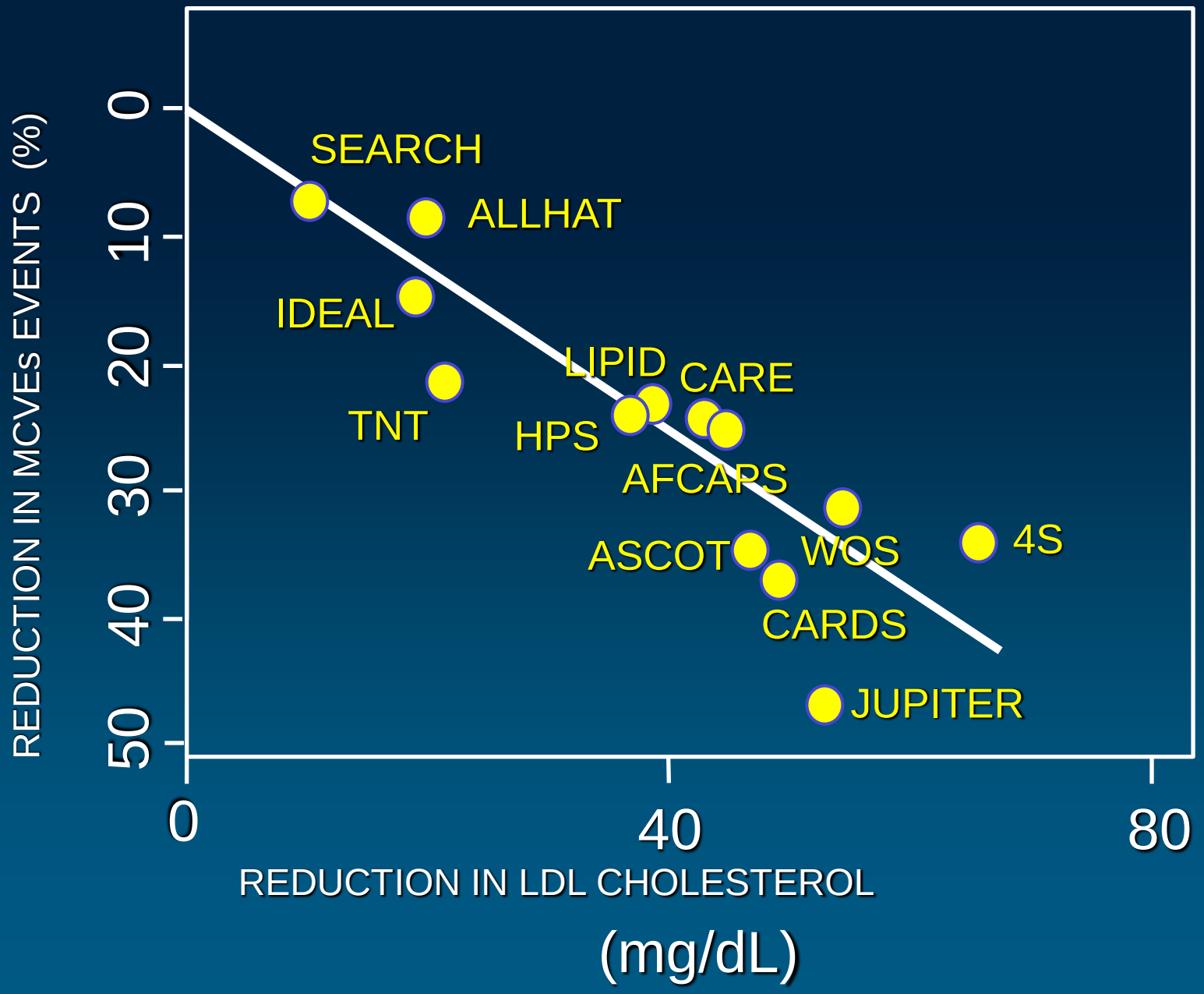
연세의대 심장내과

Evolution of NCEP-ATP

ATP I (1988)	ATP II (1993)	ATP III (2002)
• Diet • Low dose (Drug of choice : bile acid sequestrants, nicotinic acid)	• Delaying the use of drug in patients at low risk •Intensive management of LDL-C in pts with CHD (**Major drug** : bile acid sequestrants, nicotinic acid, statins vs. **Other drug** : fibric acids , probucol)	• More intensive LDL-C lowering for the patients with multiple risk factors or CHD



Major Intervention Trials



Evolution of LDL-C Goals in various guidelines

2002–2003

- HPS (2002)
- PROSPER (2002)
- ALLHAT-LLT (2002)
- ASCOT-LLA (2003)
- HPS diabetes (2003)

- **NCEP ATP III update**
- 3rd Joint Task Force ESC (2003)
  - TC<5 mmol/L
  - LDL<3mmol/L
  - Established CHD
  - TC<4.5mmol/L
  - LDL<2.5mmol/L

2004–2005

- PROVE IT (2004)
- CARDS (2004)
- TNT (2005)
- IDEAL (2005)

- ADA (2005)
  - Patients with diabetes + CVD
  - Optional LDL-C goal: <70 mg/dL

2006–2007

- **AHA/ACC (2006)**
  - **"Reasonable" to treat to LDL-C <70 mg/dL**
- NKF KDOQI (2007)
- 4th Joint Task Force ESC (2007) Established CHD
  - TC<4.5mmo/L (option of 4)
  - LDL<2.5mmol/L (option of 2)
- ESC/EASD (2007) Pts with diabetes + CVD
  - LDL<1.8-2.0mmol/L

2008-2012

- JUPITER (2008)
- SATURN (2011)

"Very High CV risk'

- **ESC/EAS (2011)**
- 5th Joint Task Force ESC (2012)
  - LDL-C <1.8 mmol/L or >50% reduction from baseline LDL-C
- ADA (2012)

NCEP-ATPIII : LDL-C Goals in Different Risk Categories

Risk Category	LDL-C Goal
CHD or CHD Risk Equivalents : **Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease)** **Diabetes** **10-year risk for CHD>20 %**	**< 100 mg/dL**
2+ Risk Factors without CHD	< 130 mg/dL
0-1 Risk Factors without CHD	< 160 mg/dL

- **LDL-C<70 mg/dL is optional : Very High Risk**

  Established CVD plus
  (1) Multiple risk factors (esp, Diabetes),
  (2) Severe and poorly controlled risk factors (esp, continued cigarette smoking),
  (3) Multiple risk factors of the metabolic syndrome (esp TG ≥ 200 mg/dL + non-HDL-C ≥ 130 mg/dL + HDL-C<40mg/dL**),**
  (4) ACS

ESC/EAS guidelines (2011)
LDL-C Goals in Difference Risk Categories

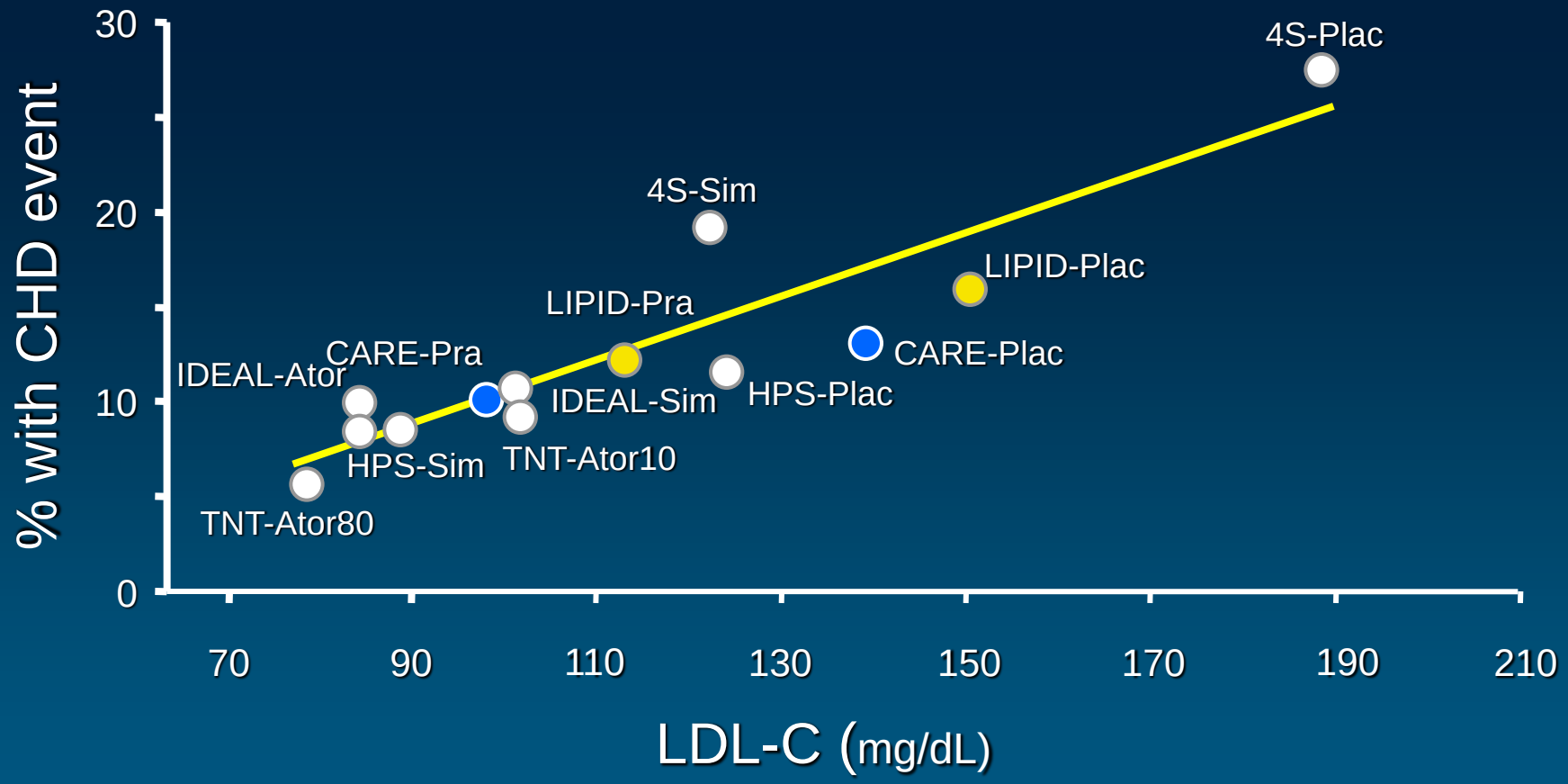
Risk Category	LDL Goal
Very High Risk : **Estabilished CVD, Previous MI, ACS,** **Coronary revascularization, Other arterial revascularization,** **Ischaemic stroke, PAD, Diabetes,** **CKD(GFR < 60 mL/min/1.73m^2),** **10 year risk SCORE ≥ 10 %**	**< 70 mg/dL** **and/or** **≥ 50 % ↓**
High Risk : Markedly elevated single risk factors (ex. Familial dyslipidaemias, severe hypertension), 10 year risk SCORE ≥ 5 % and <10 %	**< 100 mg/dL**
Moderate Risk : 10 year risk SCORE ≥ 1 % and < 5 %	< 115 mg/dL
Low Risk : 10 year risk SCORE < 1 %	

Why < 70 mg/dL?

Aggressive lipid therapy in patients at high risk

Statin for Secondary Prevention
: TNT, IDEAL, SATURN

Statin Trials: LDL-C Levels vs Events
Secondary Prevention



Secondary Prevention

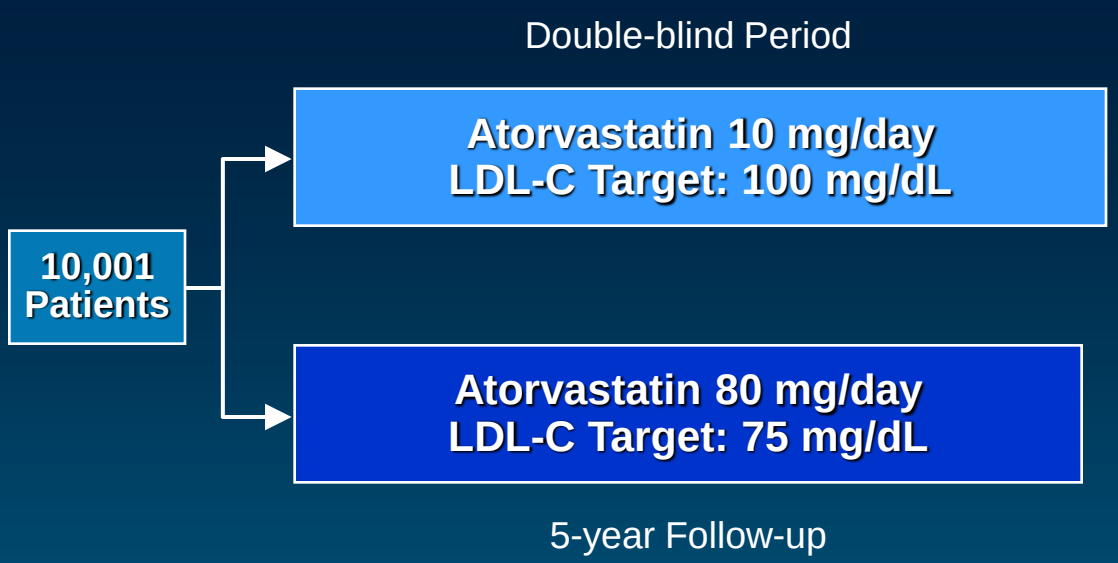
Stable CHD Patients – TNT Design

Patient Population

- Enrolled at 256 sites in 14 countries
- CHD, LDL-C >130; <250 mg/dL
- Begin open-label treatment with atorvastatin 10 mg/day at Week –8
- LDL-C levels <130 mg/dL at Week 0

Primary Endpoint

- Time to occurrence of a major CV event*

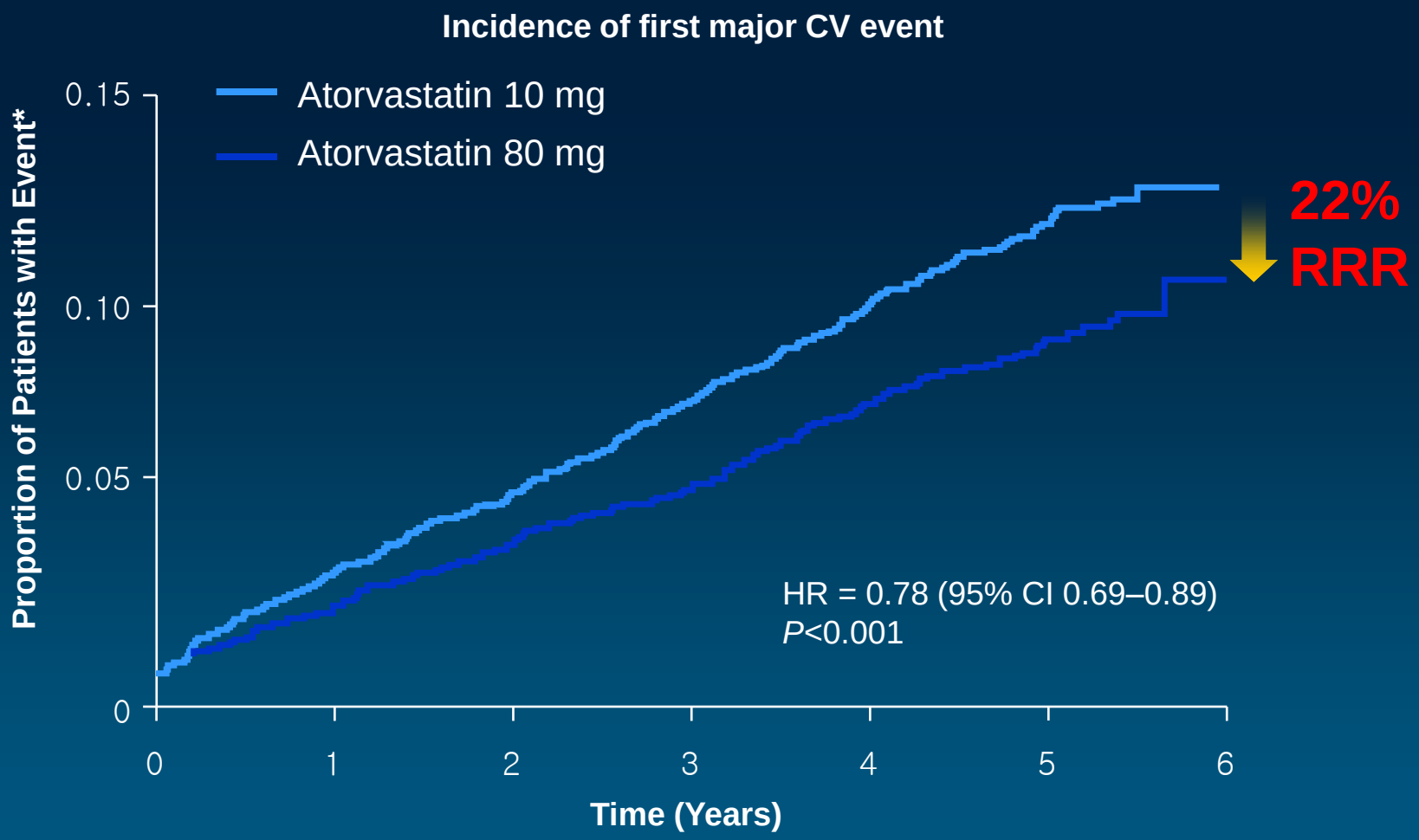


* Major CV events: death from CHD, nonfatal nonprocedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

LaRosa JC, et al. for the TNT Investigators. *N Engl J Med* 2005;352:1425–1435.

Secondary Prevention

Stable CHD Patients – TNT Results



* Major CV events: death from CHD, nonfatal nonprocedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

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

Secondary Prevention

Stable CHD Patients – TNT Sub-Analysis

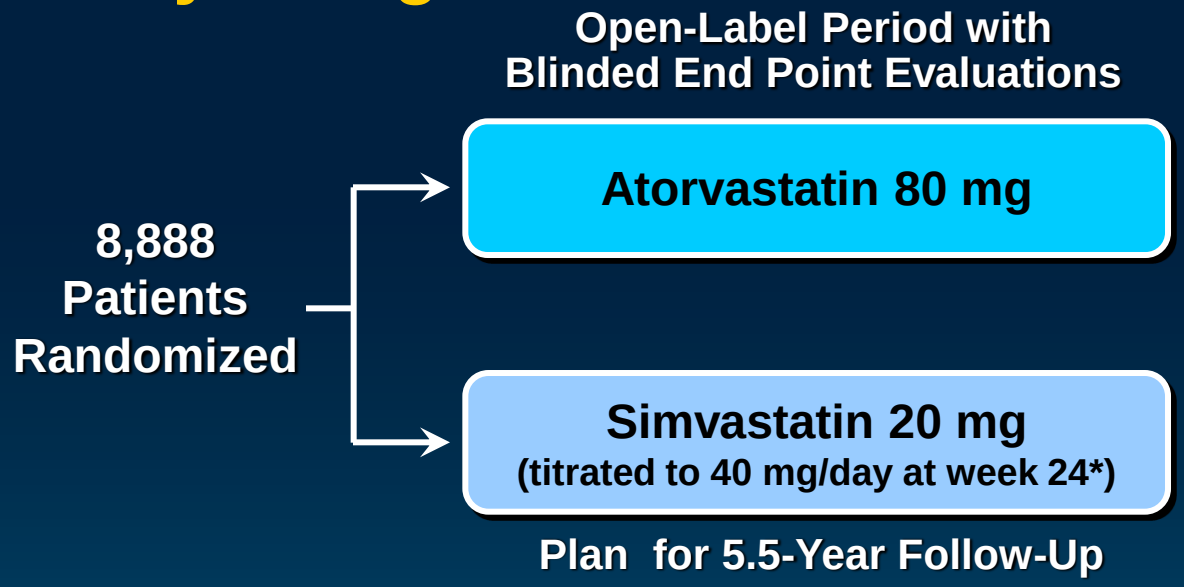
Primary endpoint result	Diabetes n=1,501	Metabolic syndrome n=5,584	Chronic kidney disease* n=3,107	Previous CABG n=4,654	Previous PCI n=5,407	Age ≥ 65 n=3,809	Heart Failure† n=781
Atorvastatin 10 mg	17.9%	13.0%	13.4%	13.0%	10.6%	17.9%	17.3%
Atorvastatin 80 mg	13.8%	9.5%	9.3%	9.7%	8.6%	13.8%	10.6%
Hazard ratio, 95% CI	0.75 0.58-0.97	0.71 0.61-0.84	0.68 0.55-0.84	27% RRR	0.79 0.67-0.94	0.75 0.58-0.97	0.59 0.40-0.88
P	0.026	<0.0001	0.0003	0.0004	0.008	0.026	Not reported

- TNT primary endpoint: Major CV events: death from CHD, nonfatal nonprocedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

* Defined as GFR <60mL/min per 1.73m^2
† Incidence of HF hospitalisation

Waters DD. *Prog Cardiovasc Dis* 2009;51:487-502

Secondary Prevention –
IDEAL: Study Design



Patient Population

- Enrolled at 190 sites
- History of MI
- Eligible for statin therapy
- 9689 screened

Primary Composite End Point

- Major coronary event

Secondary Composite End Points

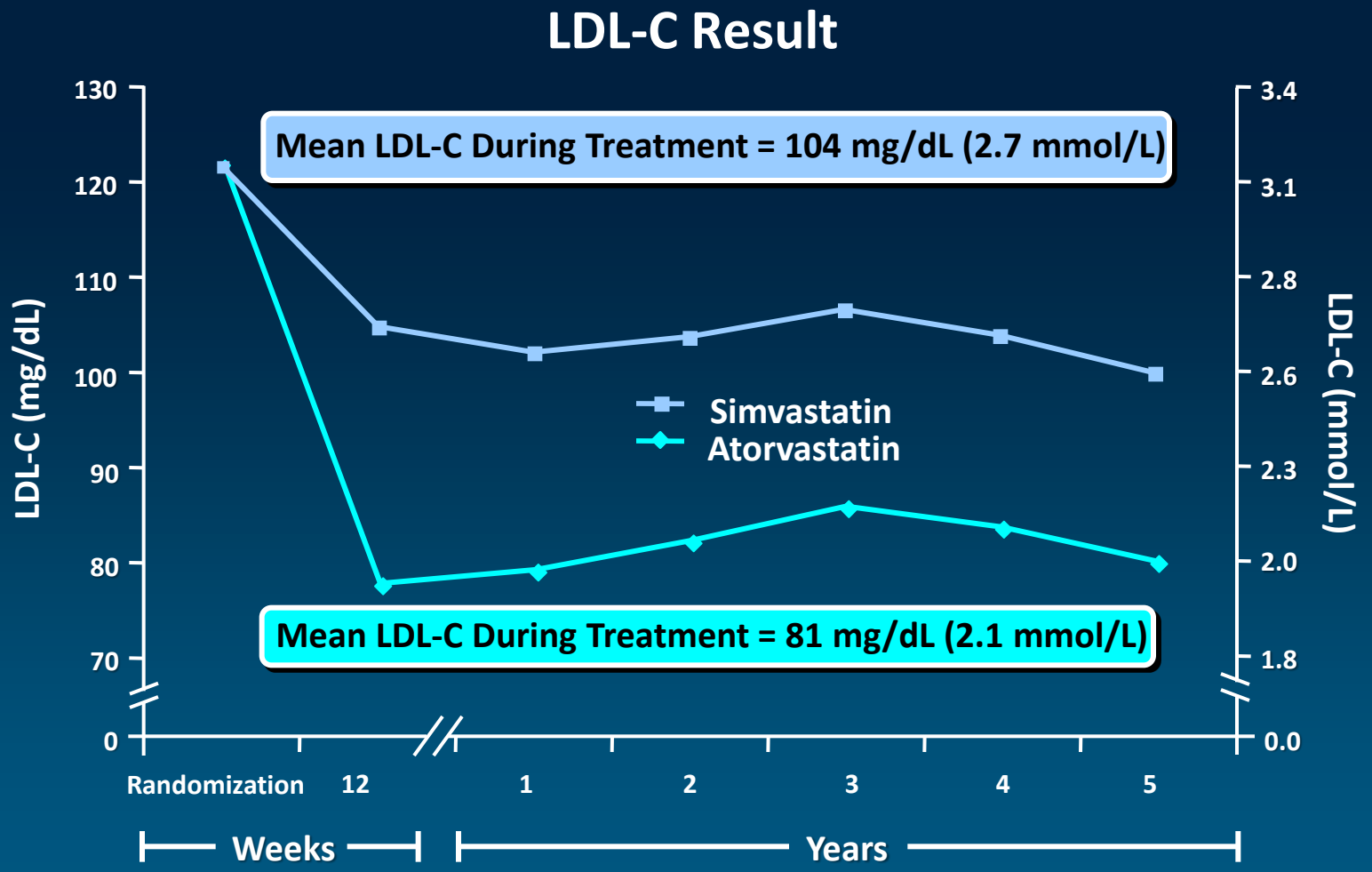
- Major CV event
- Any CHD event
- Any CV event

*Simvastatin dose was increased to 40 mg/day at week 24 in patients whose plasma total cholesterol remained >5.0 mmol/L (190 mg/dL) or whose LDL cholesterol remained >3.0 mmol/L (115 mg/dL).

Adapted from Pedersen TR, et al. *Am J Cardiol*. 2004;94:720–724.

Secondary Prevention

IDEAL Results



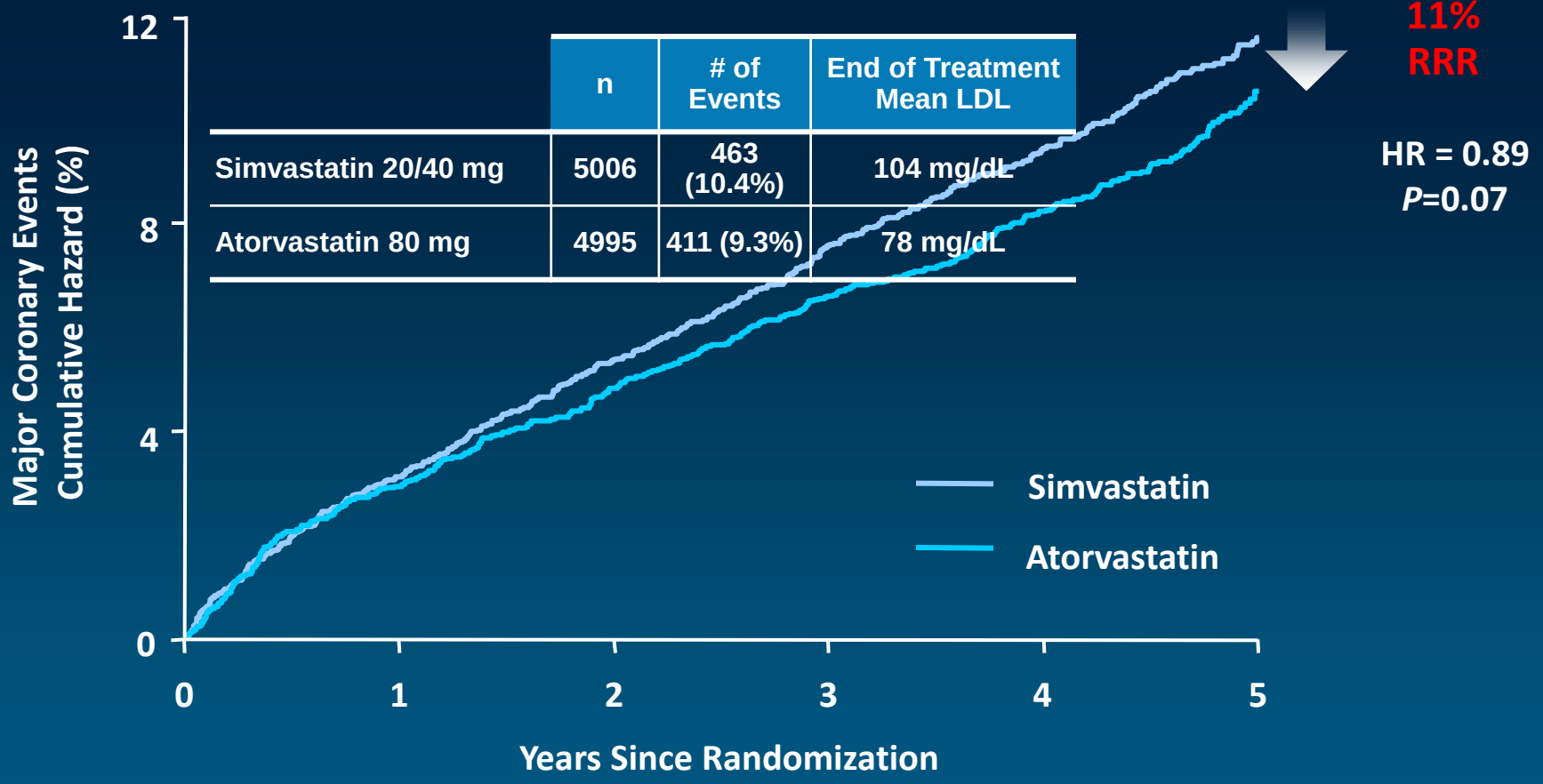
Adapted from Pedersen TR, et al. *JAMA*. 2005;294:2437-2445.

Secondary Prevention

IDEAL Results

Major Coronary Events*

	n	# of Events	End of Treatment Mean LDL
Simvastatin 20/40 mg	5006	463 (10.4%)	104 mg/dL
Atorvastatin 80 mg	4995	411 (9.3%)	78 mg/dL



*CHD death, nonfatal MI, and resuscitated cardiac arrest.

Adapted from Pedersen TR, et al. *JAMA*. 2005;294:2437-2445.

Secondary Prevention

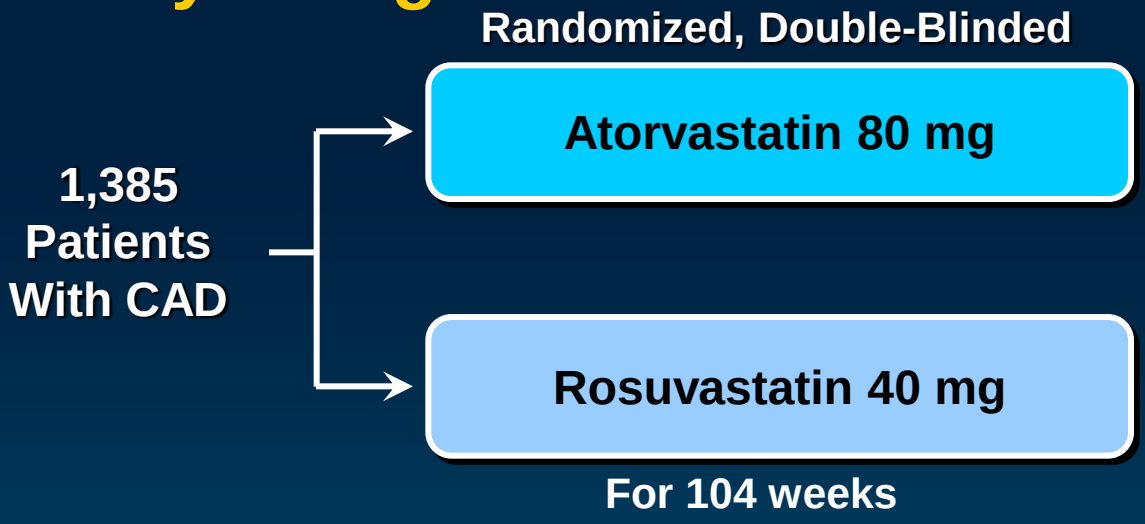
IDEAL Results

	No. of Patients (%)			
	Atorvastatin (N=4,439)	Simvastatin (N=4,449)	Hazard Ratio	*P* Value
Major coronary event	411 (9.3)	463 (10.4)	0.89	.07
CHD death	175 (3.9)	178 (4.0)	0.99	.90
Nonfatal MI	267 (6.0)	321 (7.2)	0.83	.02
Resuscitated cardiac arrest	10 (0.2)	7 (0.2)	–	–

Adapted from Pedersen TR, et al. *JAMA*. 2005;294:2437-2445.

Secondary Prevention

SATURN: Study Design



Primary End Point

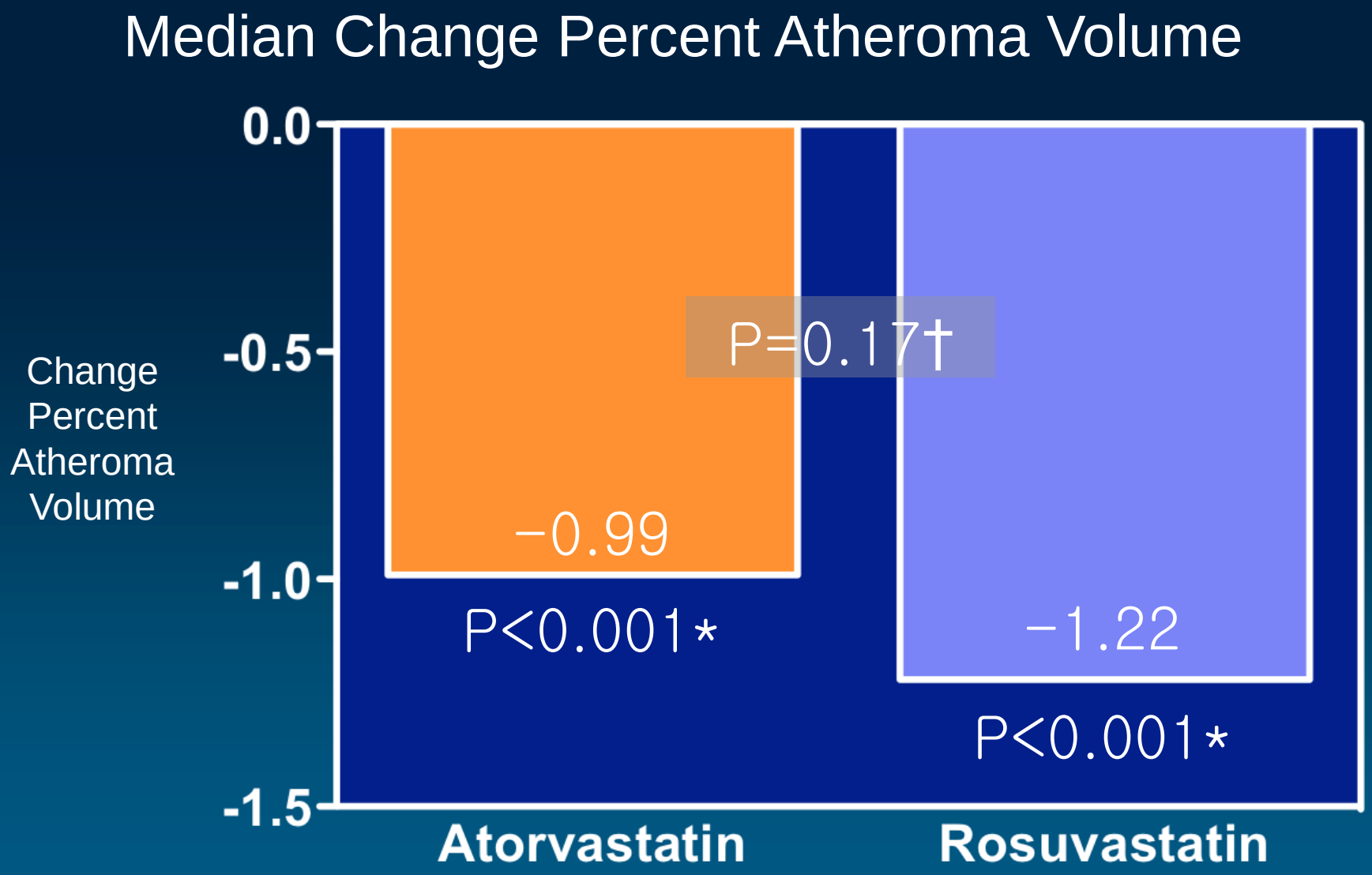
- Percent Atheroma Volume(PAV) as measured by IVUS

Secondary End Points

- Regression of PAV
- Effect on normalized Total Atheroma Volume (TAV)

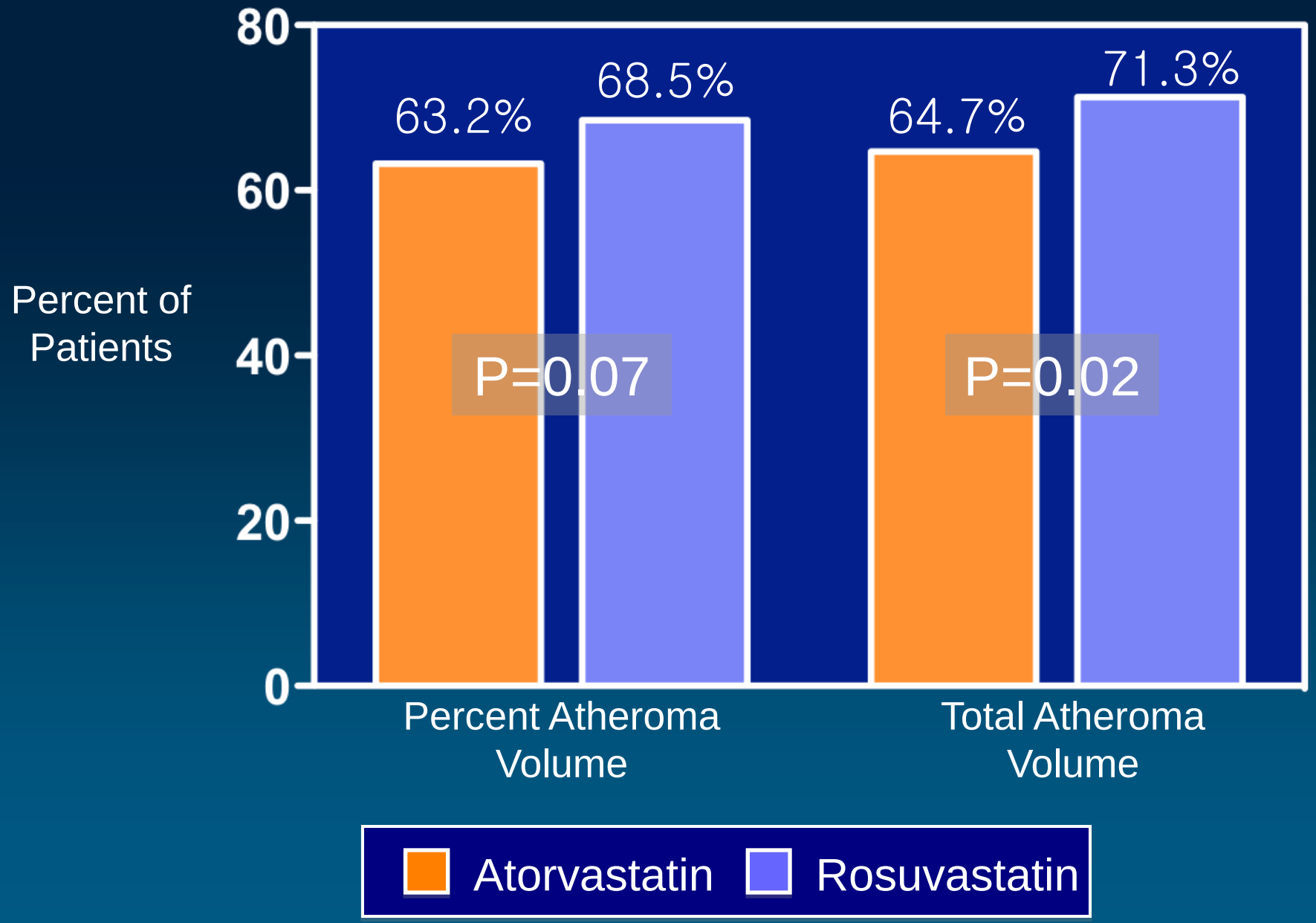
NEJM. 2011; 365: 2078-87

Primary IVUS Efficacy Parameter

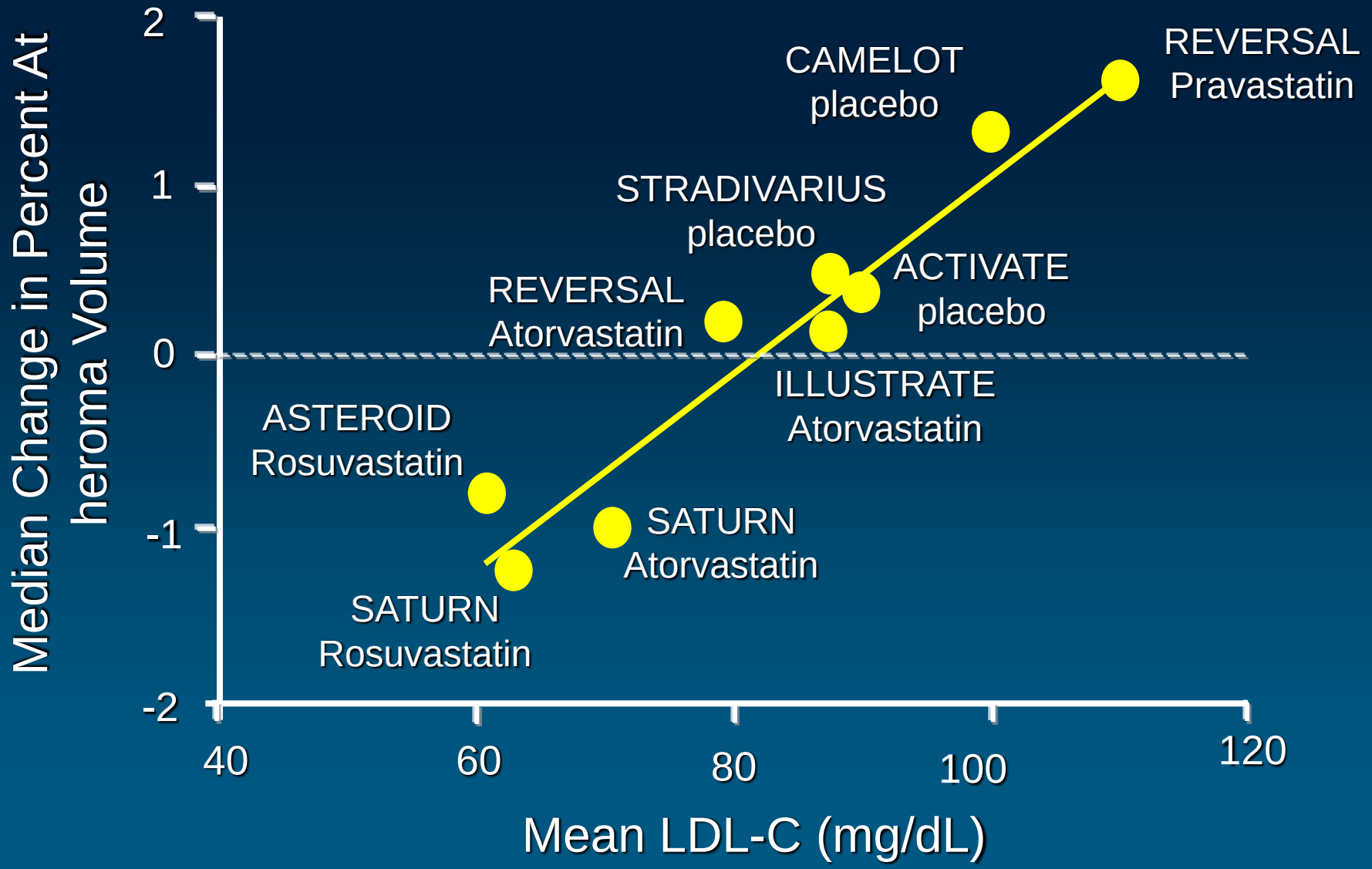


† comparison between groups. * comparison from baseline

Fraction of Patients Exhibiting Regression



Achieved LDL-C and Change in Percent Atheroma Volume



Is < *70 mg/dL* Safe in Asian?

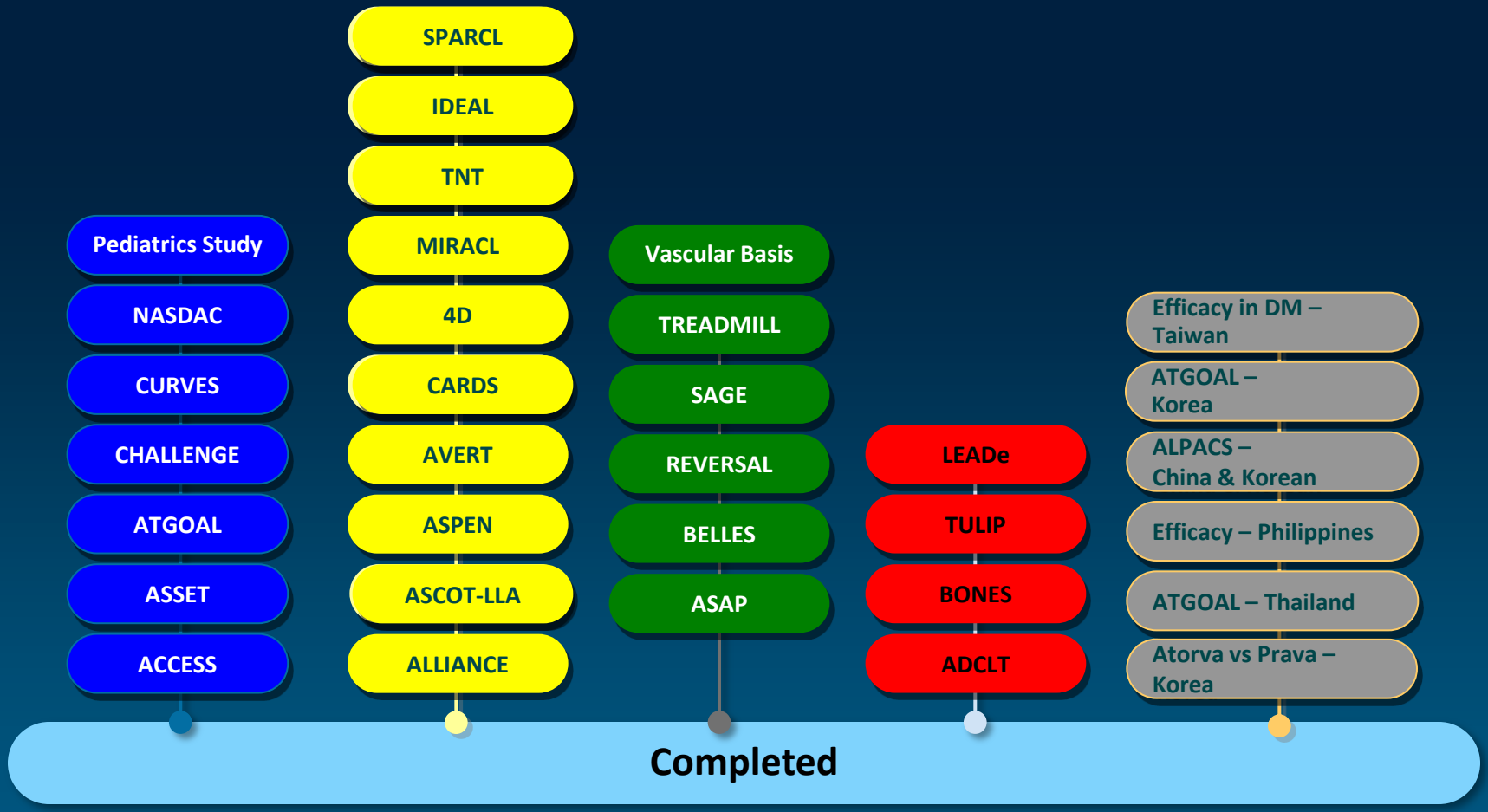
Similar Safety Profile for Atorvastatin Among Asians Compared to Total Patient Population

ASCOT, CARDS, TNT … SPARCL

Juliana Chan[1], Weihang Bao[2], Rana Fayyad[2], Rachel Laskey[2]

1. *Chinese University of Hong Kong* 2. *Pfizer Inc., New York, USA*

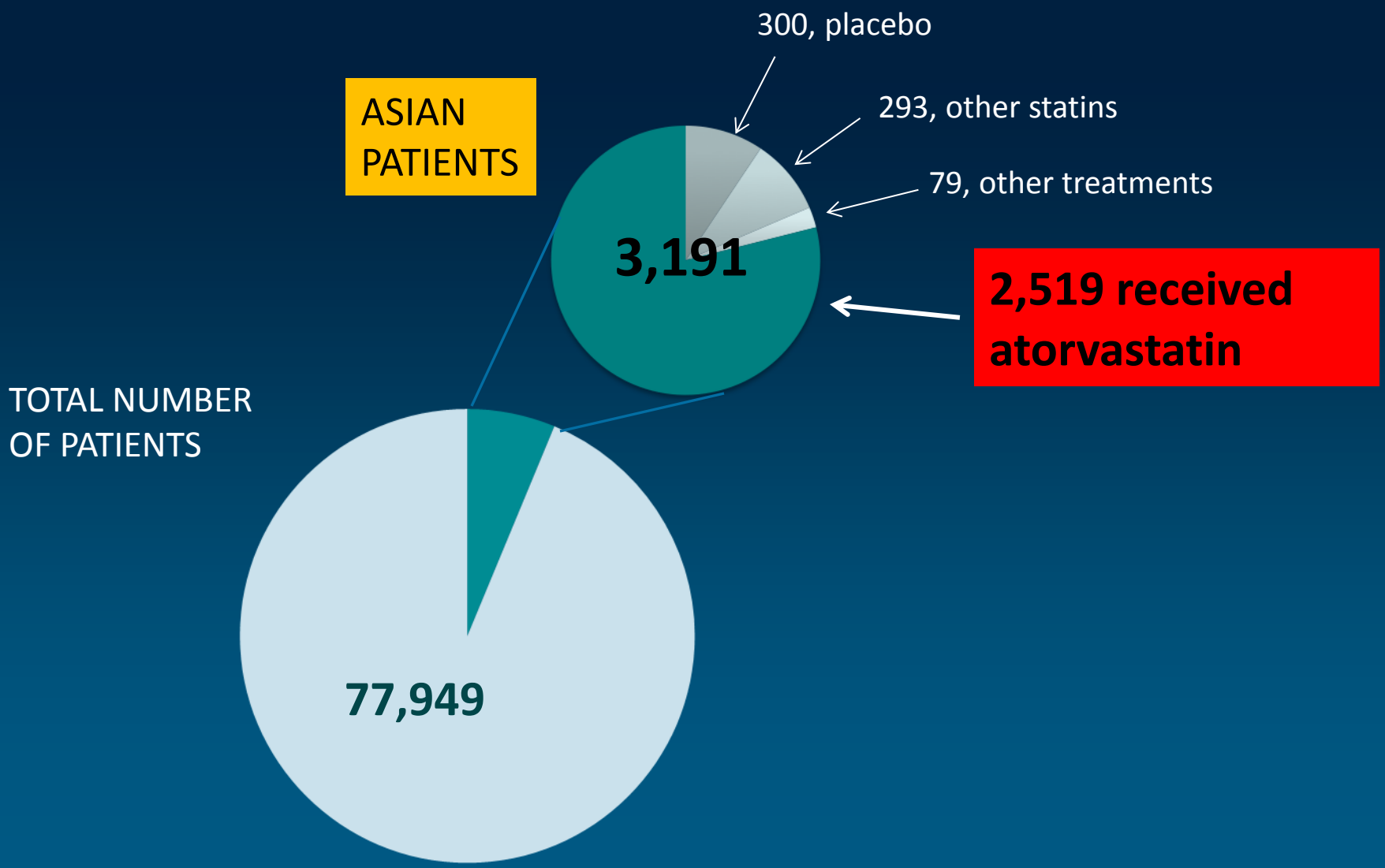
Key Atorvastatin Clinical Studies



Key to Clinical Sections:

- Lipid-Lowering Efficacy
- Clinical Endpoint
- Regression/Surrogate
- Non-cardiovascular
- Asia Region Trials

Total Number of Patients



Trials Included in Analysis

	Long-term trials	Short-term trials
Number	6	52
Median duration	3.1 to 4.9 years	4 to 72 weeks
Number of patients	39,169	38,780
Asians in study	547	2,644
Asians on atorvastatin	344	2,175

Long-term CV Outcome Trials

SPARCL	N=4,731
	Prior stroke
TNT	N=10,001
	Clinically evident coronary heart disease
IDEAL	N=8,888
	Had a myocardial infarction (MI)
CARDS	N=2,838
	Type 2 diabetes; ≥1 risk factor
ASPEN	N=2,410
	Type 2 diabetes; with or without MI
ASCOT-LLA	N=10,305
	Hypertension; ≥3 risk factors

Results: Overall Safety

- **Similar –** The incidence of AEs and SAEs for Asian patients and all patients
- **Similar –** Study discontinuations because of AEs between Asian patients and all patients
- **Rare –** Treatment-related SAEs in Asian patients
- **Not observed –** Dose relationship for AEs (all-cause and treatment-related) in Asian patients

Conclusions

- The safety profile of atorvastatin 10 mg to 80 mg is similar in Asian pts. and the overall study populations.
- In high-risk patients with coronary artery disease and the metabolic syndrome, very aggressive treatment of low-density lipoprotein (LDL) or ‘bad’ cholesterol reduces the risk for additional CV events.
- General rule: ***the lower the LDL-C, the better***
- New evidence may encourage physicians to help more people in Asia to reach cholesterol goals, particularly in high-risk patients – eg, patients with diabetes or chronic kidney disease

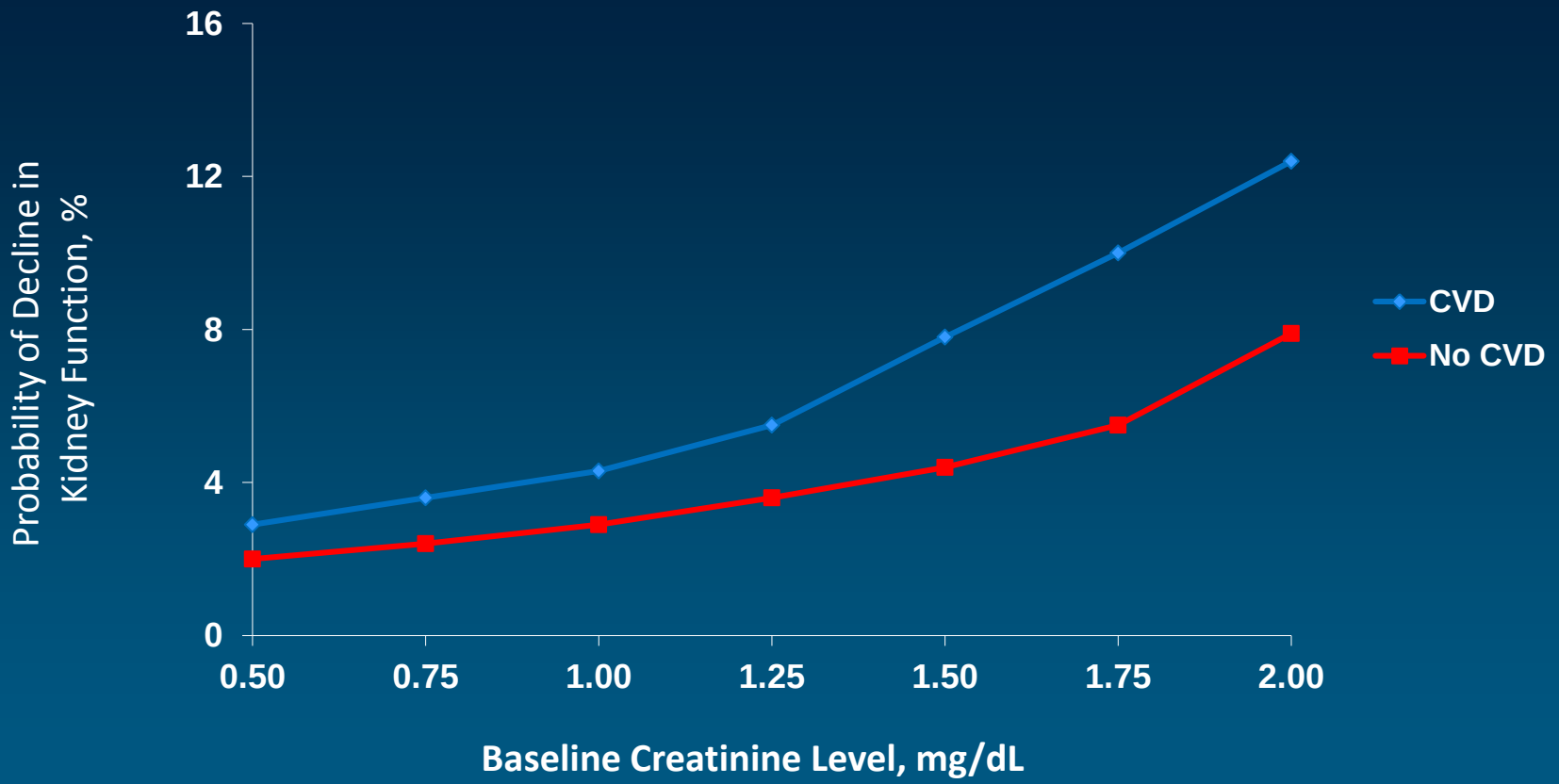
Is < *70 mg/dL* Safe in CKD patients?

Statin in CKD Patients

CARDS-CKD
TNT-eGFR
TNT-CKD
PLANET
ATV vs. RSV Meta-Analysis

CVD is an Independent Risk Factor for Renal Function Decline and Development of CKD

Adjusted Estimated Probability of Kidney Function Decline as a Function of the Baseline Serum Creatinine Level



Elsayed EF, et al. *Arch Intern Med.* 2007;167:1130-1136.

NKF Guidelines Recommend Aggressive LDL-C Management in DM & CKD

Year	Lipid Management Guidelines	LDL-C Goal
2003[1]	K/DOQI Clinical Practice Guidelines for Managing Dyslipidemia in CKD	<100 mg/dL in all CKD patients: • Initiate therapeutic lifestyle changes • Initiate a statin in LDL-C ≥130 mg/dL • May add a statin in LDL-C >100 mg/dL
2007[2]		<u><100 mg/dL in patients with diabetes and CKD stages 1-4:</u> • Initiate therapeutic lifestyle changes • Initiate a statin if LDL-C ≥100 mg/dL • <70 mg/dL is a therapeutic option

1. National Kidney Foundation. Am J Kidney Dis. 2003;41(suppl 3);S1-S91.
2. National Kidney Foundation. Am J Kidney Dis. 2007;49(suppl 2);S1-S180.

Effects of Atorvastatin on Kidney Outcomes and Cardiovascular Disease in Patients With Diabetes

CARDS-CKD Result

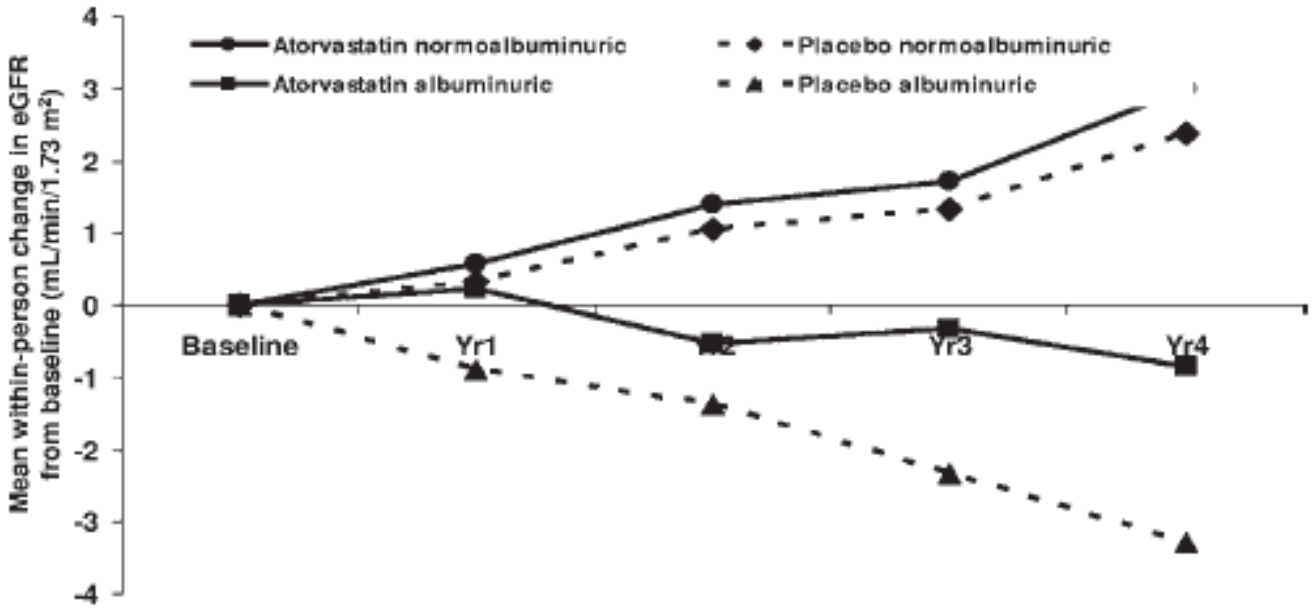


Figure 1. Yearly mean within-person change in estimated glomerular filtration rate (eGFR) by treatment group and baseline albuminuria. Net effect of atorvastatin on eGFR in those with normoalbuminuria: 0.13 mL/min/1.73 m^2/y; P = 0.1; in those with albuminuria: 0.38 mL/min/1.73 m^2/y; P = 0.03. Interaction between albuminuria and atorvastatin: β = 0.26 (95% confidence interval, −0.09 to 0.60; P = 0.1).

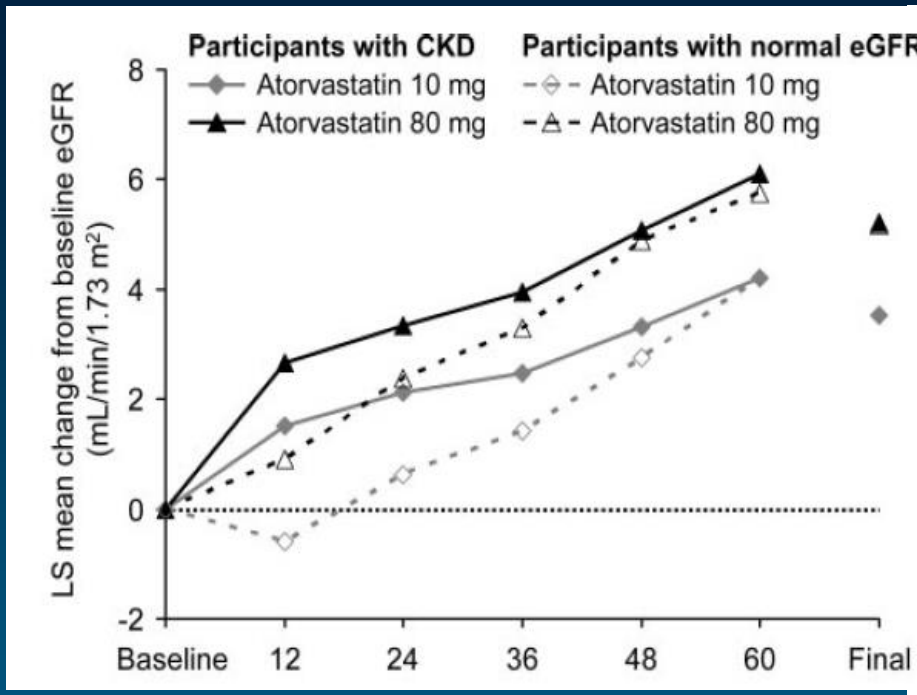
- Atorvastatin treatment was associated with **a modest improvement in annual change in eGFR**
- That was **most apparent in those with albuminuria** (net improvement, 0.38 mL/min/1.73 m2/y; P 0.03)

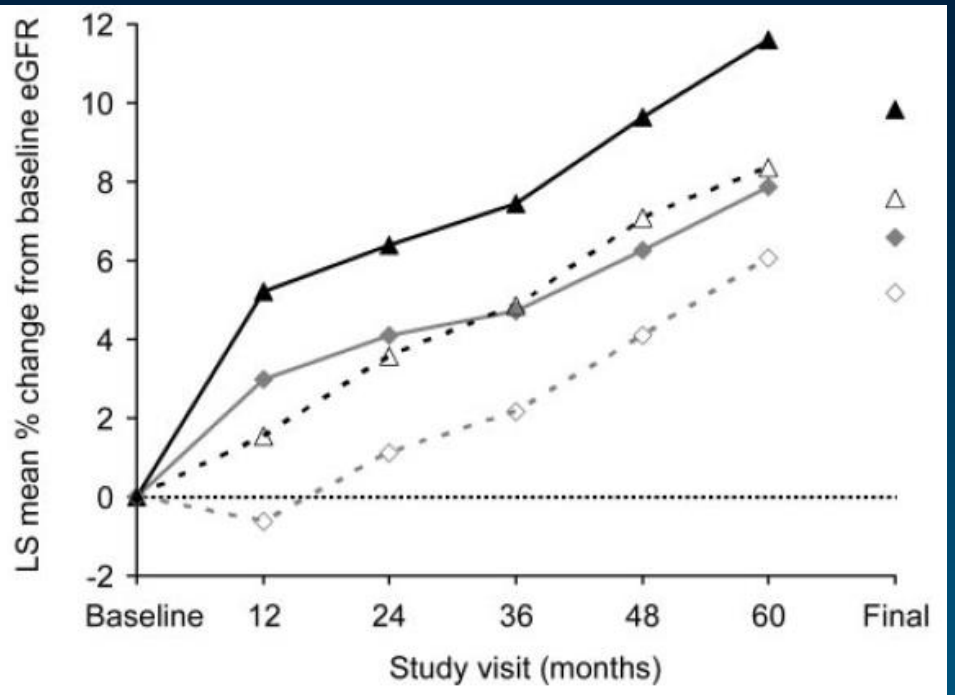
Am J Kidney Dis. 54:810-819

Effect of Intensive Lipid Lowering with Atorvastatin on Renal Function in Patients with Coronary Heart Disease

TNT-eGFR Result

LS mean change in eGFR and mean percentage change in eGFR in patients with CKD and patients with normal eGFR





- **Estimated GFR improved in both treatment groups but was significantly greater with Atorvastatin 80 mg than with 10 mg, suggesting this benefit may be dosage related**

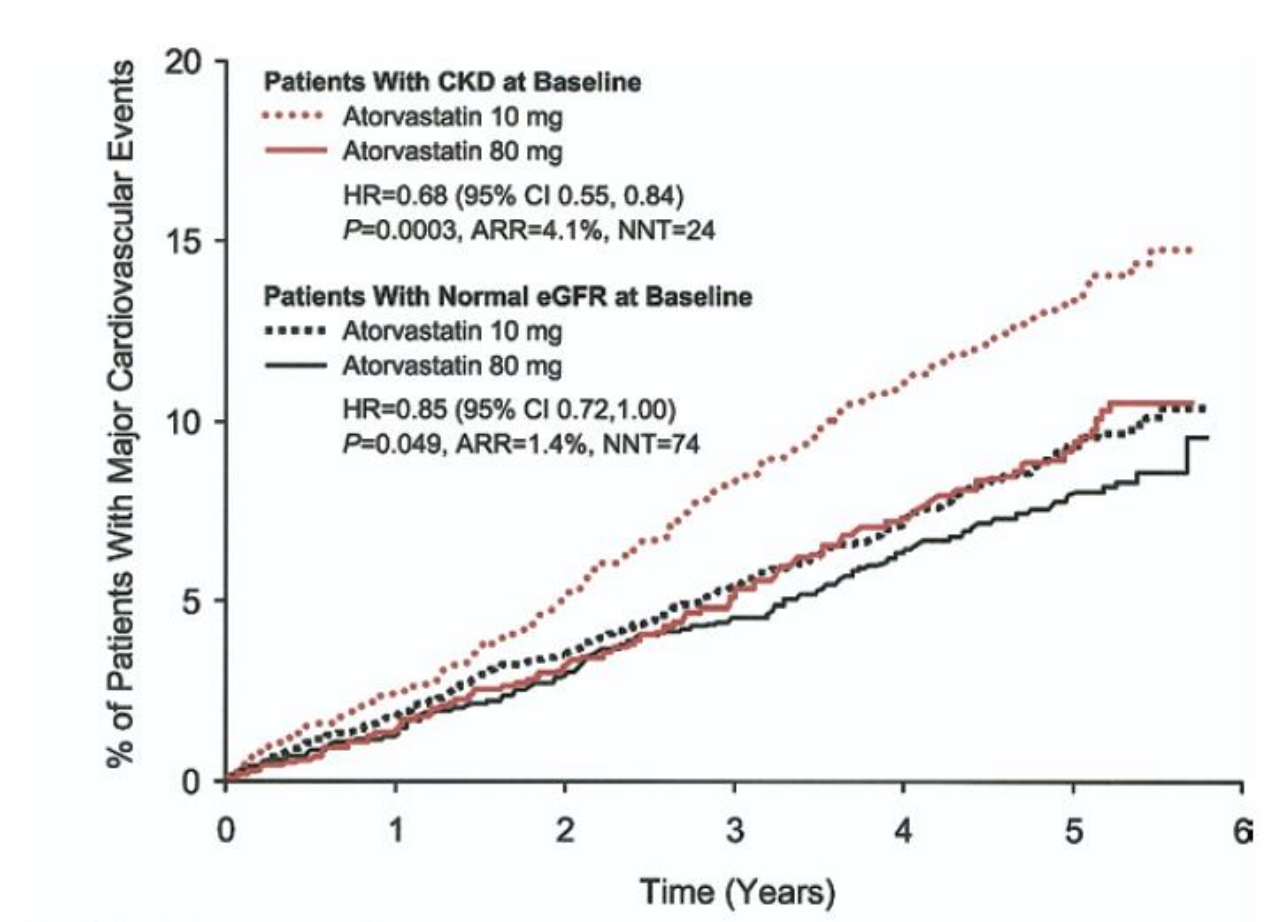
Shepherd J et al. *Clin J Am Soc Nephrol* 2: 1131–1139, 2007. doi: 10.2215/CJN.04371206

*CKD=Chronic kidney Diesase: eGFR <60 mL/min/1.73 m2

A Post hoc Analysis of TNT in Patients with CHD and CKD

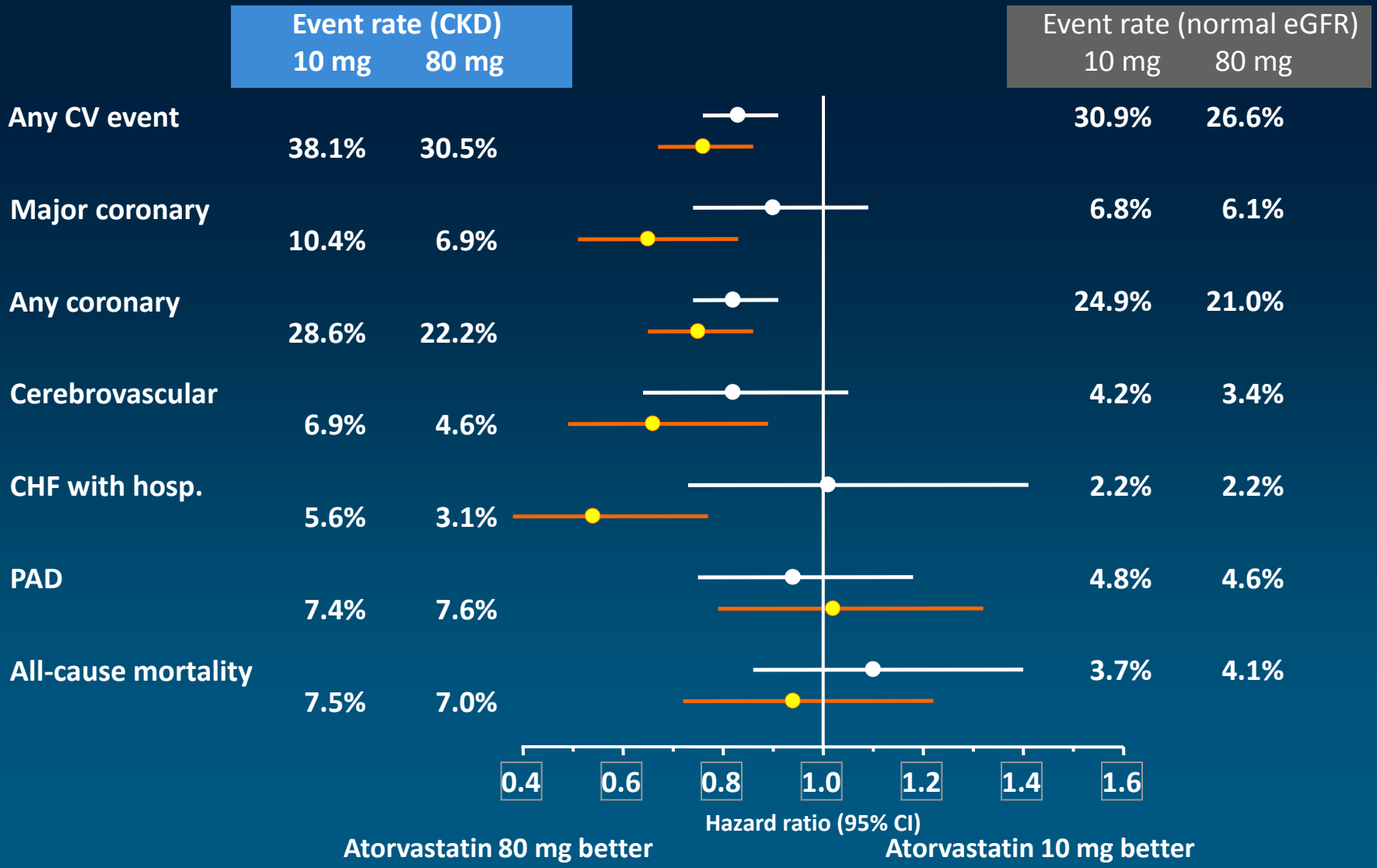
TNT-CKD Result

- Intensive lipid lowering with Atorvastatin 80 mg resulted in a **32% relative reduction in risk of major cardiovascular (CV) events** compared with 10 mg



Shepherd J et al. Am Coll Cardiol. 2008;51(15):1448-1454.

In patients with CKD, atorvastatin 80mg resulted in significant reductions in secondary event rates



Shepherd J et al. Am Coll Cardiol. 2008;51(15):1448-1454.

Safety in Patients With CKD and Patients With Normal eGFR

	No. of patients (%)			
	CKD		**Normal eGFR**	
	Atorva 10 mg (n=1505)	Atorva 80 mg (n=1602)	Atorva 10 mg (n=3324)	Atorva 80 mg (n=3225)
Hematuria (all-cause)	51 (3.4)	58 (3.6)	124 (3.7)	121 (3.8)
Albuminuria (all-cause)	25 (1.7)	28 (1.7)	47 (1.4)	53 (1.6)
CPK ≥10 × ULN*	0	0	0	0
ALT and/or AST ≥3 × ULN*	1 (0.1)	22 (1.4)	8 (0.2)	38 (1.2)

Shepherd J et al. Am Coll Cardiol. 2008;51(15):1448-1454.

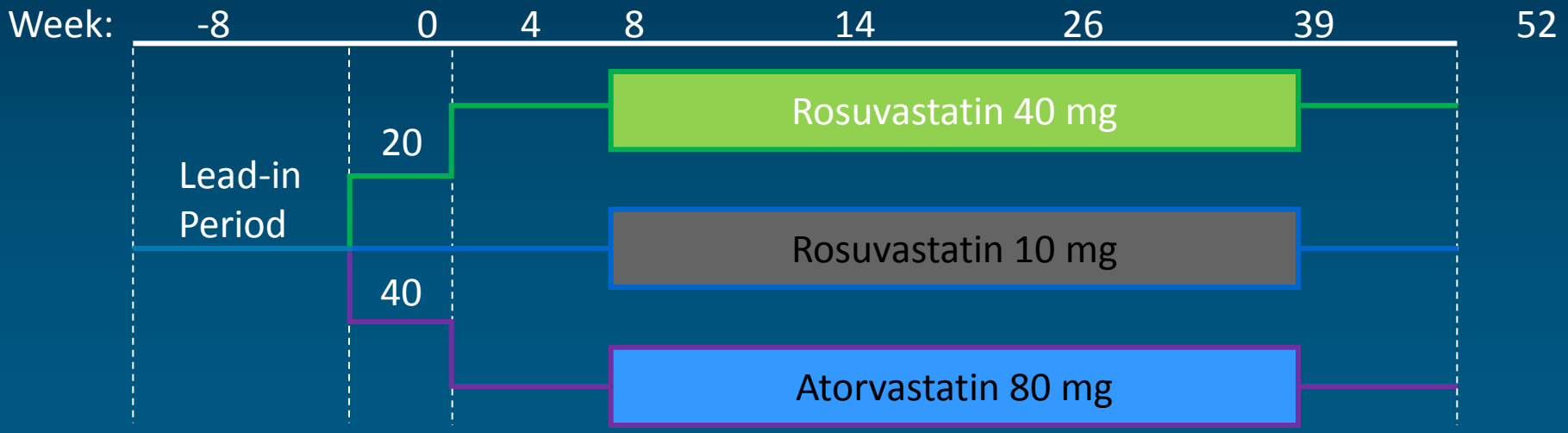
PLANET 1 and 2: Study Design

- **PLANET 1**: 325 patients with type I or II diabetes (ITT population)

- **PLANET 2**: 220 patients without diabetes (ITT population)

  - **Inclusion criteria**

    - Moderate proteinuria (urinary protein / creatinine ratio 500–5,000 mg/g)
    - Hypercholesterolaemia (fasting LDL-C ≥90 mg/dL (2.33 mmol/L)
    - ACE inhibitors or ARBs for ≥3 months prior to screening



1. Levey et al. J Am Soc Nephrol 2000; 11: 155A.

PLANET 1 and 2: Primary Endpoint - Effect on Proteinuria

Vs Baseline, **Atorvastatin 80 mg significantly reduced urinary protein ratio**, while Rosuvastatin 40 mg demonstrated no significant change in urinary protein ratio

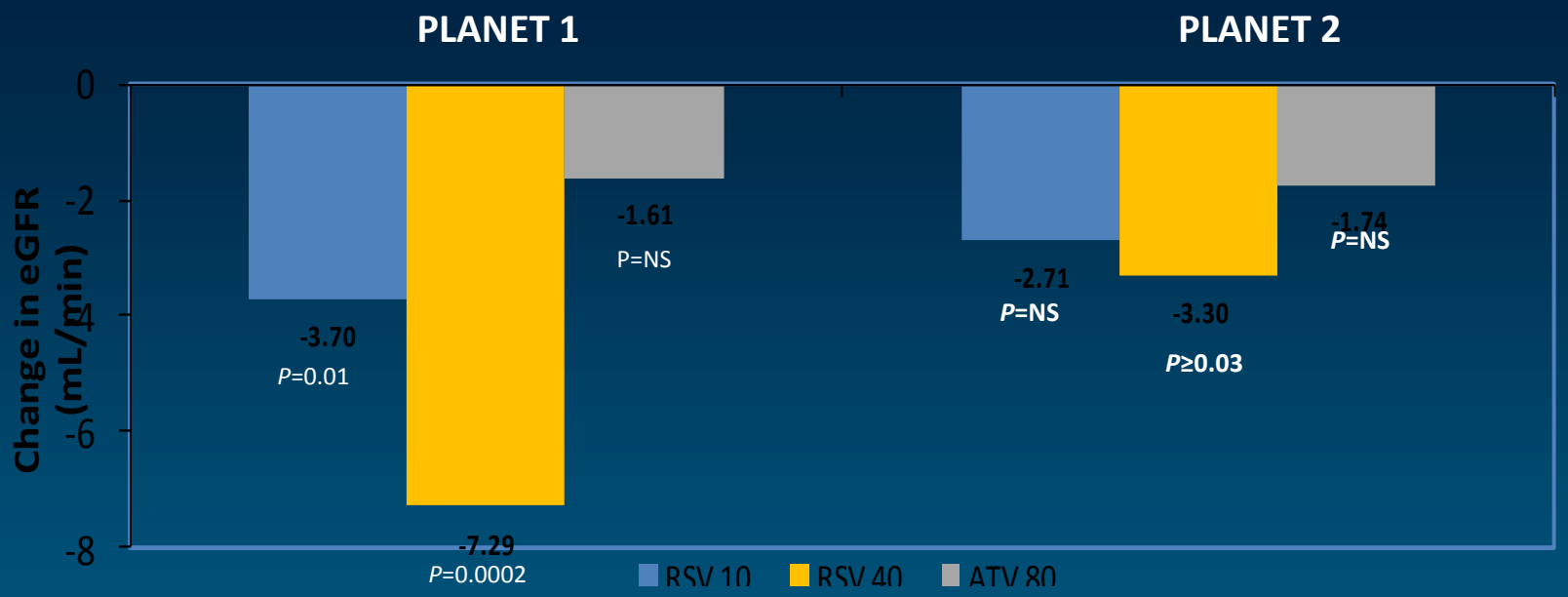
		Rosuvastatin 10 mg	Rosuvastatin 40 mg	Atorvastatin 80 mg
PLANET 1	**Urinary protein excretion**			
	Post:Pre protein / creatinine **% change** **P-value vs baseline**	– <5%* NS	– <5%* NS	**0.874** **-12.6** **0.033**
	Urinary albumin excretion			
	Post:Pre albumin / creatinine **% change** **P-value vs baseline**	– 'Small'* NS	0.836 -16.4 0.041	**0.823** **-17.7** **0.010**
PLANET 2	**Urinary protein excretion**			
	Post:Pre protein / creatinine **% change** **P-value vs baseline**	– <10%* NS	– <10% NS	**0.759** **-24.6†** **0.003**
	Urinary albumin excretion			
	Post:Pre albumin / creatinine **% change** **P-value vs baseline**	0.879 – 0.390	0.967 – 0.696	**0.719** **-28.1** **0.002**

**Not specified whether change was increase or decrease.*

†P = 0.01 vs. rosuvastatin 20/40 mg.

PLANET 1 and 2: Secondary Endpoint - Changes in eGFR

PLANET 1: Patinets on RSV lost more kidney function over 52 weeks than did those on ATV
PLANET 2: RSV 40 mg significantly decreased eGFR vs baseline



1. Clinicaltrials.gov.

PLANET 1 and 2: Summary of Reported Adverse Events

n (%)	Rosuvastatin 10 mg	Rosuvastatin 40 mg	Atorvastatin 80 mg	P-value
PLANET 1 (Diabetic patients)	n = 116	n = 123	n = 110	
Any adverse event	69 (59.5)	79 (64.2)	63 (57.3)	NS
Any serious adverse event	18 (15.5)	20 (16.3)	21 (19.1)	NS
Any renal adverse event	9 (7.8)	12 (9.8)	5 (4.5)	NS
Acute renal failure	**0**	**5 (4.1)**	**1 (0.9)**	**<0.05**
Serum creatinine doubling	**0**	**6 (4.9)**	**0**	**<0.01**
Doubling of serum creatinine or acute renal failure	**0**	**9 (7.3)**	**1 (0.9)**	**<0.01**
PLANET 2	n = 69	n = 87	n = 80	
Any adverse event	37 (53.6)	49 (56.3)	42 (52.5)	NS
Any serious adverse event	10 (14.5)	6 (6.9)	5 (6.3)	NS
Any renal adverse event	4 (5.8)	6 (6.9)	3 (3.8)	NS
Acute renal failure	0	1 (1.1)	0	NS
Doubling of Serum creatinine	1 (1.4)	0	0	NS
Doubling of serum creatinine or acute renal failure	1 (1.4)	1 (1.1)	0	NS

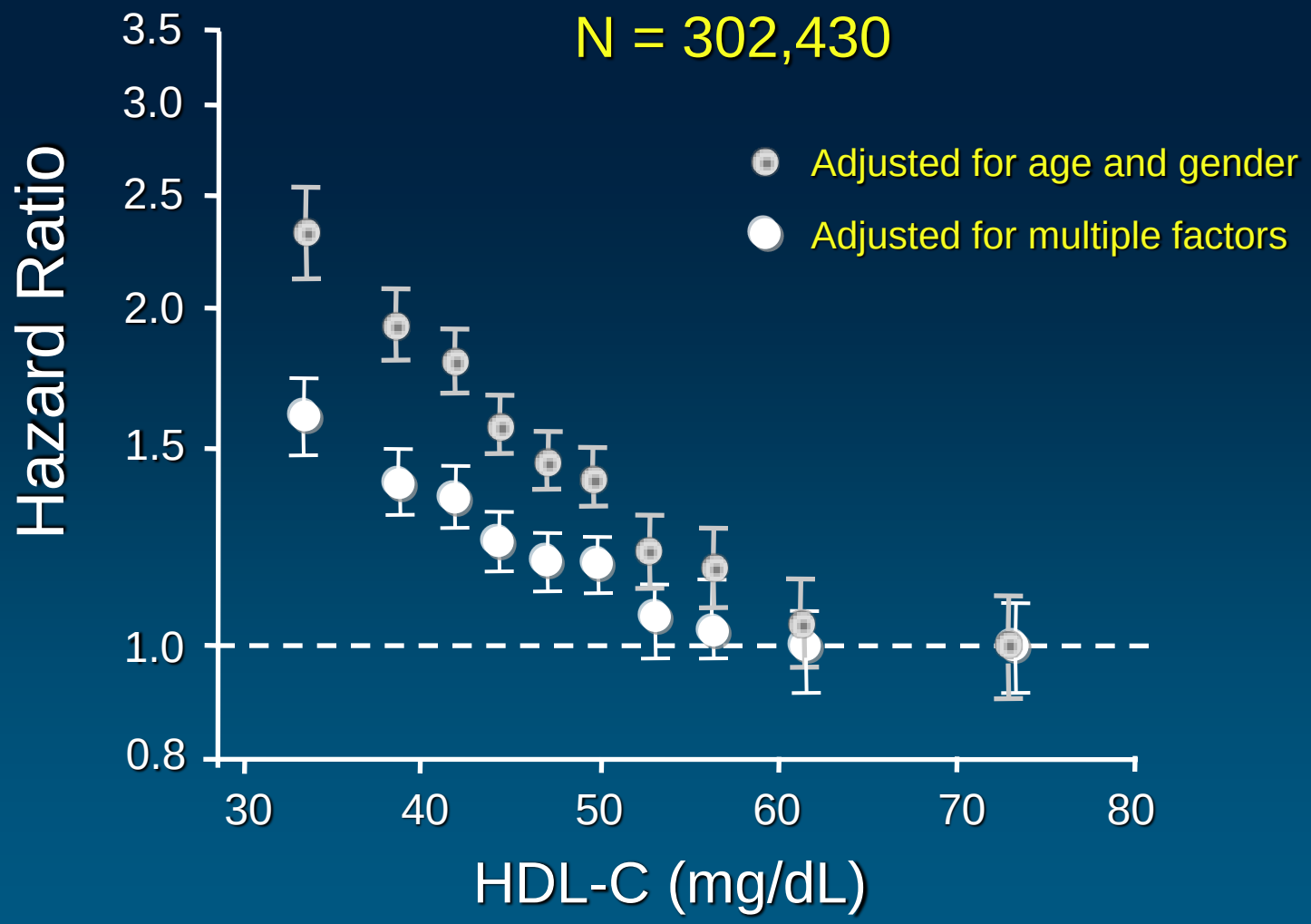
PLANET Conclusions

- In people with or without diabetes with proteinuria:
  - Rosuvastatin 10 or 40 mg had no effect on proteinuria, whereas atorvastatin 80 mg reduced proteinuria
  - Rosuvastatin 40 mg was associated with a significant decline in eGFR, whereas atorvastatin 80 mg showed no change in eGFR
  - With respect to statin-induced renal protection or renal damage, atorvastatin 80 mg had a clear advantage over rosuvastatin 40 mg in the studied renal patient populations

Despite the effective reduction in CV risk achieved by lowering LDL-C with statins, many people remain at risk and have furt her CV events

One factor responsible for this residual C V risk is a low level of **HDL-C**

Coronary heart disease and HDL-C

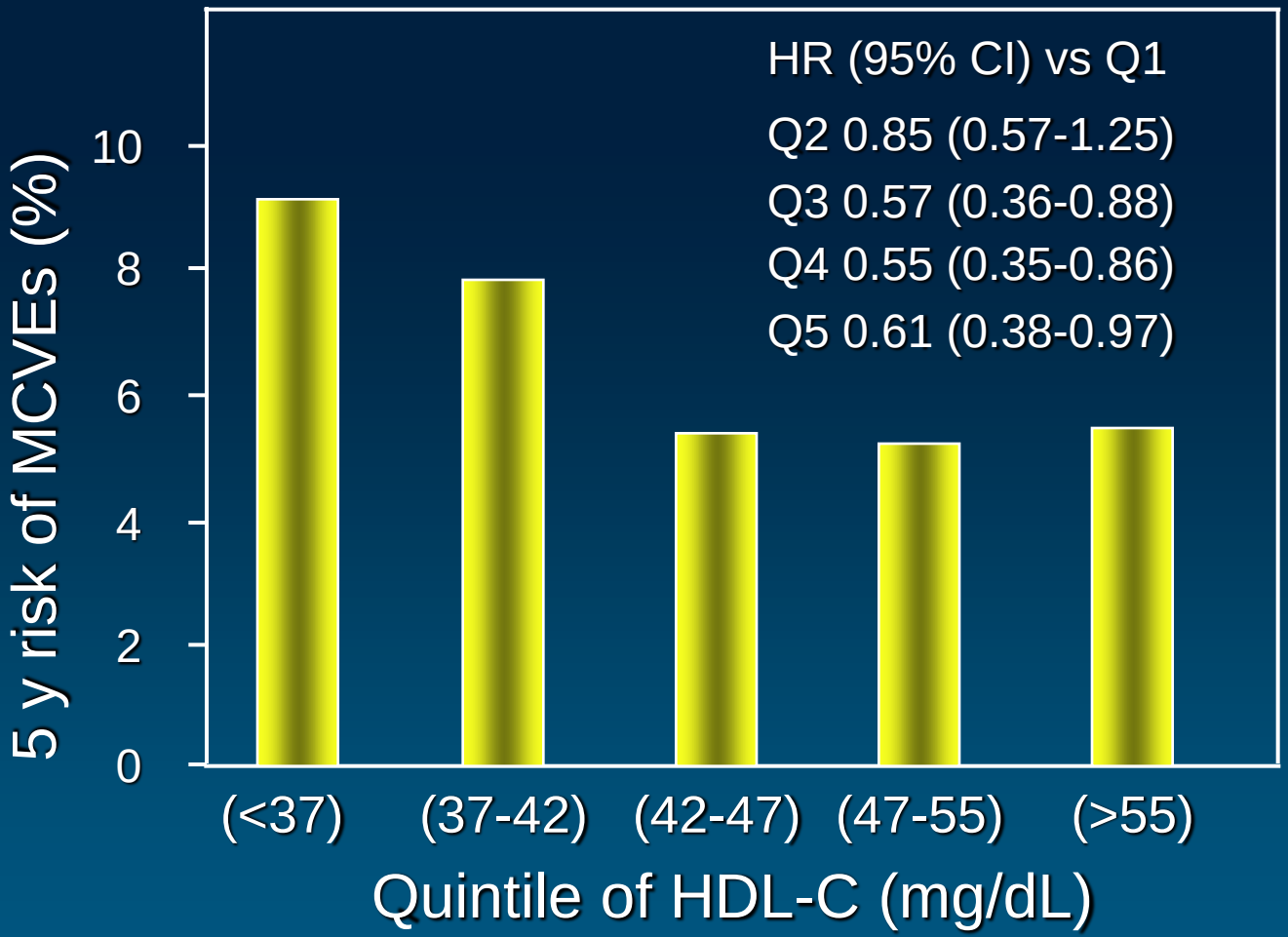


The Emerging Risk Factors Collaboration. JAMA 2009;302:1993-2000.

Question

Does the HDL level matter if the LDL-C is very low?

MCVE Frequency by HDL level in group with LD L-C < 70 mg/dL (Adjusted for baseline LDL)



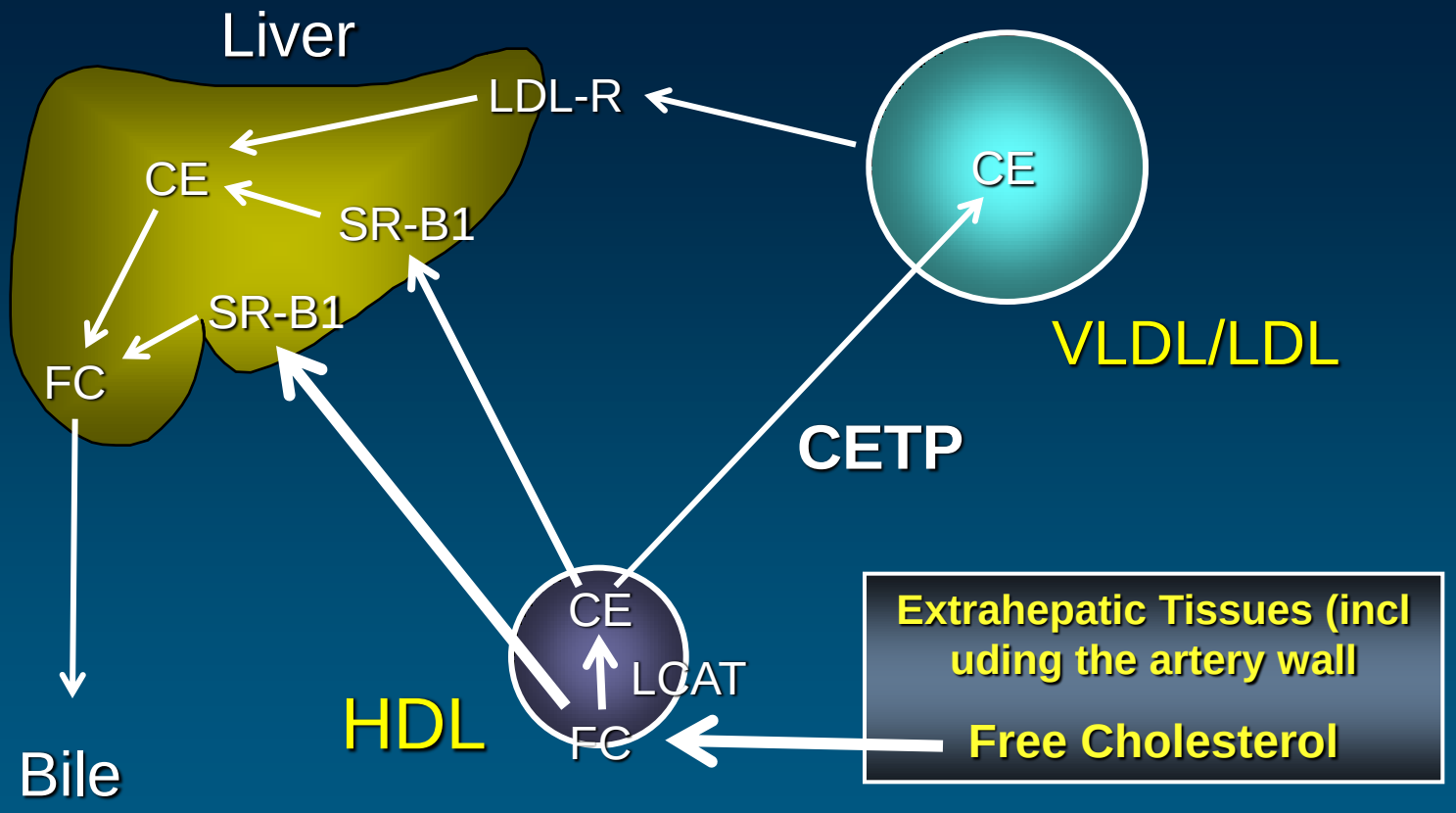
No of Events	57	50	34	34	35
No of Patients	473	525	550	569	544

Barter et al, NEJM 2007, 357; 13, 1301-1310

Potential protective properties of HDL

- Promote cholesterol efflux
- Anti-oxidant properties
- Anti-thrombotic properties
- Anti-inflammatory properties
- Improve endothelial function
- Promote endothelial repair
- Improve diabetic control
- Other

CETP
(humans, non-human primates, rabbits)



Human Genetics

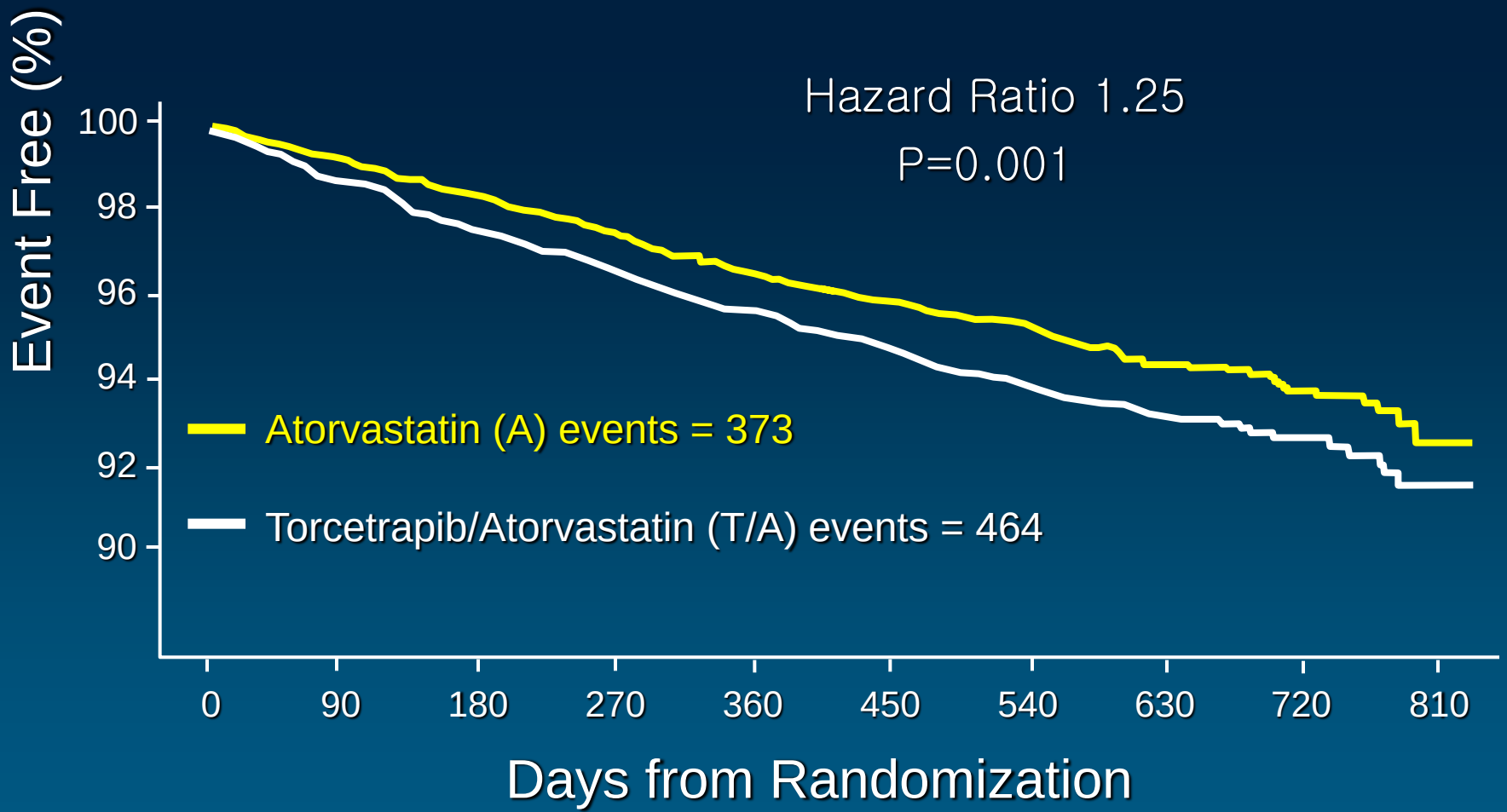
Four very large human studies found tha t genetic variants of CETP associated wi th reduced levels of CETP activity are ac companied by higher HDL-C, lower LDL-C and reduced CV risk

Thompson et al JAMA2008;299:2777-278
Voight et al Lancet, online ahead of publication, 17 May 2012
Ridker et al. Circ Cardiovasc Genet 2009; 2: 26
Johannsen et al JACC 2012; 60:2041

But

Inhibition of CETP with torcetrapib and dalcetrapib did not reduce CV events a nd, in the case of torcetrapib, caused s erious harm.

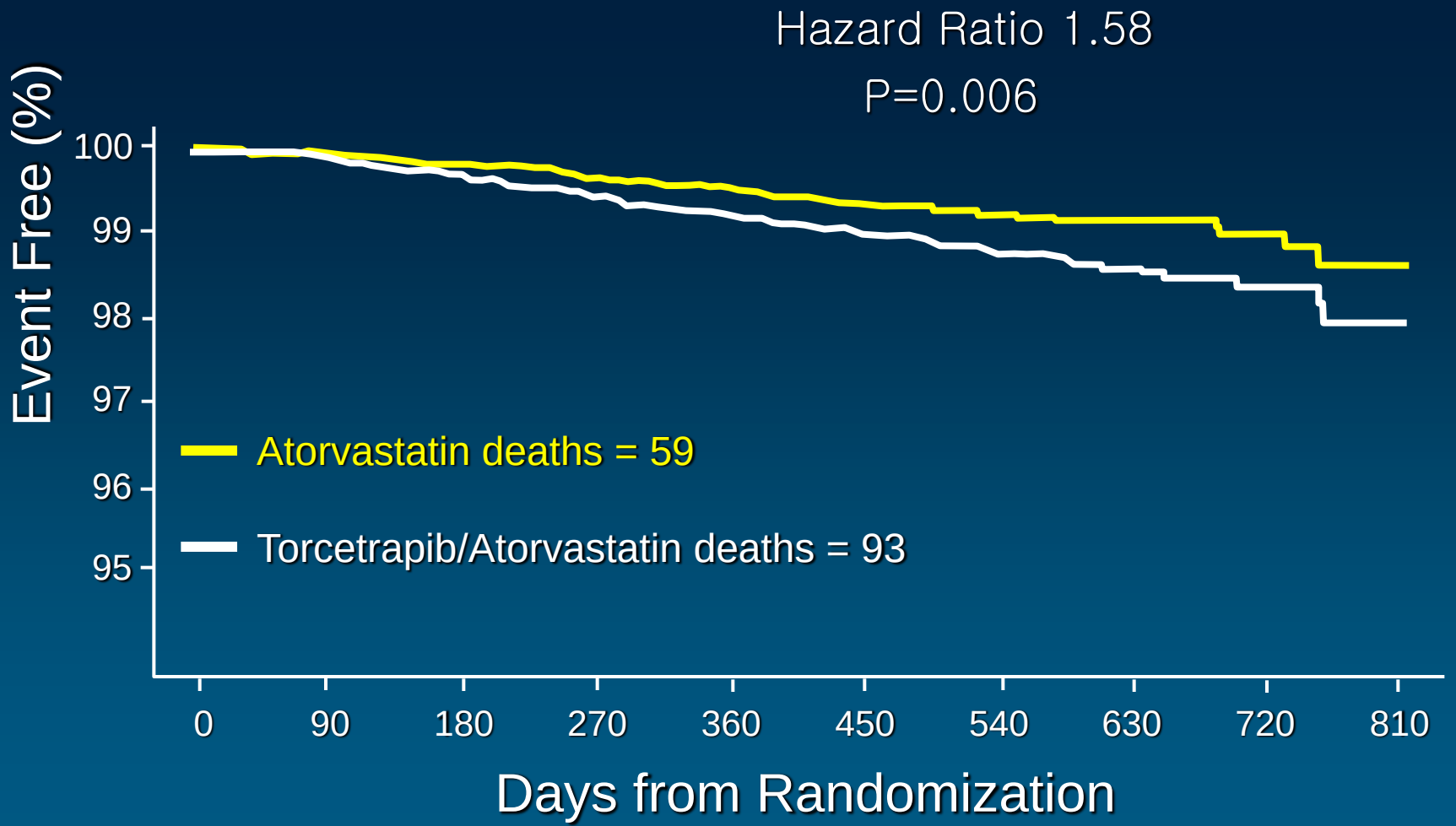
ILLUMINATE: Primary Endpoint:
Time to First MCVE*: Kaplan-Meier Plot



*Major cardiovascular event: CHD death, non-fatal MI, stroke or hospitalization for unstable angina

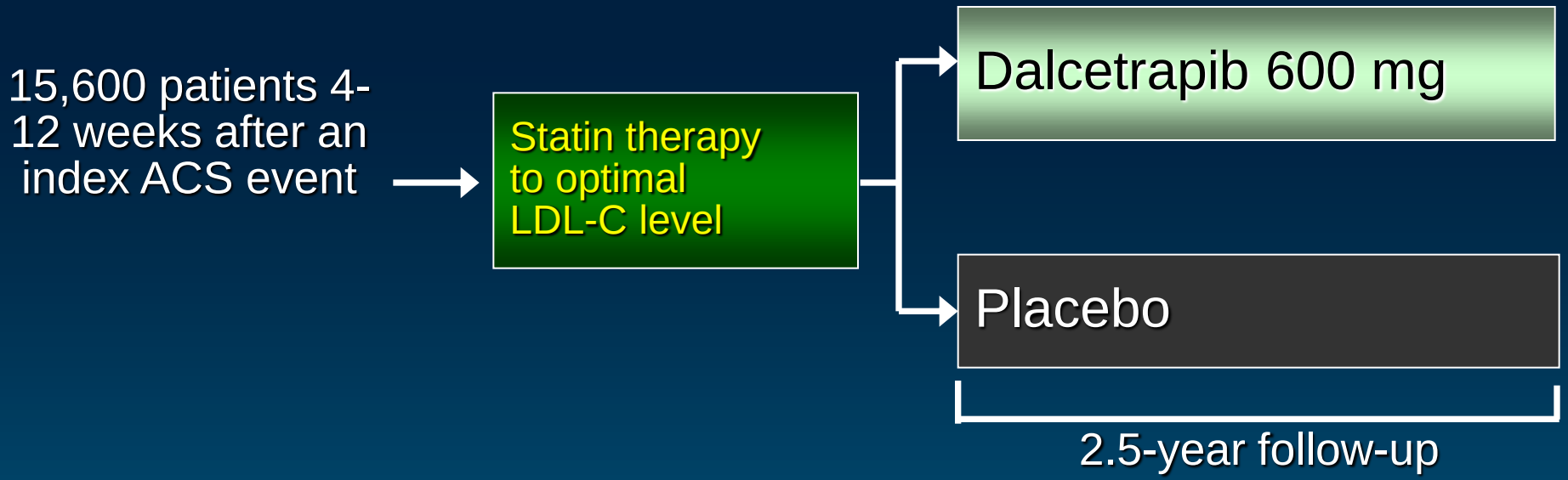
Barter et al, NEJM 2007;357:2109

ILLUMINATE: Secondary Endpoint
Time to Death: Kaplan-Meier Plot



Barter et al, NEJM 2007;357:2109

dal-OUTCOMES Trial



Primary End Point

CHD death, non-fatal MI, atherothrombotic stroke , unstable angina requiring hospitalization or resu scitated cardiac arrest

Schwartz et al. Am Heart J. 2009;158:896.

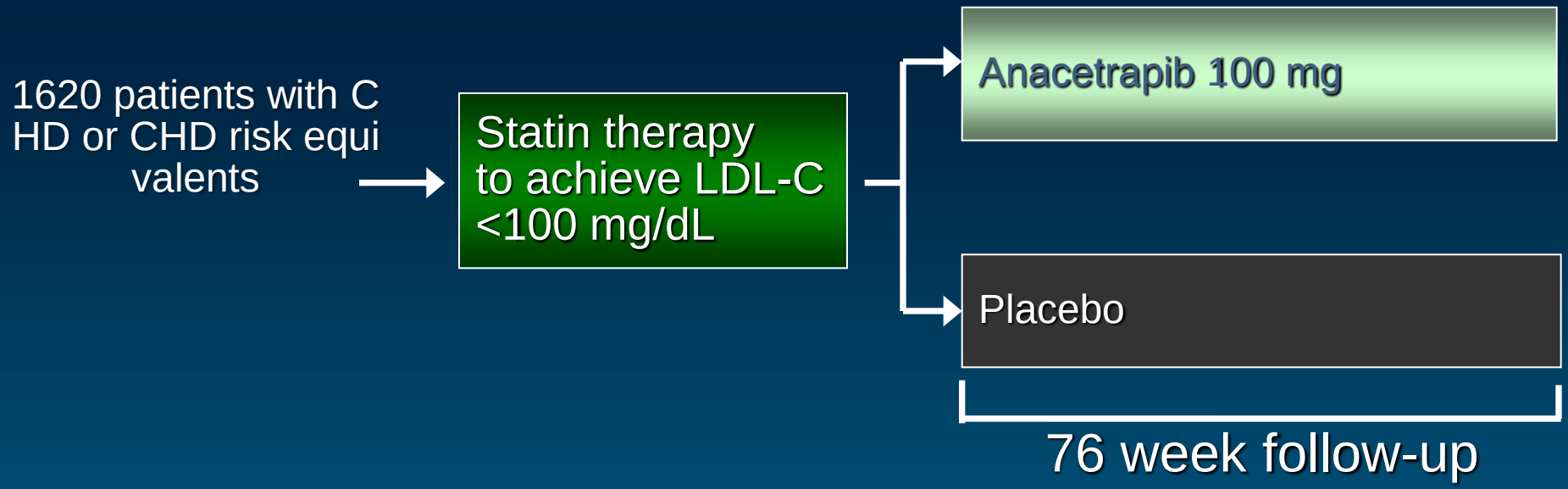
dal-OUTCOMES Trial

- It was announced in early May 2012 that the dal-OUTCOMES trial had been terminated early on the basis of futility.
- The early termination was solely on the basis of futility and not because of any safety issues.

http://www.roche.com/media_releases/med-cor-2012-05-07.htm

DEFINE trial

Determining the EFficacy and Tolerability of CETP INhibition with AnacEtrapib



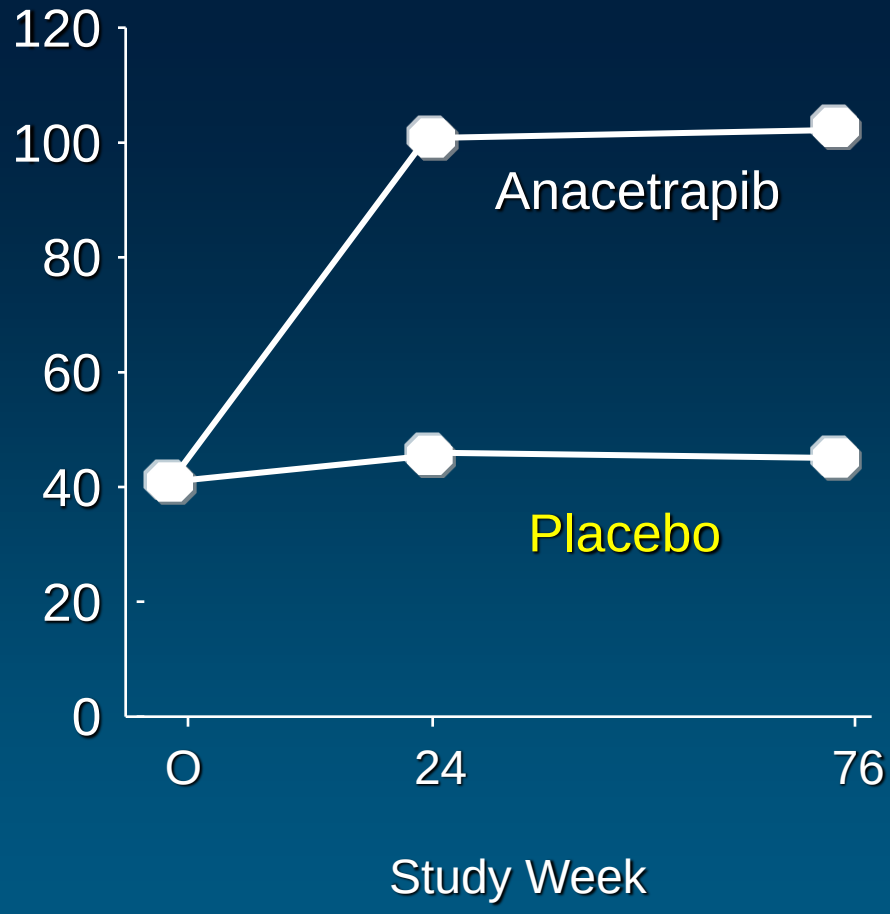
Primary End Point

Lipid efficacy and the safety

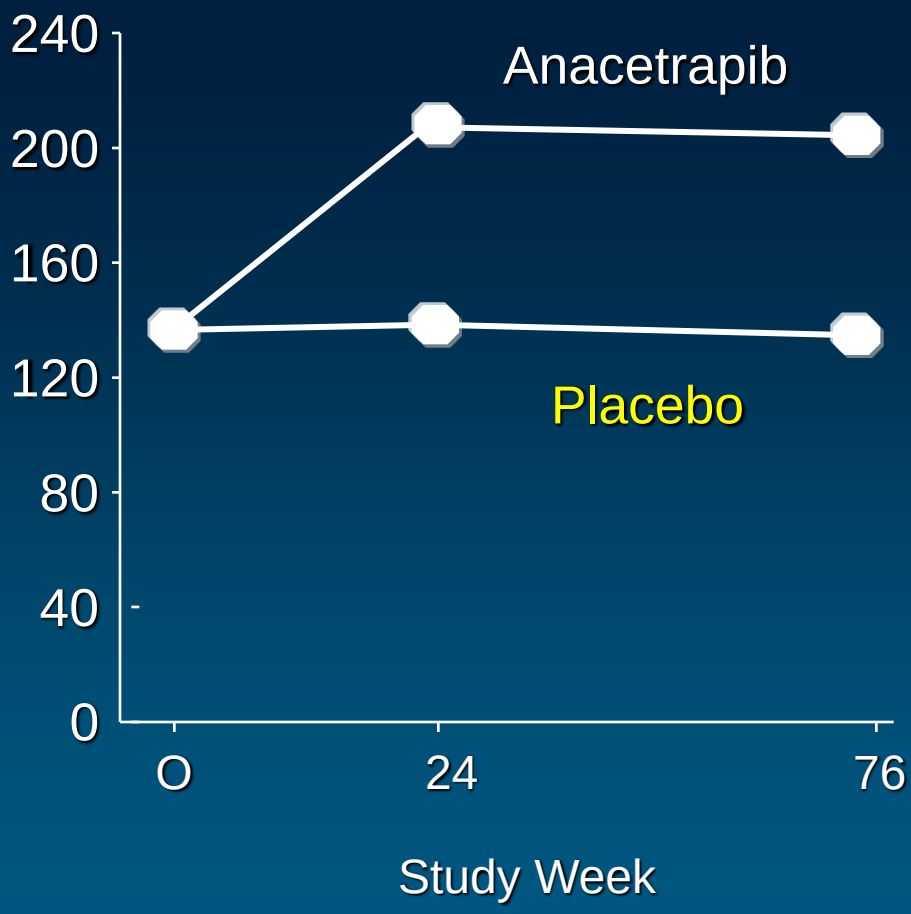
Cannon et al. NEJM. 2010; 363:2406-2415.

DEFINE trial

HDL-C (mg/dL)



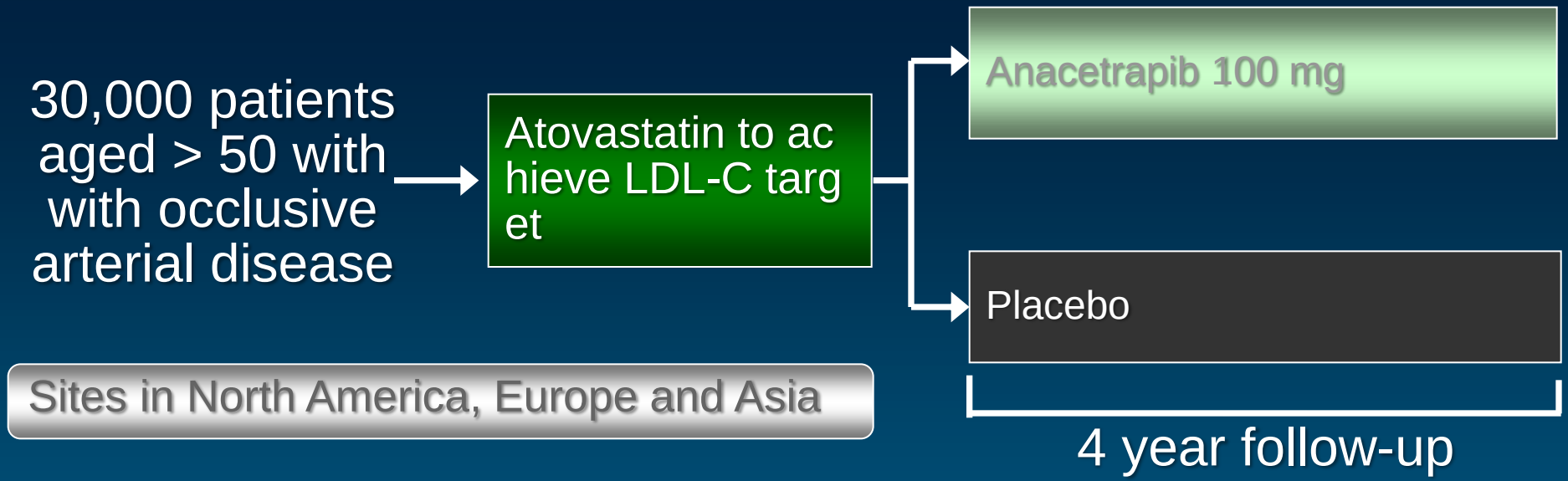
ApoA-I (mg/dL)



Cannon et al. NEJM. 2010; 363:2406

REVEAL trial

Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification



Primary End Point

Coronary death, myocardial infarction or coronary revascularization

Planned completion in 2017

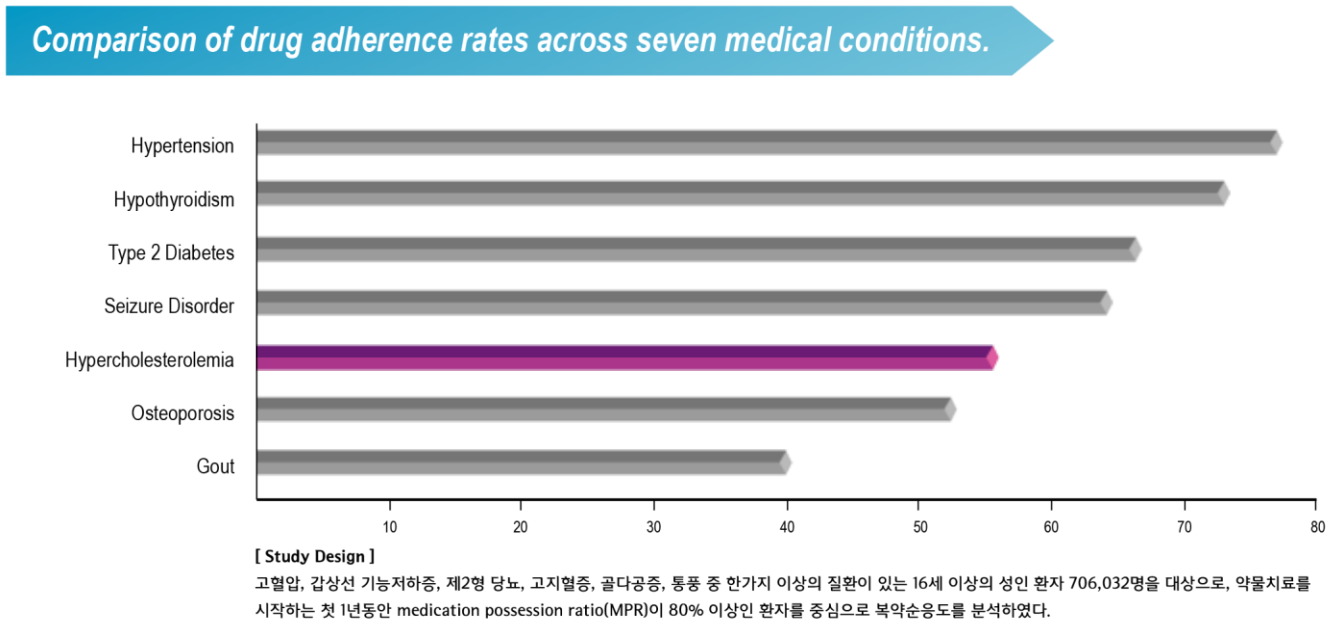
www.revealtrial.org

Better Compliance
for Better Outcome

Compliance Issues

- Side effects
- Asymptomatic disease
- Cost
- Memory
- Understanding
- Swalloing

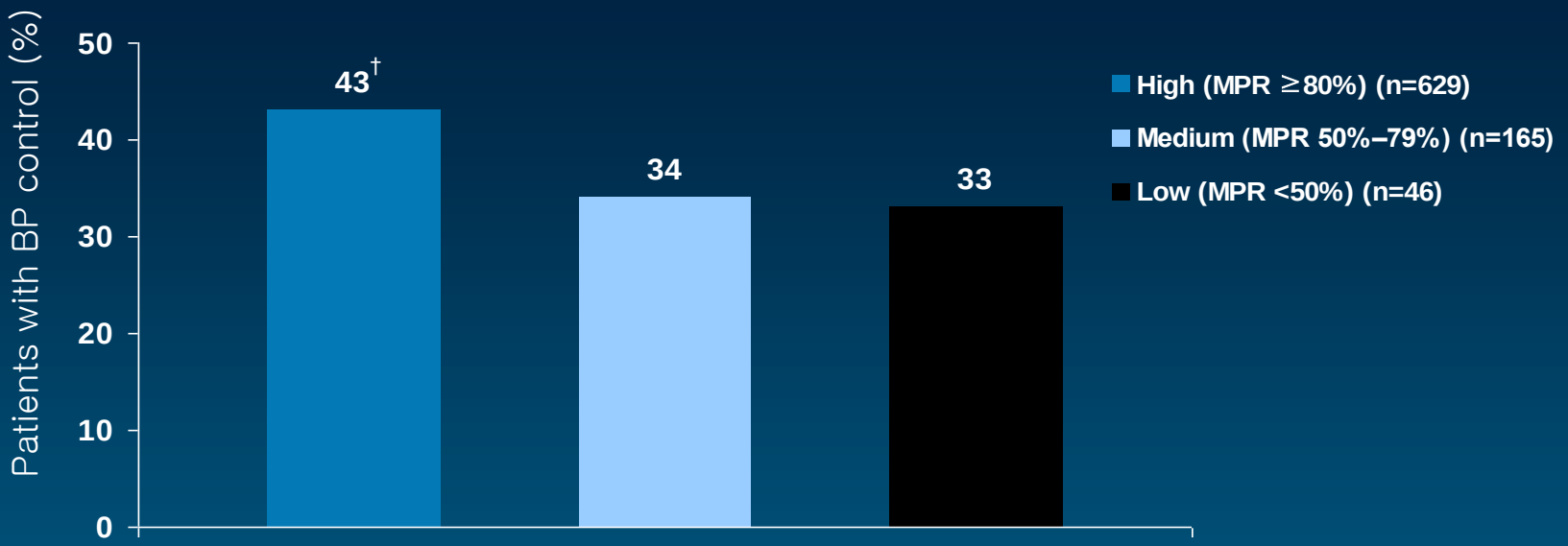
1 year after diagnosis of chronic disease, patient compliance was reduced



Dislipidemia Patients showed *45% of reduction in compliance* 1 year after diagnosis

Reference : Briesacher BA, et al. Pharmacotherapy. 2008;28(4):437–443.

Low adherence to antihypertensive therapy (AHT): *worse BP control*

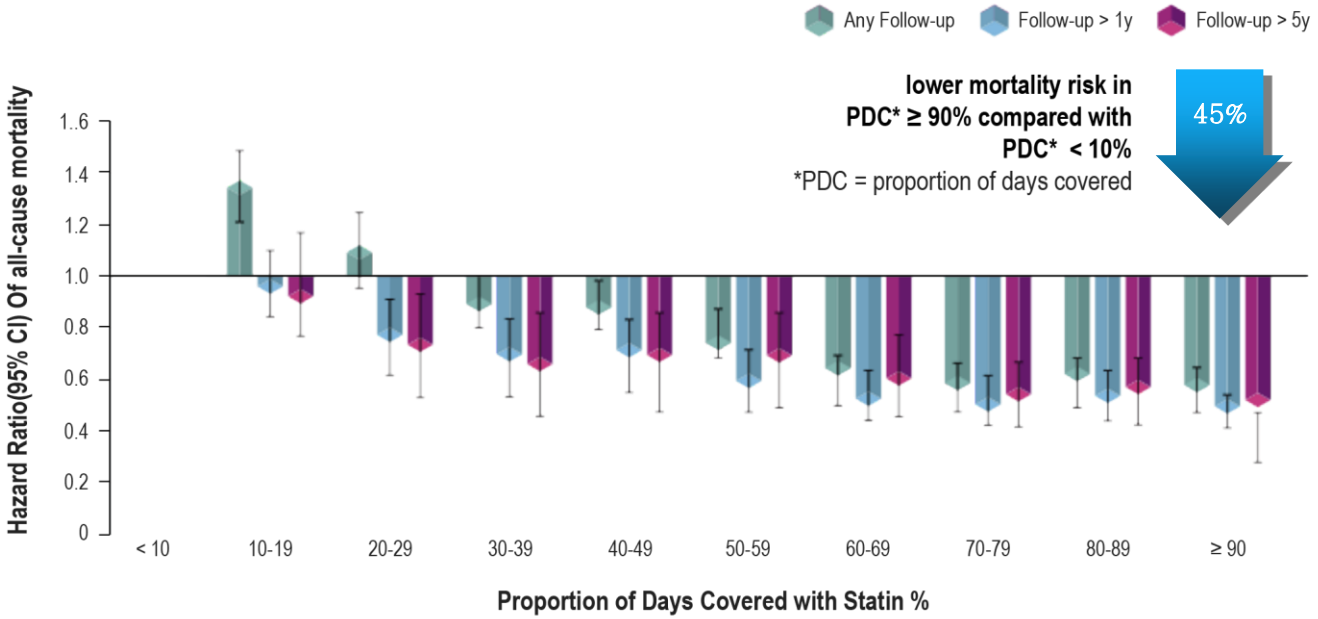


†P=0.06 prior to adjustment; P=0.026 in regression analysis

Retrospective, population-based study of medical and pharmacy claims from 13 health plans from 1999-2002 HEDIS data. N=840 patients who had received monotherapy or fixed-dose combination therapy during the time BP was measured; ≥3 AHT Rxs prior to BP measurement; and ≥1 AHT Rx after BP measurement. Medication possession ratio (MPR).

Bramley T, et al. J Managed Care Pharm. 2006:239-245.

Statin Adherence Is Associated with All-cause Mortality



Continuation Statin Treatment and All-Cause Mortality Study design

- 70만 명 규모의 이스라엘 건강보험 데이터에서 18세 이상 성인 중 1998년 1월 1일부터 2006년 12월 31일까지 스타틴 처방을 받은 환자를 대상으로 실행된 retrospective cohort 연구
- 총 299,918 중 CHD 및 기타 심혈관계 질환이 없는 primary prevention cohort(136,052명)와 CHD가 있는 secondary prevention cohort(93,866명)에서 순응도(PDC*)와 All-Cause Mortality의 연관성을 평가함

* PDC : 스타틴을 처음 처방받은 날짜로부터 연구 종료 시점까지 처방받은 스타틴의 총 개수로 측정함

PDC≥90% group showed **45% lower all-cause mortality** compared to PDC<10% Group

Reference : Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD, Continuation of statin Treatment and All-Cause Mortality. Arch Intern Med 2009;169(3):260-268.

Physicians have varying degrees of control over factors that impact adherence

Modifiable causes of nonadherence

Less able to control		More able to control
Patients are forgetful and/or stubborn	Patients do not understand that they are at significant risk and must take medication	High pill burden and unsynchronized initiation make it difficult to take medication

Potential solutions to nonadherence

Address nonadherent behaviours with patients	Communicate patients' global risk	Prescribe treatment regimens that optimize adherence

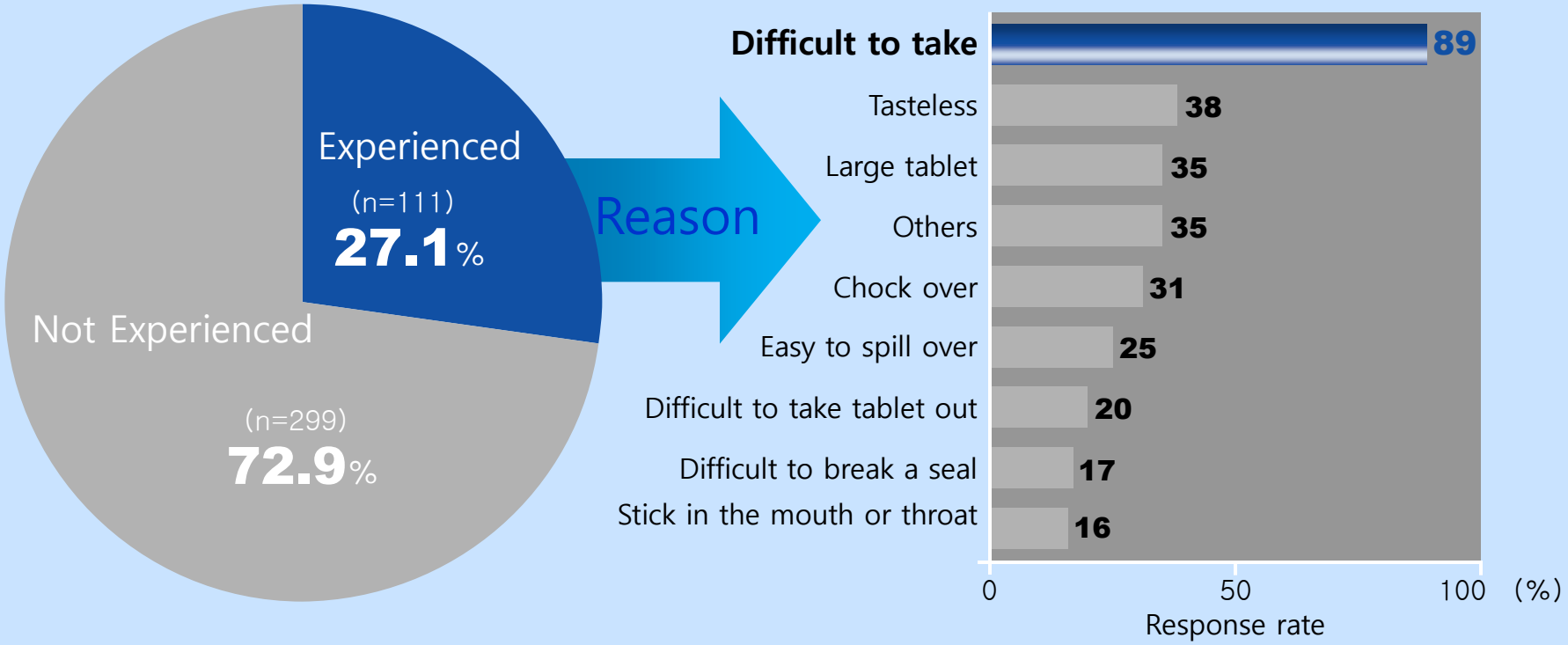
Enhanced Formulation of Statin is Expected to Improve Patient's Compliance.

Lipitor becomes
Round and smaller
for better compliance

One out of four elderly experiences choking on a drug in administration

Reason to choke on drugs is “difficult to take drugs.”

Experience and reason to choke on drugs



【Respondents】 410 elderly people aged 65 or older (Self-help, Needed support or Needed nursing care) taking one or more tablets daily who live in nursing home, special elderly nursing home or elderly housing.

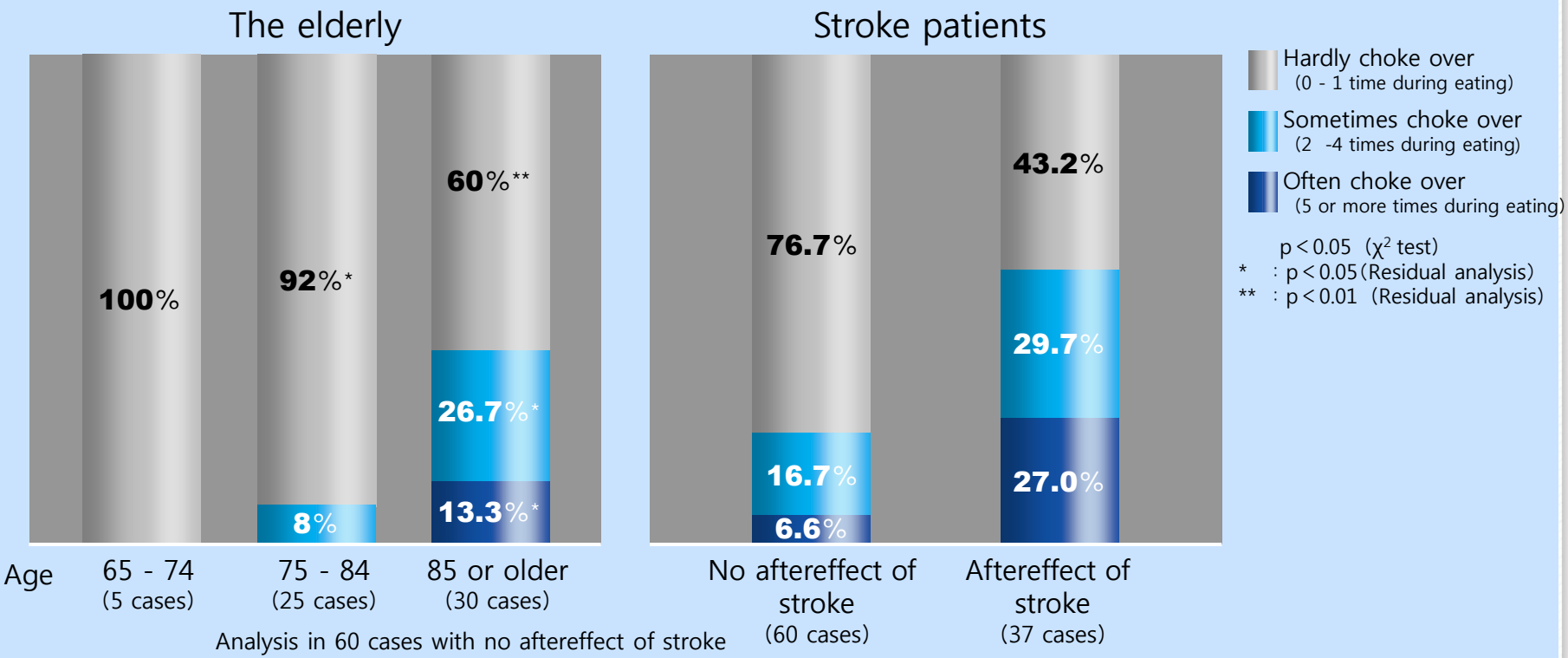
【Method】 An interview survey was conducted to grasp drug administration and awareness about dosage form among the elderly.

Takao Hashimoto: Based on Ther Res 27(6): 1219, 2006 [L20060710145]

What kind of patients would suffer from swallowing difficulties?

Elderly or stroke patients would suffer. If patient are aged at 75 or older, or suffer from the after effect of stroke, they are highly likely to choke over as an indicator of swallowing difficulties.

Choking frequencies in the elderly and stroke patients



【Subjects】 97 people in need of care aged 65 or older who live in the care health facility. (37 cases with aftereffect of stroke and 60 cases with no aftereffect of stroke)

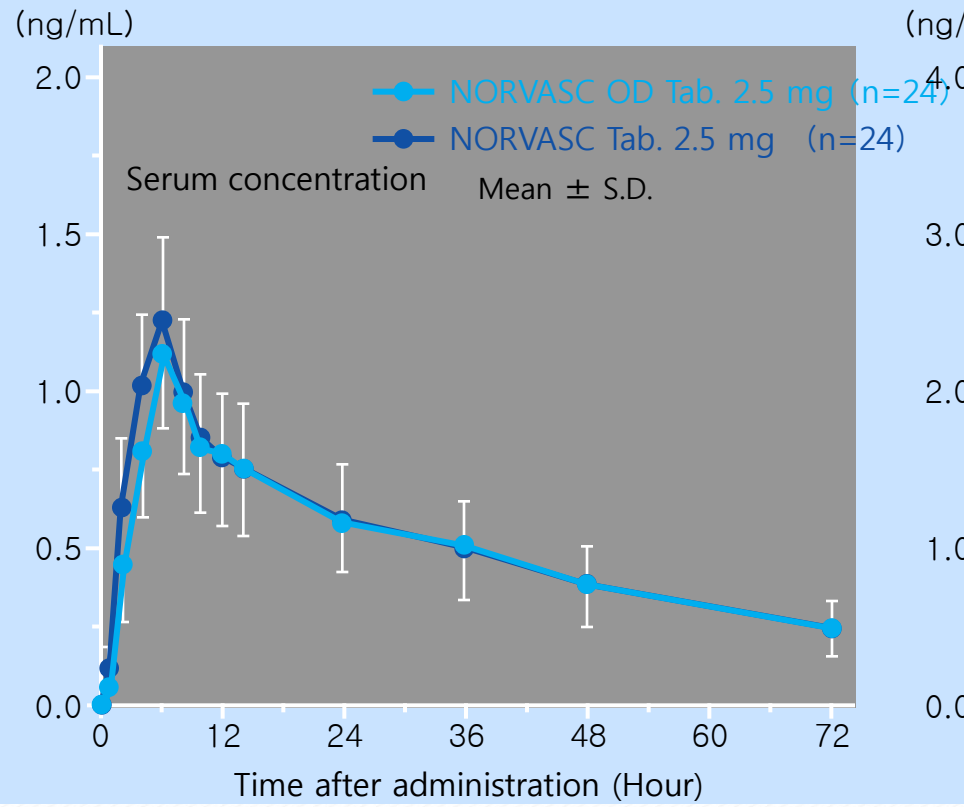
【Method】 Relation between older age or stroke and choking frequencies as a indicator of eating or swallowing difficulties is considered.

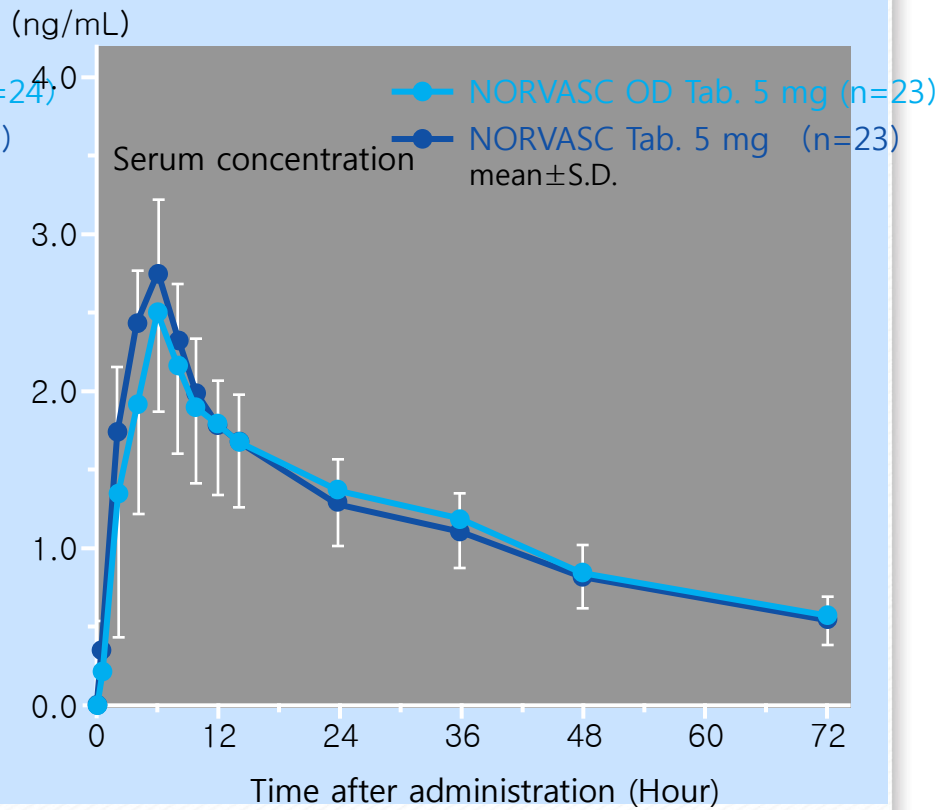
Teruo Yokoi and others: Based on physical therapy science 19(4): 347, 2004[L20080130043]

NOVASC OD tab. is expected to achieve similar efficacy to NORVASC tab.

NORVASC OT tab. is bioequivalent to the traditional NORVASC tab.

Serum concentration Trend in NORVASC OD tablet and NORVASC tablet





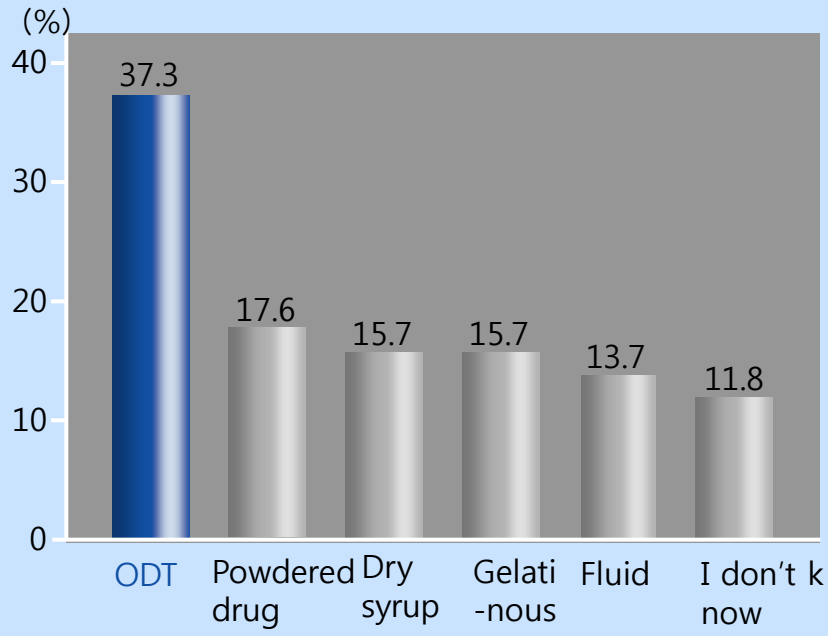
【Subjects】 Healthy adults
【Method】 Single oral administration of NORVASC OD tablet or NORVASC 2.5mg or 5mg by cross-over method

社内資料

OD tab. is accepted by patients and caretakers

If it is easy for patients to take drugs, caretakers will reduce their burden. ※

Dosage form requested by patients

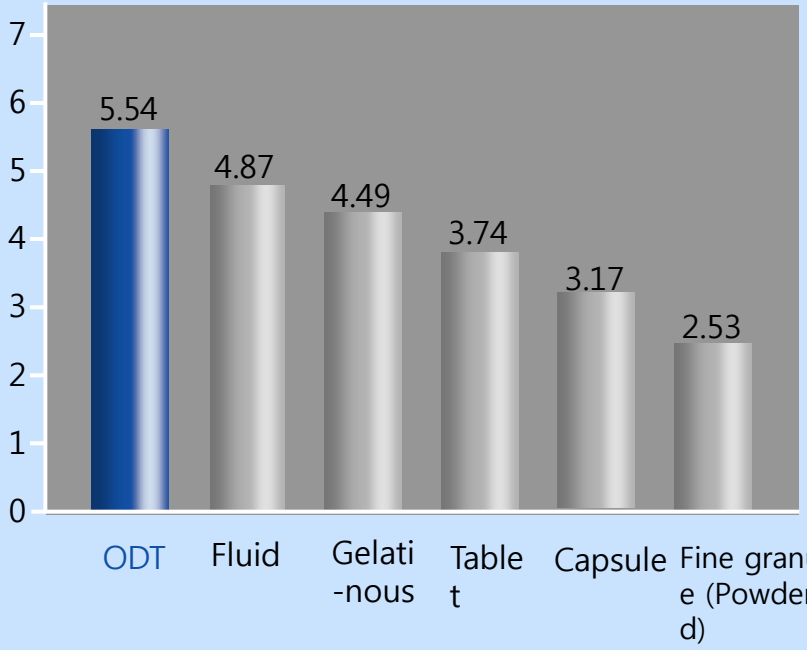


Takao Hashimoto: Based on Ther Res 27(6): 1219, 2006[L20060710145]

【Respondents】 Those who request dosage form change among 410 elderly people aged 65 or older (Self-help, Needed support or Needed nursing care) taking one or more tablets daily, living in nursing home, special elderly nursing home or elderly housing.

【Method】 An interview survey was conducted to grasp drug administration and the awareness about dosage form among the elderly.

Dosage form that caretakers can easily administer



Yukimichi Imai: Created based on Treatment 87(2): 433, 2005[L20050215027]

【Respondents】 210 caretakers responded among 404 caretakers providing home care for senile elderly

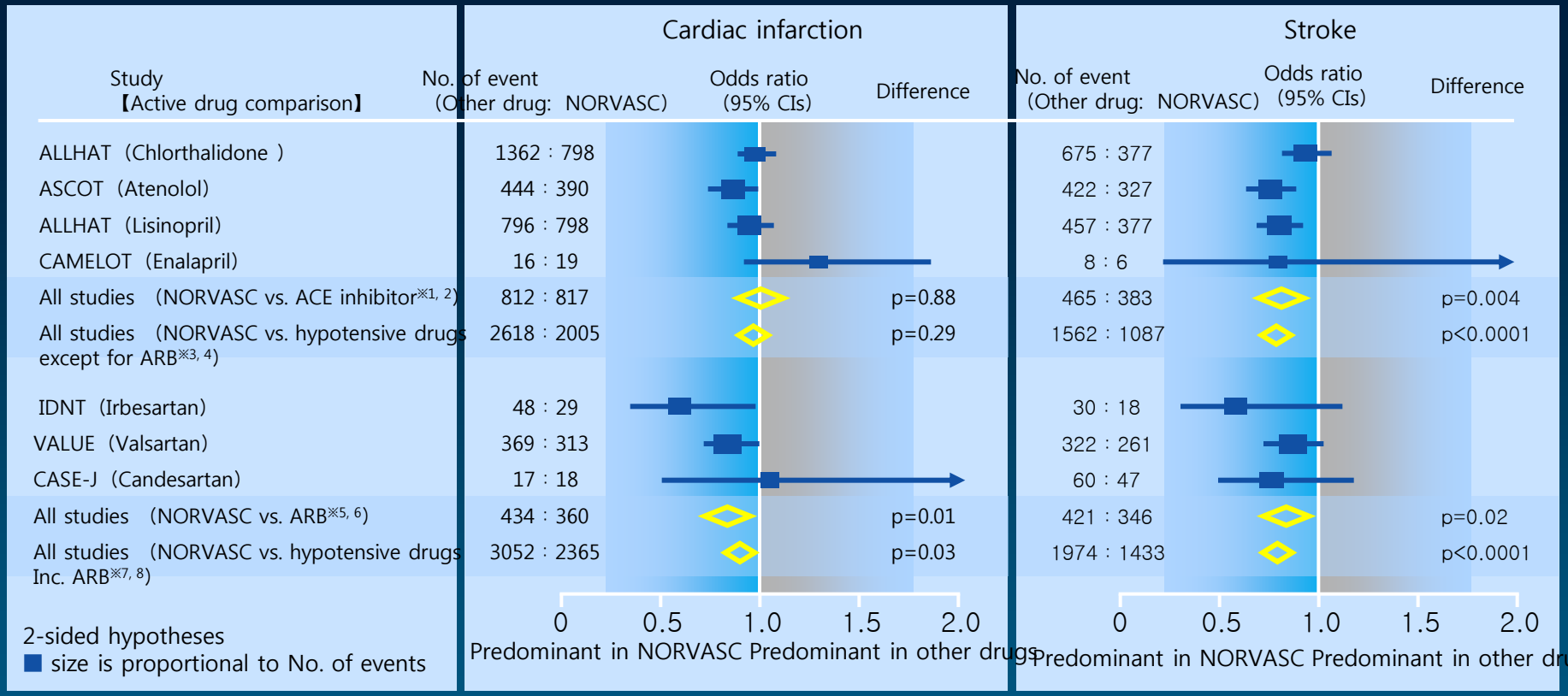
【Method】 An online survey was conducted to grasp administration management among home care caretakers.

* Caretakers are asked about administration after explaining each dosage form to evaluate on a 7-point scale: 1. Difficult to administer to 7. Easy to administer

NORVASC OD tab. is also expected to suppress cerebral and cardiovascular events like NORVASC

NORVASC is one of the most effective hypotensive drugs to suppress cerebral and cardiovascular events.

Cardiac infarction (CI) and stroke risk (NORVASC vs. other hypotensive drugs)



※1 Heterogeneity against CI : P=0.60 ※3 Heterogeneity against CI : P=0.21 ※5 Heterogeneity against CI : P=0.28 ※7 Heterogeneity against CI : P=0.12
※2 Heterogeneity against stroke : P=0.99 ※4 Heterogeneity against stroke : P=0.79 ※6 Heterogeneity against stroke : P=0.48 ※8 Heterogeneity against stroke : P=0.79

【Method】 Meta-Analysis with 12 studies (94,338 cases) to measure suppressive effects of stroke and cardiac infarction among patients suffering from hypertention, coronary disease and diabetic nephropathy, using NORVASC, Angiotensin receptor antagonist or others.

Wang, J. G. et al. : Based on Hypertens 50(1): 181, 2007 [L20070809046]

Take Home Message

- According to guideline, more aggressive treatment is needed for dyslipidemia treatment
- High dose statin treatment is safe in Asian population
- Atorvastatin is effective in patients with CKD
- CETP inhibitor need more outcome data
- Compliance issue is important for reducing cardiovascular event

SEVERANCE HOSPITAL

CARDIOVASCULAR HOSPITAL

Thank You For Your Attention !