REAL CAD study : What would be the clinical benefit from high dose PIV ?

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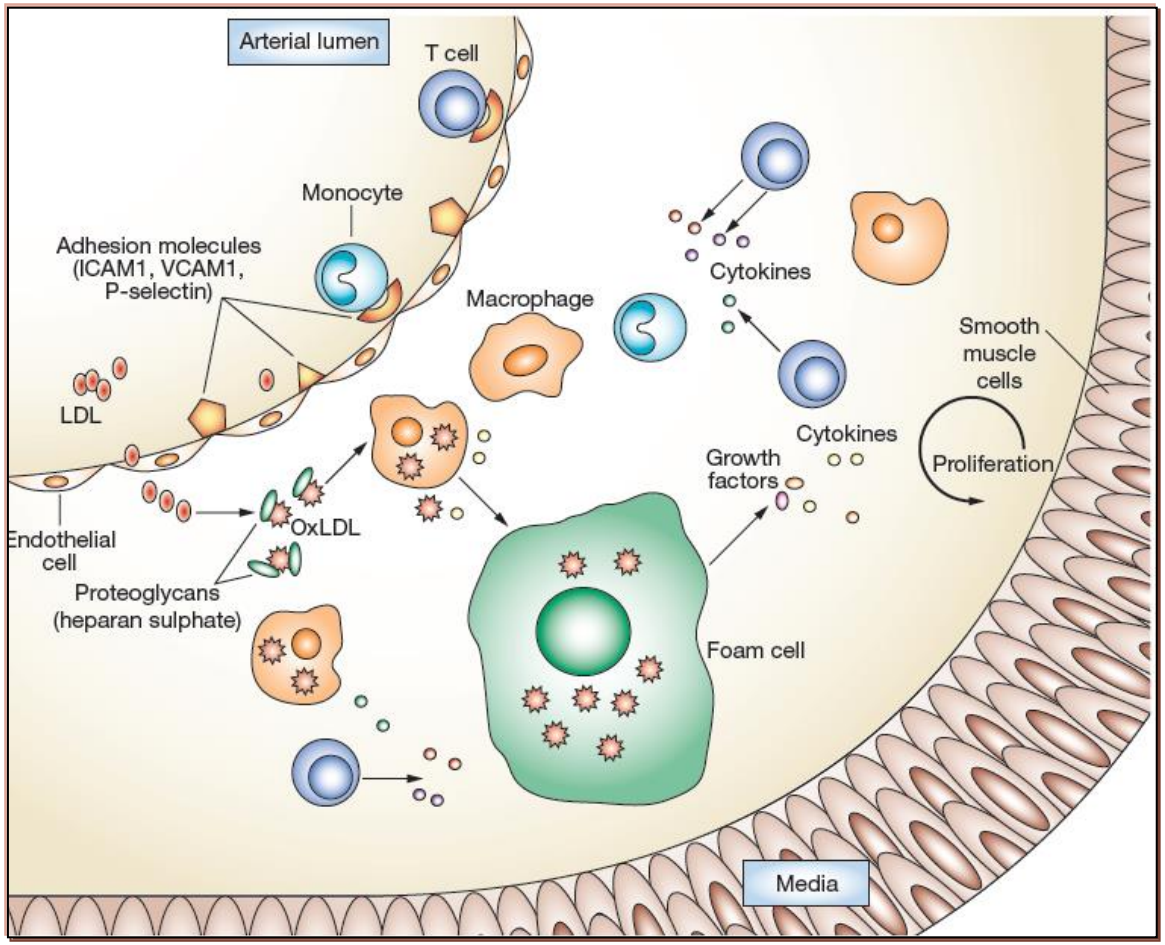
Contents

Atherosclerosis is the most common pathologic condition leading to cardiovascular disease



- A dynamic disease process clinically characterized by narrowing of the arterial lumen due to **accumulation of atherogenic lipoproteins and inflammatory cells**
- Complex interaction of **lipoproteins, inflammatory cells, and the arterial wall**

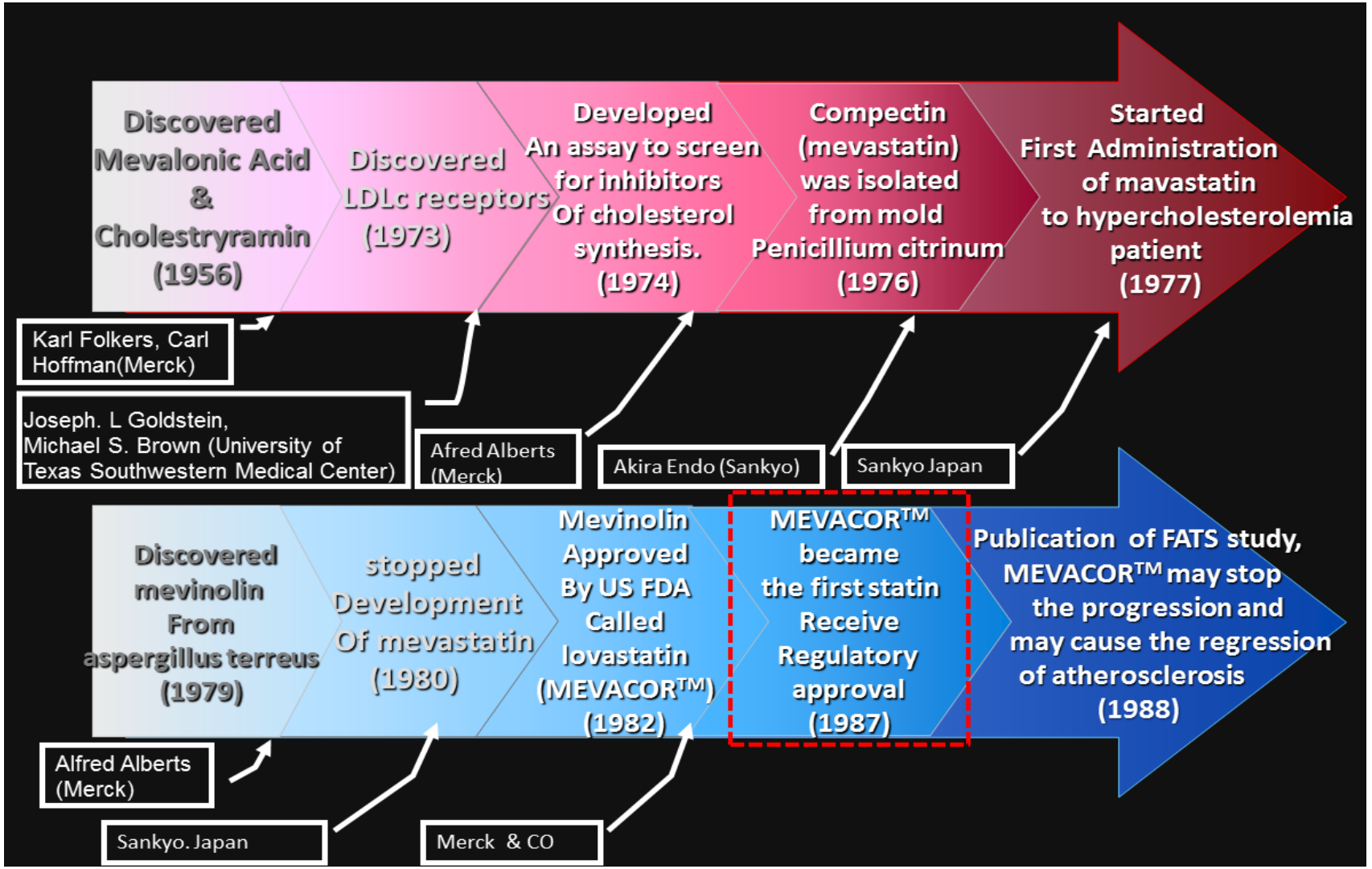
Nat Clin Pract Rheumatol. 2006;2:99

Relationship of atherosclerosis & cardiovascular disease

- **Cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall and to thrombosis is the foremost cause of premature mortality and of disability-adjusted life years (dalys) .**
- **The management of dyslipidemias as an essential and integral part of CVD prevention.**
- **Dyslipidemias cover a broad spectrum of lipid abnormalities, some of which are of great importance in CVD prevention.**

Eur Heart J. 2011;32:1769

Birth of Statin



Statin established solid evidence based on landmark trials

Landmark Statin Trials

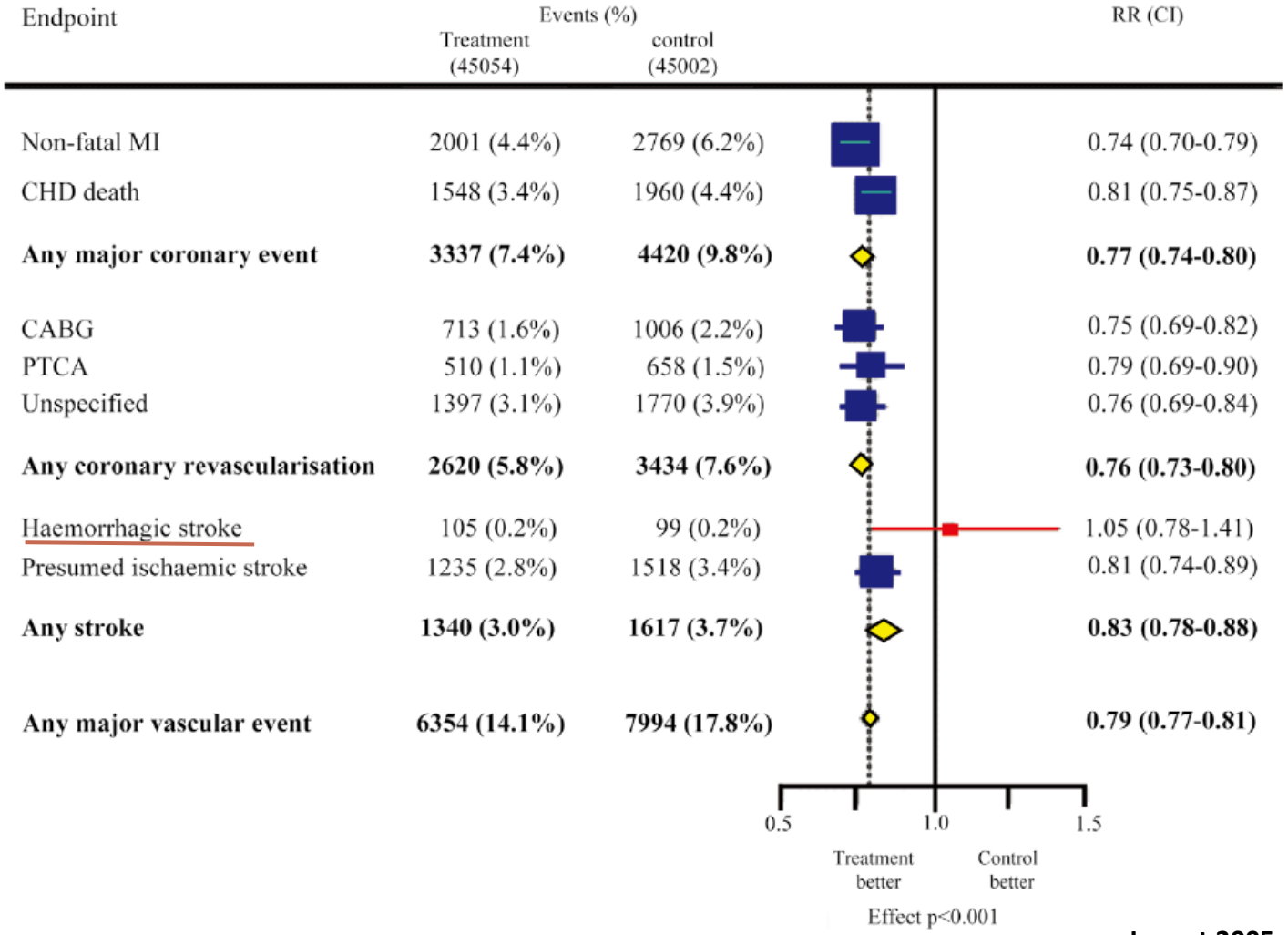
Lots of Evidence

AFCAPS/TexCaps, WOSCOPS, ALLHAT, CARE, LIPID, PROSPER, 4S, HPS, A-to-Z MIRACL, CARDS, PROVE-IT, ALLIANCE, 4D, ASCOT-LLA, IDEAL, TNT, SPARCL, AURORA, CORONA, GISSI-HF, JUPITER, SEAS, SHARP, IMPROVE-IT

- **Statin**
  - **The only proven medicine in 1° & 2° prevention and atheroscleorsis**

Effect on vascular events reduction in LDL-C

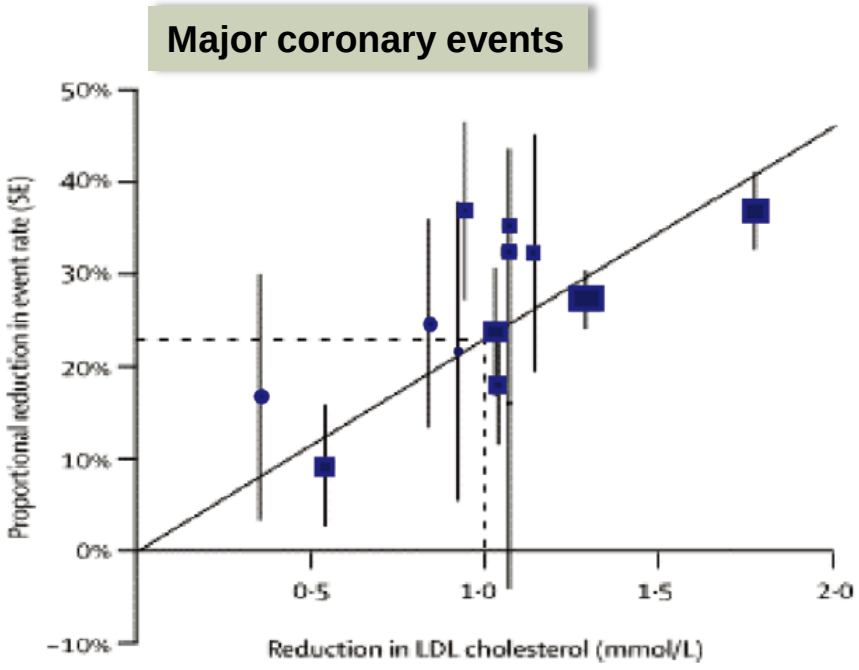
- **Proportional effect on major vascular events per mmol/L reduction in LDL-C.**

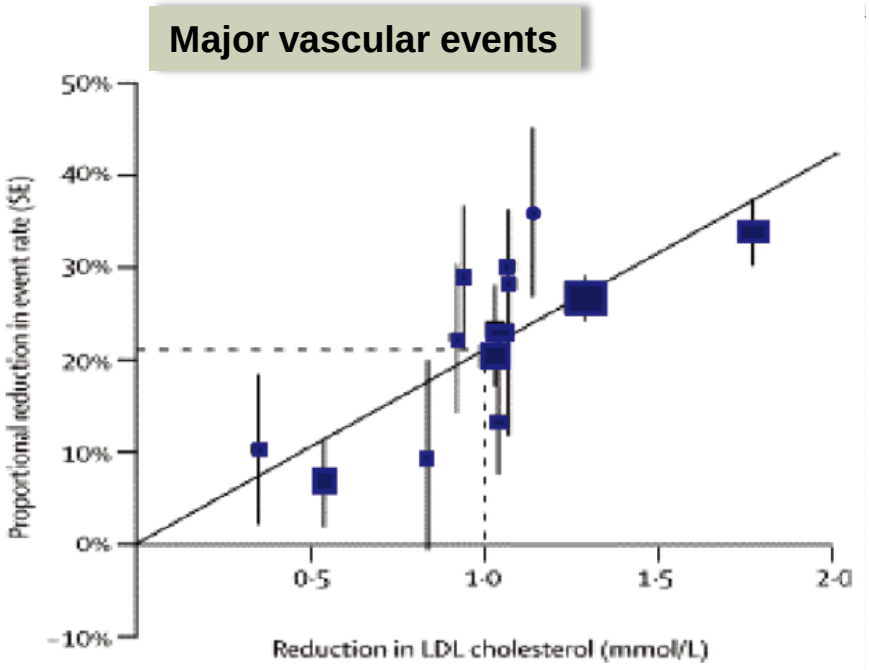


Lancet 2005; 366: 1267 – 1278.

Relationship between proportional reduction in the incidence of events

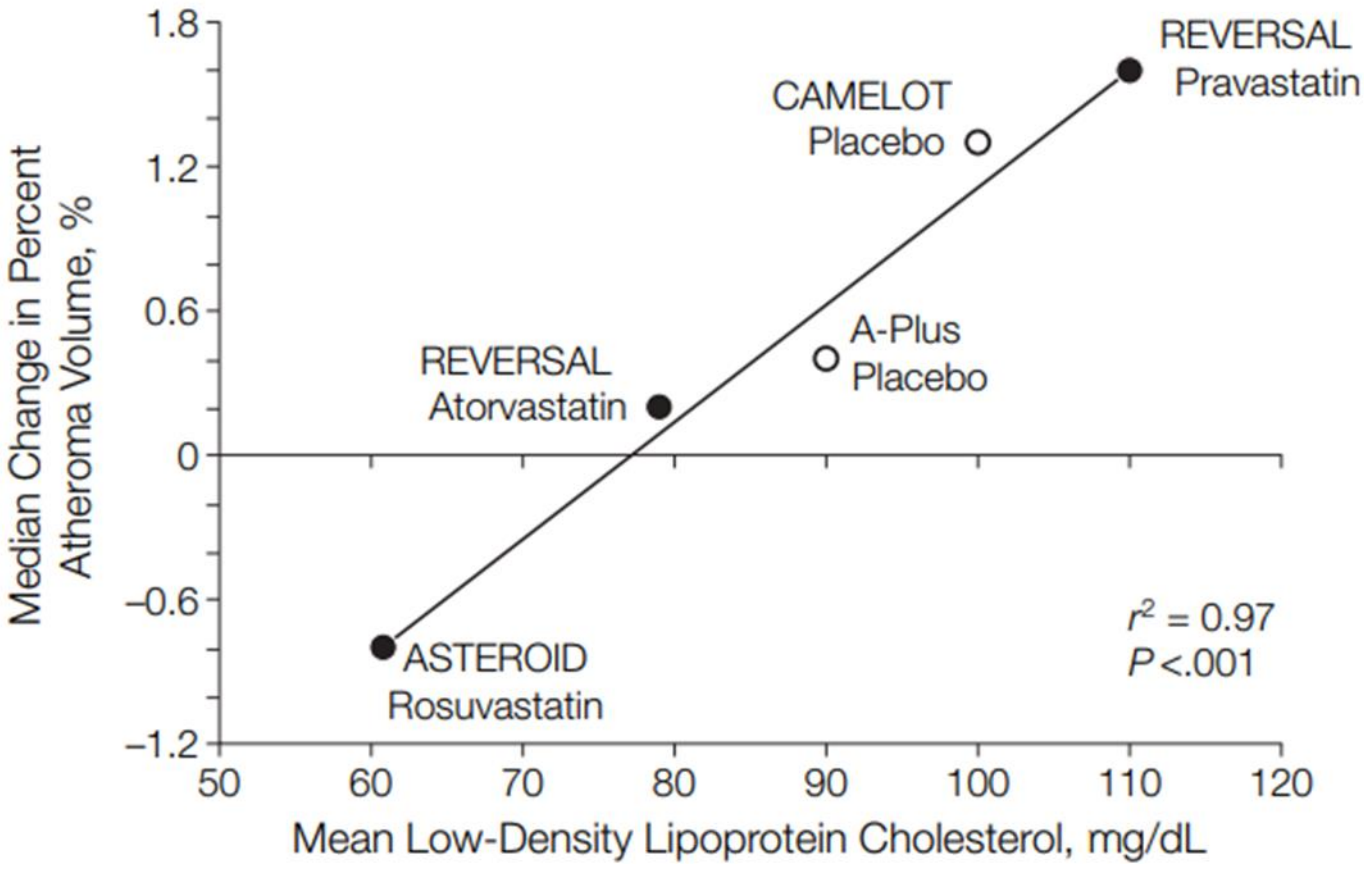
- **Relationship between proportional reduction in the incidence of major coronary events (Left) and major vascular events (Right) and mean absolute LDL-C at 1 year.**





Lancet 2005; 366: 1267 – 1278.

Relationship between mean LDL-C levels and mean % change in plaque volume



Lower LDL-C is better.

JAMA 2006; 295: 1556 – 1565.

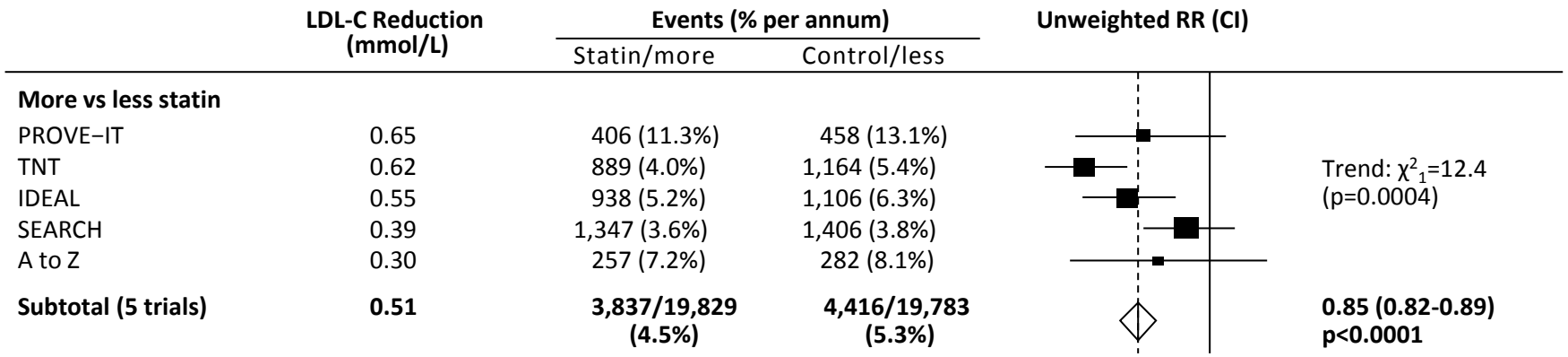
Recommendation of statin therapy

- **Recommendations for Lipid-lowering Therapy in Patients with Established CAD**

ACC/AHA guideline: High-intensity statin therapy

atorvastatin 40/80 mg, rosuvastatin 20/40 mg, or simvastatin 80 mg

- **Previous "More versus Less" Statins Trials**



Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet 2010; 376: 1670-81.

Primary Outcome in White and East Asian Populations

- **HOPE-3 trial- supplementary appendix**

Table 1. Primary Outcome in the White and East Asian Populations at a Median Follow-up of 5.6 Years.*

Population	No. of Patients	Rosuvastatin	Placebo	Relative Risk Reduction	Absolute Risk Reduction
		no./total no. (%)		%	*percentage points*
White	2546	36/1286 (2.8)	58/1260 (4.6)	39.2	1.8
East Asian	3691	53/1854 (2.9)	69/1837 (3.8)	23.9	0.9

* The primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Rosuvastatin was administered at a dose of 10 mg once daily. White indicates persons of European descent, and East Asian persons of Chinese descent.

HOPE-3 trial shows that **among persons of European descent(whites), the absolute risk reduction in cardiovascular events with rosuvastatin was almost twice as much as that among Chinese persons(East Asians)** (1.8% points vs. 0.9% points).

n engl j med 375;12 nejm.org September 22, 2016

REAL-CAD study

REAL-CAD study

Does High-Intensity Pitavastatin Therapy Further Improve Clinical Outcomes?

The REAL-CAD Study in 13,054 Patients With Stable Coronary Artery Disease

Takeshi Kimura, Teruo Inoue, Isao Taguchi, Hiroshi Iwata, Satoshi Iimuro, Takafumi Hiro, Yoshihisa Nakagawa, Yukio Ozaki, Yasuo Ohashi, H iroyuki Daida, Hiroaki Shimokawa, Ryozo Nagai,

on behalf of the **REAL-CAD Study Investigators**

Circulation. 2018 May 8;137(19):1997-2009

Backgrounds and Objectives

The high-intensity statins are not widely used in daily clinical practice, particularly in Asi a. **No clear evidence** regarding “more versus less” statins has been established in **Asian population**. Furthermore, maximum approved doses of statins are prescribed only very infrequently in Korea.

Therefore, we sought to determine whether **higher-dose statin therapy would be bene ficial in Asian patients in the largest-ever trial** comparing the efficacy of high-dose vers us low-dose statin therapy in patients with established stable CAD.

Circulation. 2018 May 8;137(19):1997-2009

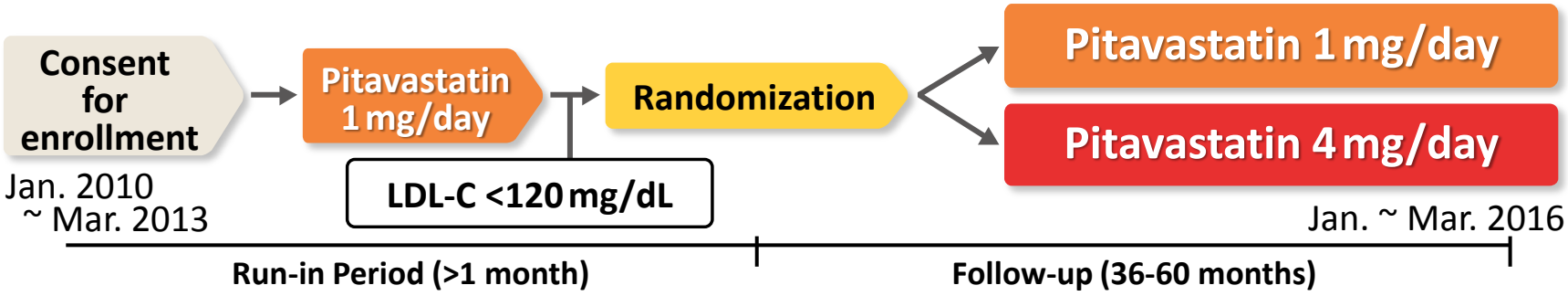
REAL-CAD study

- **Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease**

A prospective, multi-center, randomized, open-label, blinded endpoint, physician-initiated trial to determine whether high-dose as compared with low-dose pitavastatin therapy within the approved dose range could reduce CV events in Japanese patients with stable CAD.

Eligibility:

- Men and women, 20-80 years of age
- Stable CAD:
  - ACS or PCI/CABG >3 months
  - Clinical diagnosis of CAD with coronary stenosis ≥50 % diameter stenosis
- LDL-C <120 mg/dL on pitavastatin 1 mg/day during the run-in period



Pitavastatin 1 mg and 4 mg have LDL-C lowering effect comparable to atorvastatin 5 mg and 20 mg, respectively.

Circulation. 2018 May 8;137(19):1997-2009

Study Design

PEP： composite of CV death, non-fatal MI, non-fatal ischemic stroke, or unstable angina requiring emergency hospitalization

Sample size calculation

Hypothesis: 16% relative risk reduction with the high-dose pitavastatin Tx

Assumptions: Annual primary endpoint event rate of 2.5%, Drop-out rate of 10%

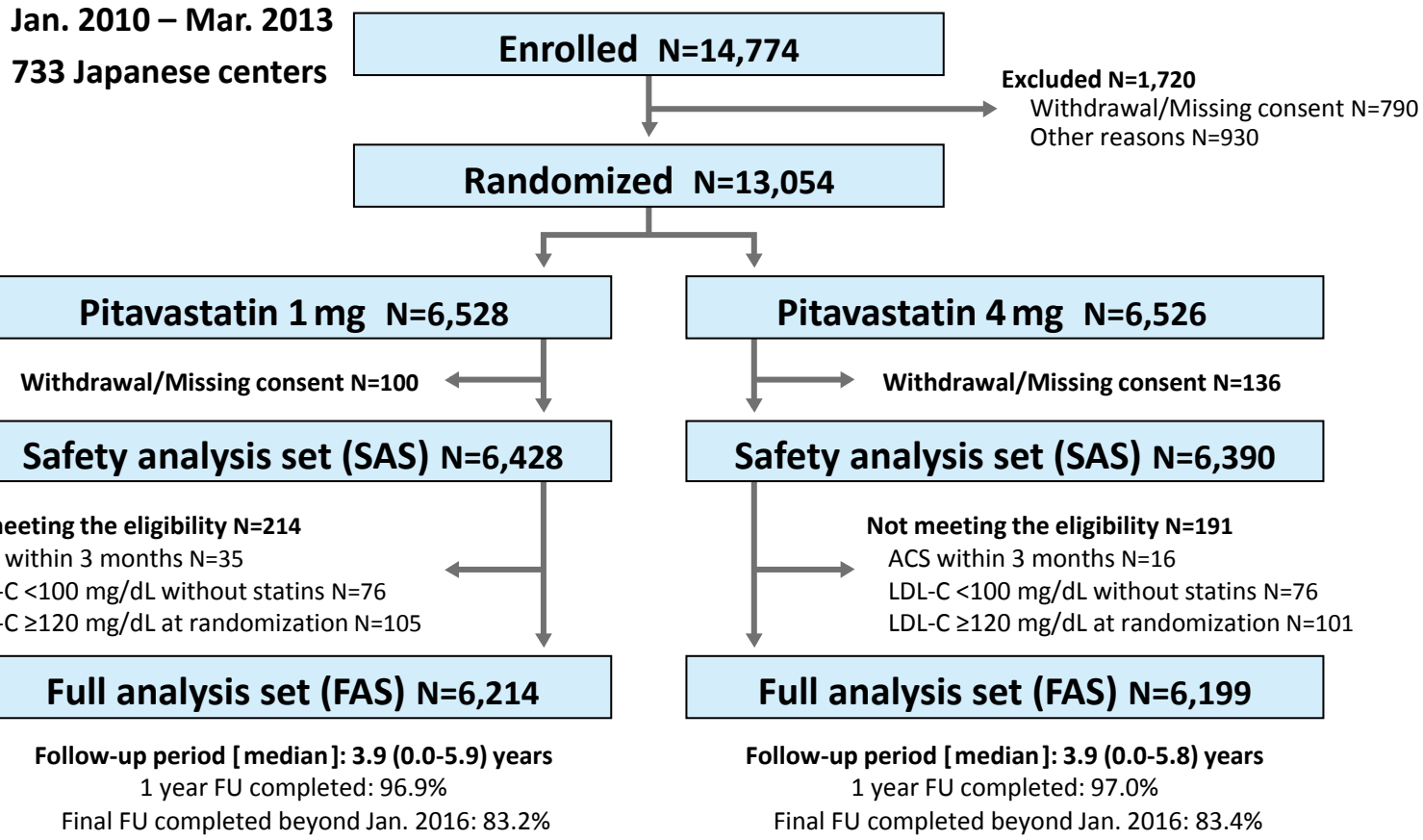
Sample size: 12,600 patients were to be enrolled with anticipated 1,033 events during the planned 3 years of enrollment and at least 3 years of follow-up.

Power: 80%, Alpha: 0.05

The actual event rate was lower than anticipated. On October 27, 2015, the steering committee decide d not to extend the study further despite the original event-driven trial design, because substantial nu mber of centers were reluctant to extend the study further.

Circulation. 2018 May 8;137(19):1997-2009

Study Patient Flow



Circulation. 2018 May 8;137(19):1997-2009

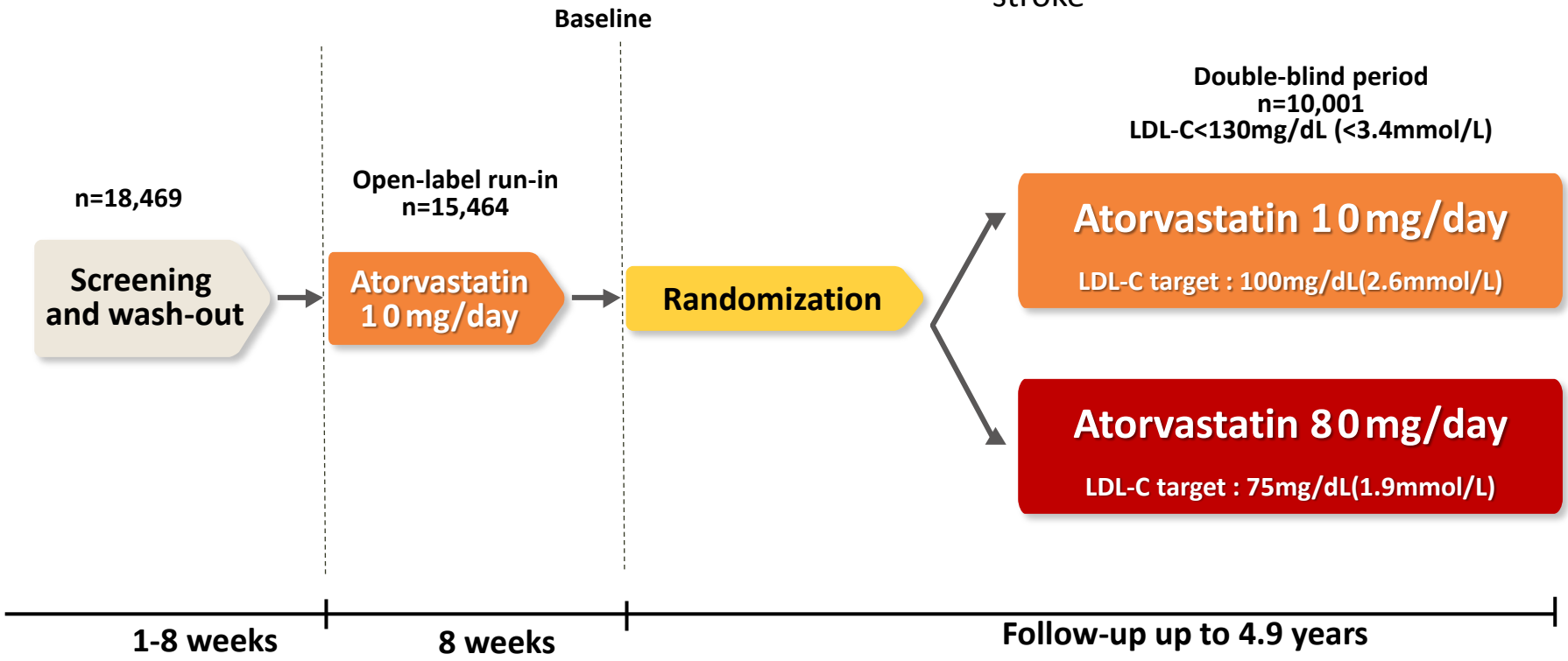
Design : REAL-CAD vs. TNT

Patient population :

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

Primary endpoint

- Time to occurrence of a major CV event
  - coronary heart disease death
  - nonfatal myocardial infarction
  - resuscitated cardiac arrest
  - stroke



LaRosa JC et al,. N Engl J Med. 2005 Apr 7;352(14):1425-35

Baseline Characteristics

Variables	Pitavastatin 1 mg (N=6,214)	Pitavastatin 4 mg (N=6,199)
Age — years	**68.1±8.3**	**68.0±8.3**
Male sex	83%	83%
BMI — kg/m^2	24.6±3.4	24.6±3.3
Hypertension	**75%**	**76%**
Diabetes mellitus	**40%**	**40%**
Current smoking	16%	17%
History of ACS	72%	72%
ACS within 1 year before randomization	24%	24%
Coronary revascularization	**91%**	**90%**
Revascularization within 1 year before randomization	28%	28%
Ischemic stroke	7%	7%
Peripheral vascular disease	7%	7%
CKD (eGFR <60 mL/min/1.73m^2)	**36%**	**35%**
Aspirin	**93%**	**92%**
DAPT	45%	44%
Statins before enrollment	**91%**	**91%**

Circulation. 2018 May 8;137(19):1997-2009

Baseline Characteristics : REAL-CAD vs. TNT

REAL-CAD

10 yrs older

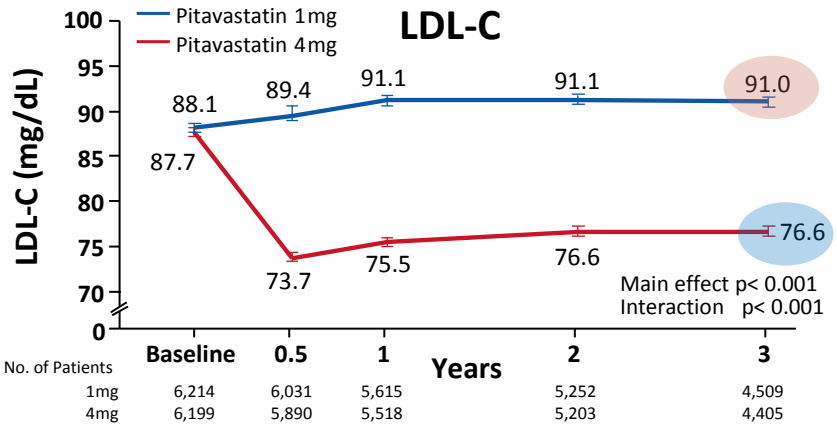
All ASIAN

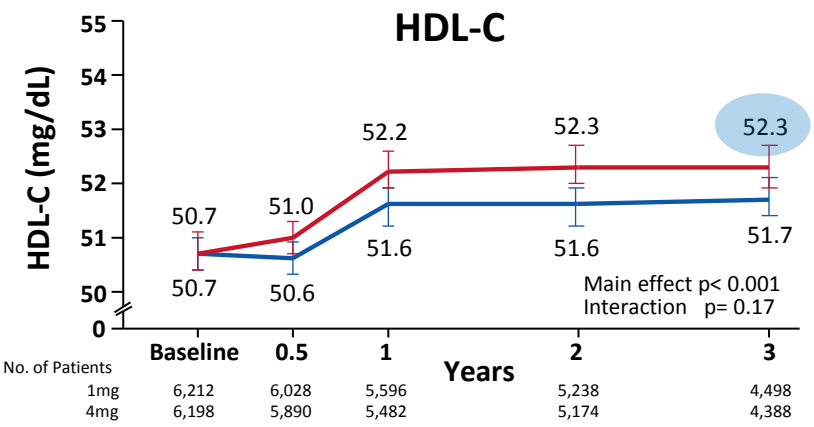
More HT (75%)

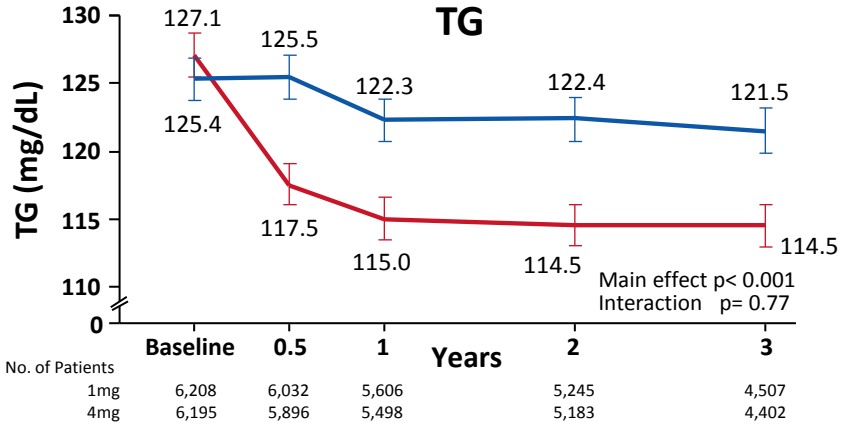
More DM (40%)

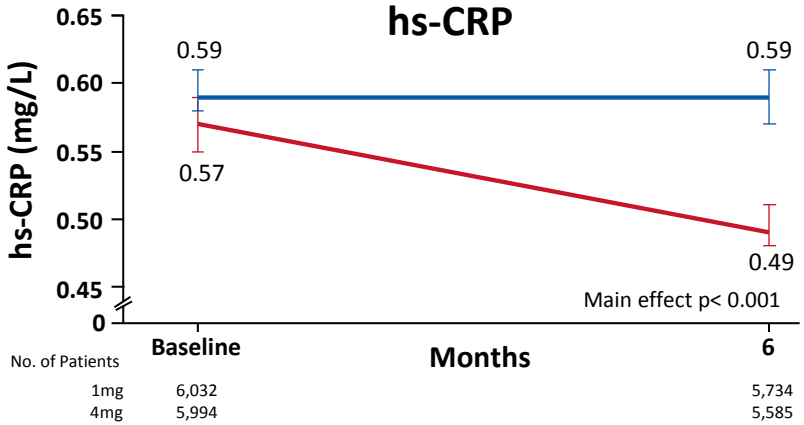
Characteristic	Atorvastatin 10 mg (N=5,006)	Atorvastatin 80 mg (N=4,995)
Age — years	**60.9±8.8**	**61.2±8.8**
Male sex – no. (%)	4045 (80.8)	4054 (81.2)
White race – no. (%)	**4711 (94.1)**	**4669 (94.1)**
Systolic blood pressure - mmHg	131±17	131±17
Diastolic blood pressure - mmHg	78±10	78±10
Body mass index	28.6±4.7	28.4±4.5
Cardiovascular history – no. (%)		
Current smoker	672 (13.4)	669 (13.4)
Former smoker	3167 (63.3)	3155 (63.2)
Systemic hypertension	**2721 (54.4)**	**2692 (53.9)**
History of diabetes mellitus	**753 (15.0)**	**748 (15.0)**
Myocardial infarction	2888 (57.7)	2945 (59.0)
Angina	4067 (81.2)	4084 (81.8)
Cerebrovascular accident	263 (5.3)	255 (5.1)
Peripheral-artery disease	570 (11.4)	603 (12.1)
Congestive heart failure	404 (8.1)	377 (7.6)
Arrhythmia	927 (18.5)	907 (18.2)
Coronary revascularization		
Angioplasty	2719 (54.3)	266 (53.8)
Bypass	233 (46.7)	2317 (46.4)

Serial Changes in Lipid Parameters & hs-CRP



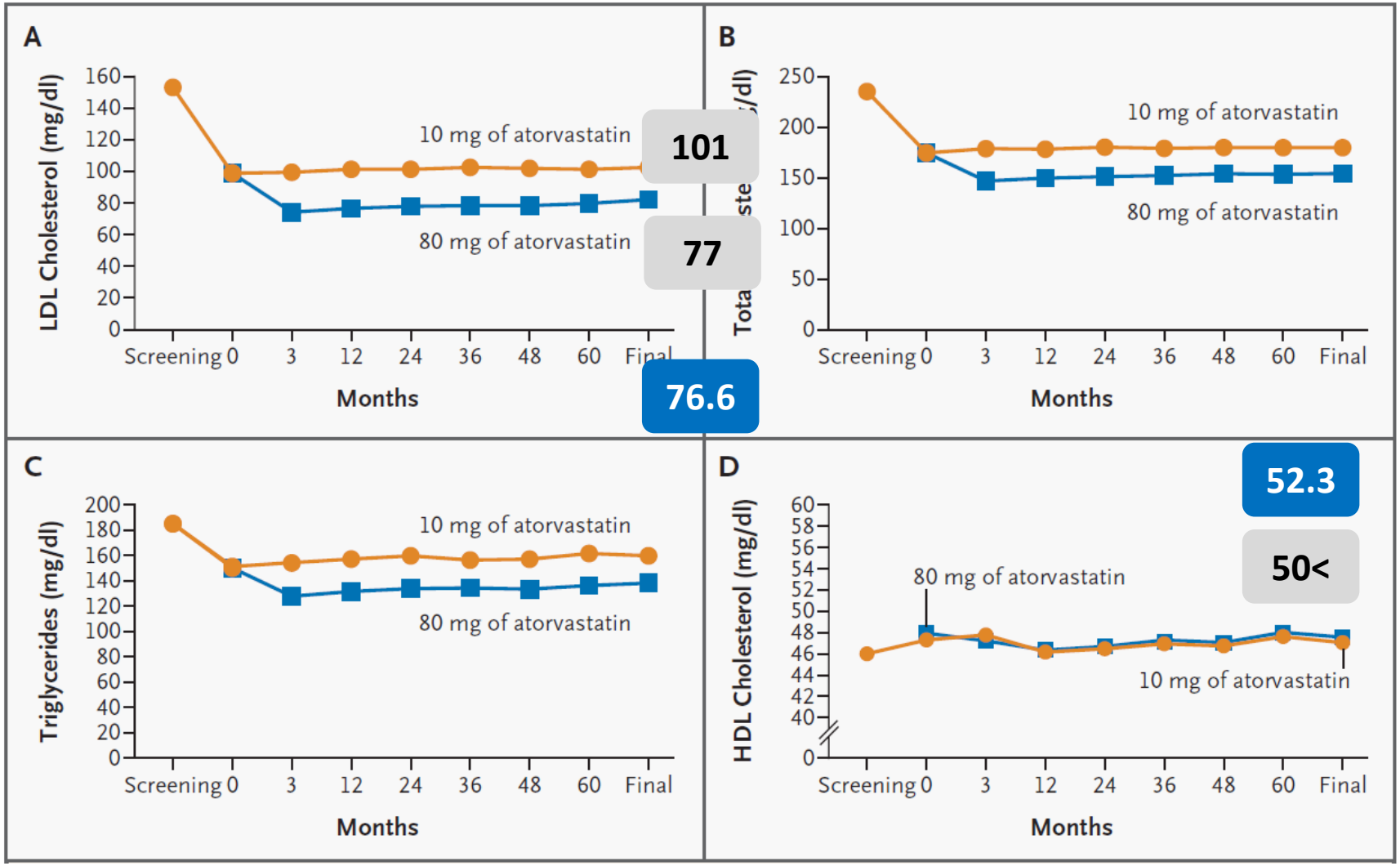






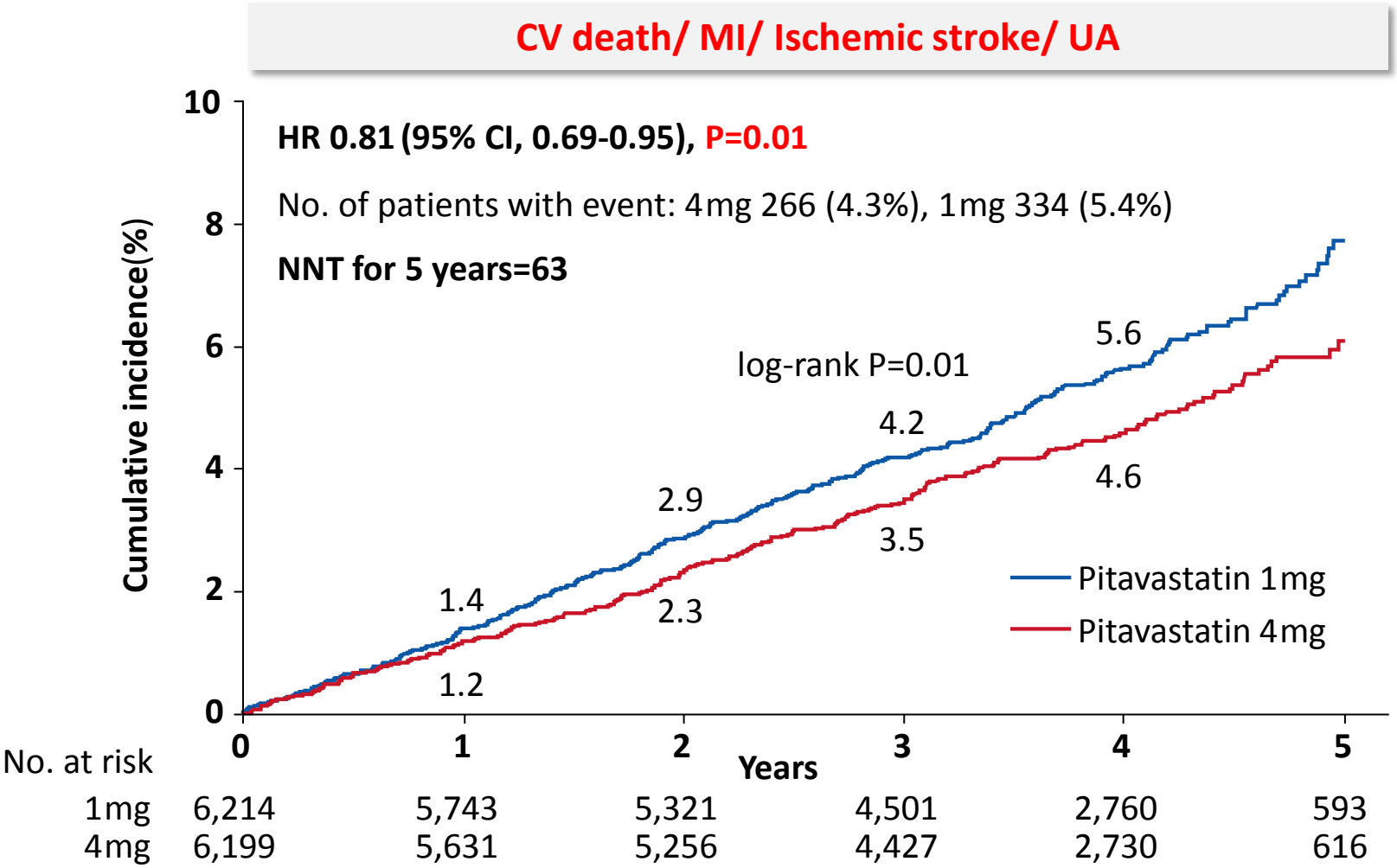
Circulation. 2018 May 8;137(19):1997-2009

Lipid profile : REAL-CAD vs. TNT



LaRosa JC et al,. N Engl J Med. 2005 Apr 7;352(14):1425-35

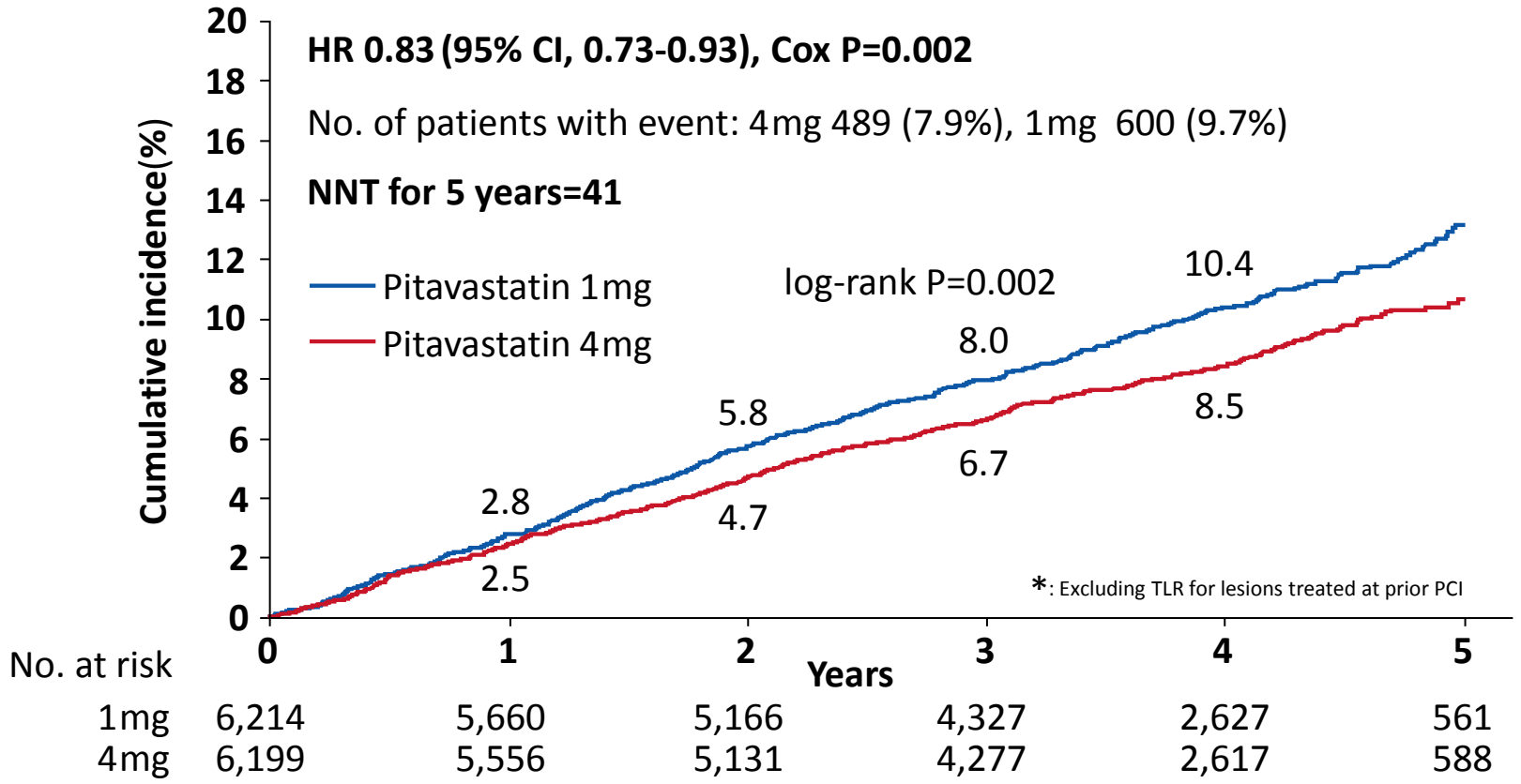
Primary Endpoint



Circulation. 2018 May 8;137(19):1997-2009

Secondary Endpoint

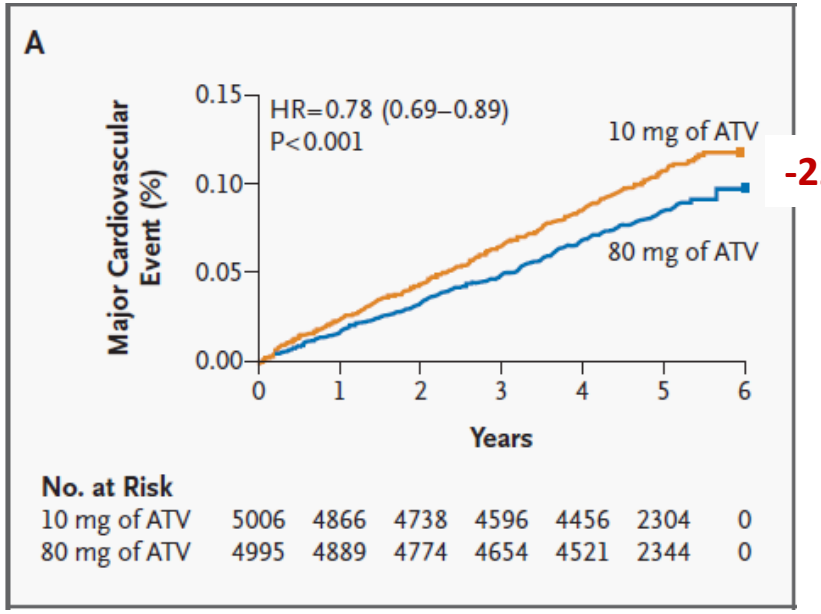
Primary Endpoint plus Coronary Revascularization*



Circulation. 2018 May 8;137(19):1997-2009

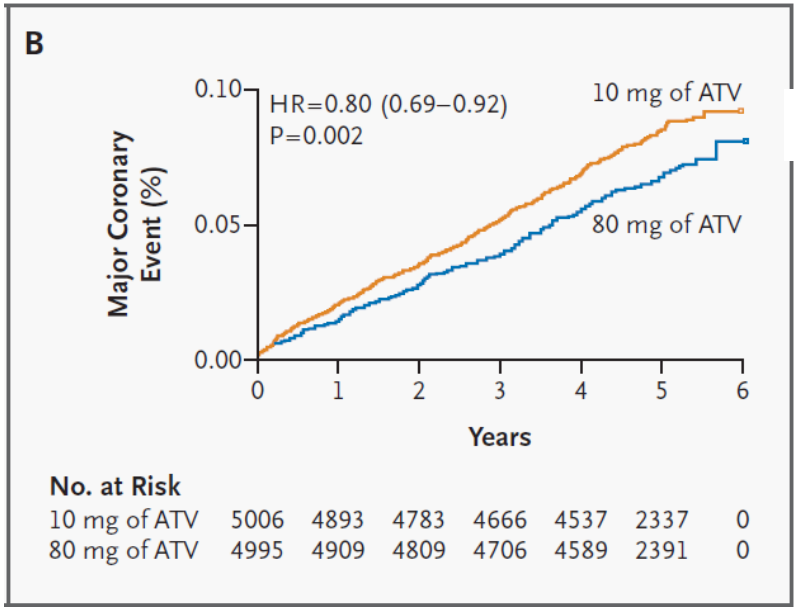
Primary Endpoint : REAL-CAD vs. TNT

- The relative **reduction in the risk** of the **primary** composite end point of death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, and fatal or nonfatal stroke was **22 percent** in the group given 80 mg of atorvastatin, as compared with the group given 10 mg of atorvastatin.



-22%

A : Cumulative Incidence of a First Major Cardiovascular Event



-20%

B : Cumulative Incidence of a First Major Coronary Event

LaRosa JC et al,. N Engl J Med. 2005 Apr 7;352(14):1425-35

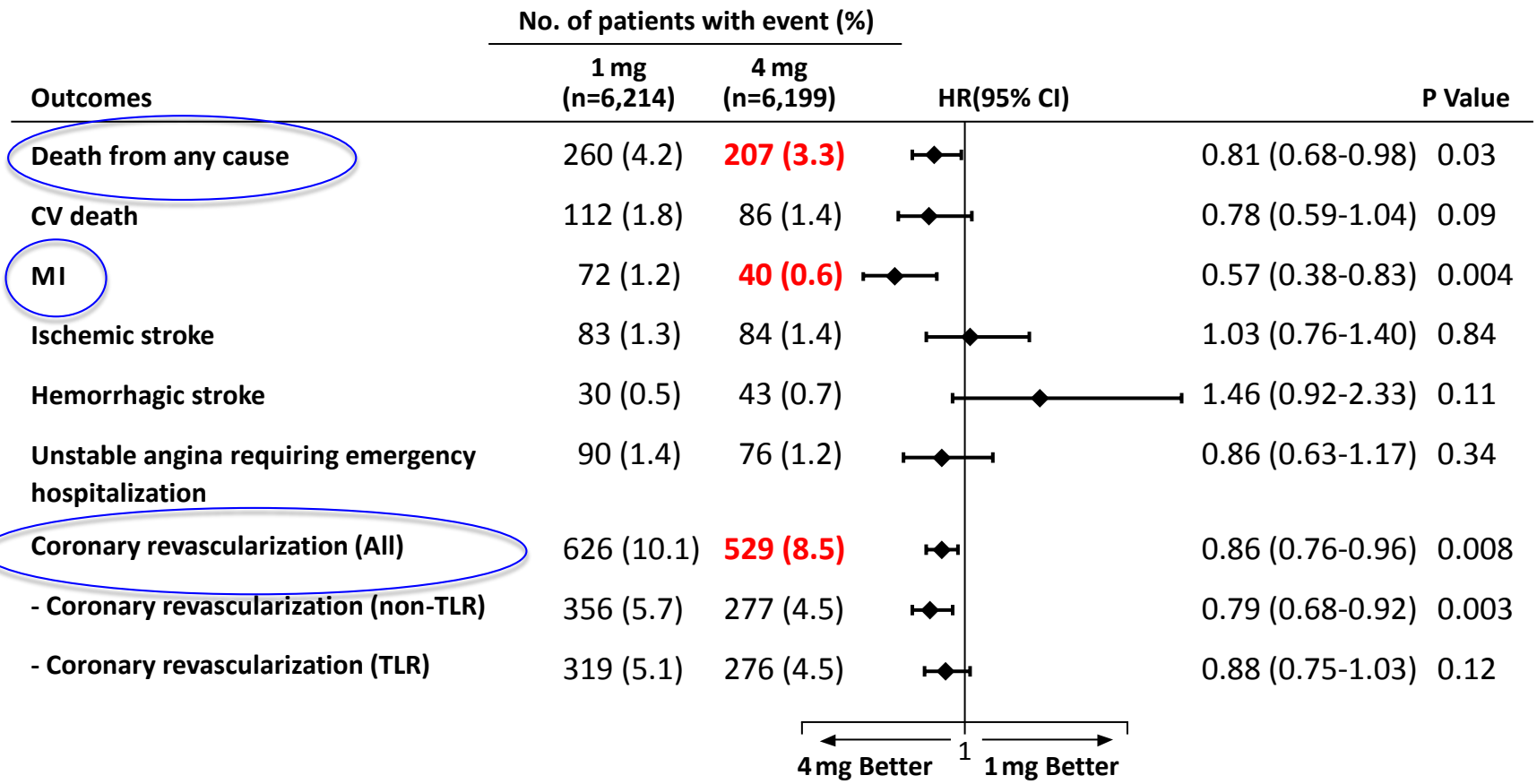
Other Secondary Endpoint : REAL-CAD vs. TNT

- The study was **not** adequately powered to detect changes in the **risk of death from any cause.**

Outcomes	No. with first event (%) 10 mg ATV (n=5,006)	80 mg ATV (n=4,995)	HR(95% CI)	P Value
Primary outcome				
Total major cardiovascular events	548 (10.9)	434 (8.7)	0.78 (0.69 – 0.89)	<0.001
Death from CHD	127 (2.5)	101 (2.0)	0.80 (0.61 – 1.03)	0.09
Nonfatal, non-procedure-related MI	308 (6.2)	243 (4.9)	0.78 (0.66 – 0.93)	0.004
Resuscitation after cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56 – 1.67)	0.89
Fatal or nonfatal stroke	155 (3.1)	117 (2.3)	0.75 (0.59 – 0.96)	0.02
Secondary outcome				
Major coronary event	418 (8.3)	334 (6.7)	0.80 (0.69 – 0.92)	0.002
Cerebrovascular event	250 (5.0)	196 (3.9)	0.77 (0.64 – 0.93)	0.007
Hospitalization for congestive heart failure	164 (3.3)	122 (2.4)	0.74 (0.59 – 0.94)	0.01
Peripheral-artery disease	282 (5.6)	275 (5.5)	0.97 (0.83 – 1.15)	0.76
Death from any cause	282 (5.6)	284 (5.7)	1.01 (0.85 – 1.19)	0.92
Any cardiovascular event	1677 (33.5)	1405 (28.1)	0.81 (0.75 – 0.87)	<0.001
Any coronary event	1326 (26.5)	1078 (21.6)	0.79 (0.73 – 0.86)	<0.001

LaRosa JC et al,. N Engl J Med. 2005 Apr 7;352(14):1425-35

Other Secondary Endpoints



Outcomes	No. of patients with event (%) 1 mg (n=6,214)	4 mg (n=6,199)	HR(95% CI)	P Value
Death from any cause	260 (4.2)	**207 (3.3)**	0.81 (0.68-0.98)	0.03
CV death	112 (1.8)	86 (1.4)	0.78 (0.59-1.04)	0.09
MI	72 (1.2)	**40 (0.6)**	0.57 (0.38-0.83)	0.004
Ischemic stroke	83 (1.3)	84 (1.4)	1.03 (0.76-1.40)	0.84
Hemorrhagic stroke	30 (0.5)	43 (0.7)	1.46 (0.92-2.33)	0.11
Unstable angina requiring emergency hospitalization	90 (1.4)	76 (1.2)	0.86 (0.63-1.17)	0.34
Coronary revascularization (All)	626 (10.1)	**529 (8.5)**	0.86 (0.76-0.96)	0.008
- Coronary revascularization (non-TLR)	356 (5.7)	277 (4.5)	0.79 (0.68-0.92)	0.003
- Coronary revascularization (TLR)	319 (5.1)	276 (4.5)	0.88 (0.75-1.03)	0.12

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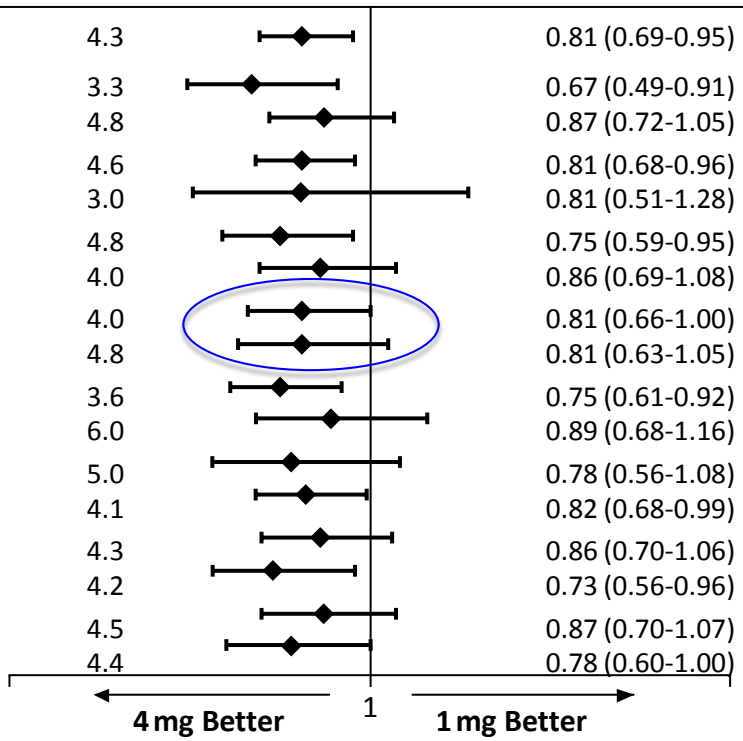
Subgroup Analyses

- **Primary Endpoint** (CV death/ MI/ Ischemic stroke/ UA)

Subgroup		No. of patients	Event rate (%) 1 mg	4 mg	HR (95% CI)	P value for interaction
Overall		12,413	5.4	4.3	0.81 (0.69-0.95)	
Age	<65	4,009	5.0	3.3	0.67 (0.49-0.91)	0.16
	≥65	8,404	5.6	4.8	0.87 (0.72-1.05)	
Sex	Male	10,253	5.7	4.6	0.81 (0.68-0.96)	0.99
	Female	2,160	3.8	3.0	0.81 (0.51-1.28)	
Diabetes	Yes	4,978	6.5	4.8	0.75 (0.59-0.95)	0.39
	No	7,435	4.6	4.0	0.86 (0.69-1.08)	
LDL-C	<95 mg/dL	7,865	5.0	4.0	0.81 (0.66-1.00)	0.97
	≥95 mg/dL	4,548	5.9	4.8	0.81 (0.63-1.05)	
hs-CRP	<1 mg/L	8,510	4.9	3.6	0.75 (0.61-0.92)	0.32
	≥1 mg/L	3,516	6.7	6.0	0.89 (0.68-1.16)	
HDL-C	≤40 mg/dL	2,607	6.5	5.0	0.78 (0.56-1.08)	0.78
	>40 mg/dL	9,803	5.1	4.1	0.82 (0.68-0.99)	
TG	<150 mg/dL	8,045	5.1	4.3	0.86 (0.70-1.06)	0.34
	≥150 mg/dL	4,358	5.9	4.2	0.73 (0.56-0.96)	
BMI	<25	6,693	5.3	4.5	0.87 (0.70-1.07)	0.53
	≥25	4,788	5.7	4.4	0.78 (0.60-1.00)	



Circulation. 2018 May 8;137(19):1997-2009

Safety Outcome

Event	Pitavastatin 1 mg (N=6,428)	Pitavastatin 4 mg (N=6,390)	P value
Adverse events — N (%)			
Rhabdomyolysis	1 (0.0)	2 (0.0)	0.62
Muscle complaints	45 (0.7)	121 (1.9)	<0.001
New onset of diabetes mellitus	279 (4.3)	285 (4.5)	0.76
Laboratory test abnormalities — N (%)			
Elevation of ALT, AST, or both ≥3ULN	174 (2.7)	187(2.9)	0.46
Elevation of CK ≥5ULN	40 (0.6)	42 (0.7)	0.83

Circulation. 2018 May 8;137(19):1997-2009

Conclusions and Implications

- REAL-CAD is currently the largest randomized trial to compare high-dose and low-dose statin therapy.
- It was also the first such trial performed in Asia.
- High-dose (4 mg/day) as compared with low-dose (1 mg/day) pitavastatin therapy significantly reduced CV events in Asian patients with stable CAD.
- All-cause death, myocardial infarction, and clinically indicated coronary revascularization were also significantly reduced.
- Rates of serious adverse events were similar in the 2 treatment groups.


Thank you