REAL-CAD

: Cardiovascular benefit of pitavastatin in stable coronary artery disease

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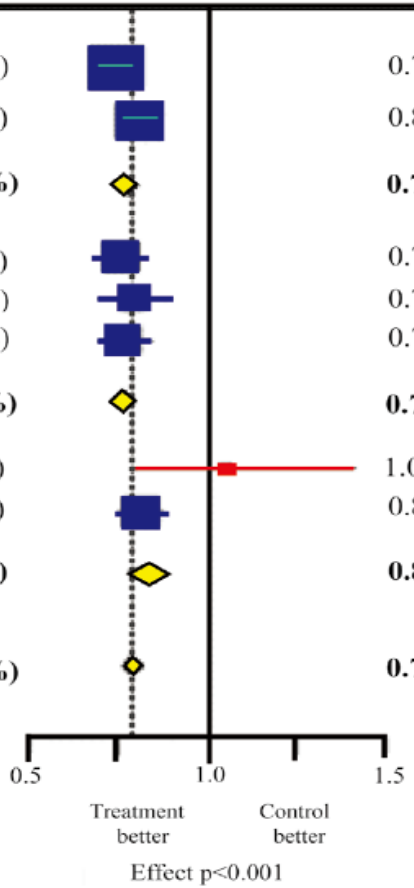
I have nothing to be disclosed

Contents

Effect of LDL-C reduction on major vascular events

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

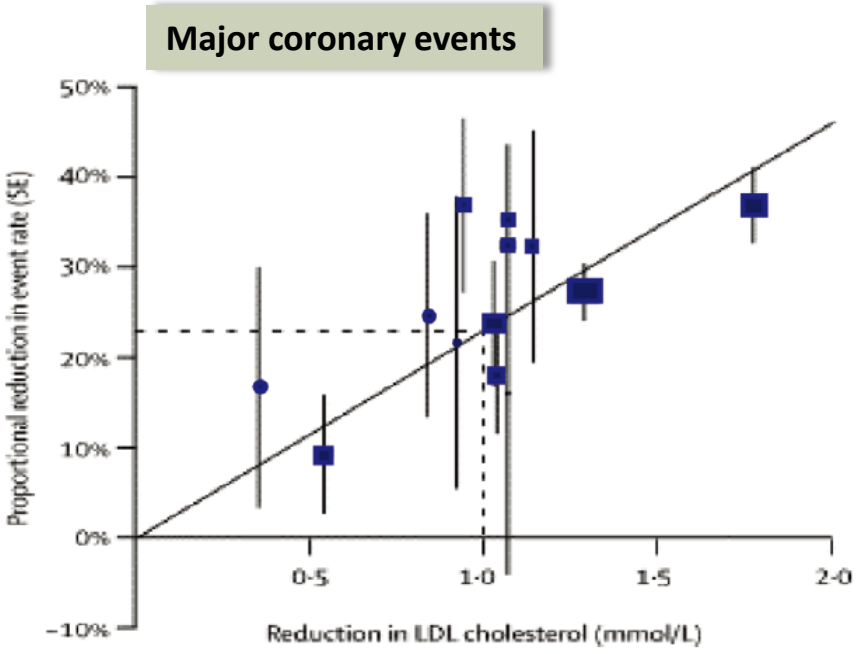
Endpoint	Events (%) Treatment (45054)	control (45002)	RR (CI)
Non-fatal MI	2001 (4.4%)	2769 (6.2%)	0.74 (0.70-0.79)
CHD death	1548 (3.4%)	1960 (4.4%)	0.81 (0.75-0.87)
Any major coronary event	**3337 (7.4%)**	**4420 (9.8%)**	**0.77 (0.74-0.80)**
CABG	713 (1.6%)	1006 (2.2%)	0.75 (0.69-0.82)
PTCA	510 (1.1%)	658 (1.5%)	0.79 (0.69-0.90)
Unspecified	1397 (3.1%)	1770 (3.9%)	0.76 (0.69-0.84)
Any coronary revascularisation	**2620 (5.8%)**	**3434 (7.6%)**	**0.76 (0.73-0.80)**
Haemorrhagic stroke	105 (0.2%)	99 (0.2%)	1.05 (0.78-1.41)
Presumed ischaemic stroke	1235 (2.8%)	1518 (3.4%)	0.81 (0.74-0.89)
Any stroke	**1340 (3.0%)**	**1617 (3.7%)**	**0.83 (0.78-0.88)**
Any major vascular event	**6354 (14.1%)**	**7994 (17.8%)**	**0.79 (0.77-0.81)**

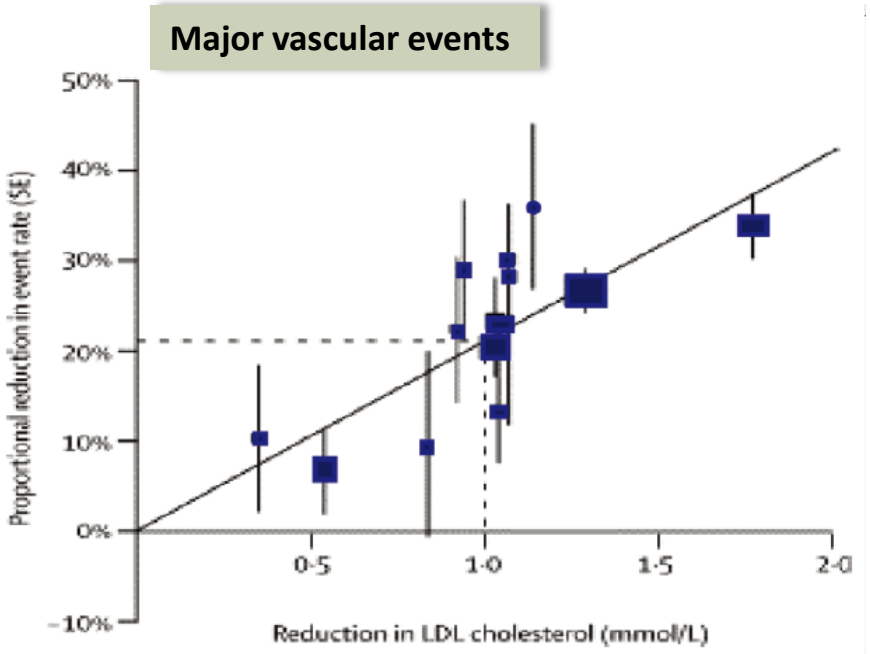


Lancet 2005; 366: 1267 – 1278.

Relationship between proportional reduction in the incidence of events

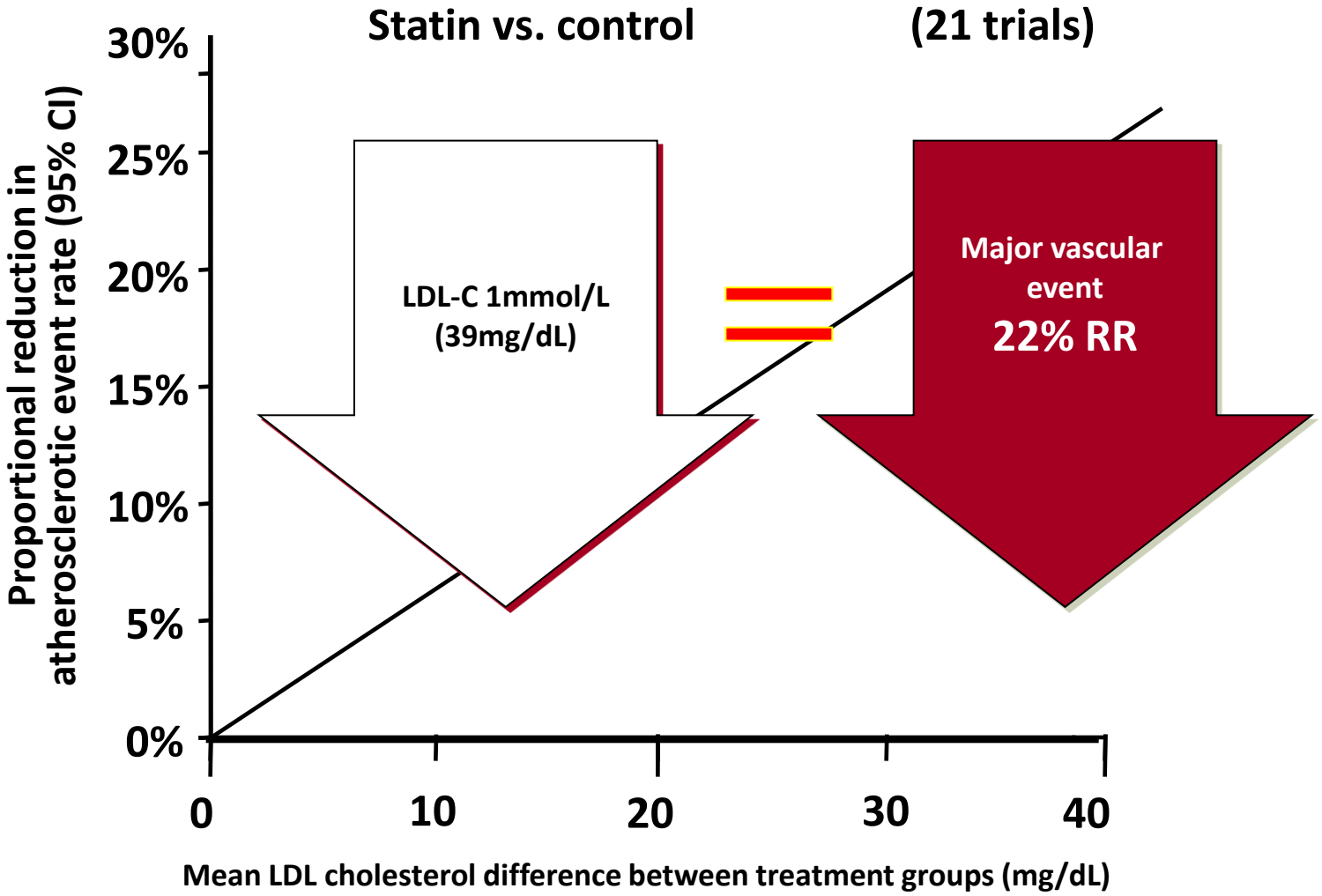
Relationship between proportional reduction in the incidence of major coronary events (Left) and major vascular events (Right) and mean absolute LDL-C at 1 year.





Lancet 2005; 366: 1267 – 1278.

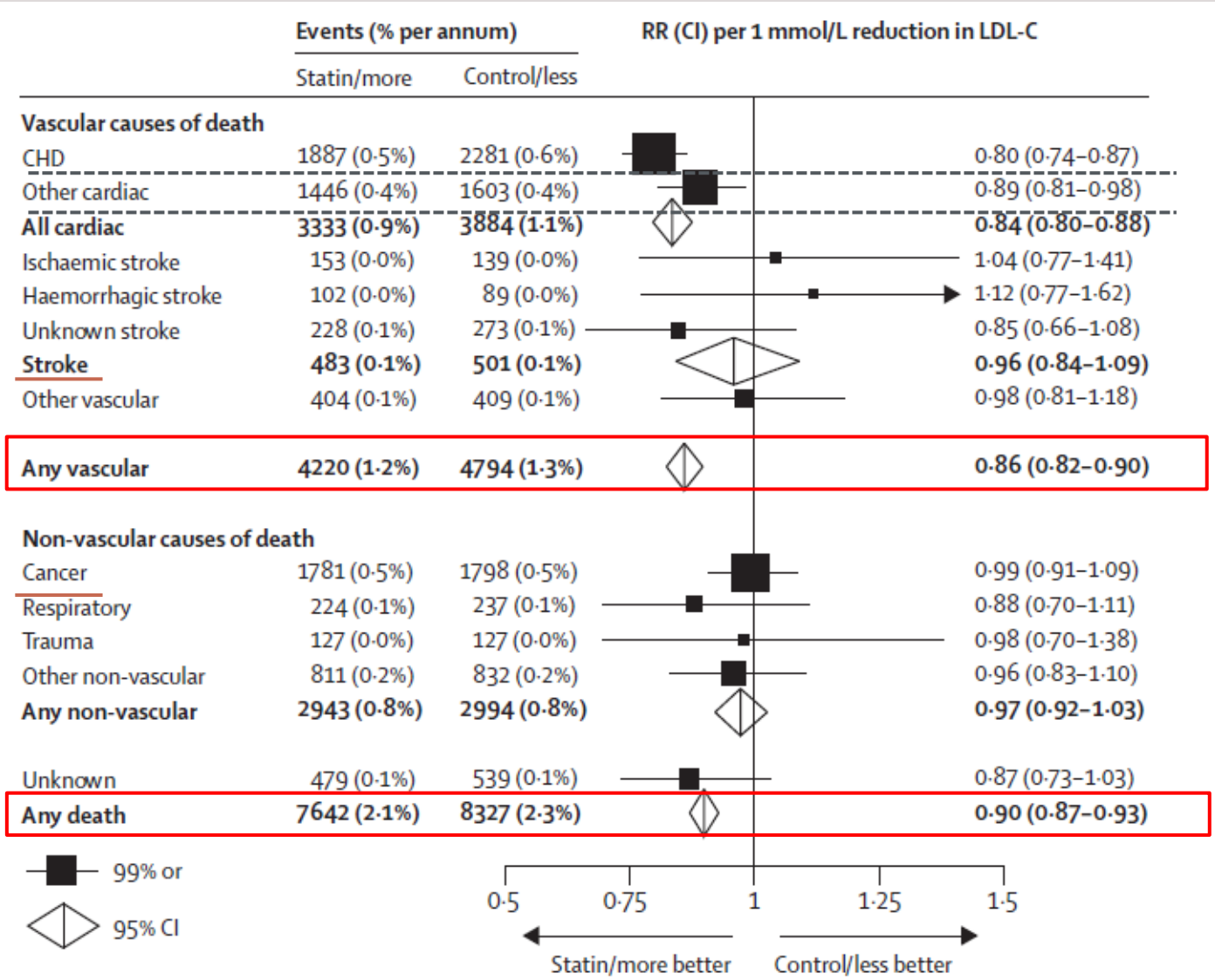
Cholesterol Treatment Trialists (CTT)



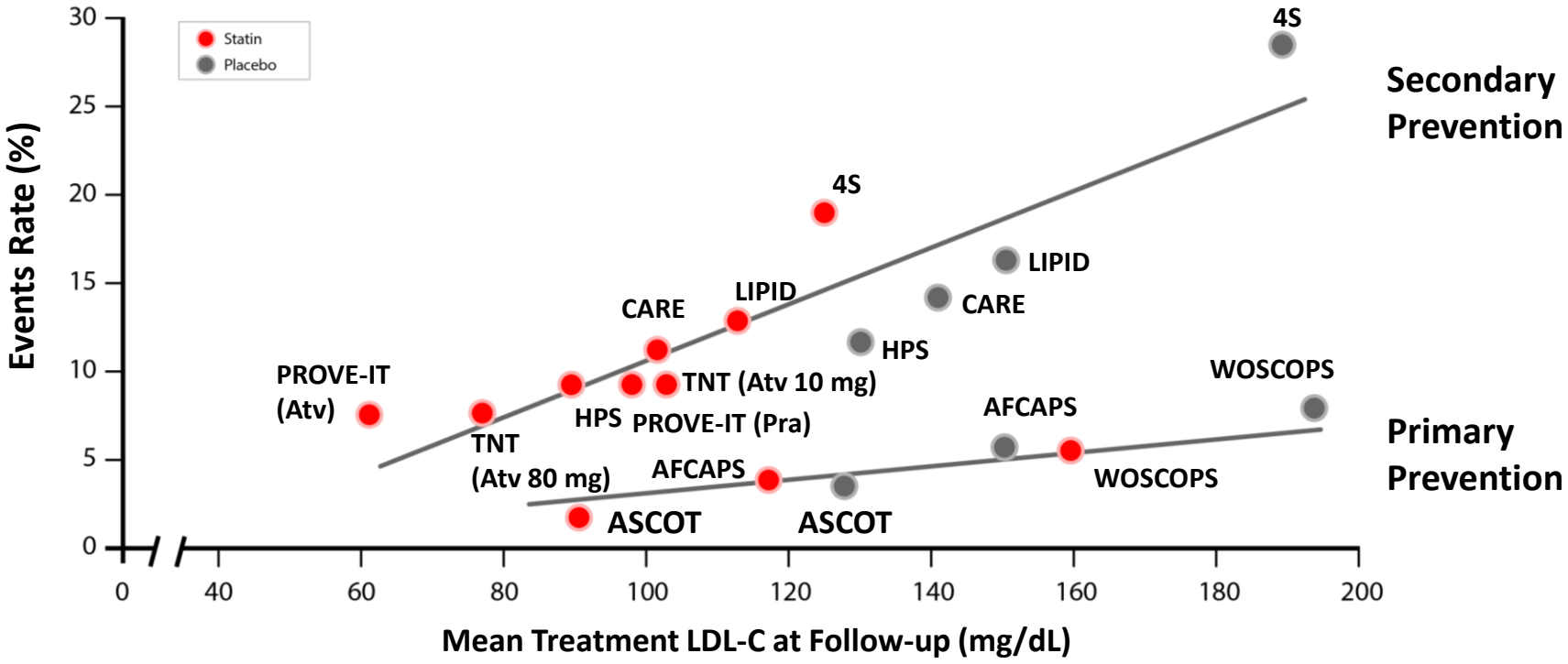
Lancet 2010;376:1670-1681.

Mortality Benefit in 26 trials in CTT

Vascular mortality : 14 % further reduction per 1 mmol/L reduction in LDL-C



On-treatment LDL-C is closely related to CHD events in statin trials.

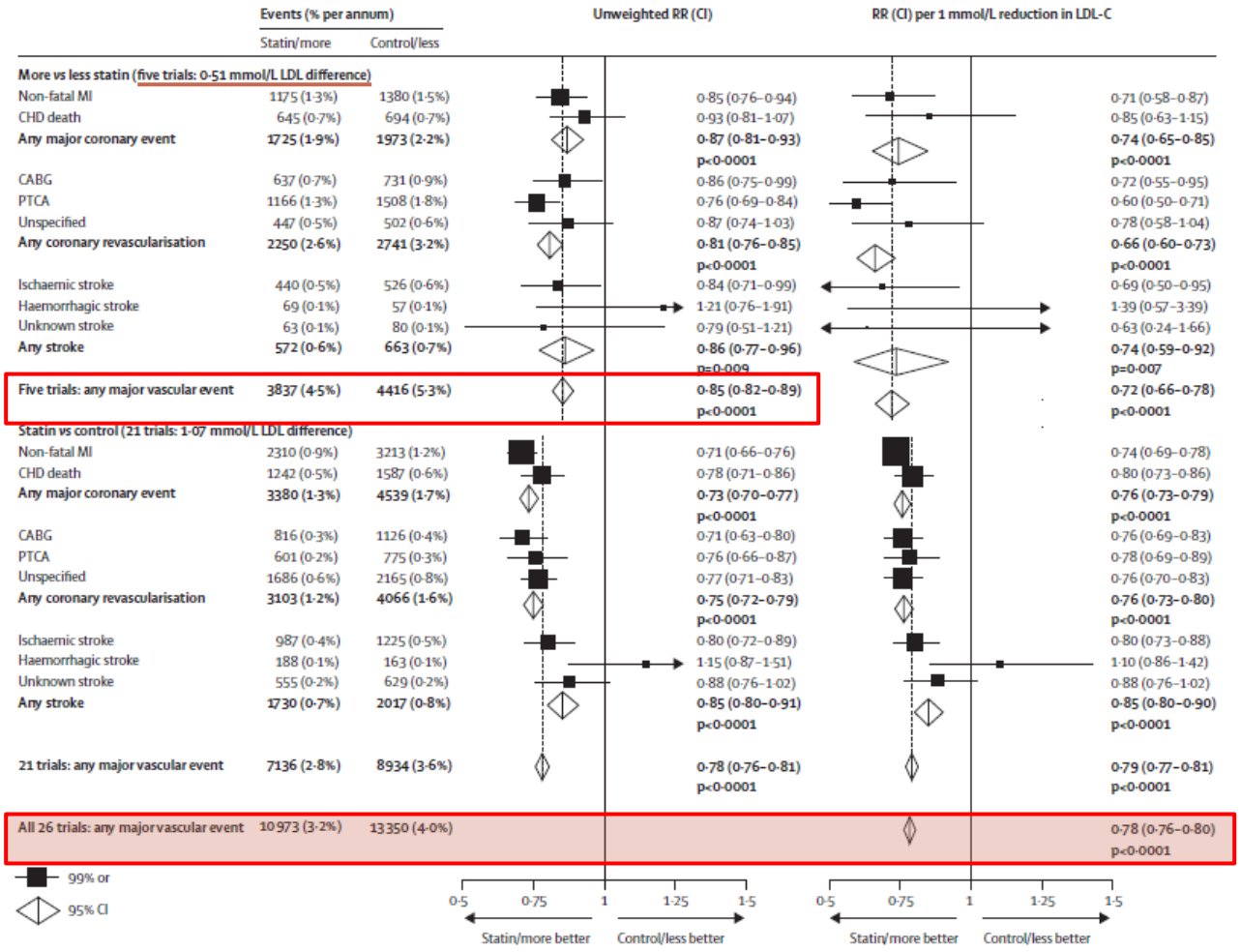


Atv, atorvastatin; Pra, pravastatin; PROVE-IT, Pravastatin or AtorVastatin Evaluation and Infection Therapy; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS, Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS, West of Scotland Coronary Prevention Study; TNT, Treating to New Targets; HPS, Heart Protection Study; CARE, Cholesterol and Recurrent Events Trial; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; 4S, Scandinavian Simvastatin Survival Study

Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9:269–279. 2. LaRosa JC, et al. *N Engl J Med.* 2005;352:1425–1435.

Efficacy and safety of more intensive lowering of LDL cholesterol : meta-analysis (CTT Collaboration)

Major Vascular Events : 15 % further reduction in more intensive regimen



weighted mean further reduction in LDL at 1 year : 19.7 mg/dL

- **coronary death or non-fatal MI of 13%**
- **coronary ReVasc of 19%**
- **ischaemic stroke of 16%**

Lancet. 2010;376: 1670-81

Recommendation of statin therapy

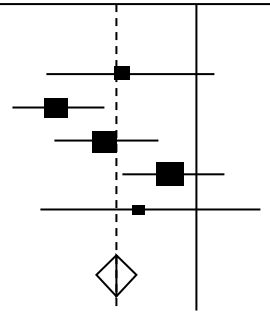
Recommendations for Lipid-lowering Therapy in Patients with Established CAD

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

	LDL-C Reduction (mmol/L)	Events (% per annum)		Unweighted RR (CI)
		Statin/more	Control/less	
More vs less statin				
PROVE–IT	0.65	406 (11.3%)	458 (13.1%)	
TNT	0.62	889 (4.0%)	1,164 (5.4%)	
IDEAL	0.55	938 (5.2%)	1,106 (6.3%)	
SEARCH	0.39	1,347 (3.6%)	1,406 (3.8%)	
A to Z	0.30	257 (7.2%)	282 (8.1%)	
Subtotal (5 trials)	**0.51**	**3,837/19,829 (4.5%)**	**4,416/19,783 (5.3%)**	**0.85 (0.82-0.89) p<0.0001**



Trend: χ^2_1=12.4 (p=0.0004)

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

4 statin benefit groups

Acute coronary syndrome
History of MI or angina,
Coronary or other arterial Revascularization,
stroke, TIA, PAD

1. Patients who have cardiovascular disease (clinical ASCD*)
2. Patients with an LDL level of 190 mg/dL or higher
3. Patients with DM who are between 40 and 75 years of age (LDL-C 70 to 189 mg/dL)
4. Patients with an estimated 10-year risk of cardiovascular disease of 7.5 % or higher who are between 40 and 75 years of age (the report provides formulas for calculating 10-year risk)

ASCVD = Atherosclerotic cardiovascular disease
Clinical ASCVD is defined by the inclusion criteria for the secondary prevention statin RCTs (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin).

2013 ACC/AHA Blood Cholesterol Guideline based on Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30-50%	Daily dose lowers LDL–C on average, by <30%
• Atorvastatin (40†)–80 mg Rosuvastatin 20 *(40)* mg	• Atorvastatin 10 *(20)* mg • Rosuvastatin *(5)* 10 mg • Simvastatin 20–40 mg‡ • Pravastatin 40 *(80)* mg • Lovastatin 40 mg • *Fluvastatin XL 80 mg* • Fluvastatin 40 mg bid • *Pitavastatin 2–4 mg*	• *Simvastatin 10 mg* • Pravastatin 10–20 mg • Lovastatin 20 mg • *Fluvastatin 20–40 mg* • *Pitavastatin 1 mg*

Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

† Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL

‡ Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

ACC: American College of Cardiology. AHA: American Heart Association. LDL-C: low-density lipoprotein cholesterol. RCT: randomized controlled trials. FDA: Food and Drug Administration. U.S: United States of America

1. Stone NJ, et al. JACC. 2013 ACC/AHA Blood Cholesterol Guideline.

Management of Dyslipidemia

Statin Safety Recommendations

Recommendation	NHLBI Grade
Safety	
1. To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD* risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present. Characteristics predisposing individuals to statin adverse effects include, but are not limited to: • Multiple or serious comorbidities, including impaired renal or hepatic function. • History of previous statin intolerance or muscle disorders. • Unexplained ALT elevations >3 times ULN. • Patient characteristics or concomitant use of drugs affecting statin metabolism. • >75 years of age. Additional characteristics that may **modify the decision to use higher statin intensities** may include, but are not limited to: • History of hemorrhagic stroke. **• Asian ancestry.**	**A (strong)** There is high certainty based on evidence that the net benefit† is substantial.

Circulation. 2014;129:S1-S45

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, Hiroyuki Daida, Hi
roaki Shimokawa, Ryozo Nagai,

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

AHA SCIENAMERICAN HEART ASSOCIATION'S
AHA SCIENTIFIC SESSIONS 2017

▶ 학회 : THE AMERICAN HEART ASSOCIATION, Annual Meeting 2017
▶ 일시 : 2017년 11월 11일-15일
▶ 장소 : 미국 캘리포니아 애너하임

SESSION LBS.02 - Late Breaking Science in Prevention

November 13, 2017, 9:00 - 10:15 AM | Ballroom CD, 3rd Level (Main Building)

9:00-9:12 AM	Dose High-Intensity Pitavastatin Therapy Further Improve Clinical Outcome? The **REAL-CAD study** in 13,054 Patients With Stable Coronary Artery Disease **Takeshi Kimura** et al, REAL-CAD investigators

2017 ACC/AHA guideline limitation

However, the high-intensity statins are not widely used in daily clinical practice, particularly in Asia. No clear evidence regarding "more versus less" statins has been established in Asian population. Most of the doses of high-intensity statin therapy defined in the ACC/AHA guideline are not approved in Japan. Furthermore, maximum approved doses of statins are prescribed only very infrequently in Japan.

Therefore, we sought to determine whether higher-dose statin therapy would b e beneficial in Japanese patients in the largest-ever trial comparing efficacy of h igh-dose vs low-dose statin therapy in patients with established stable CAD.

Statin therapy in Asian patients

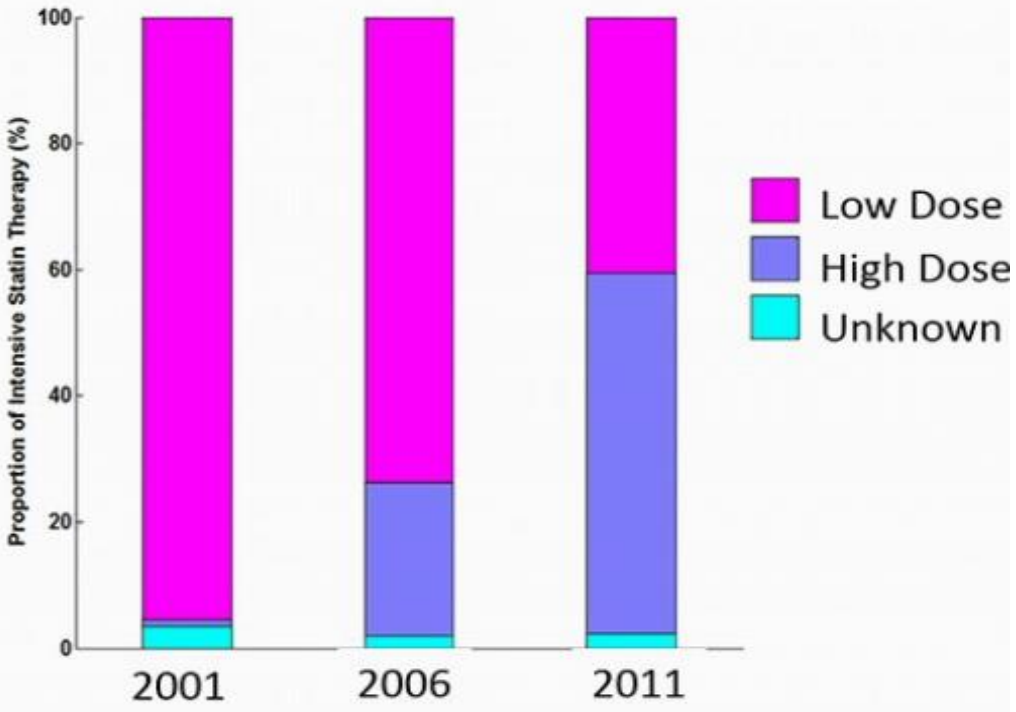
- Pharmacokinetic studies have noted higher plasma levels of statins in patients of Asian descent as compared to other ethnic groups, even when comparable doses of statins are used

- For this reason, some statin labels and some regulatory bodies suggest using lower doses of statins in Asian patients

Karol Watson, MD, PhD, FAHA, UCLA medical center

Statin therapy in asian pts

- Patients of Asian descent are often not treated with high dose statin therapy, even in clinically appropriate situations
- Demonstrating safety and efficacy of high dose statin therapy in Asian populations is therefore, of utmost importance



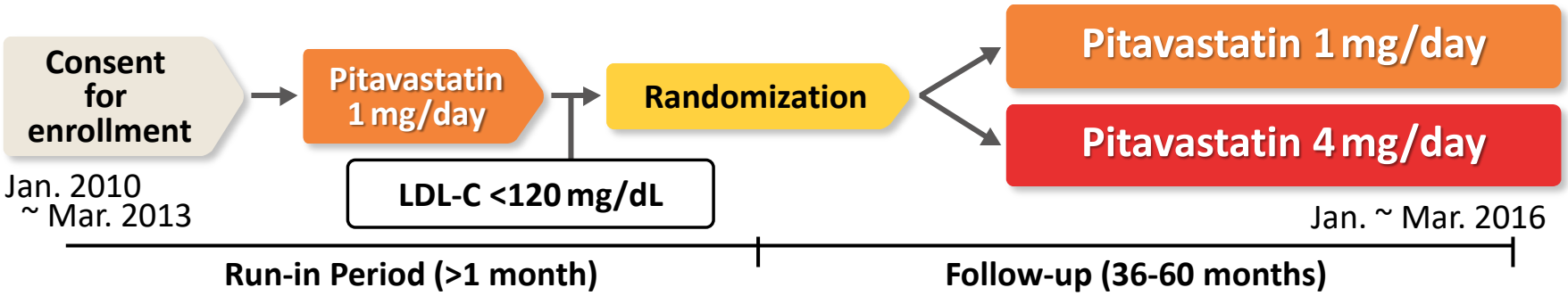
Statin Intensity in Patients Hospitalized with Acute Myocardial Infarction in China

Zhang L et. a. PLoS ONE 11(4): e0150806.

REAL-CAD STUDY

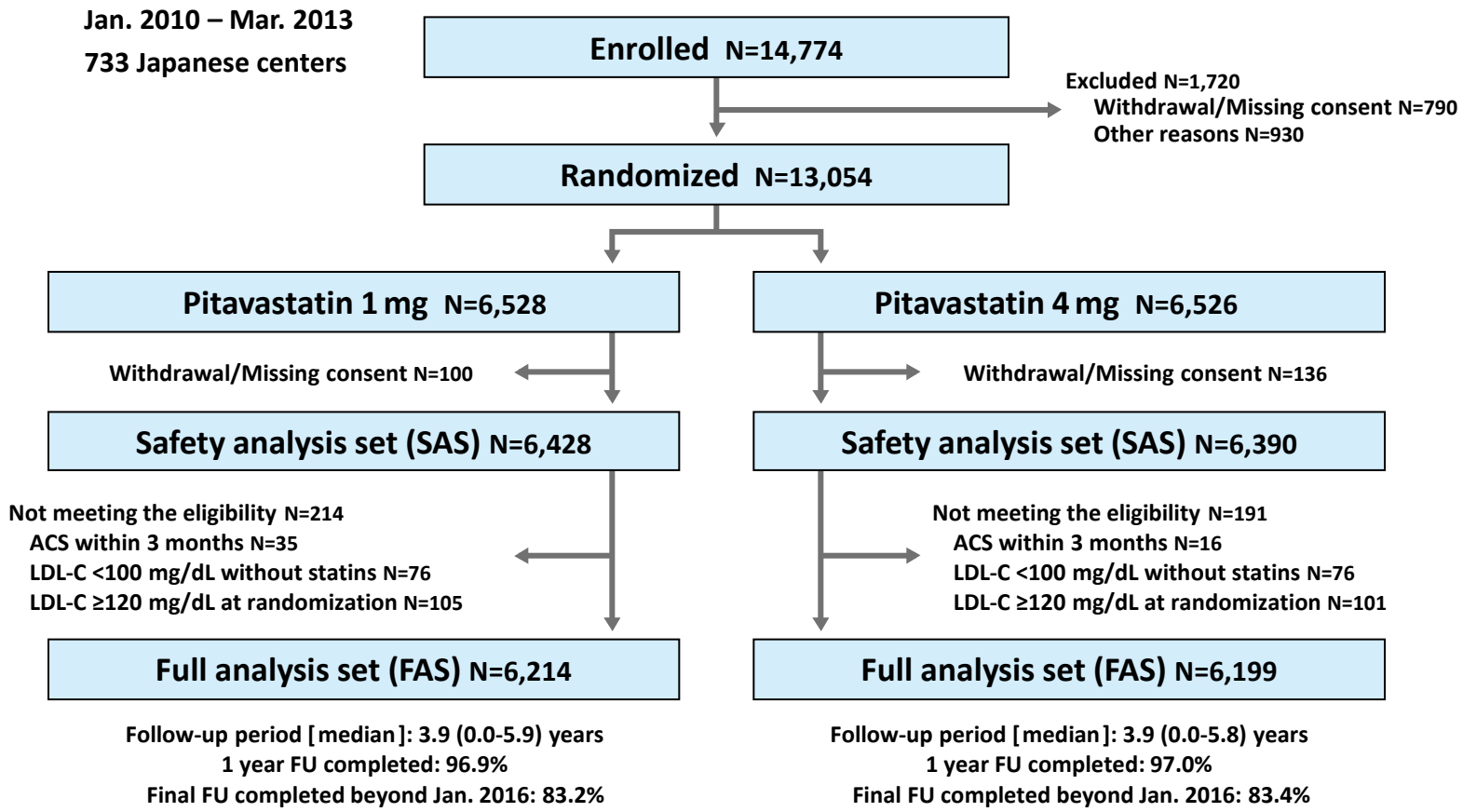
(Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease)

연구 목적	대부분의 statin 무작위 배정 연구에서 아시아 환자의 비율이 8%정도로 동양인 환자에게 기존의 고지혈 치료 진료 지침을 그대로 적용하기 어려웠다. 이번 연구를 통해 아시아 관상동맥 환자에서의 고용량 statin의 효용성과 안전성을 확인하고자 한다.
연구 방법	A prospective, multi-center, randomized, open-label, blinded endpoint, physician-initiated trial
대상 환자	관상동맥 협착이 50% 이상인 일본 관상동맥 환자 14,774명 ・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
Primary Endpoint	심장사망, 비치명적 MI, 비치명적 허혈성 뇌졸중, 입원을 요하는 불안정형 협심증
Secondary Endpoint	Primary endpoint + 관상동맥 재협착술



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

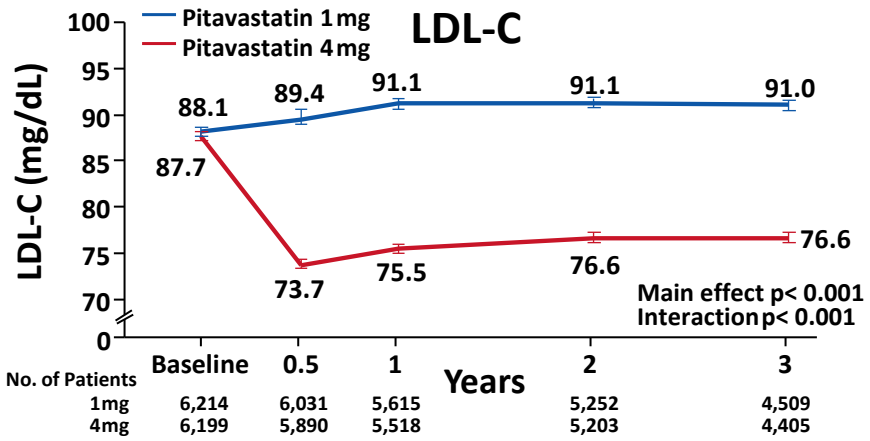
Study flow

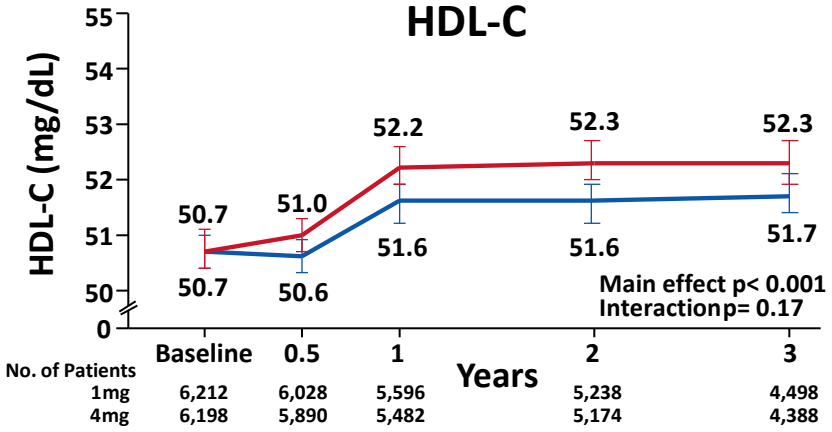

Jan. 2010 – Mar. 2013
733 Japanese centers
Enrolled N=14,774
Excluded N=1,720
Withdrawal/Missing consent N=790
Other reasons N=930
Randomized N=13,054
Pitavastatin 1 mg N=6,528
Pitavastatin 4 mg N=6,526
Withdrawal/Missing consent N=100
Withdrawal/Missing consent N=136
Safety analysis set (SAS) N=6,428
Safety analysis set (SAS) N=6,390
Not meeting the eligibility N=214
ACS within 3 months N=35
LDL-C <100 mg/dL without statins N=76
LDL-C ≥120 mg/dL at randomization N=105
Not meeting the eligibility N=191
ACS within 3 months N=16
LDL-C <100 mg/dL without statins N=76
LDL-C ≥120 mg/dL at randomization N=101
Full analysis set (FAS) N=6,214
Full analysis set (FAS) N=6,199
Follow-up period [median]: 3.9 (0.0-5.9) years
1 year FU completed: 96.9%
Final FU completed beyond Jan. 2016: 83.2%
Follow-up period [median]: 3.9 (0.0-5.8) years
1 year FU completed: 97.0%
Final FU completed beyond Jan. 2016: 83.4%

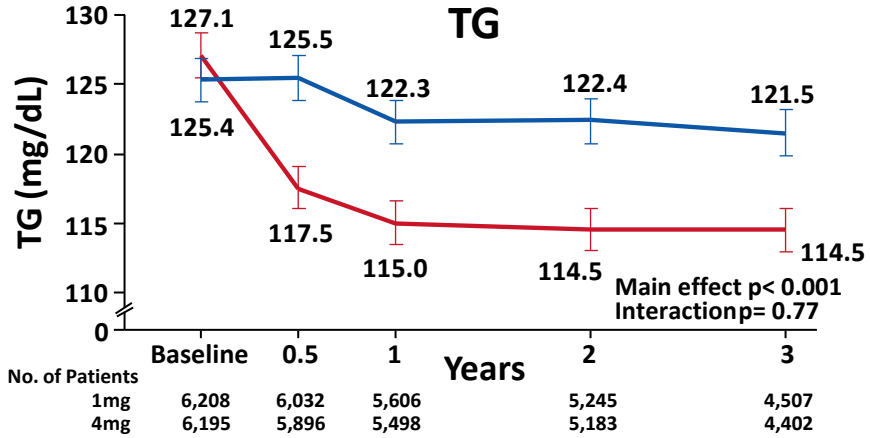
Baseline characteristics

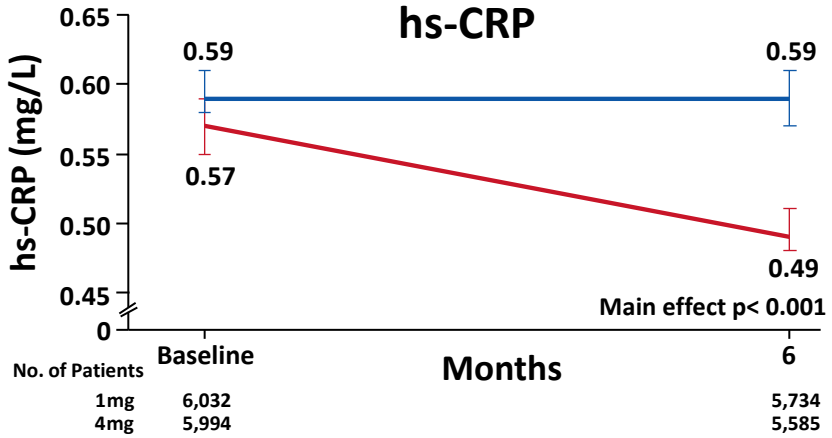
Variables	Pitavastatin 1 mg (N=6,214)	Pitavastatin 4 mg (N=6,199)
Age — years	68.1±8.3	68.0±8.3
Male sex	83%	83%
BMI — kg/m^2	24.6±3.4	24.6±3.3
Hypertension	75%	76%
Diabetes mellitus	40%	40%
Current smoking	16%	17%
History of ACS	72%	72%
ACS within 1 year before randomization	24%	24%
Coronary revascularization	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%

Lipid Parameters and hs-CRP



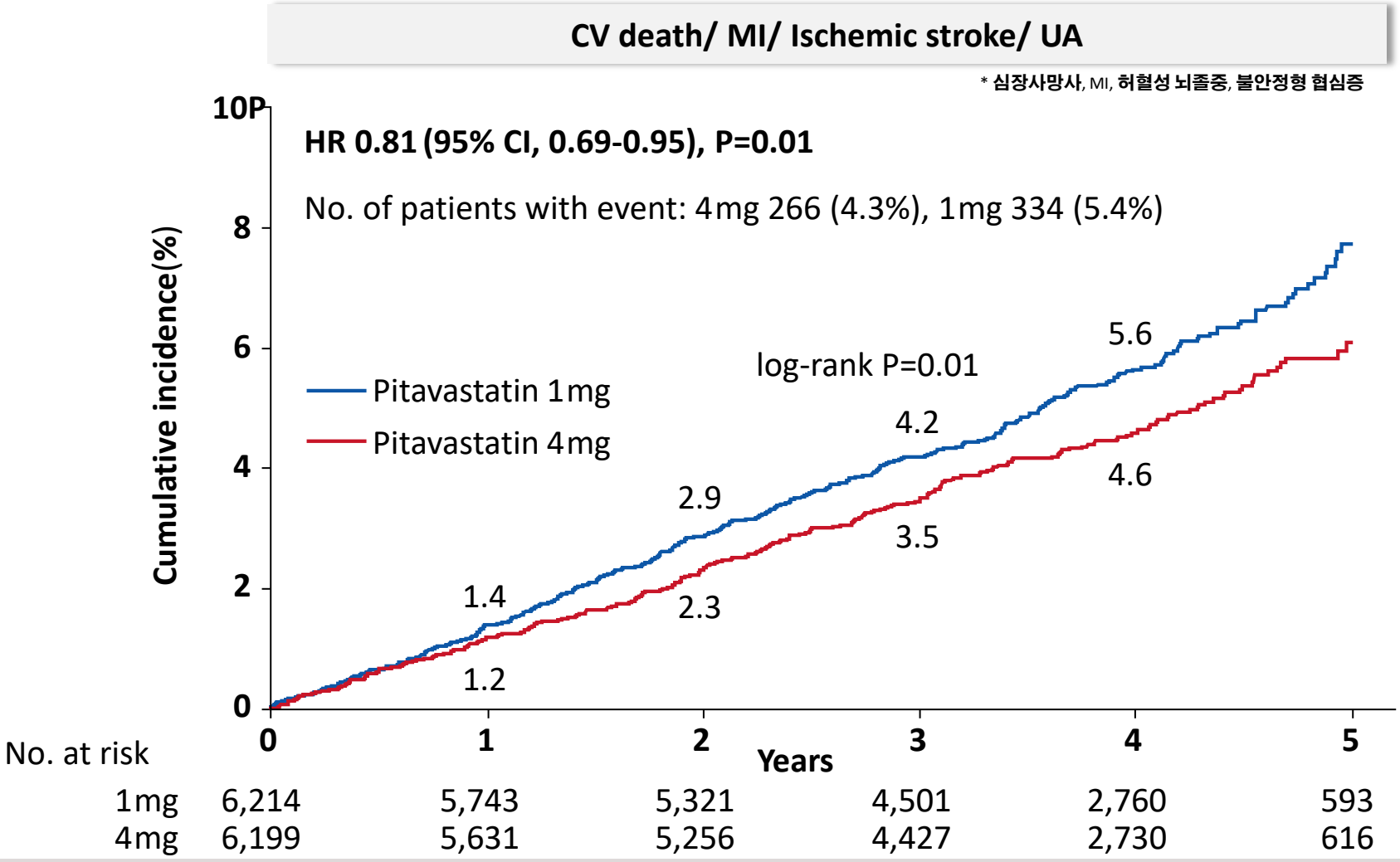






Primary endpoint

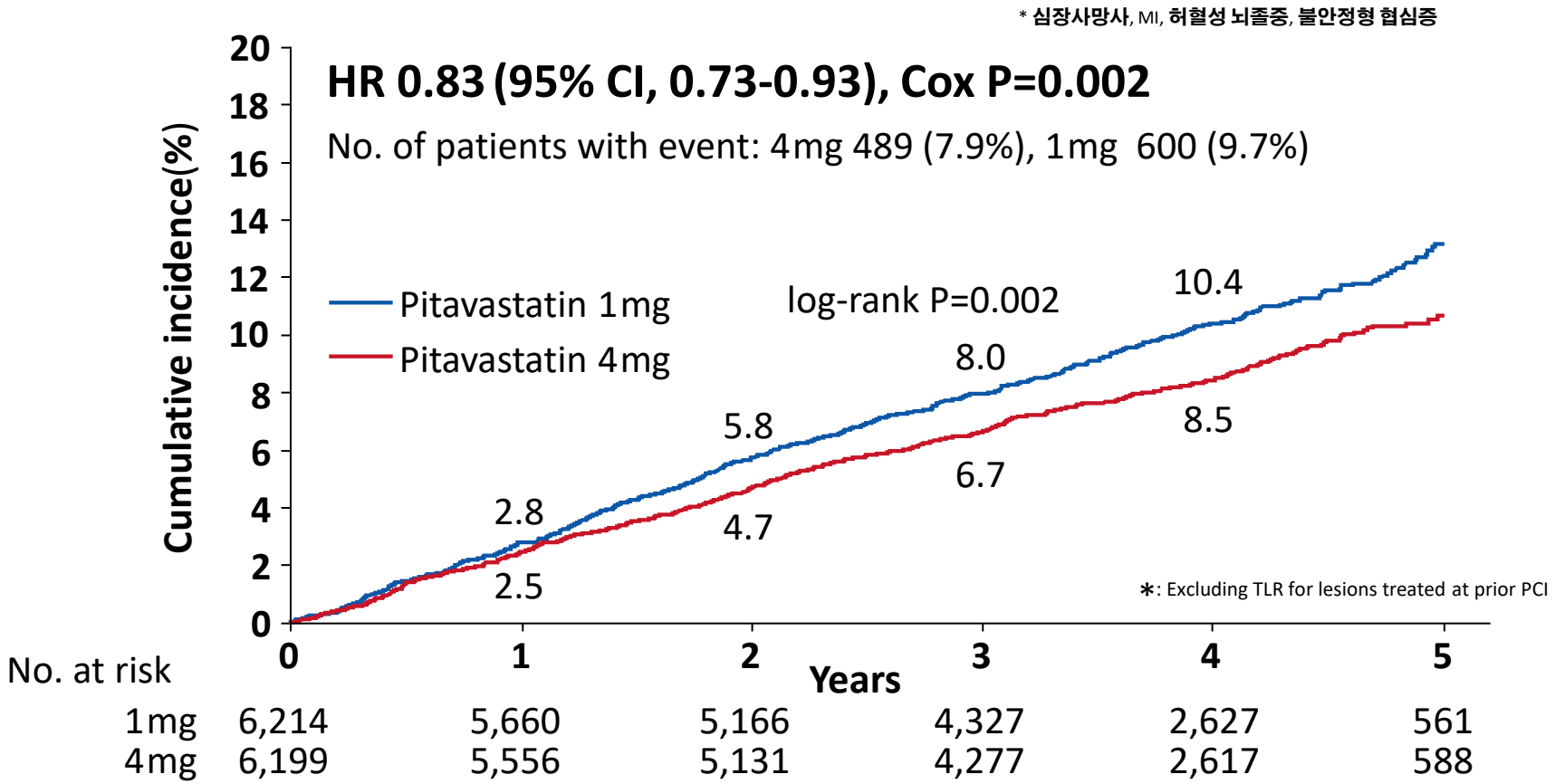
Pitavastatin 4mg은 1mg 대비 심혈관 사건*의 발생을 19% 유의하게 감소 시켰습니다.



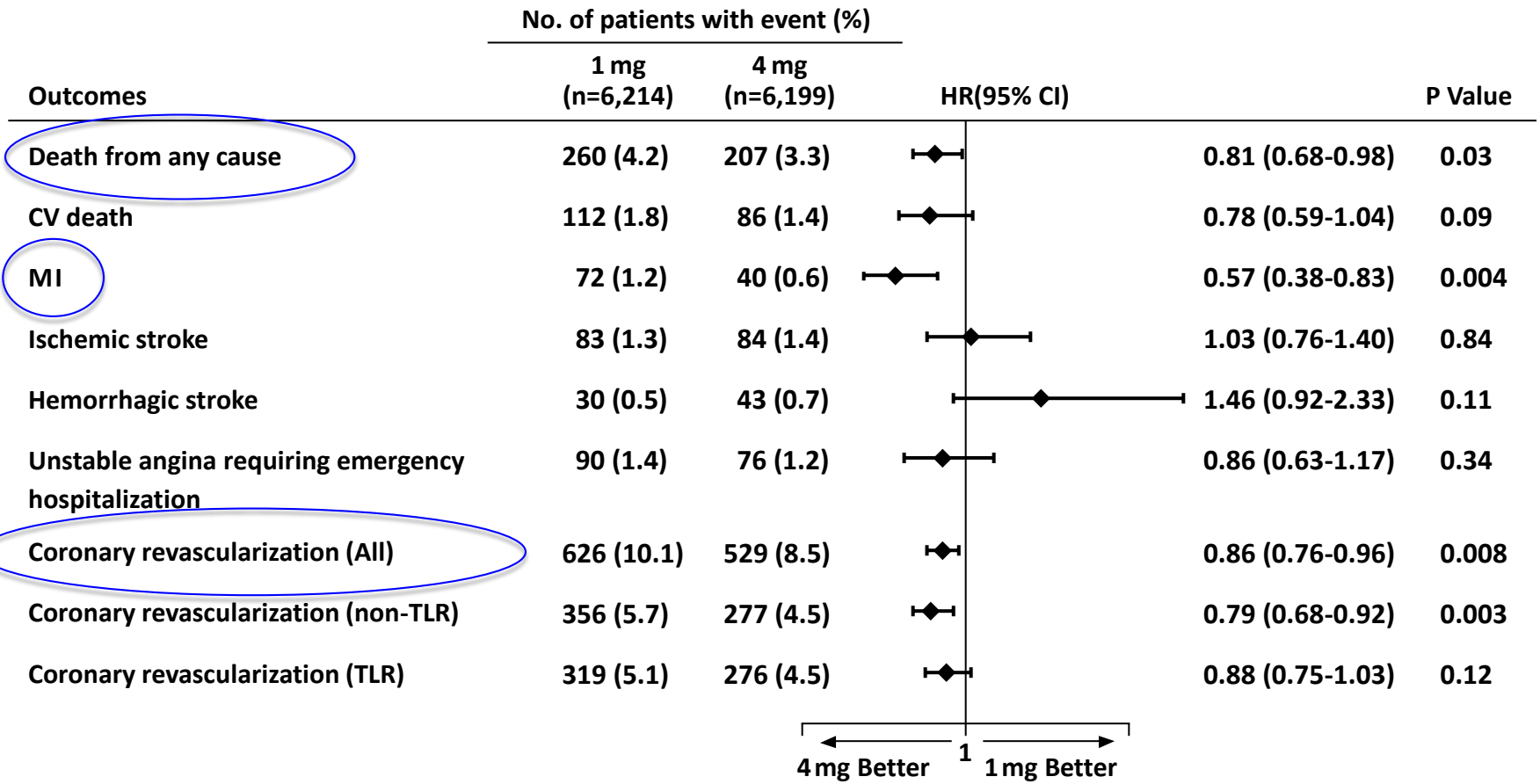
Secondary endpoint

Pitavastatin 4mg은 1mg 대비 관상동맥 혈관 재생술을 포함한 심혈관 사건*의 발생을 17% 유의하게 감소 시켰습니다.

Primary Endpoint plus Coronary Revascularization*



Other secondary endpoints

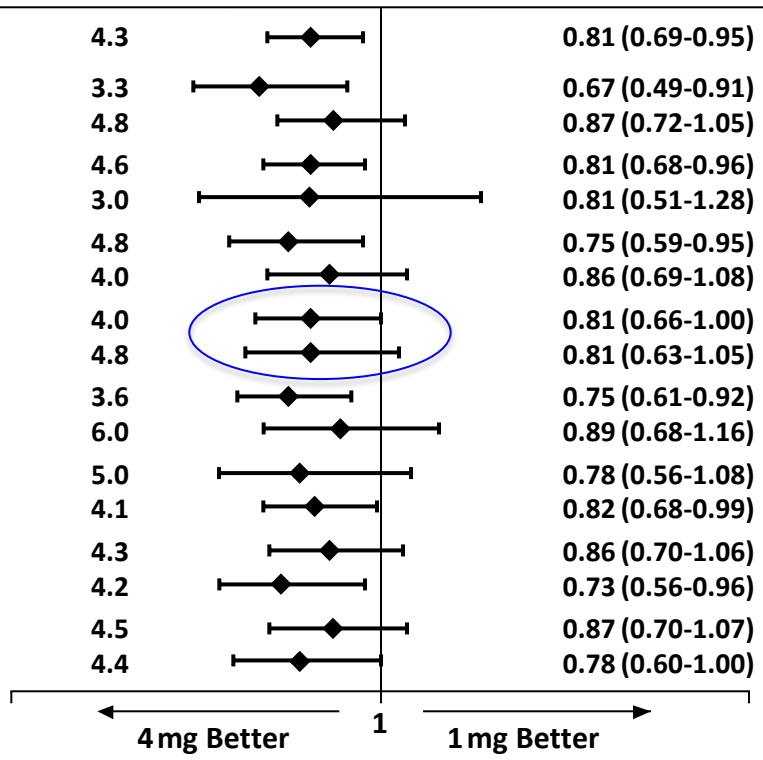


Outcomes	No. of patients with event (%) 1 mg (n=6,214)	4 mg (n=6,199)	HR(95% CI)	P Value
Death from any cause	260 (4.2)	207 (3.3)	0.81 (0.68-0.98)	0.03
CV death	112 (1.8)	86 (1.4)	0.78 (0.59-1.04)	0.09
MI	72 (1.2)	40 (0.6)	0.57 (0.38-0.83)	0.004
Ischemic stroke	83 (1.3)	84 (1.4)	1.03 (0.76-1.40)	0.84
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

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)	



Safety outcomes

Pitavastatin 4mg과 1mg은 우수한 내약성을 입증하였으며
NODM발생에서 용량의존적 차이가 없었습니다.**

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
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

ISSUE of STATIN

FDA warning

Cardiovascular

FDA Adds Diabetes Warning to Statin Label

Published: Feb 28, 2012

By Peggy Peck , Executive Editor, MedPage Today

WASHINGTON -- The FDA said today that all statins must carry warnings about increased risks of elevated blood sugar and possible transient memory and cognition problems, but at the same time the agency removed a standing recommendation for routine liver function tests for patients taking the cholesterol-lowering drugs.

http://www.medpagetoday.com/Cardiology/Dyslipidemia/31408

Based on clinical trial meta-analyses and epidemiological data from the published literature, information concerning an effect of statins on incident diabetes and increases in HbA1c and/or fasting plasma glucose was added to statin labels.

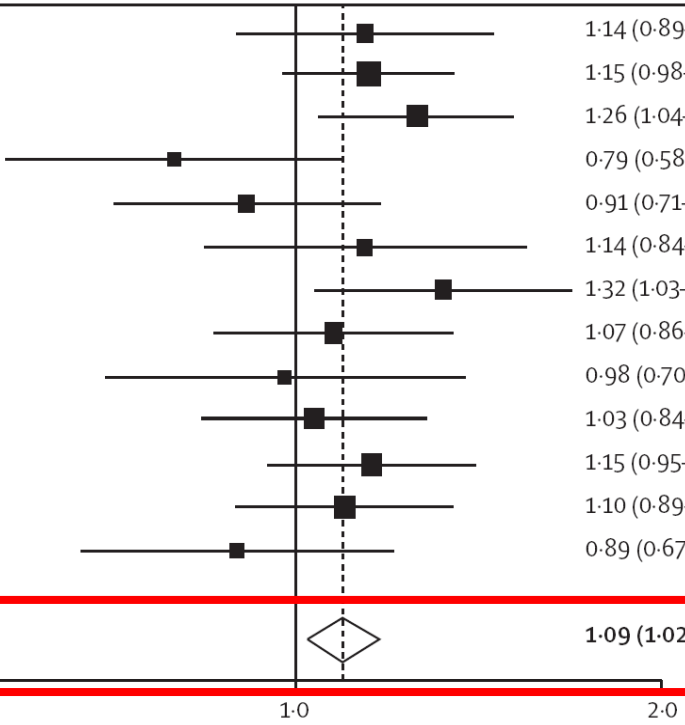
http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm

Statin and new onset of diabetes in meta-analysis

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Naveed Sattar, David Preiss, Heather M Murray, Paul Welsh, Brendan M Buckley, Anton J M de Craen, Sreenivasa Rao Kondapally Seshasai, John J McMurray, Dilys J Freeman, J Wouter Jukema, Peter W Macfarlane, Chris J Packard, David J Stott, Rudi G Westendorp, James Shepherd, Barry R Davis, Sara L Pressel, Roberto Marchioli, Rosa Maria Marfisi, Aldo P Maggioni, Luigi Tavazzi, Gianni Tognoni, John Kjekshus, Terje R Pedersen, Thomas J Cook, Antonio M Gotto, Michael B Clearfield, John R Downs, Haruo Nakamura, Yasuo Ohashi, Kyoichi Mizuno, Kausik K Ray, Ian Ford

	n	Statin		Placebo or control		OR (95% CI)	Weight (%)
		Events	Rate	Events	Rate		
ASCOT-LLA[7]	7773	154	11·9	134	10·5	1·14 (0·89–1·46)	7·07%
HPS[8]	14573	335	9·2	293	8·0	1·15 (0·98–1·35)	13·91%
JUPITER[4]	17802	270	16·0	216	12·8	1·26 (1·04–1·51)	11·32%
WOSCOPS[5]	5974	75	5·2	93	6·5	0·79 (0·58–1·10)	4·24%
LIPID[6]	6997	126	6·0	138	6·6	0·91 (0·71–1·71)	6·53%
CORONA[9]	3534	100	20·9	88	18·5	1·14 (0·84–1·55)	4·65%
PROSPER[12]	5023	165	20·5	127	15·8	1·32 (1·03–1·69)	6·94%
MEGA[13]	6086	172	10·8	164	10·1	1·07 (0·86–1·35)	8·03%
AFCAPS/TEXCAPS[18]	6211	72	4·5	74	4·6	0·98 (0·70–1·38)	3·76%
4S[15]	4242	198	17·3	193	16·8	1·03 (0·84–1·28)	8·88%
ALLHAT[14]	6087	238	16·4	212	14·4	1·15 (0·95–1·41)	10·23%
GISSI HF[16]	3378	225	34·8	215	32·1	1·10 (0·89–1·35)	9·50%
GISSI PREV[16]	3460	96	27·5	105	30·6	0·89 (0·67–1·20)	4·94%
Overall (I^2=11·2% [95% CI 0·0–50·2%])						1·09 (1·02–1·17)	100%



Lancet 2010;375:735

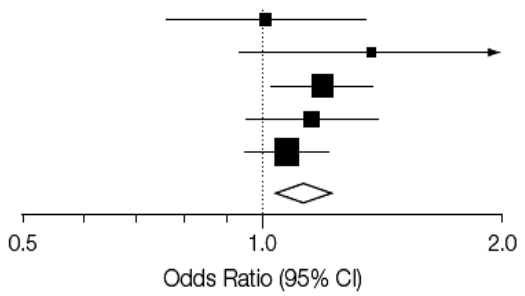
The association between Higher doses of statins and new-onset Diabetes

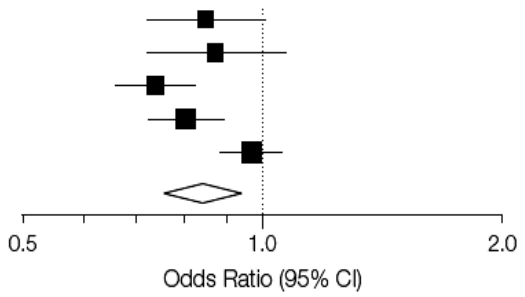
In a pooled analysis, intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy.

- **As compared with moderate-dose statin, the number needed to harm per year for intensive-dose statin was 498 for new-onset DM while the number needed to treat per year for intensive-dose statin was 155 for CV events.**

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16 408 (8.8)	1300/16 344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2 = 0\%$; $P = .60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16 408 (19.1)	3550/16 344 (21.7)	0.84 (0.75-0.94)
Heterogeneity: $I^2 = 74\%$; $P = .004$			





Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

Preiss D, JAMA. 2011;305:2556-2564

Pitavastatin, 당뇨병 위험징후 없음 정부기관 공식 승인 !!

유럽 7개국 아시아 1개국, 총 8개 국가에서 리바로® 허가공문(SmPC)에 당대사, 당뇨병 발생에 부정적 영향 없음 공인

- 영국 2016.03.07
- 그리스 2016.03.07
- 포르투갈 2016.03.07
- 독일 2016.03.14
- 스페인 2016.03.29
- 스웨덴 2016.06.29
- 네덜란드 2016.07.03
- 대만 2016.09.07

영국을 시작으로 유럽 7개국 아시아 1개국, 총 8개 국가에서 피타바스타틴 당뇨병 안전성 내용 추가

- 피타바스타틴 제품설명서(SmPC)에 당대사나 당뇨병 발생에 부정적 영향 없음 공인 -

4.4 Special warnings and precautions for use[1)]

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk of hyperglycaemia (fasting glucose 5.6 to 6.9 mmol/L, BMI>30 kg/m2, raised triglycerides, hypertension), should be monitored both clinically and biochemically according to national guidelines. **However, there has been no confirmed signal of a diabetes risk for pitavastatin either in post-marketing safety surveillance studies or in prospective studies** (see section 5.1).

1) SmPC of Pitavastatin in UK

MHRA가 인정한 당뇨병에 안전한 유일한 스타틴

MEDICINES & HEALTHCARE PRODUCTS REGULATORY AGENCY

영국식약처(MHRA), 2016년 3월 7일

리바로® 제품설명서(SmPC)에 당뇨병 안전성 인정

리바로만이 PMS와 임상시험 자료를 근거로 당뇨병 위험 징후가 없음을 언급

4.4 Special warnings and precautions for use

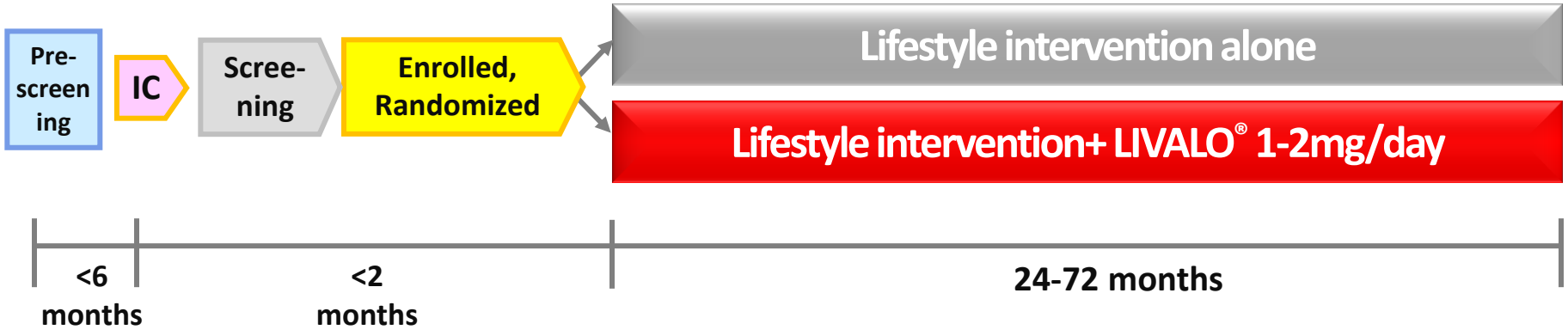
Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk of hyperglycaemia (fasting glucose 5.6 to 6.9 mmol/L, BMI>30 kg/m2, raised triglycerides, hypertension), should be monitored both clinically and biochemically according to national guidelines. **However, there has been no confirmed signal of a diabetes risk for pitavastatin either in post-marketing safety surveillance studies or in prospective studies** (see section 5.1).

J-PREDICT study

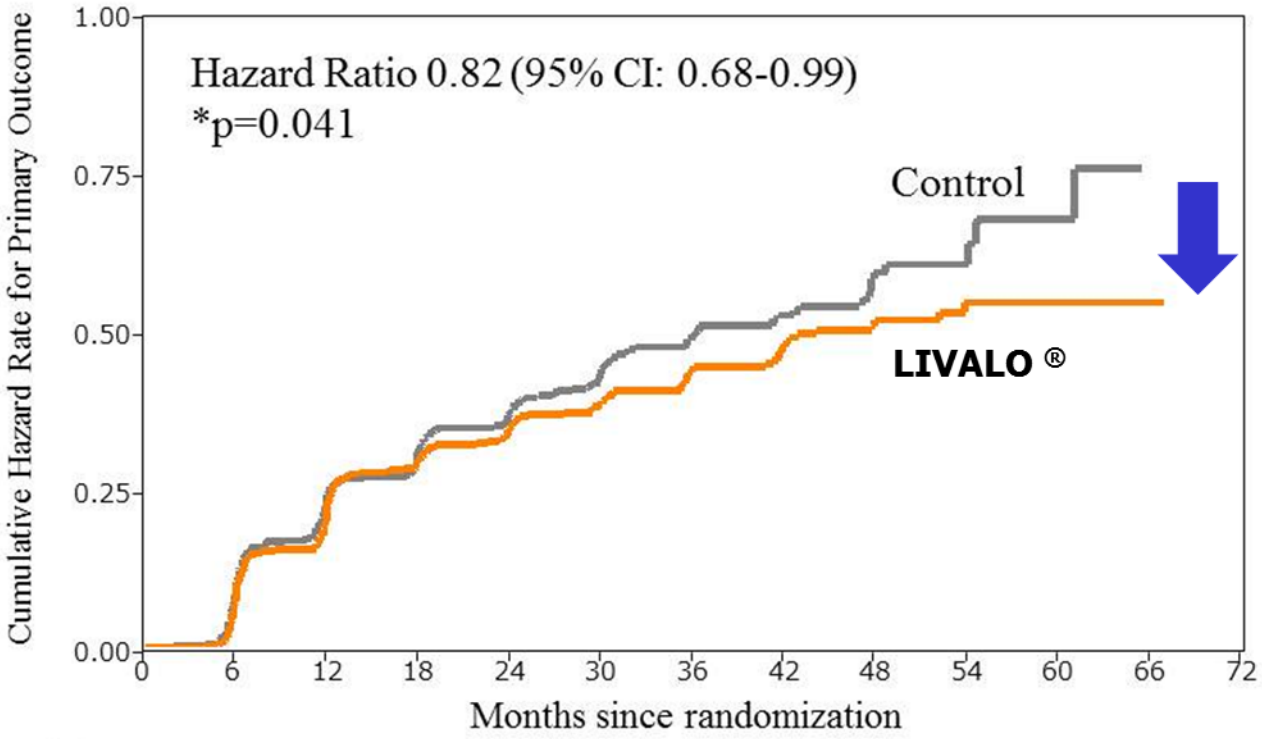
Subject	IGT
Primary outcome	Cumulative incidence of diabetes
Secondary outcome	Incidence of any cardiovascular diseases, etc
Study drug	LIVALO® 1-2mg/day vs. control group
Sample size	1,240
Study period	Apr. 2007 to Mar. 2013 (recruitment closure Mar. 31,2010)
Principal investigator	Takashi Kadowaki (the university of Tokyo)

Prospective, Randomized, Open - label, Blinded – Endpoint (PROBE)



J-PREDICT study

Effect of LIVALO® on the incidence of diabetes



No. at Risk											
Control	556	500	405	350	277	190	123	77	42	15	5
Pitavastatin	534	475	385	320	263	178	124	101	68	30	23

*P value was calculated using a log-rank test that was stratified according to the 5 assignment factors (sex, age, Body mass index, 2-h plasma glucose, and presence of hypertension).

2013 ADA

Pitavastatin meta-analysis

Title	**Effect of pitavastatin on glucose, HbA1c and incident diabetes: A meta-analysis of randomized controlled clinical trials in individuals without diabetes**
Methods	**Until 2014 for ≥12-week follow-up placebo or statin-controlled RCT of pitavastatin that included participants without diabetes and reported on fasting blood glucose (FBG), HbA1c or NOD. -> 15 studies (approx. 1600 person-years)**
Results	**No significant differences associated with pitavastatin (vs. control) were observed for FBG (MD -0.01 mg/dL [95%CI -0.77, 0.74], I^2 = 0%), HbA1c (MD -0.03% [95%CI -0.11, 0.05], I^2= 43%) or NOD (RR 0.70 [95%CI 0.30, 1.61]; RD 0.0 [95%CI -0.004, 0.003]; I^2 = 0%). Sensitivity and subgroup analyses (including type of control [placebo or other statin], pitavastatin dose or follow-up] did not yield significant results.**

Atherosclerosis. 2015 Aug;241(2):409-18

Pitavastatin meta-analysis

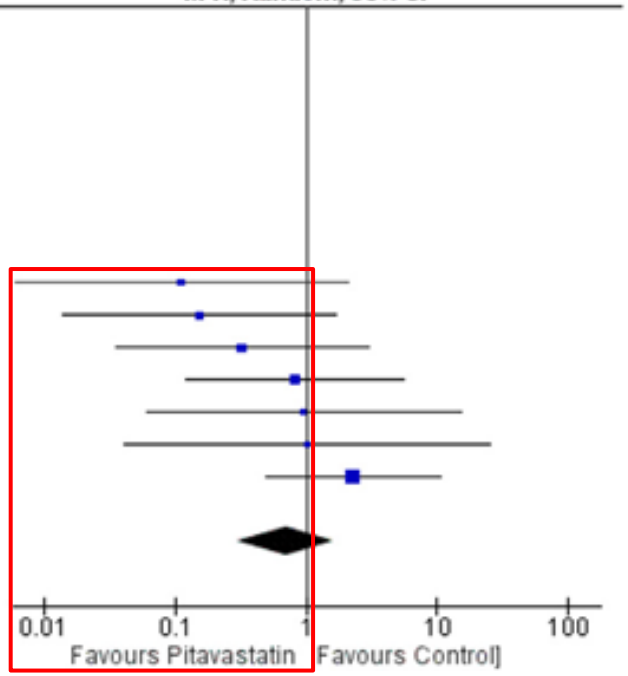
다른 스타틴과 비교해서 LIVALO® 은 당뇨병발생에 부정적인 영향을 미치지 않습니다.

C. New onset diabetes – Risk Ratio

Study or Subgroup	Pitavastatin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Eriksson M et al, 2011	0	218	0	111		Not estimable
NK-104-203	0	202	0	49		Not estimable
PREVAIL-US	0	143	0	131		Not estimable
NK-104-202	0	206	0	54		Not estimable
PAPAGO-T	0	50	0	50		Not estimable
PEACE	0	70	0	81		Not estimable
VISION	0	21	0	21		Not estimable
Stender S et al, 2013	0	597	0	288		Not estimable
INTREPID	0	123	4	124	8.2%	0.11 [0.01, 2.06]
Budinski D et al, 2009	1	576	2	179	12.1%	0.16 [0.01, 1.70]
COMPACT-CAD	1	36	3	35	14.2%	0.32 [0.04, 2.97]
TRUTH	2	38	2	31	19.3%	0.82 [0.12, 5.46]
Saito Y et al, 2002	1	84	1	81	9.2%	0.96 [0.06, 15.16]
Ose L et al, 2009	1	592	0	202	6.8%	1.03 [0.04, 25.11]
NK-104-4.01CH	9	280	2	142	30.2%	2.28 [0.50, 10.42]
Total (95% CI)		**3236**		**1579**	**100.0%**	**0.70 [0.30, 1.61]**
Total events	15		14			

Heterogeneity: Tau² = 0.00; Chi² = 5.97, df = 6 (P = 0.43); I² = 0%

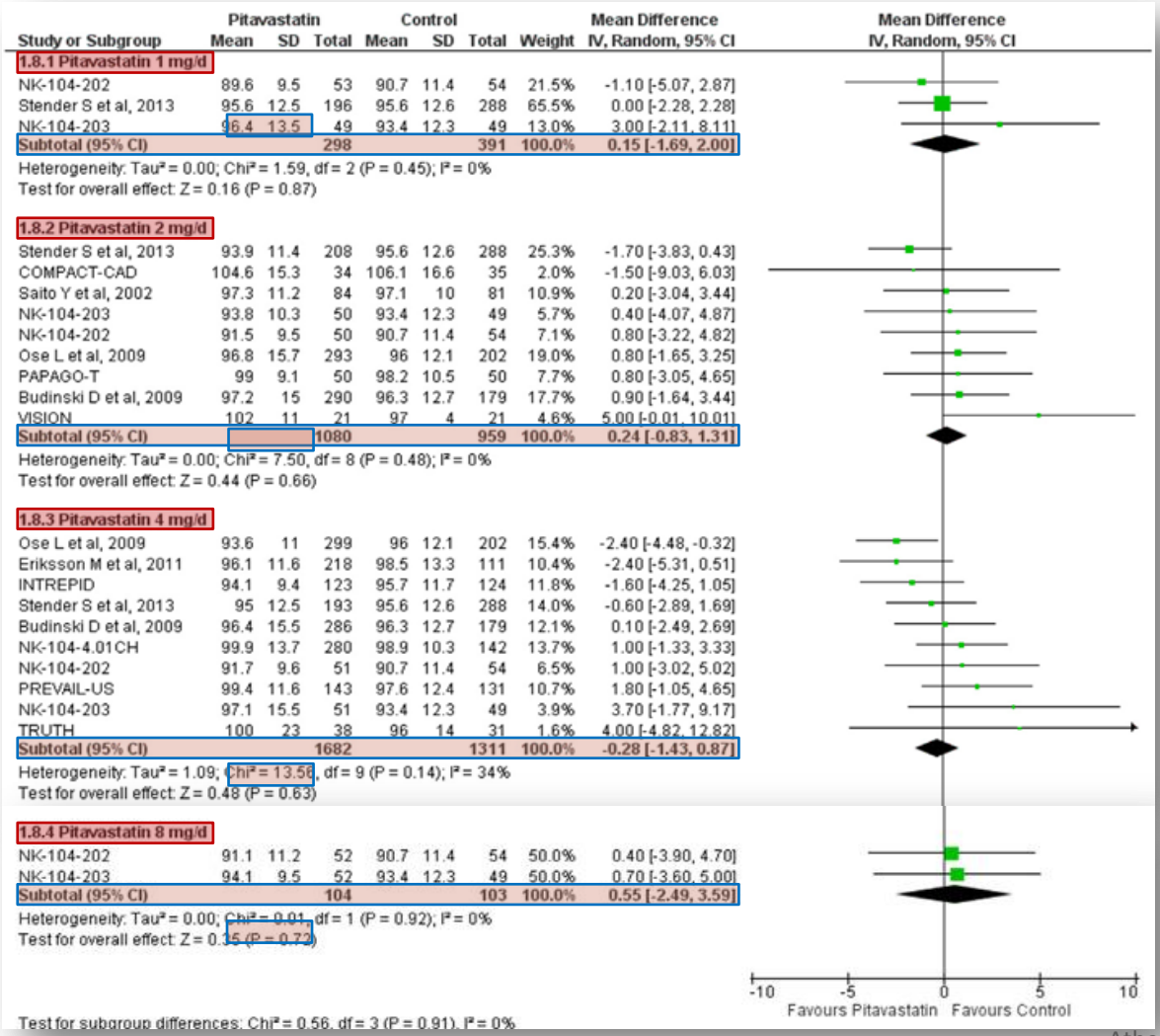
Test for overall effect: Z = 0.84 (P = 0.40)



Atherosclerosis. 2015 Aug;241(2):409-18

Pitavastatin meta-analysis

Dose-dependent한 혈당(FBG)에의 영향은 나타나지 않았습니다.



Study or Subgroup	Pitavastatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.8.1 Pitavastatin 1 mg/d								
NK-104-202	89.6	9.5	53	90.7	11.4	54	21.5%	-1.10 [-5.07, 2.87]
Stender S et al, 2013	95.6	12.5	196	95.6	12.6	288	65.5%	0.00 [-2.28, 2.28]
NK-104-203	96.4	13.5	49	93.4	12.3	49	13.0%	3.00 [-2.11, 8.11]
Subtotal (95% CI)			298			391	100.0%	0.15 [-1.69, 2.00]
Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 2 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.16 (P = 0.87)								
1.8.2 Pitavastatin 2 mg/d								
Stender S et al, 2013	93.9	11.4	208	95.6	12.6	288	25.3%	-1.70 [-3.83, 0.43]
COMPACT-CAD	104.6	15.3	34	106.1	16.6	35	2.0%	-1.50 [-9.03, 6.03]
Saito Y et al, 2002	97.3	11.2	84	97.1	10	81	10.9%	0.20 [-3.04, 3.44]
NK-104-203	93.8	10.3	50	93.4	12.3	49	5.7%	0.40 [-4.07, 4.87]
NK-104-202	91.5	9.5	50	90.7	11.4	54	7.1%	0.80 [-3.22, 4.82]
Ose L et al, 2009	96.8	15.7	293	96	12.1	202	19.0%	0.80 [-1.65, 3.25]
PAPAGO-T	99	9.1	50	98.2	10.5	50	7.7%	0.80 [-3.05, 4.65]
Budinski D et al, 2009	97.2	15	290	96.3	12.7	179	17.7%	0.90 [-1.64, 3.44]
VISION	102	11	21	97	4	21	4.6%	5.00 [-0.01, 10.01]
Subtotal (95% CI)			1080			959	100.0%	0.24 [-0.83, 1.31]
Heterogeneity: Tau² = 0.00; Chi² = 7.50, df = 8 (P = 0.48); I² = 0%								
Test for overall effect: Z = 0.44 (P = 0.66)								
1.8.3 Pitavastatin 4 mg/d								
Ose L et al, 2009	93.6	11	299	96	12.1	202	15.4%	-2.40 [-4.48, -0.32]
Eriksson M et al, 2011	96.1	11.6	218	98.5	13.3	111	10.4%	-2.40 [-5.31, 0.51]
INTREPID	94.1	9.4	123	95.7	11.7	124	11.8%	-1.60 [-4.25, 1.05]
Stender S et al, 2013	95	12.5	193	95.6	12.6	288	14.0%	-0.60 [-2.89, 1.69]
Budinski D et al, 2009	96.4	15.5	286	96.3	12.7	179	12.1%	0.10 [-2.49, 2.69]
NK-104-4.01CH	99.9	13.7	280	98.9	10.3	142	13.7%	1.00 [-1.33, 3.33]
NK-104-202	91.7	9.6	51	90.7	11.4	54	6.5%	1.00 [-3.02, 5.02]
PREVAIL-US	99.4	11.6	143	97.6	12.4	131	10.7%	1.80 [-1.05, 4.65]
NK-104-203	97.1	15.5	51	93.4	12.3	49	3.9%	3.70 [-1.77, 9.17]
TRUTH	100	23	38	96	14	31	1.6%	4.00 [-4.82, 12.82]
Subtotal (95% CI)			1682			1311	100.0%	-0.28 [-1.43, 0.87]
Heterogeneity: Tau² = 1.09; Chi² = 13.56, df = 9 (P = 0.14); I² = 34%								
Test for overall effect: Z = 0.48 (P = 0.63)								
1.8.4 Pitavastatin 8 mg/d								
NK-104-202	91.1	11.2	52	90.7	11.4	54	50.0%	0.40 [-3.90, 4.70]
NK-104-203	94.1	9.5	52	93.4	12.3	49	50.0%	0.70 [-3.60, 5.00]
Subtotal (95% CI)			104			103	100.0%	0.55 [-2.49, 3.59]
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.72)								
Test for subgroup differences: Chi² = 0.56, df = 3 (P = 0.91), I² = 0%								

Mean Difference IV, Random, 95% CI

-10 -5 0 5 10

Favours Pitavastatin Favours Control

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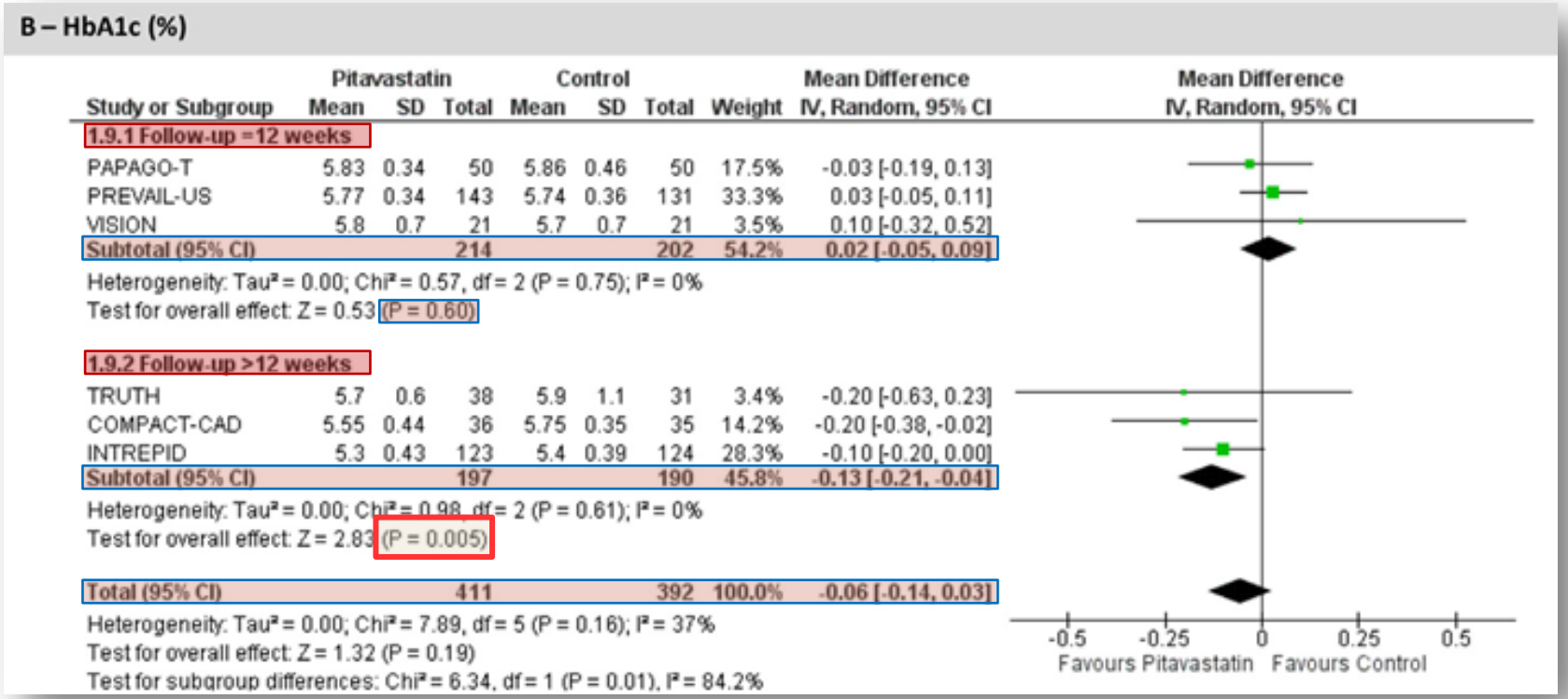
Pitavastatin meta-analysis

F/U > 12주 하위그룹 분석 시, control군 대비 PTV군에서HbA1c가 유의적으로 감소하였습니다.



Atherosclerosis. 2015 Aug;241(2):409-18

Summary

1. *REAL-CAD trial* adds important clinical evidence in support of high dose statin therapy in Asian population.
2. In Asian CAD population, *pitavastatin 4mg daily* reduced the composite primary outcomes more than *pitavastatin 1mg daily*
   – at 3 years, ARR = 1.1%, RRR = 19% ; NNT = 63
3. *Pitavastatin 4mg daily* reduced total mortality
   – at 3 years, ARR = 0.9%, RRR = 27%, NNT = 111
4. *High dose pitavastatin* is well tolerated in Asian CAD patients.

Thank you for your attention^^.