The New Reliable Options to Treat Dyslipidemia with Diabetes Mellitus

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서 지 아

Contents

- Diabetes as a CVD risk factor
- Pharmacokinetics of Pitavastatin
- Clinical Benefit of Pitavastatin in Type 2 DM
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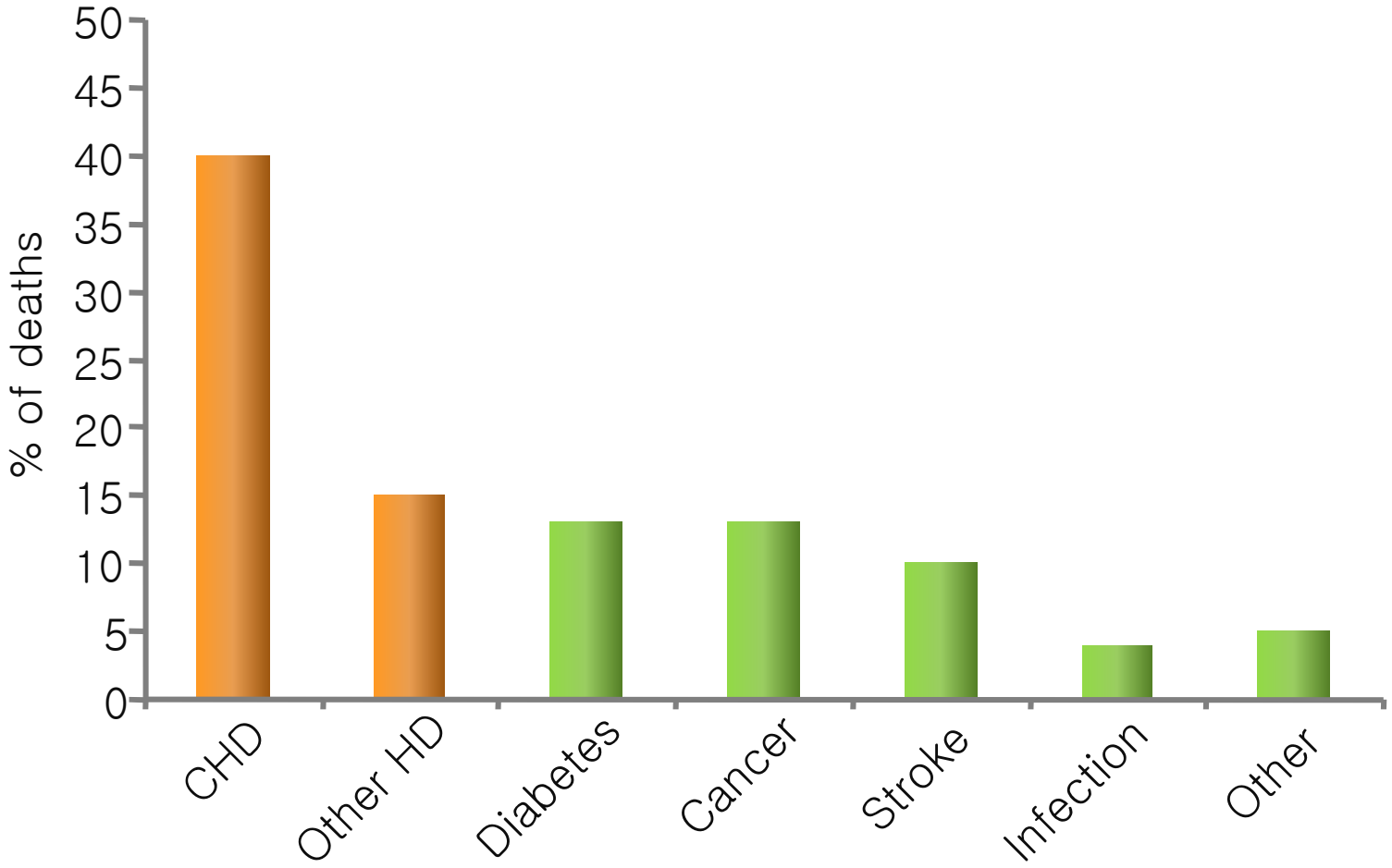
  - Effects on the glucose metabolism including PROPIT results
  - Effects on the surrogate markers
  - Effects on the prevention of CV events
- On-going Clinical Trials

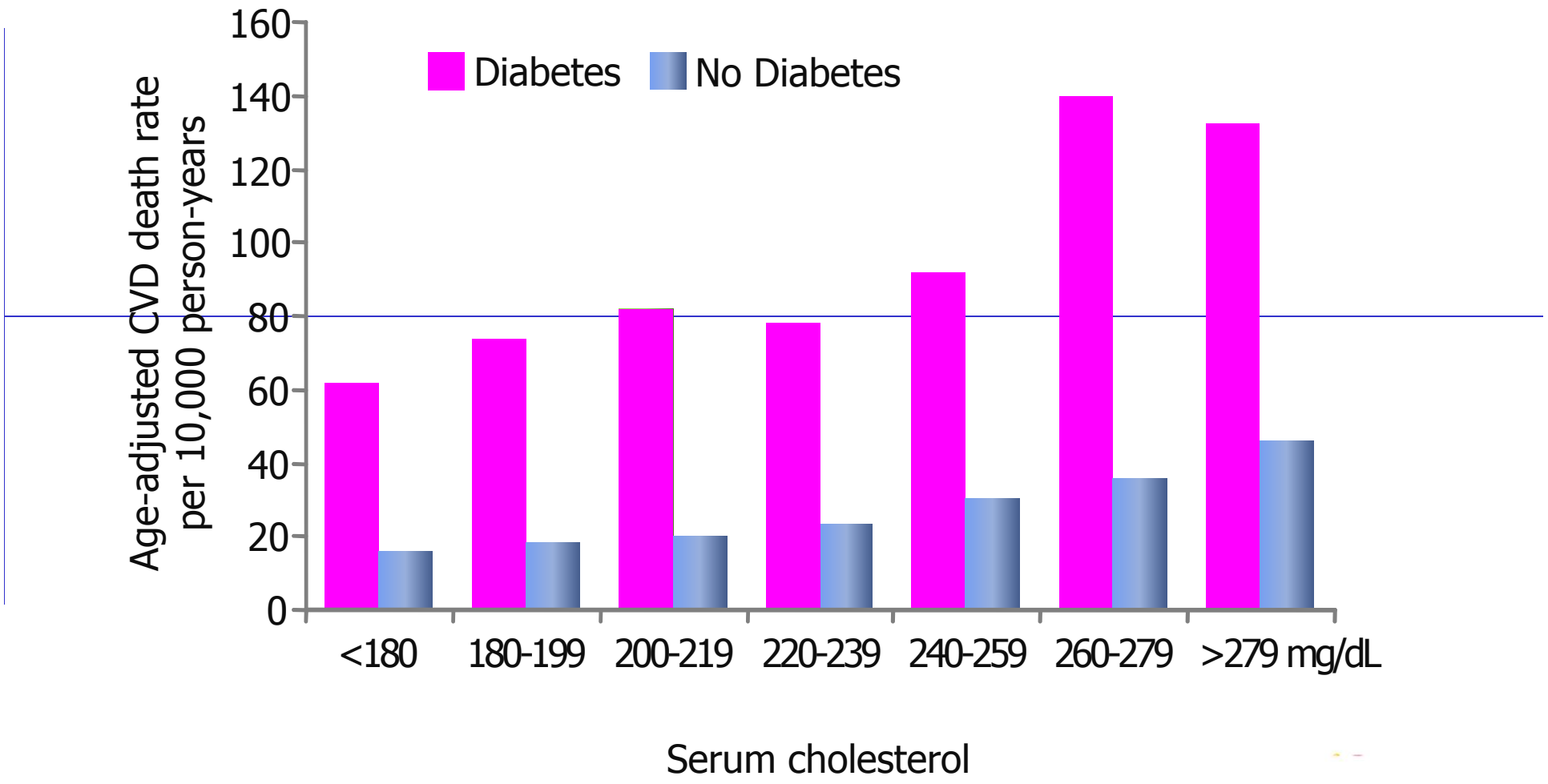
CVD Is the Major Listed Cause of Death in Patients With T2DM



HD, heart disease.

Geiss LS, et al. In: National Diabetes Data Group. *Diabetes in America*. 2nd ed. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995:233–257.

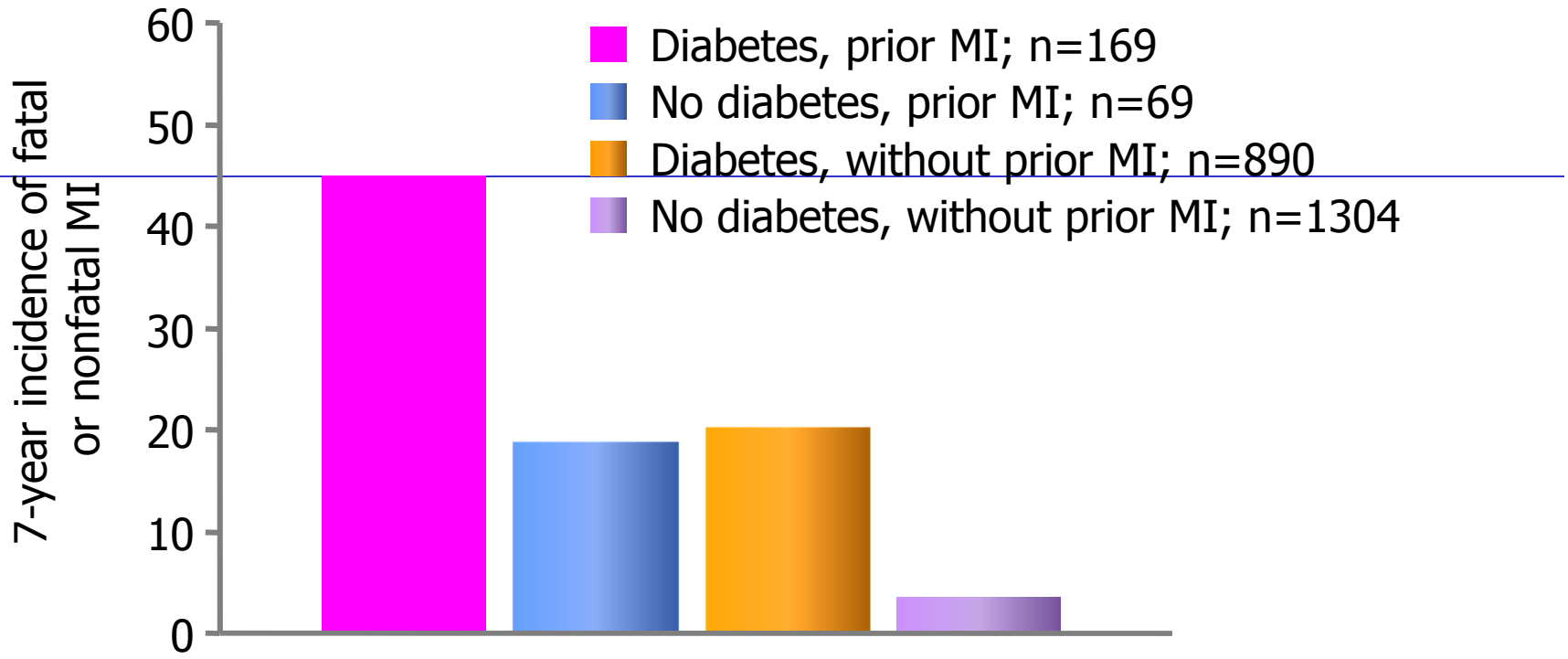
Risk of CVD Death Increases With TC Levels in Men With Diabetes: MRFIT



Stamler J. Vaccaro O. Neaton JD. Wentworth D. Diabetes Care. 1993:16:434-444.

Patients with Diabetes are at 2-4 Times Greater Risk for CVD

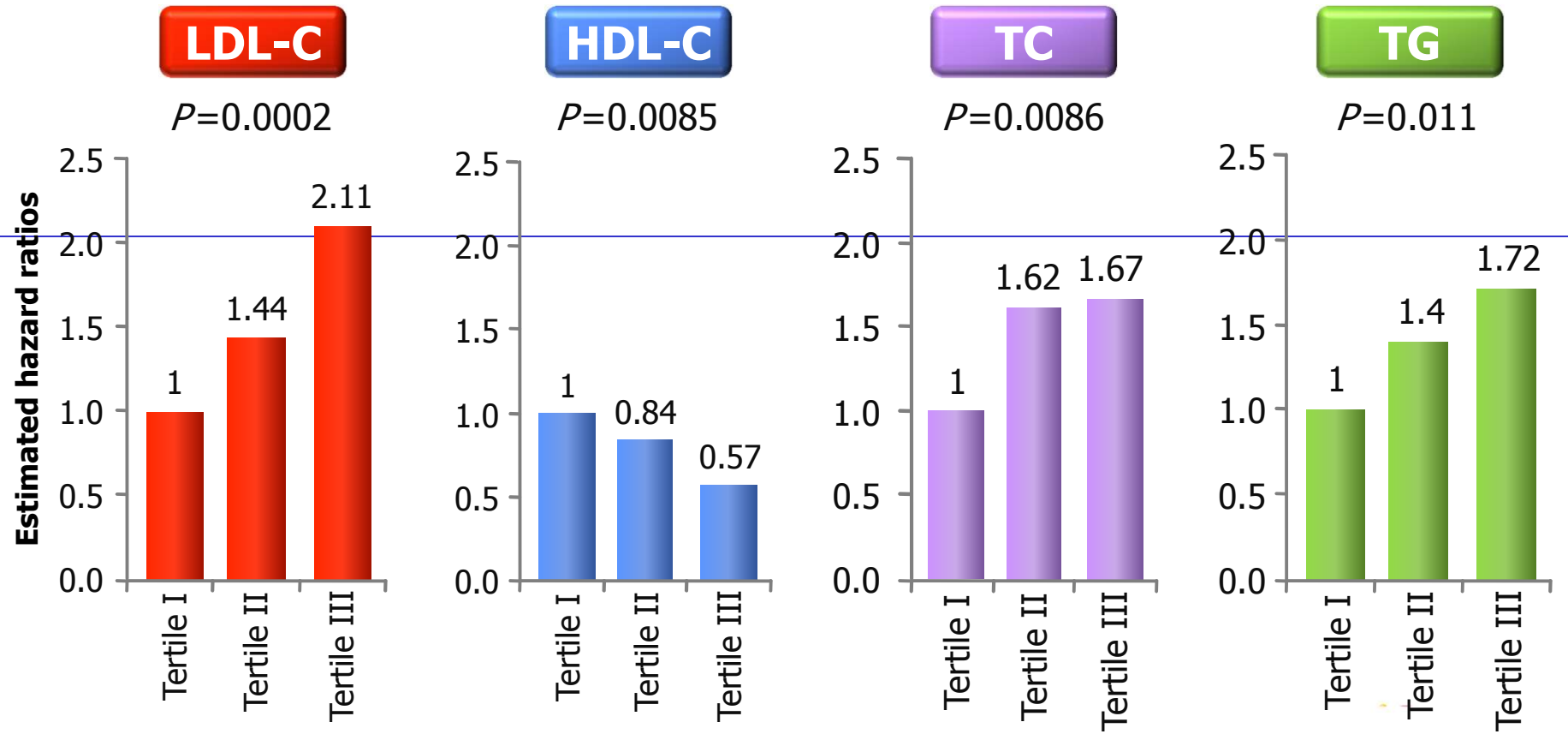
In this study, patients with diabetes without previous myocardial infarction (MI) have as high a risk of MI as patients without diabetes with previous MI



Haffner SM, N Engl J Med. 1998;339:229-234

LDL-C Is a Very Strong Predictor of CHD Risk
in Patients With Diabetes: UKPDS 23

Relation of dyslipidemia (hazard ratios) to nonfatal or fatal MI after adjustment for age and sex in 2693 patients with type 2 diabetes



Turner RC, BMJ. 1998;316:823-828

Guidelines for Glycemic, BP, & Lipid Control

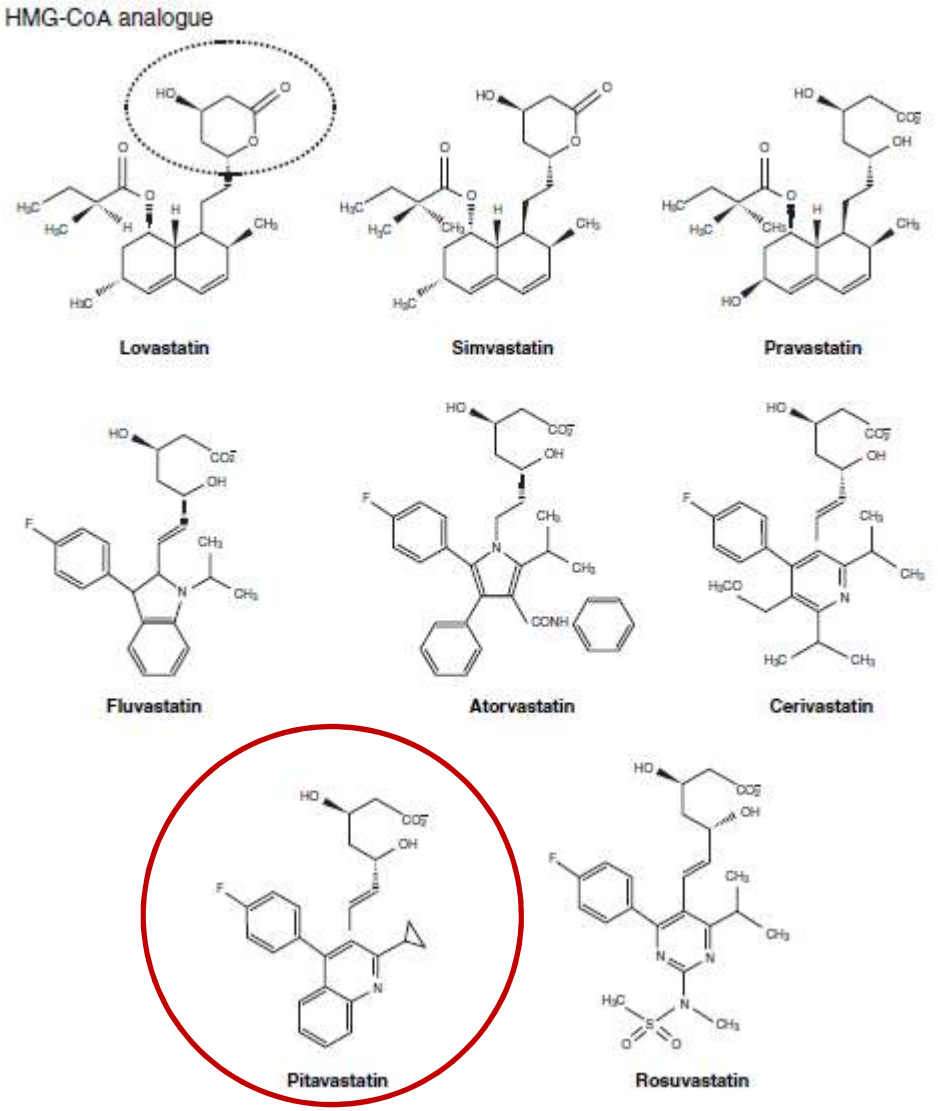
	American Diabetes Assoc. Goals
HbA1C	**< 7.0%** *(individualization)*
Preprandial glucose	**70-130** mg/dL (3.9-7.2 mmol/l)
Postprandial glucose	**< 180** mg/dL
Blood pressure	**< 130/80** mmHg
Lipids	**LDL: < 100** mg/dL (2.59 mmol/l) **< 70** mg/dL (1.81 mmol/l) (with overt CVD) **HDL: > 40** mg/dL (1.04 mmol/l) ♂ **> 50** mg/dL (1.30 mmol/l) ♀ **TG: < 150** mg/dL (1.69 mmol/l)

HDL = high-density lipoprotein; LDL = low-density lipoprotein; PG = plasma glucose; TG = triglycerides.

ADA. *Diabetes Care.* 2012;35:S11-63

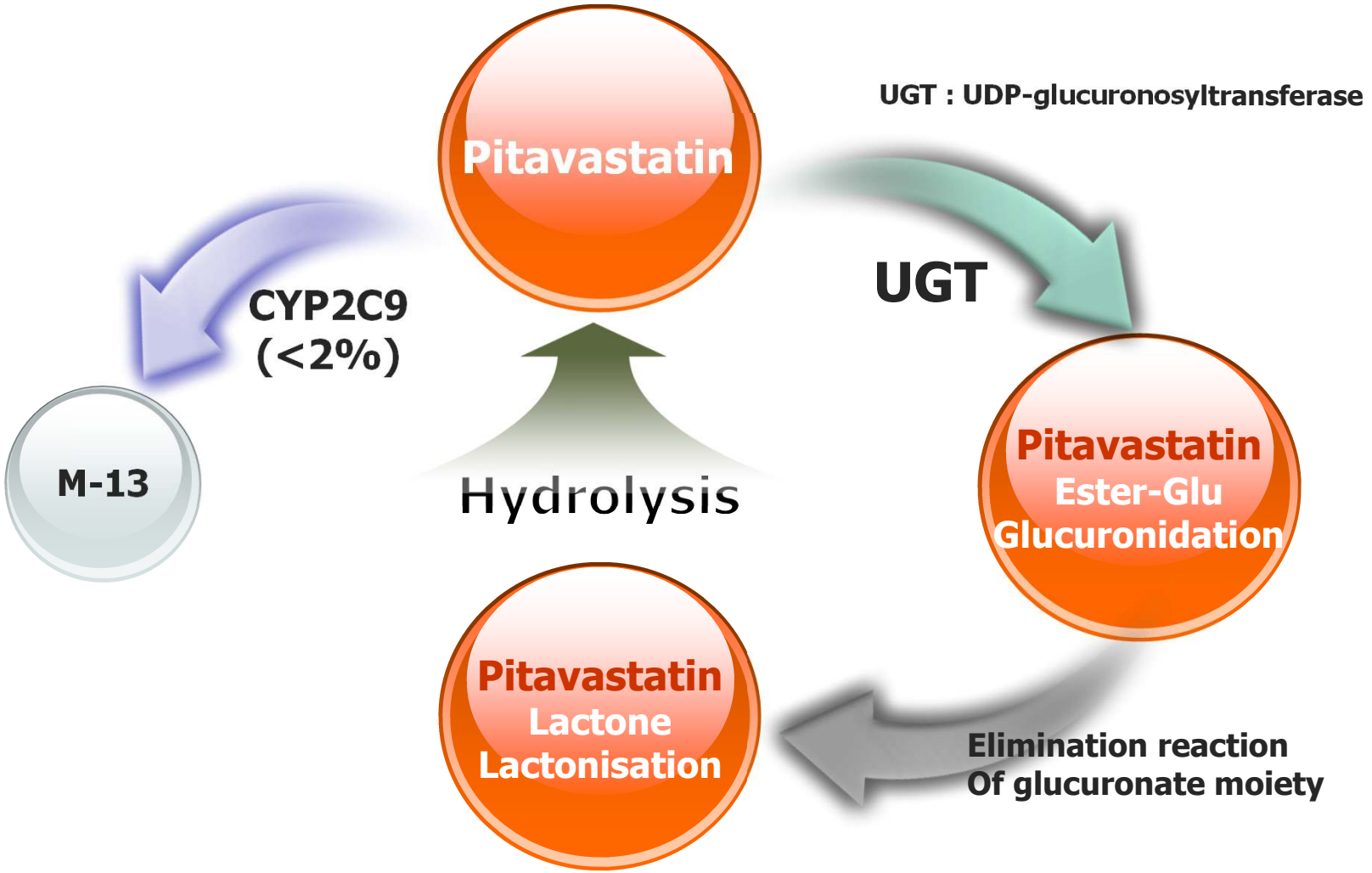
Metabolism of Statins

Statin	Primary metabolic pathway
Atorvastatin	CYP3A4
Fluvastatin	CYP2C9
Lovastatin	CYP3A4
Pitavastatin	Minimally CYP2C9
Pravastatin	Minimally CYP3A4
Rosuvastatin	Minimally CYP2C9
Simvastatin	CYP3A4



RYA Mukhtar et.al Int J Clin Pract 2005. 599(2):239-52

Metabolism of pitavastatin



RYA Mukhtar et.al Int J Clin Pract 2005. 599(2):239-52

Pharmacokinetic parameters of statins

	Pitavastatin	**Rosuvastatin**	**Atorvastatin**	**Pravastatin**	**Simvastatin**	**Lovastatin**	**Fluvastatin**
Origin	**Synthetic**	Synthetic	Synthetic	Semi-synthetic	Semi-synthetic	Microbial	Synthetic
Racemic	**No**	No	No	No	No	No	Yes
Prodrug	**No**	No	No	No	Yes	Yes	No
log *P*	**1.49**	-0.3	4.1	-0.2	4.7	4.3	3.2
Hepatic excretion (%)	**NA**	90	>70	66	78~87	>70	68
Bioavailability(%)	**>60**[1]	20	12	17	<5	<5	10~35
Effect of food on bioavailablity	**Yes (36% decrease)**	No	Yes (13% decrease)	Yes (30% decrease)	No	Yes (50% decrease)	Yes (15~25% decrease)
Protein binding(%)	**>99**	90	>98	48	95	95	>99
T_{max} (h)	**0.5~0.8**	3	2~4	0.9~1.6	1.3~2.4	2.8	0.5~1.5
$T_{1/2}$ (h)	**11**	20	11~30	0.8~3	1.9~3	2.5~3	0.5~2.3
Renal excretion	**<2**	10	2	60	13	30	6
50% Inhibitory concentration(nM)	**6.8**	12	15.2	55.1	18.1	2.7~11.1	17.9
Metabolites contribute to lipid lowering effect	**No**	No	Active	Yes, mainly inactive	Yes	Yes	Yes, mainly inactive
Dosage range(mg)	**1~4**	5~80	10~80	5~40	5~80	10~80	20~80
Primary metabolic pathway[2]	**CYP2C9 Minimally**	CYP2C9 Minimally	CYP3A4	CYP3A4 Minimally	CYP3A4	CYP3A4	CYP2C9

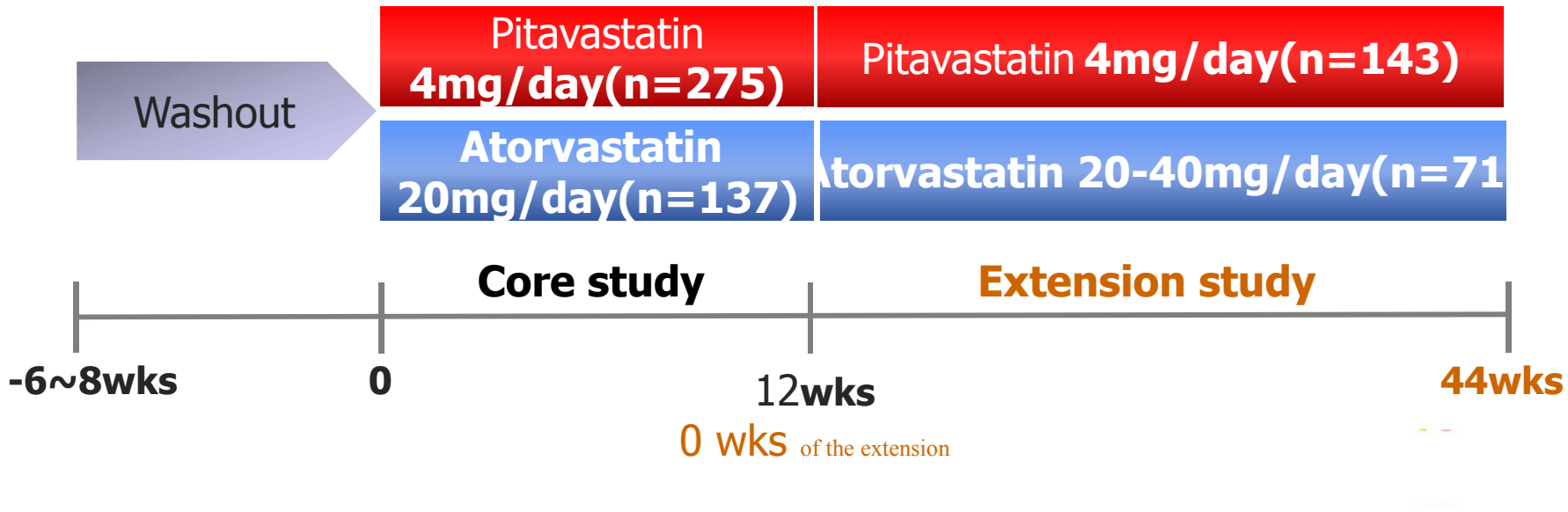
Cardiovascular Drug Reviews 2003;21(3):199-215.
1. Fundamental & clinical pharmacology 2004;19:117-25.
2. Vasc Health Risk Manag. 2009; 5: 921–936.

Clinical benefits of Pitavastatin in T2DM

1. Lipid lowering efficacy

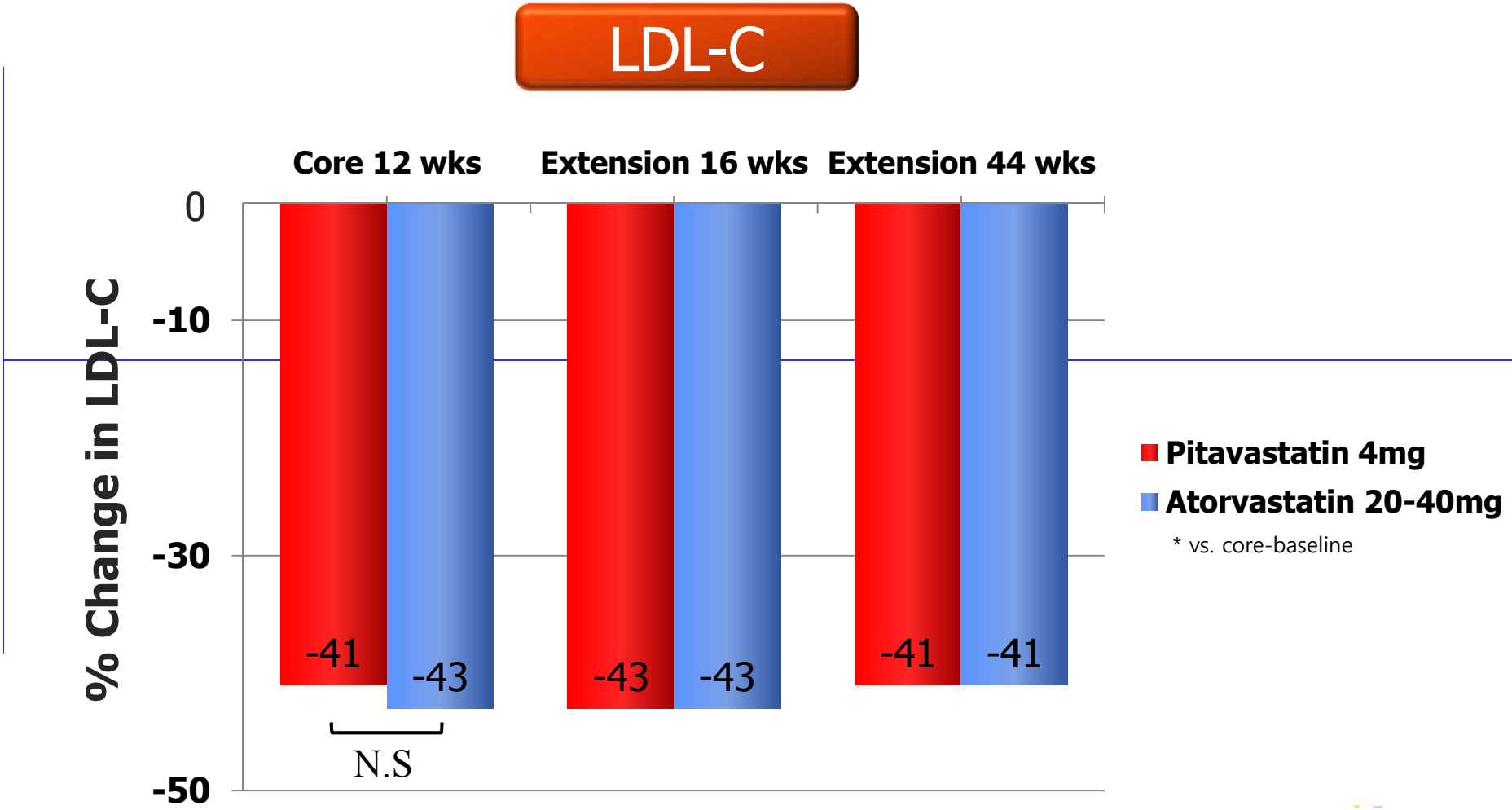
Phase 3 study in Europe 2011
with T2DM patients

Subjects	**Type 2 diabetes and combined (mixed) dyslipidaemia.**
Outcome	**Percent Change in LDL-C**
Drugs	**Pitavastatin 2-4mg/day vs Atorvastatin 10-40mg/day**
No. of Subjects	**418 (Pitavastatin:279, Atorvastatin:139)**
Country	**Denmark, Germany, India, the Netherlands, Poland, UK**



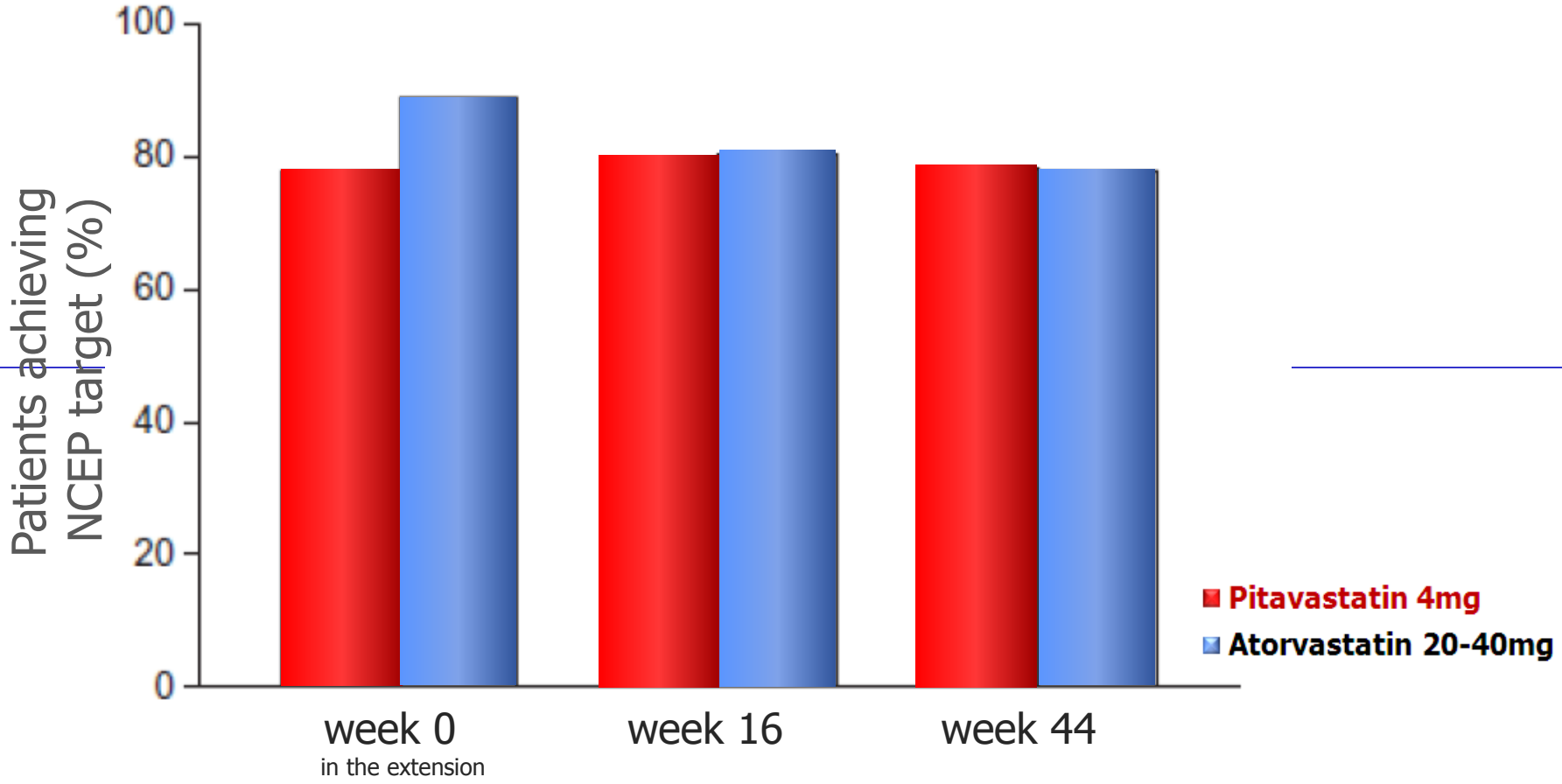
Gumprecht J. et al. Diabetes Obes Metab. 2011;13(11):1047-55.

Effects on LDL-C With T2DM patients



Gumprecht J. et al. Diabetes Obes Metab. 2011;13(11):1047-55.

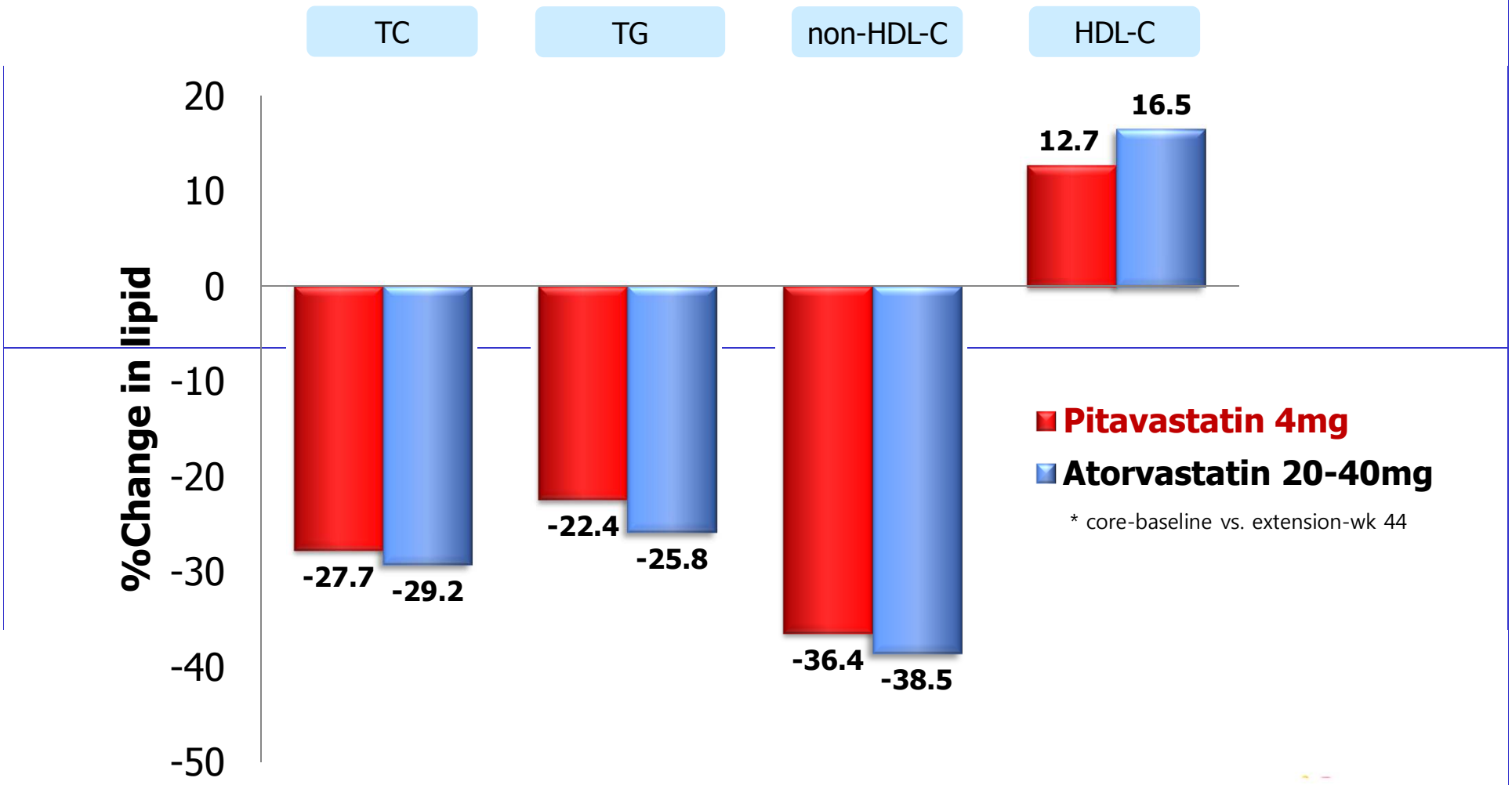
Lipid target attainment in the extension study



* The rate of goal attainment was stable or tended to increase slightly during the extension study in the only pitavastatin group

Gumprecht J. et al. Diabetes Obes Metab. 2011;13(11):1047-55.

Effects on lipid profile with T2DM patients

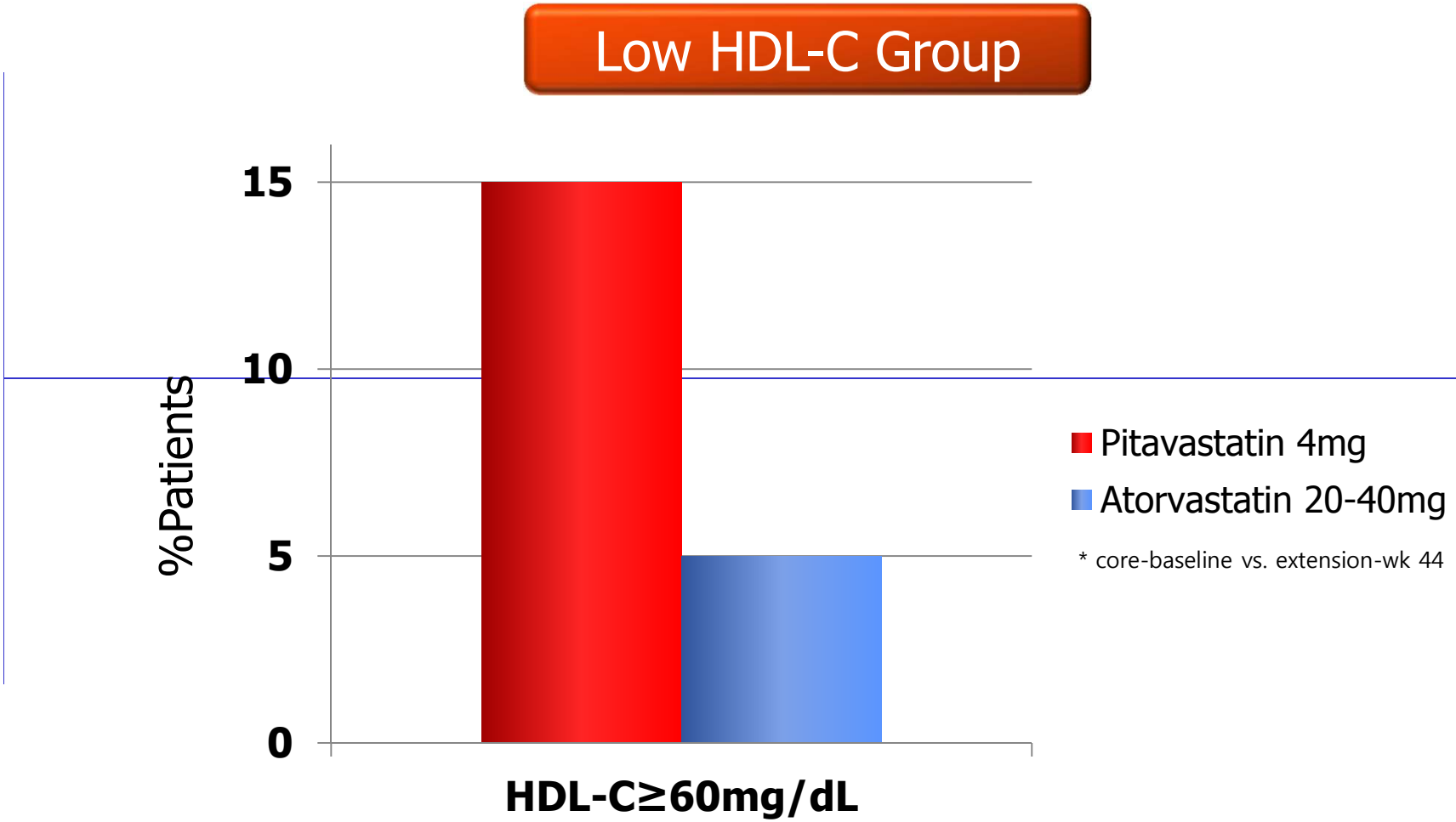


* a similar extent in both treatment groups

Gumprecht J. et al. Diabetes Obes Metab. 2011;13(11):1047-55.

Effects on low HDL-C group (HDL-C<60mg/dL)

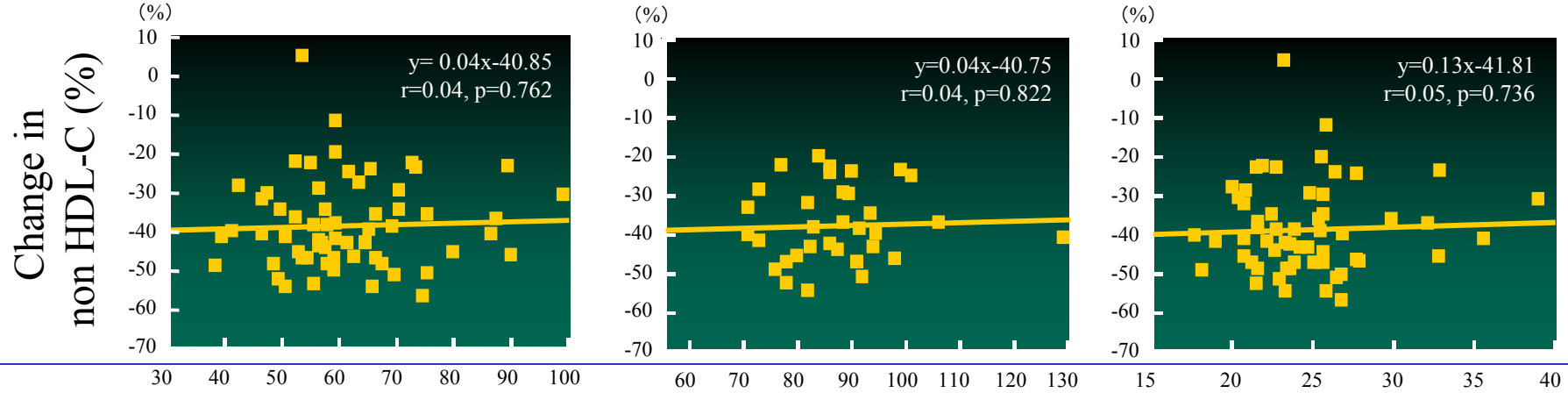
with T2DM patients



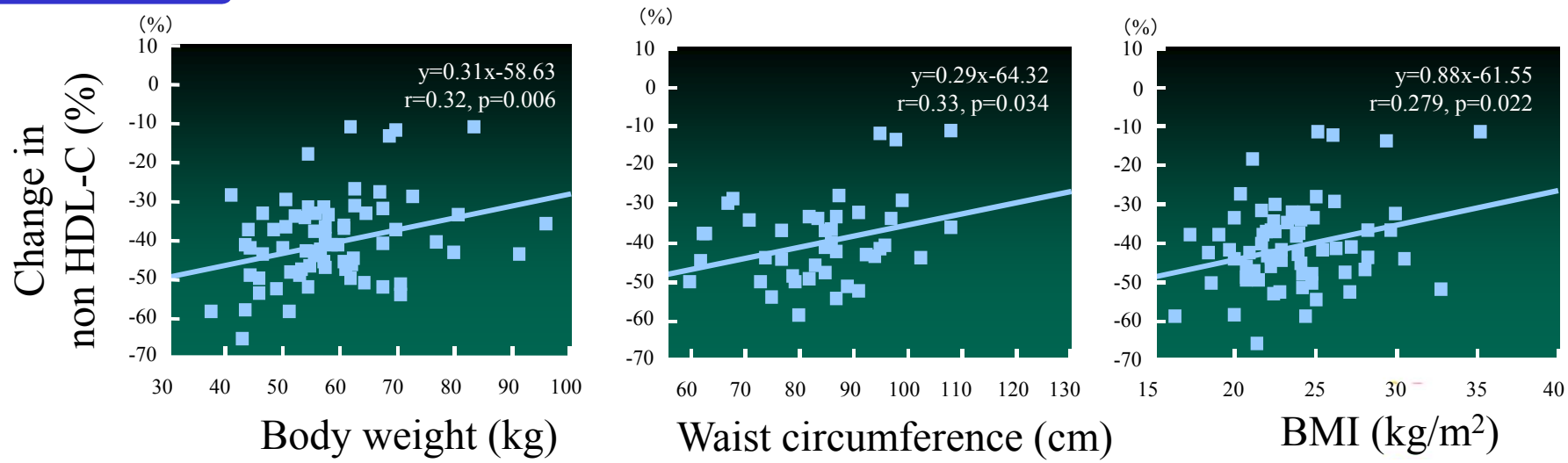
Gumprecht J. et al. Diabetes Obes Metab. 2011;13(11):1047-55.

CHIBA study -12wk, hypercholesterolemia pt. DM(~48%)
Body weight/Waist circumference/BMI & non HDL-C decreasing rate

Pitavastatin

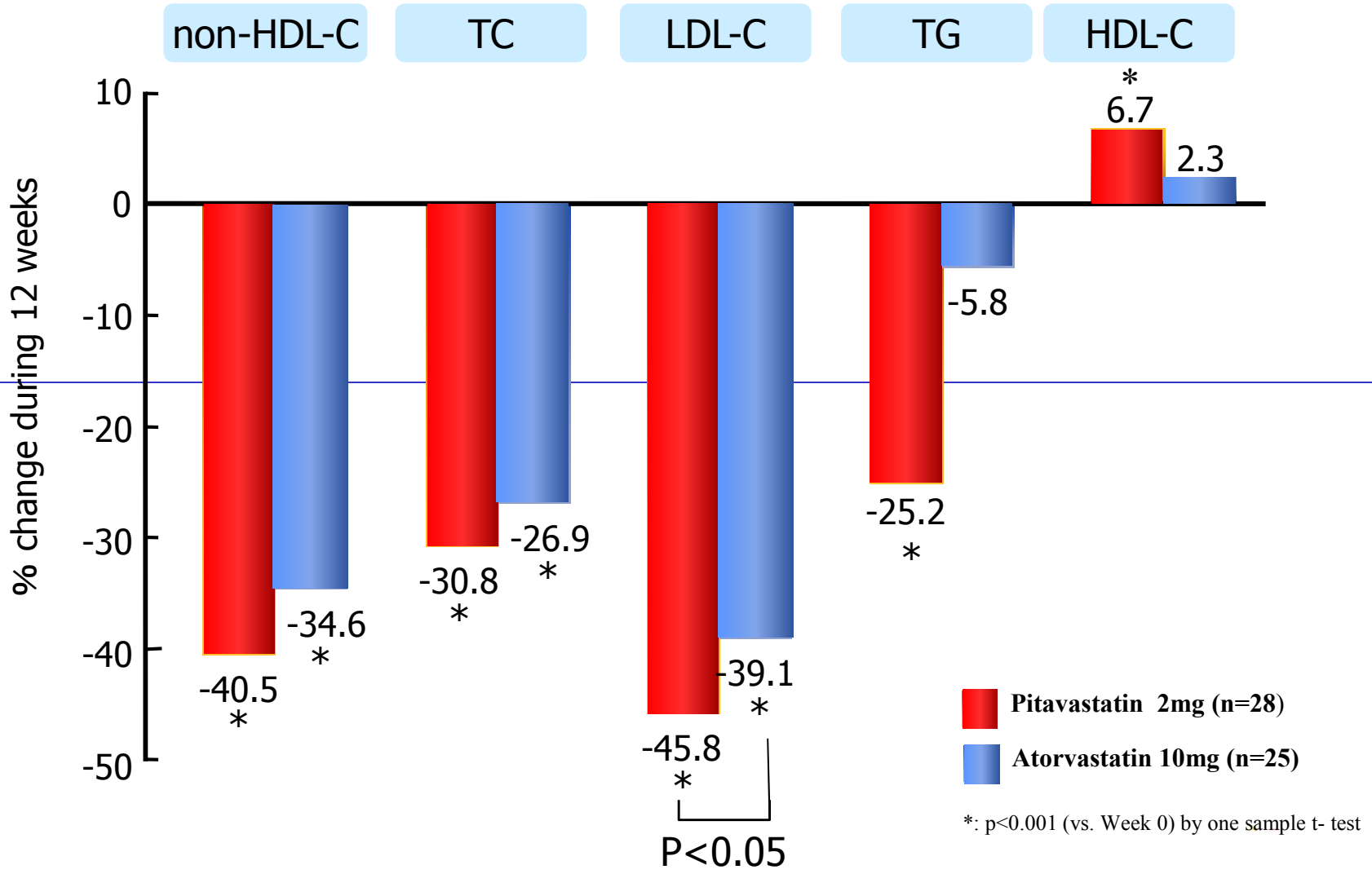


Atorvastatin



Yokote K Atherosclerosis 2008, 201(2):345-352

CHIBA Study
- Cases with Metabolic Syndrome -



Patients: hypercholesterolemia with MS (n=53)
Methods: pitavastatin 2mg/day or atorvastatin 10mg/day for 12weeks

Yokote K Atherosclerosis 2008, 201(2):345-352

Clinical benefits of Pitavastatin in T2DM

2. Effects on the glucose metabolism

Statins & development of diabetes

"Statin therapy was associated with a **9% increased** risk for incident diabetes"

	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%

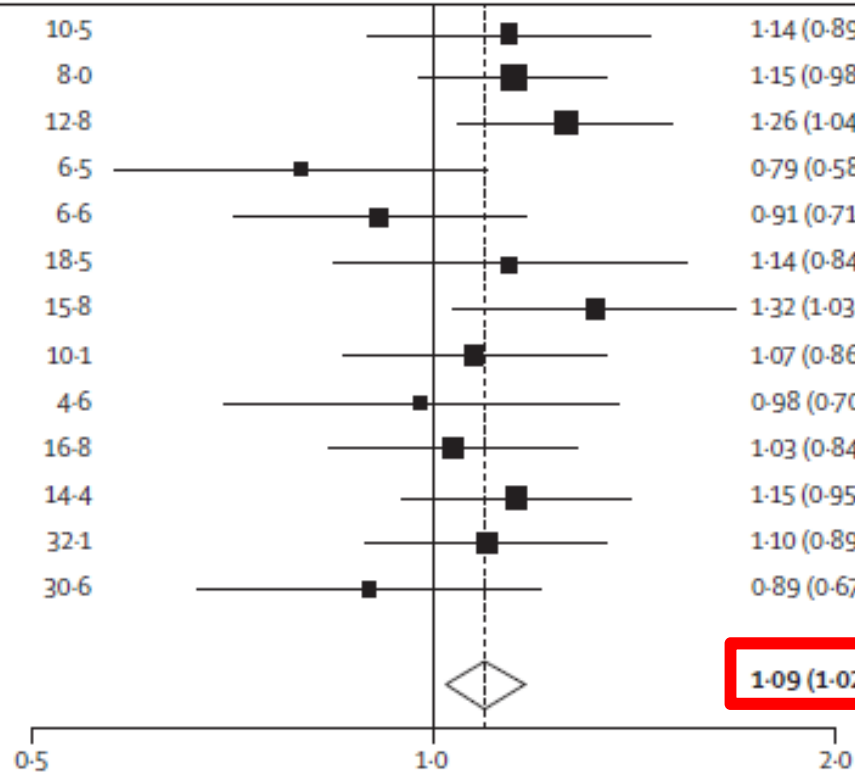


Figure 2: **Association between statin therapy and incident diabetes in 13 major cardiovascular trials†**

*Events per 1000 patient-years. †Weights are from random-effects analysis.

Data Sources: In 13 trials(Placebo-controlled and standard-care-controlled statin trials) with 91,140 participants

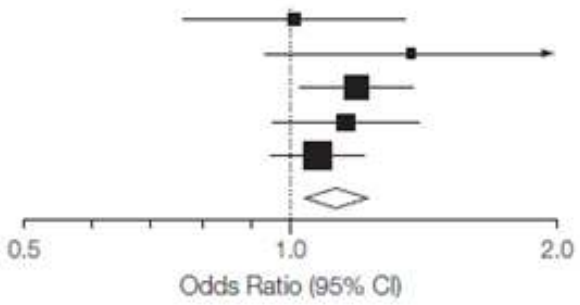
Lancet. 2010;375(9716):735-42.

Statins and risk of incident diabetes

The use of **intensive-dose statin therapy** compared with moderate-dose statin therapy was associated with **a higher incidence of new-onset diabetes (OR, 1.12)**

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

Incident Diabetes	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
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	1449/16408 (8.8)	1300/16344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2 = 0\%$; $P = .60$			



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

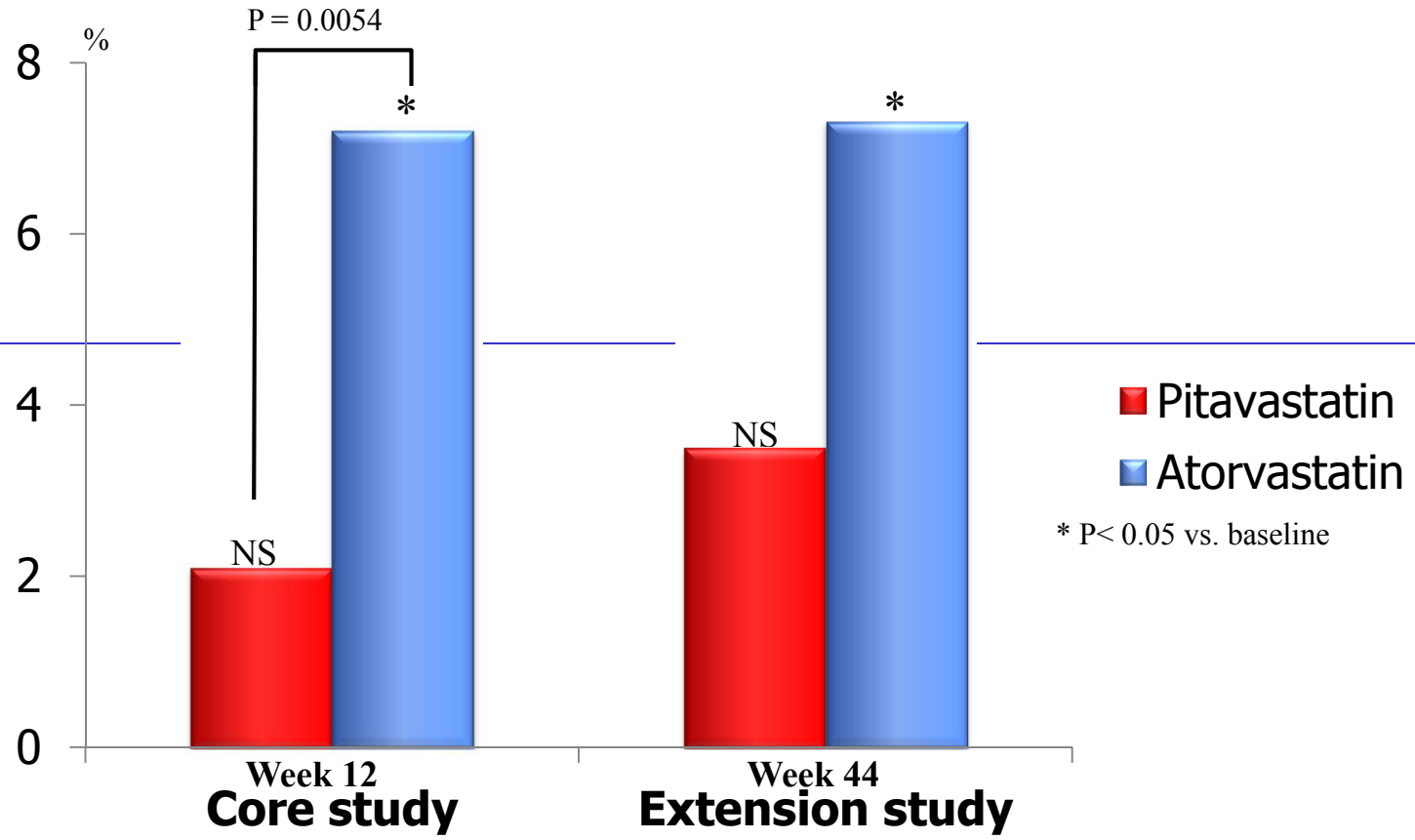
Data Sources: In 5 statin trials with 32 752 participants without diabetes at baseline

JAMA. 2011;305(24):2556-2564.

Effects on blood glucose

With T2DM patients –post hoc analysis

Change in blood glucose

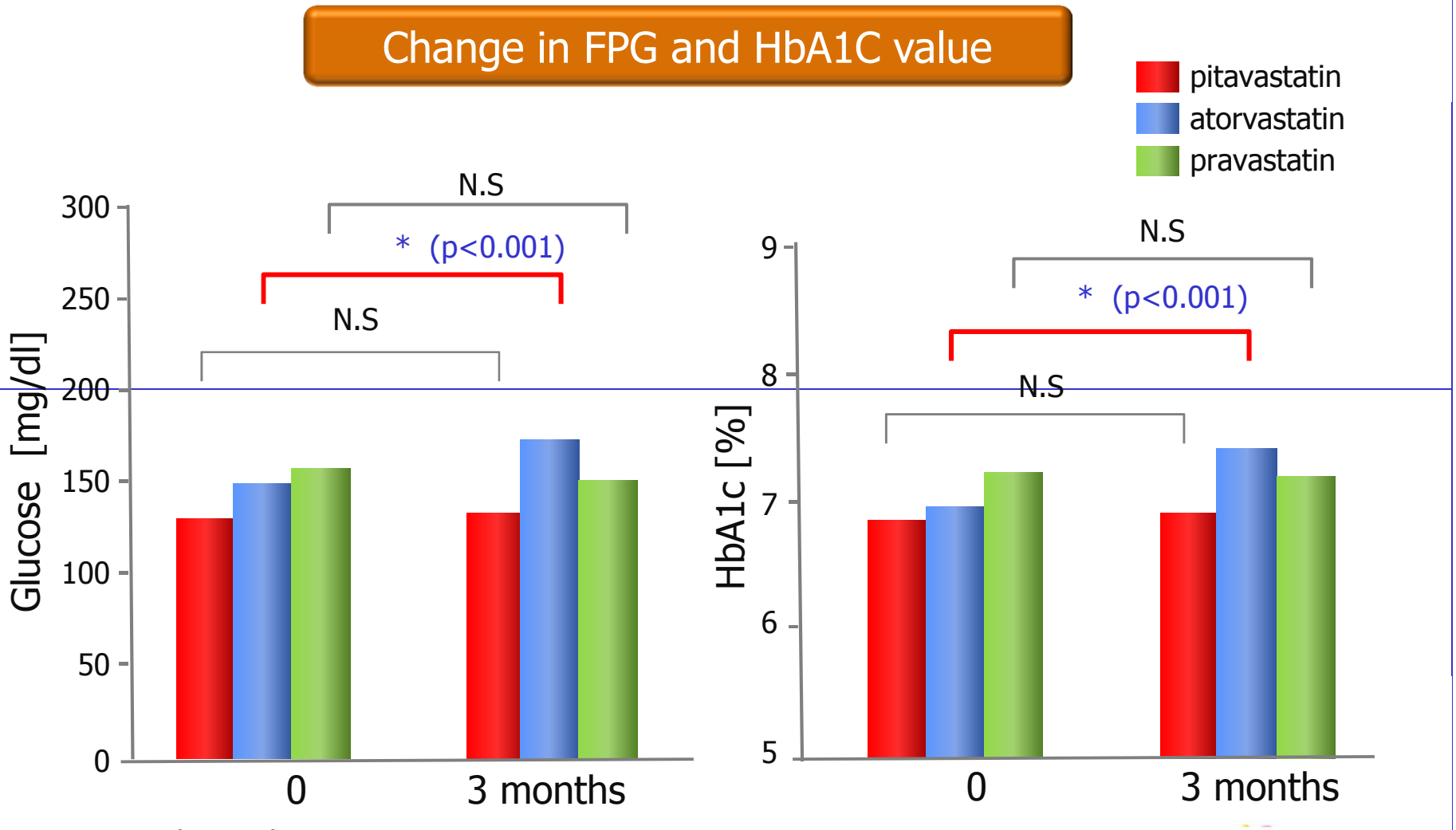


Patients: Dyslipidaemia with T2DM (n=418)
Method: Core study - Pitavastatin(n=275);4mg/day, Atorvastatin(n=137);20mg/day for 12 weeks
Extension study - Pitavastatin(n=143);4mg/day, Atorvastatin(n=71);20-40mg/day for a further 44 weeks

Gumprecht J. et al. Diabetes Obes Metab. 2011;13(11):1047-55.

Influence of Pitavastatin on glucose tolerance

in patients with T2DM -retrospective study

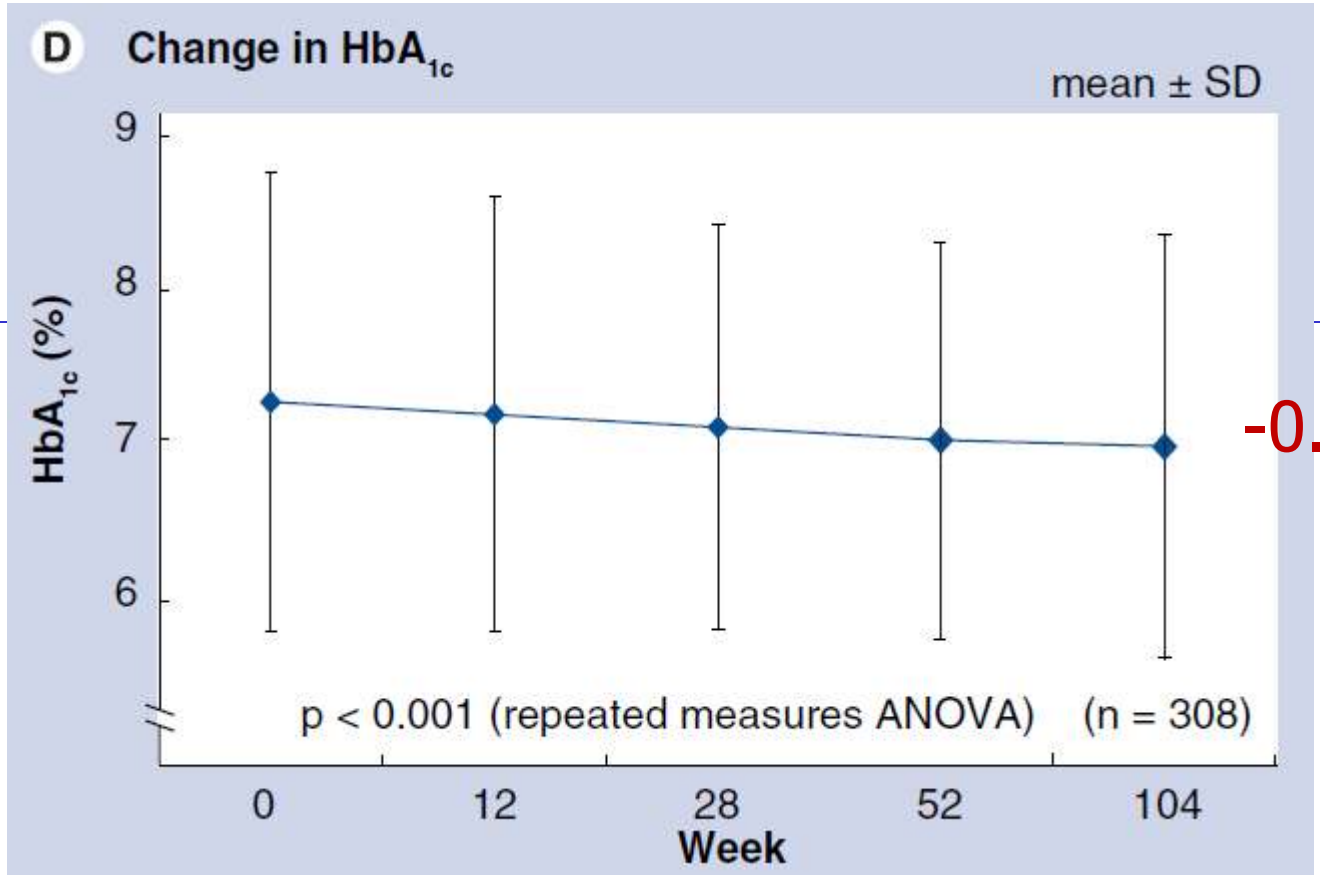


Patients: T2DM (n=279)
Method: Pitavastatin(n=95);2mg/day, Atorvastatin(n=99);10mg/day, Pravastatin(n=85):10mg/day for 3month

Yamakawa T et.al J Atheroscler Tromb 2008:15(5):269-275

Sub-Analysis of LIVES study
Effect of Pitavastatin on HbA_{1C} in DM patients

(n=1127)



-0.28%*

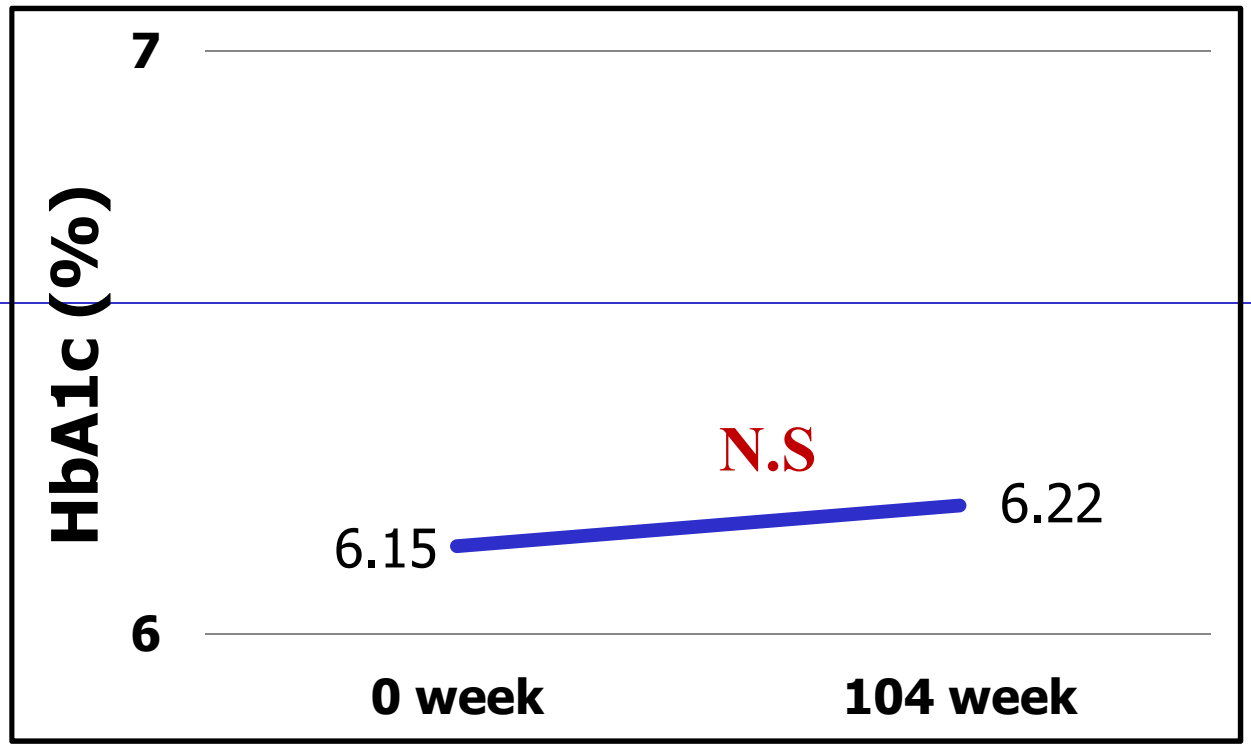
* P<0.001 vs. Baseline

T. Teramoto et al, Expert Opin. Pharmacother. 2010

Sub-Analysis of LIVES study

Effect of Pitavastatin on HbA_{1c} in DM patients without medication

DM Patients WITHOUT anti-DM therapy (n=205)



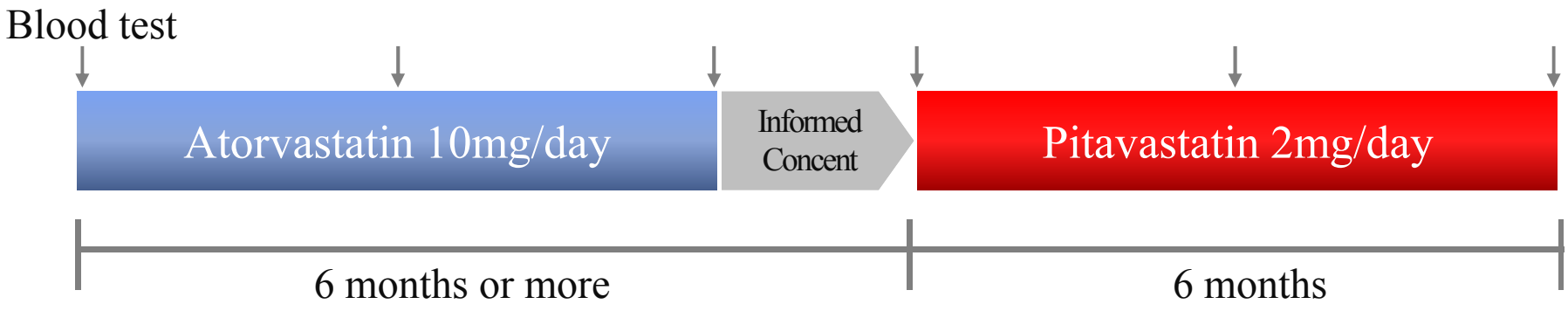
Patients: Hypercholesterolemia patients (n=19,925) among T2DM patients
Method: Pitavasatin/day, 3 months as PMS + 2 years period as long-term special study

T. Teramoto et al, Expert Opin. Pharmacother. 2010

Evaluation of effect on glycemic control

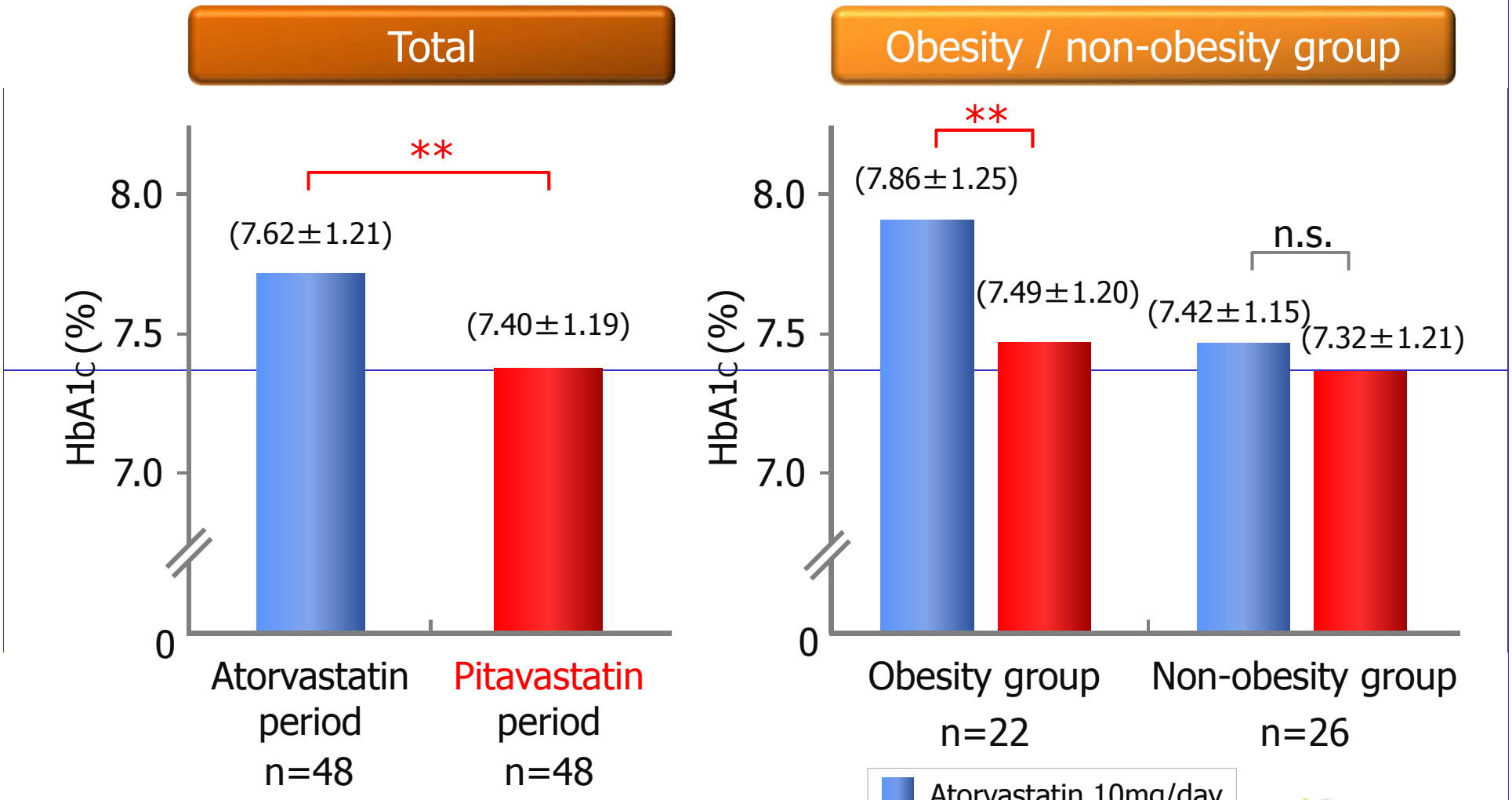
- Switch from ATV to PTV -

Study population	**Hypercholesterolemic patients with Type 2 DM**
Outcomes	**(1) HbA_{1c}** **(2) Serum lipid (TC, LDL-C, TG and HDL-C)**
Test drugs	**Pitavastatin 2mg/day** **(Switch from ATV 10mg/day to PTV 2mg/day)**
Study period	**6 months (blood tests every 2 months)**
No. of subjects	**48**



Pharma medica 2007 25(5) 155-160

Change in HbA1c value



mean±S.D.
n.s.= not significant, ** p<0.01

Pharma medica 2007 25(5) 155-160

ProPit

: A PROspective comparative clinical study to evaluate efficacy and safety of PITavastatin in patients with a metabolic syndrome

PROPIT study team:

SH Choi, S Lim, JA Seo, CY Park,

JH Noh, JO Mok, KY Lee, JS Park, DJ Kim,
CB Lee, SR Kim, HC Jang

ProPit study

Objective

: To investigate the effect of **pitavastatin treatment + life style modification** vs. **life style modification only** in patients with metabolic syndrome on the progression of MS scores

Proactive management of dyslipidemia with pitavastatin from the early phase of MS can improve the disease progression?

ProPit study

Subjects

Enrollment Criteria

- Age : 18~75 yrs old
- Agreed to participate in this study with informed consent
- LDL ≥ 100mg/dl -essential
- Metabolic Syndrome (Central Obesity –essential)

① IFG: fasting glucose ≥ 100mg/dL

② Waist circumference : men ≥90cm, women ≥ 85cm

③ 1 or above : below conditions

- TG ≥ 150 mg/dl
- HDL : men < 40mg/dl, women < 50mg/dl
- Blood pressure : SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or anti-hypertensive medication

ProPit study

Exclusion Criteria

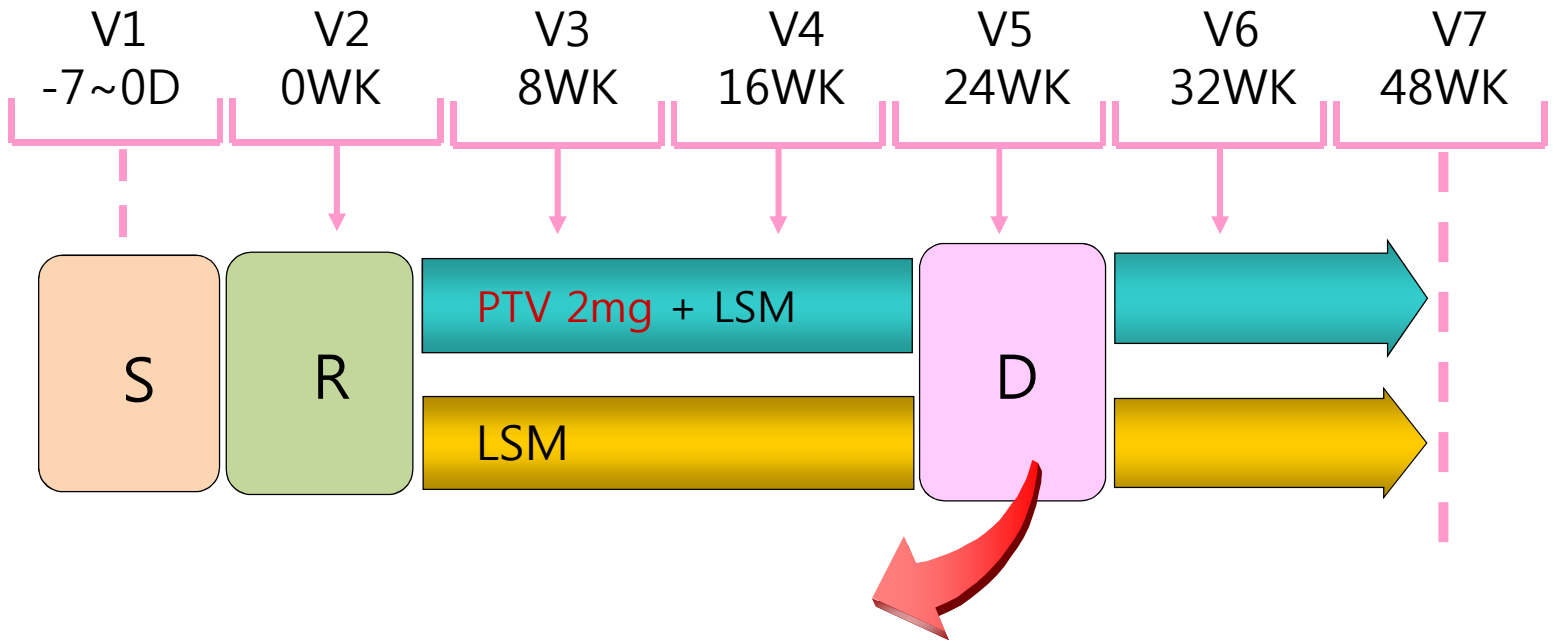
- 다른 임상시험의 시험약을 복용한 지 3개월 미만인 자
- 등록 전 3개월 이내에 statin 제제를 복용한 자
- 조절되지 않는 고혈압 환자(DBP ≥ 95mmHg)
- 당뇨 약물을 복용 중이거나 HbA1c > 8% 인 자
- LDL ≥ 190mg/dl 또는 TG ≥ 400mg/dl 인 자
- 관상동맥질환 또는 다른 동맥경화로 인한 질병이 있는 자
- 6개월 이내 종양학적 병력이 있는 자
- 생명을 위협하는 감염질환과 같이 시험을 수행하기 어려운 심각한 질환이 있는 자
- 신기능 장해가 의심되는 자(serum creatinine ≥ 2.0mg/dL)
- 간기능 장해가 의심되는 자(AST 또는 ALT ≥ ULN * 2.5)
- CPK가 정상 상한치의 2배 이상인 자
- 조절되지 않는 갑상선기능저하증이 있는 자(TSH ≥ ULN * 1.5)
- 수유중, 임신중 또는 임신을 희망하는 여성
- 기타 시험자가 부적합하다고 판단한 자

ProPit study : Study Design

Treated Group : Intensive LSM* + Pitavastatin

Control : Intensive life style modification only

48 weeks
Prospective
Randomized



- LDL ≥ 190mg/dL or
- HbA1c > 8 %

▪S: Screening, R: Randomization D: Drop-out

ProPit study : Study Outcomes

Outcome Variables

- **Primary Outcomes**
  Changes in Metabolic Syndrome Scores

- **Secondary Outcomes**

Changes in cardiometabolic risk profiles:

① **LDL-C, Apo B/Apo A1, hs-CRP, Adiponectin, HMW adiponectin**

② **Visceral Fat & SQ fat by fat CT**

③ **0 min, 30min, 120 min : insulin, glucose & HOMA**

④ **Framingham risk score**

⑤ **The percentage of patients who are HbA1c>7%**

Safety

Lab, vital signs, adverse reactions

ProPit

Enrollment

	PTV+LSM 군	LSM 군	Total
Screening			289
Randominization	**92**	**95**	**187**
Drug treated	92	0	92
LSM	0	95	95
Patients	92	95	187
Finish study	64	73	137
Drop out	28	22	50
Reasons for drop out			
Drop out criteria after 6months	2	4	6
Enroll/criteria : mismatch	3	2	5
Adverse effects	2	0	2
Other Tx needed	0	1	1
Disagreement	9	6	15
Late registration	1	0	1
others	11	9	20
안전성 평가 대상례	**92**	**95**	**187**
유효성 평가 대상례			
ITT (Intention-To Treat)	**80**	**84**	**164**
PP (Per Protocol)	**58**	**61**	**119**

Baseline characteristics of study subjects

Category		PTV+LSM군	LSM군	p-value
Sex: N (%)	Male	50(62.50)	51(60.71)	0.8142
	Female	30(37.50)	33(39.29)	
Age (yr)	Mean(SD)	51.68(9.17)	50.79(10.18)	0.5581
Weight (Kg)		73.43(11.82)	75.81(12.50)	0.2119
BMI (kg/m^2)		**26.96(3.14)**	**27.43(3.18)**	0.3362
Waist circumference (cm)		**92.84(5.63)**	**94.36(6.74)**	0.1208
Fasting Glucose (mg/dL)		**114.21(12.31)**	**118.40(15.33)**	**0.0560**
post 2hr OGTT glucose (mg/dL)		164.93(61.93)	178.35(59.37)	0.1584
HOMA-IR		**2.90(1.32)**	**3.52(1.76)**	**0.0109**
TG (mg/dL)		**157.46(56.73)**	**178.62(72.09)**	**0.0379**
HDL-C (mg/dL)		47.72(9.45)	47.01(10.41)	0.6496
LDL-C (mg/dL)		139.56(22.09)	137.12(23.94)	0.4979
SBP (㎜Hg)		129.76(10.62)	127.83(10.97)	0.2544
DBP (㎜Hg)		81.06(7.61)	81.14(7.89)	0.9472

Baseline characteristics of study subjects

Category		PTV+LSM군	LSM군	p-value
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	Male	50(62.50)	51(60.71)	0.8142
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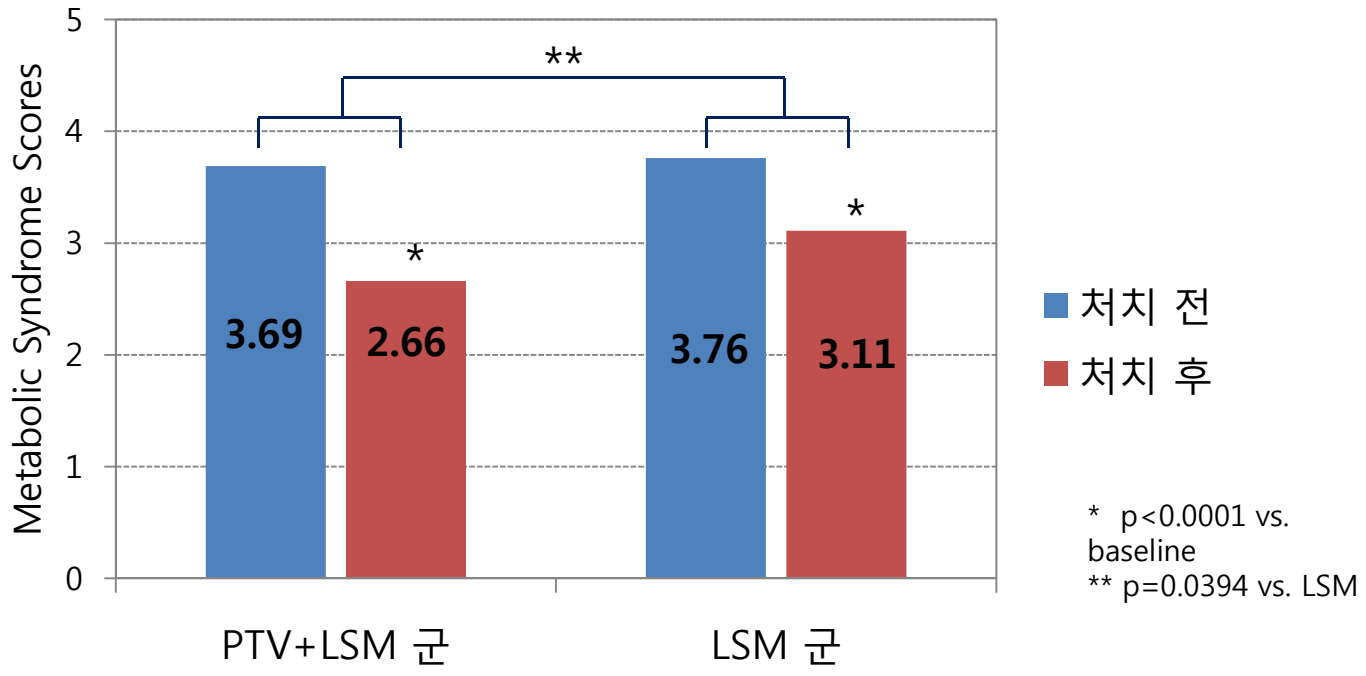
SBP (㎜Hg)		129.76(10.62)	127.83(10.97)	0.2544
DBP (㎜Hg)		81.06(7.61)	81.14(7.89)	0.9472
DM* (n/%)		**32(40.00)**	**40(47.62)**	0.3257

* : FBS≥126mg/dL or post 2hr OGTT glucose≥200mg/dL or HbA1c≥6.5%

ProPit

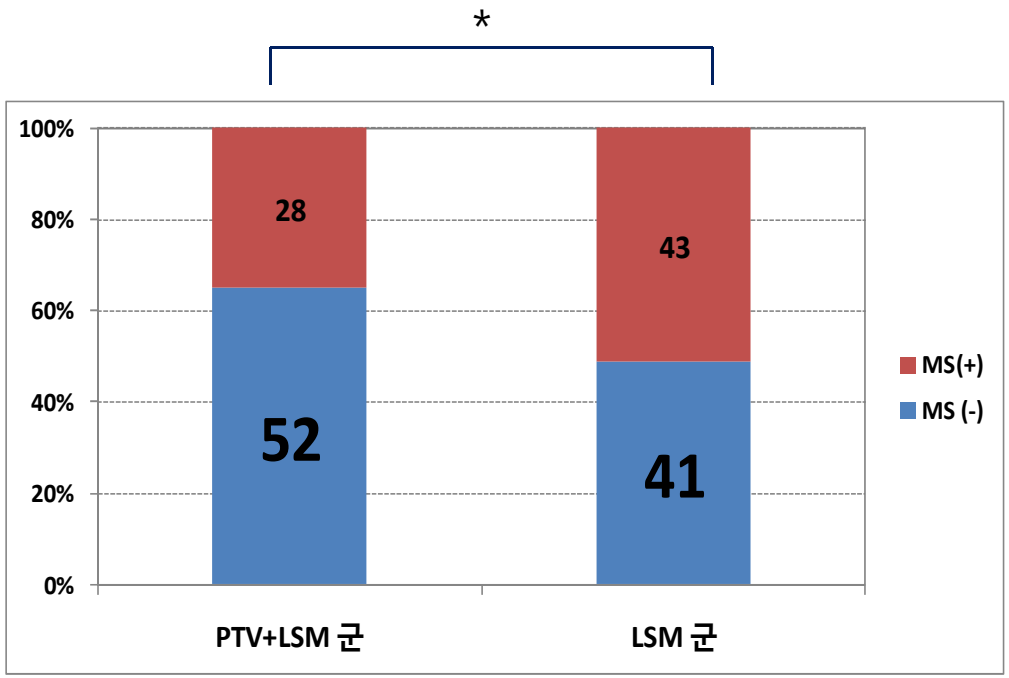
Primary Endpoint : Metabolic Syndrome Score



Pitavastatin+LSM group showed significant reduction of MS scores compared to LSM only group (p=0.0394)

ProPit

Patients with MS(-) (MS score<3) after treatment

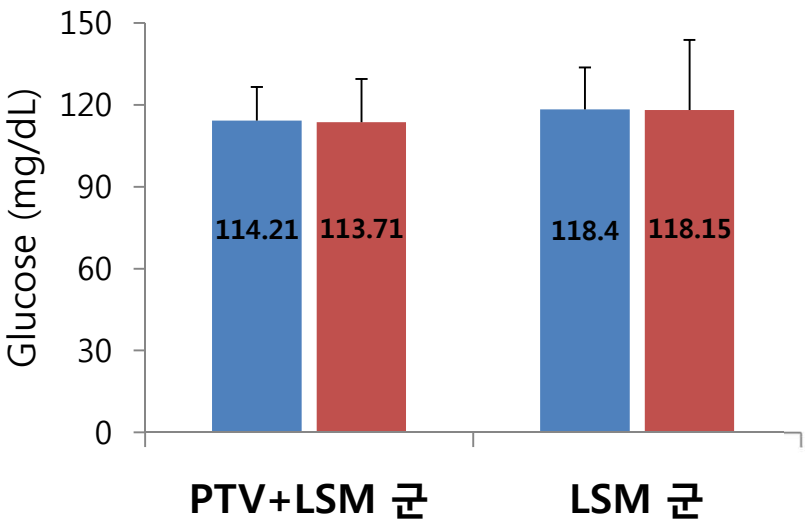


* P=0. 037

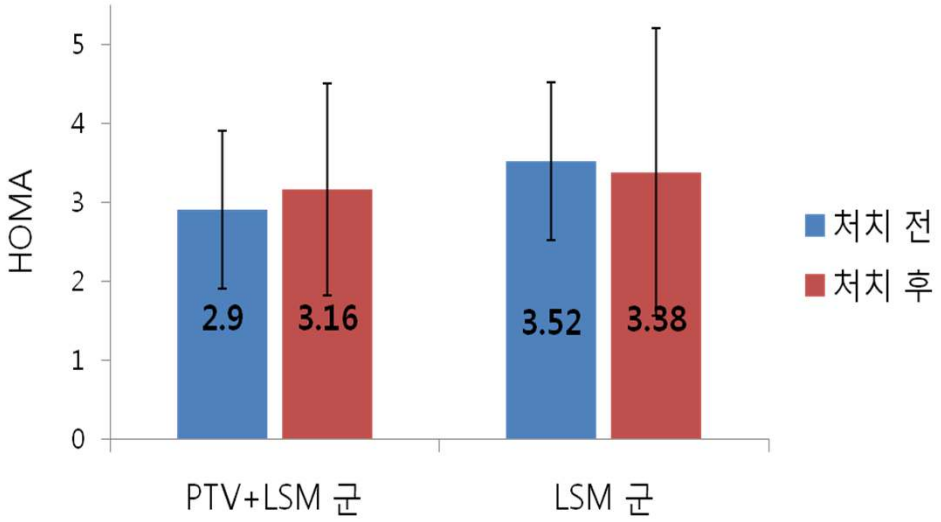
The proportion of (-) converter of MS (MS score <3) after tx. was significantly higher in PTV+LSM group vs. LSM group

ProPit

Fasting glucose



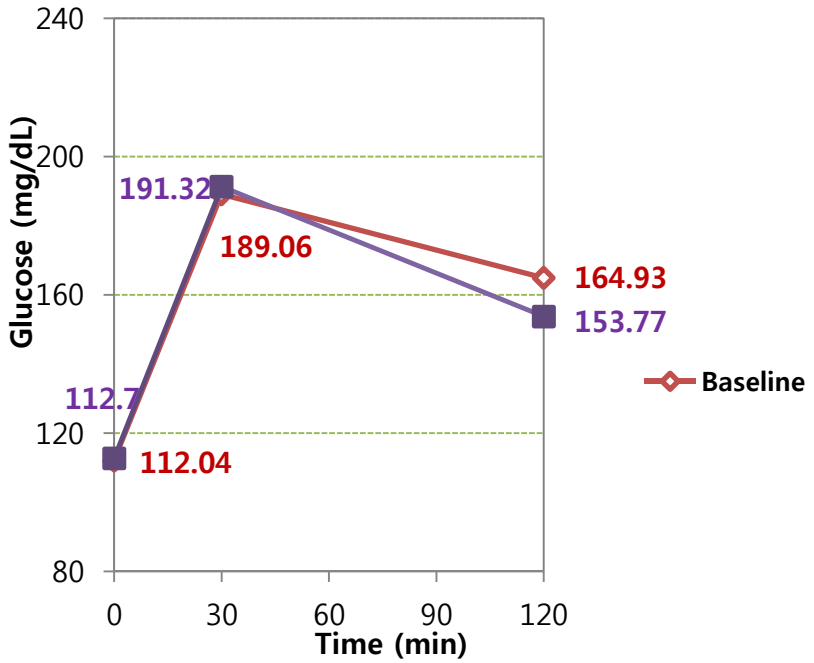
HOMA-IR



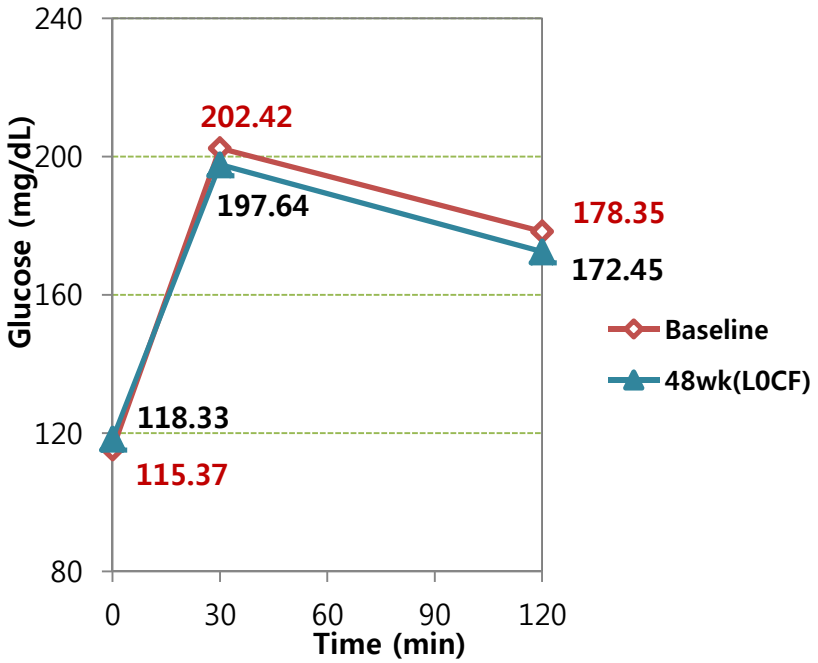
Both fasting glucose level and HOMA-IR have not been changed during trial in both groups. Also, there was no difference in changes between groups.

ProPit

Glucose : 75g OGTT



PTV+LSM 군

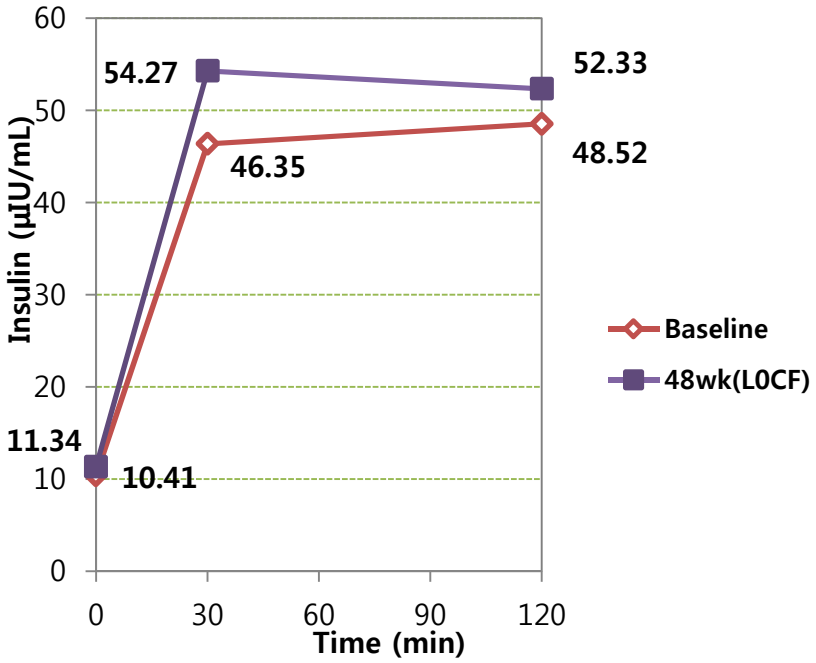


LSM 군

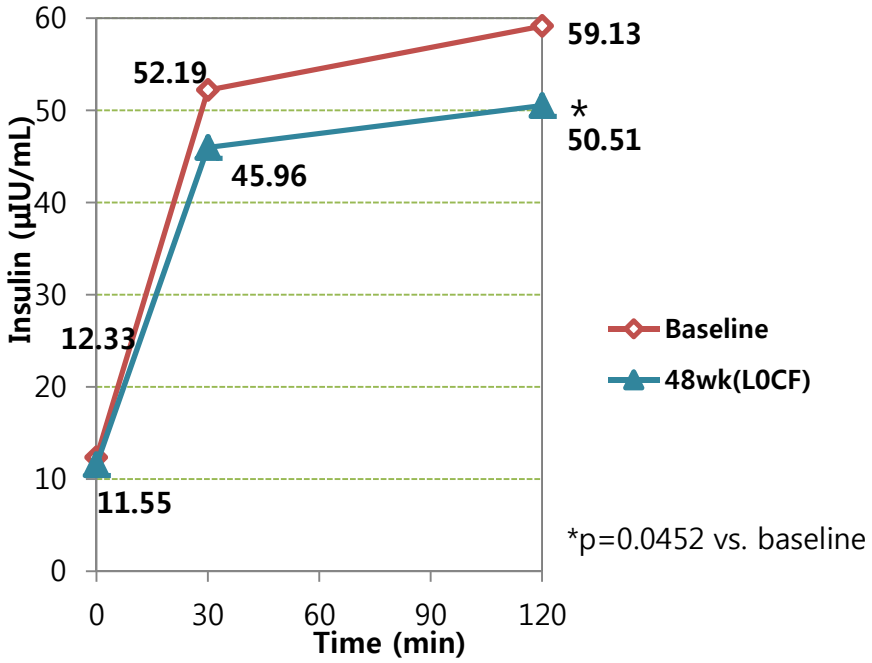
Post 2hr OGTT glucose was decreased in PTV+LSM group without statistical significance

ProPit

Insulin : 75g OGTT



PTV+LSM 군



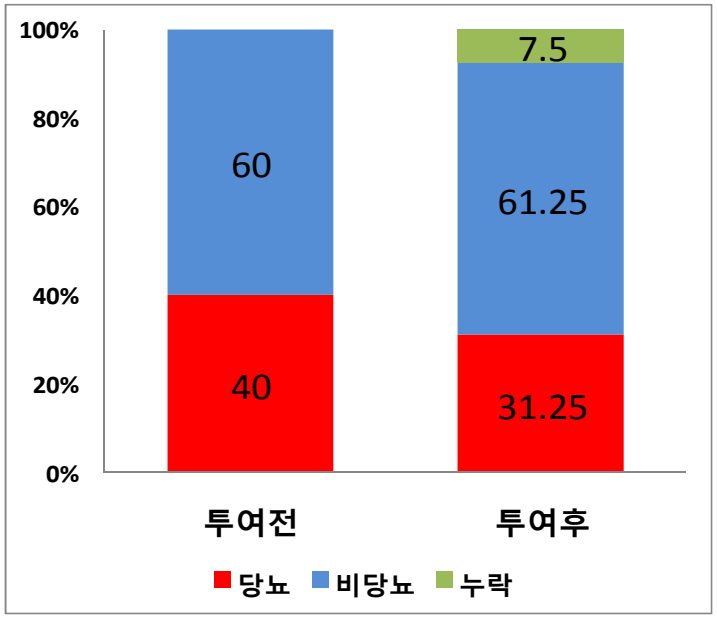
LSM 군

Post 2hr OGTT insulin was decreased in LSM group. However, there was no difference between PTV+LSM and LSM groups.

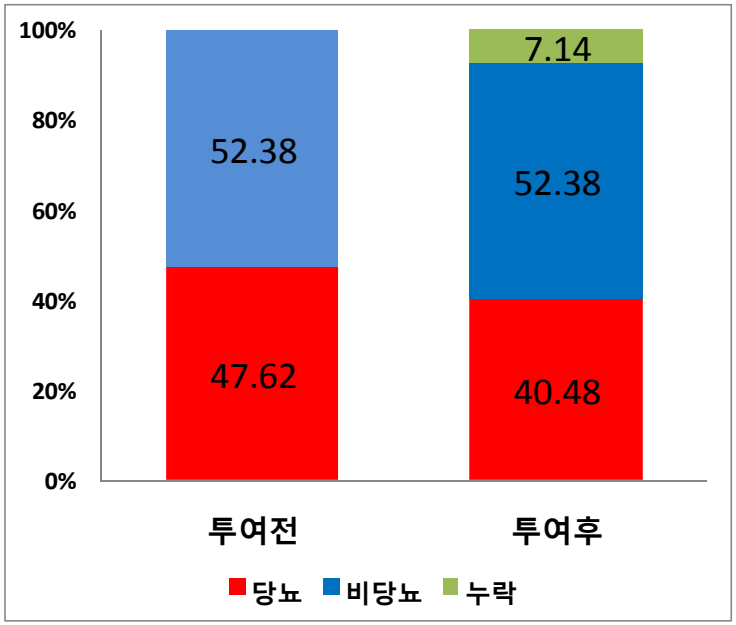
ProPit

투여군별 시험 전, 후 당뇨병 환자 비율의 변화

PTV+LSM 군



LSM 군



시험 전 당뇨병(-) -> 시험 후 당뇨병(+) 발생 비율

	PTV+LSM군	LSM군
시험 전 당뇨병(-) -> 시험 후 당뇨병(+)	4/46 (8.7%)	7/40 (17.5%)
p-value	0.2227	

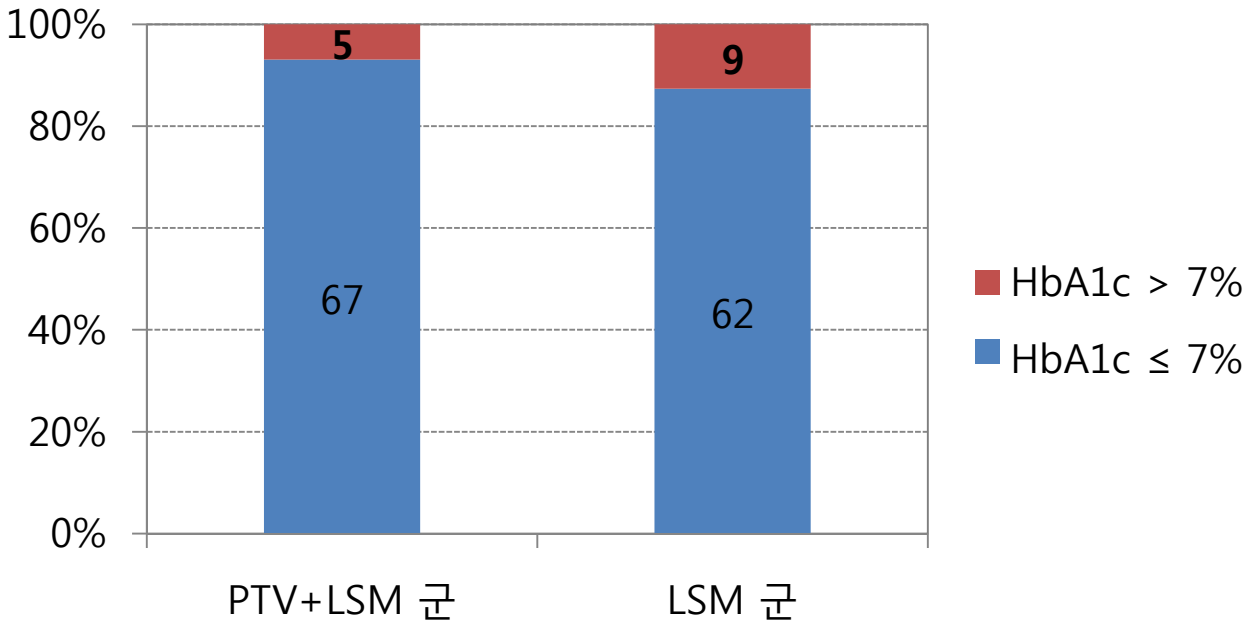
*:FBS≥126mg/dL or post 2hr OGTT glucose≥200mg/dL or HbA1c ≥ 6.5%

투여군별 시험 전, 후 당뇨병 환자 비율의 변화

	PTV+LSM 군 N=74	LSM 군 N=78
비당뇨 -> 당뇨	4 (5.41)	7 (8.97)
비당뇨 -> 비당뇨	42 (56.76)	33 (42.31)
당뇨 -> 당뇨	21 (28.38)	27 (34.62)
당뇨 -> 비당뇨	7 (9.46)	11 (14.10)
p-value	0.3294	

ProPit

Patients with A1c >7.0%



The % of patients who showed A1c >7.0% after finishing the trial was not different between PTV+LSM vs. LSM group

Safety : Adverse events

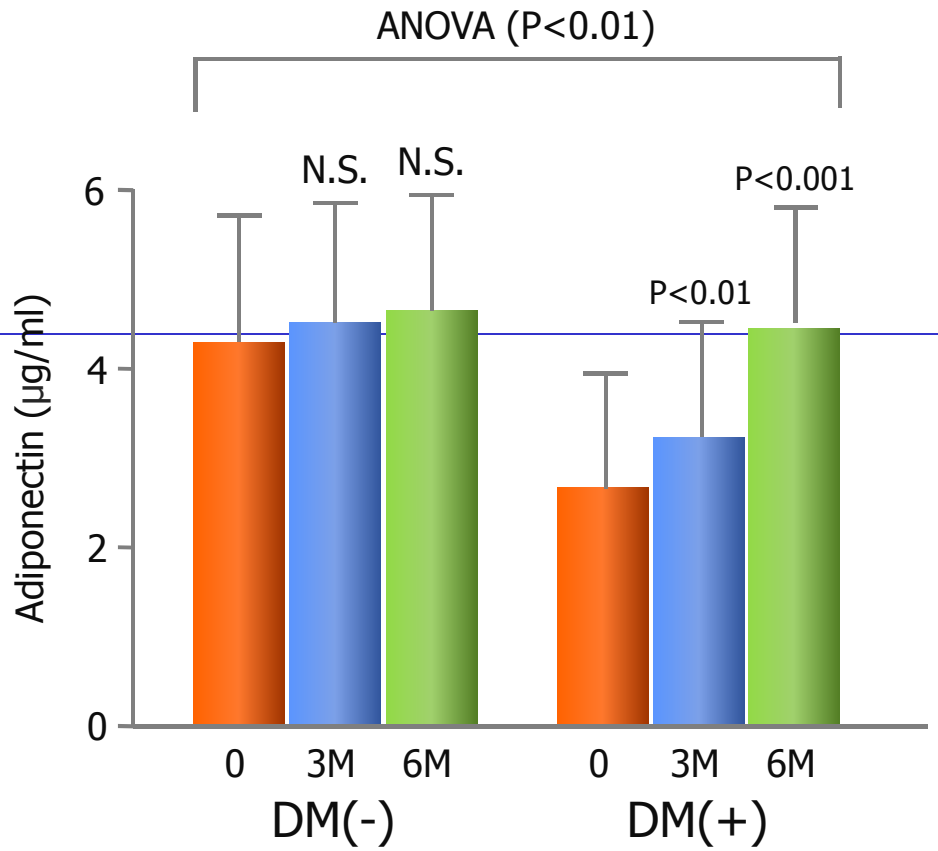
System Organ Class	Adverse Events		Adverse Drug Reaction	
	PTV+LSM 군 (N=92)		PTV+LSM 군 (N=92)	
	n	%	n	%
Body as a whole-General Disorders	9	9.78	**1**	**1.09**
Cardiovascular Disorders, General	1	1.09	-	-
Central & Peripheral Nervous System Disorders	6	6.52	-	-
Gastro-Intestinal System Disorders	12	13.04	**2**	**2.17**
Hearing & Vestibular Disorders	1	1.09	-	-
Heart rate and Rhythm Disorders	1	1.09	-	-
Metabolic and Nutritional Disorders	4	4.35	-	-
Musculo-Skeletal System Disorders	7	7.61	-	-
Myo Endo Pericardial & Valve Disorders	1	1.09	-	-
Neoplasm	2	2.17	-	-
Reproductive Disorders, Female	2	2.17	-	-
Resistance Mechanism Disorders	1	1.09	-	-
Respiratory System Disorders	13	14.13	-	-
Urinary System Disorders	1	1.09	-	-
Vascular(Extracardiac) Disorders	1	1.09	-	-
Vision Disorders	1	1.09	-	-
Others	2	2.17	-	-
Total (Person-based)	**34**	**36.96**	**3**	**3.26**
Total (Spell-based)	**65**	**70.65**	**3**	**3.26**

Clinical benefits of Pitavastatin in T2DM

3. Effects on the surrogate markers

Effect of Pitavastatin on adiponectin

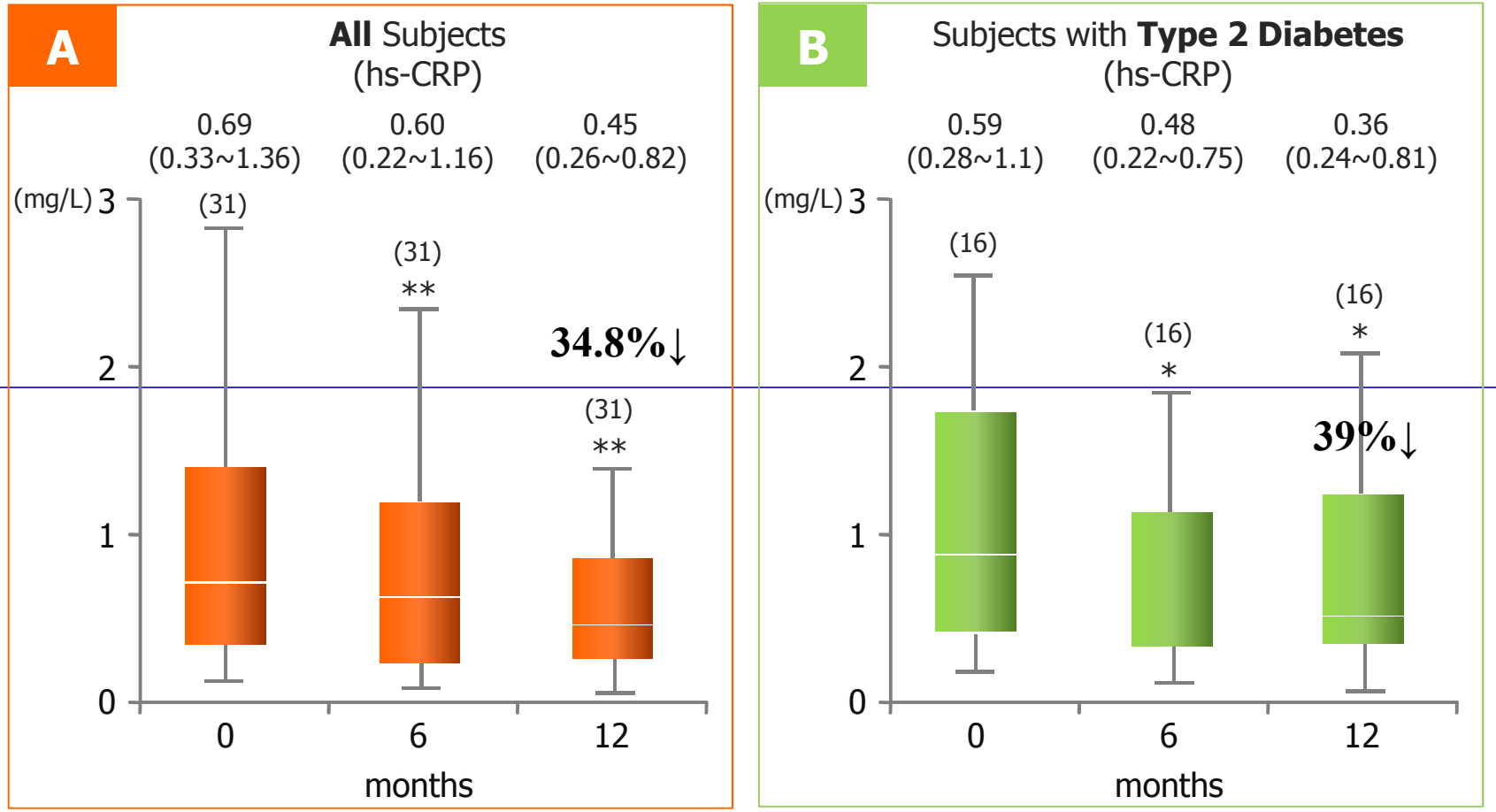
Change in adiponectin value



Patients: Hyperlipidemic patients 75 (w T2DM & w/o T2DM) Normolipidemic controls 35
Method : Pitavastatin 2mg/day for 6month

Nomura S et.al Thrombo Res 2008; 122(1):39-45

Effects of Pitavastatin on hs-CRP (KISHIMEN study)



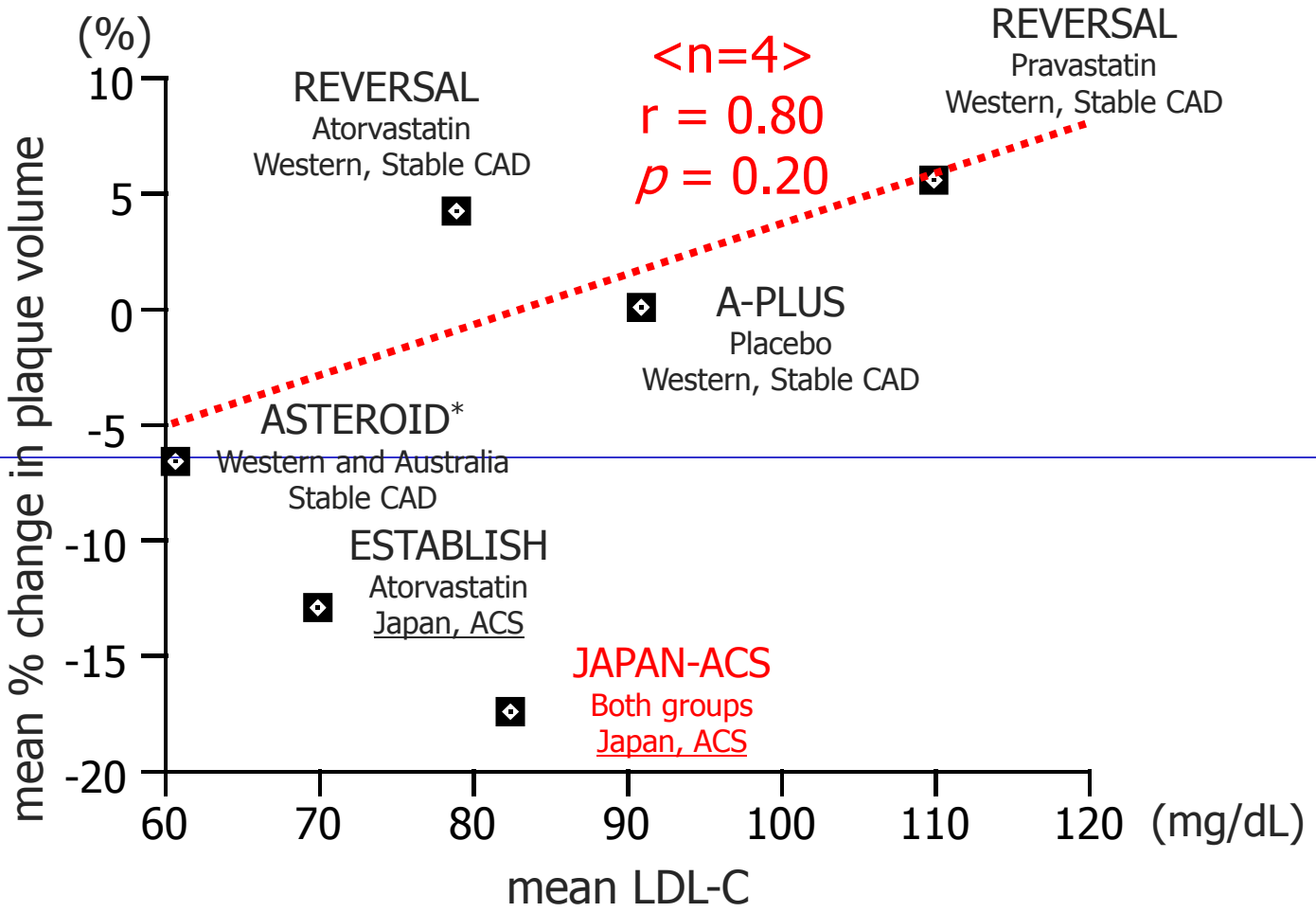
Patients: Hypercholesterolemia 178 (**including T2DM 103**)
Method: Pitavastatin 1-2mg/day (1mg/day-44, 2mg/day-134) **for 12month**

* $p<0.05$ vs baseline, ** $p<0.01$ vs baseline

Koshiyama H et.al J Atheroscle Thromb 2008;15:345-350

Previous Coronary IVUS Progression Trials

Relationship between LDL-C and Progression Rate



* normalized total plaque volume

ESTABLISH : Circulation 2004; 110: 1061–1068.
REVERSAL : JAMA 2004; 291: 1071– 1080.
ASTEROID : JAMA 2006; 295: 1556– 1565.
A-PLUS : Circulation. 2004;110:3372-3377

JAPAN-ACS
Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome

JACC publication

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CLINICAL RESEARCH **Clinical Trials**

Effect of Intensive Statin Therapy on Regression of Coronary Atherosclerosis in Patients With Acute Coronary Syndrome

A Multicenter Randomized Trial Evaluated by Volumetric Intravascular Ultrasound Using Pitavastatin Versus Atorvastatin (JAPAN-ACS [Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome] Study)

Takafumi Hiro, MD,* Takeshi Kimura, MD,† Takeshi Morimoto, MD,‡ Katsumi Miyauchi, MD,§ Yoshihisa Nakagawa, MD,‖ Masakazu Yamagishi, MD,¶ Yukio Ozaki, MD,# Kazuo Kimura, MD,** Satoshi Saito, MD,†† Tetsu Yamaguchi, MD,‡‡ Hiroyuki Daida, MD,§ Masunori Matsuzaki, MD,* for the JAPAN-ACS Investigators

Ube, Kyoto, Tokyo, Nara, Kanzawa, Toyoake, and Yokohama, Japan

JAPAN-ACS

JAPAN-ACS
Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome

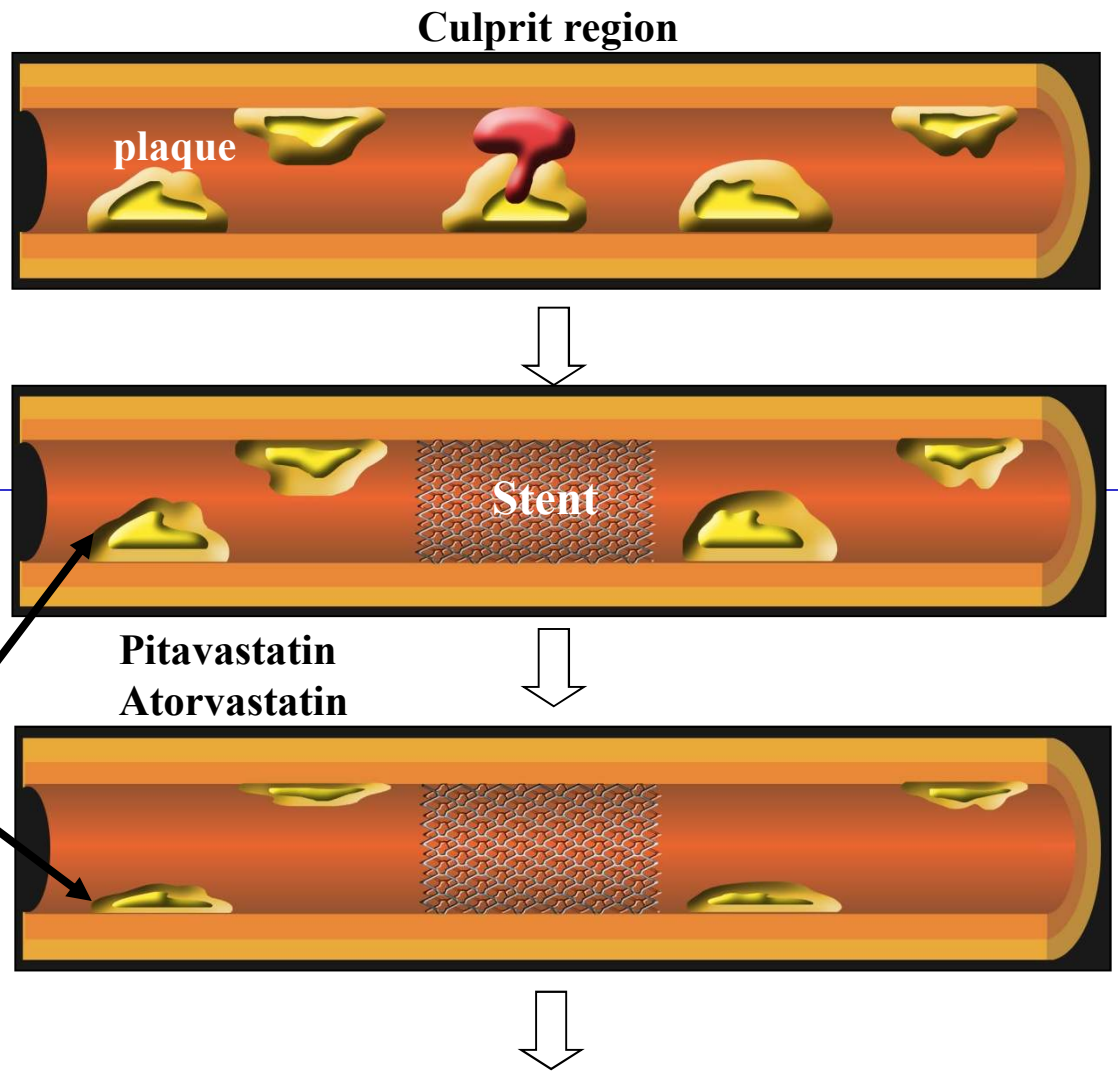
Study population	**Patients with acute coronary syndrome and with successful PCI by IVUS guidance**
Primary endpoints	**The percent change in coronary plaque volume**
Secondary endpoints	**Absolute and percentage in serum lipids and inflammatory markers**
Study drug	**Pitavastatin 4mg/day vs Atorvastatin 20mg/day**
Target No. of patients	**300（150 in each group）**
Study period	**Nov. 1, 2005 - Oct. 31, 2007**

Open-label, randomized, parallel-group comparison study

Takafumi Hiro, J Am Coll Cardiol. 2009 Jul 21;54(4):293-302.

JAPAN-ACS
Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome

Target region
- Culprit vessel, Non culprit region -

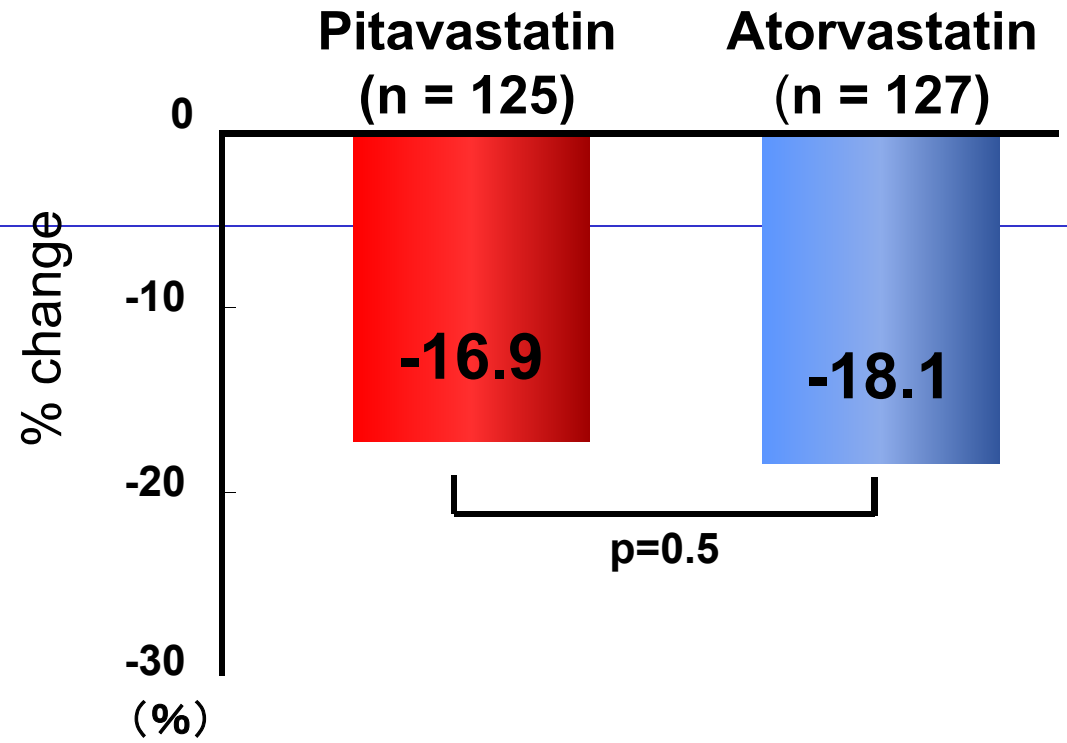


Takafumi Hiro, J Am Coll Cardiol. 2009 Jul 21;54(4):293-302.

JAPAN-ACS
Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome

No significant difference
between PTV and ATV in **Plaque Volume change –primary endpoint**

Plaque Volume



Takafumi Hiro, J Am Coll Cardiol. 2009 Jul 21;54(4):293-302.

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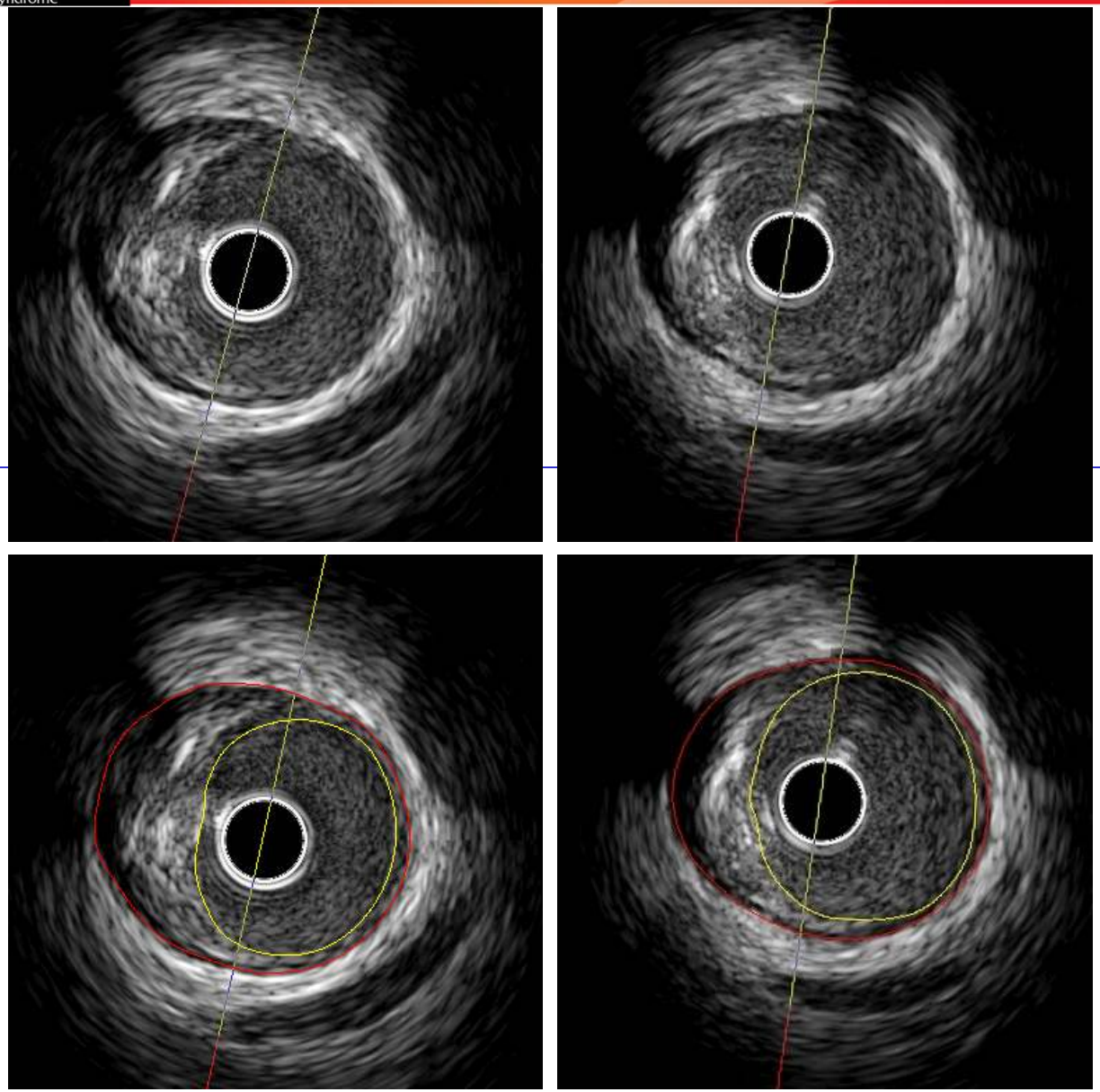
Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome

Baseline Follow Up



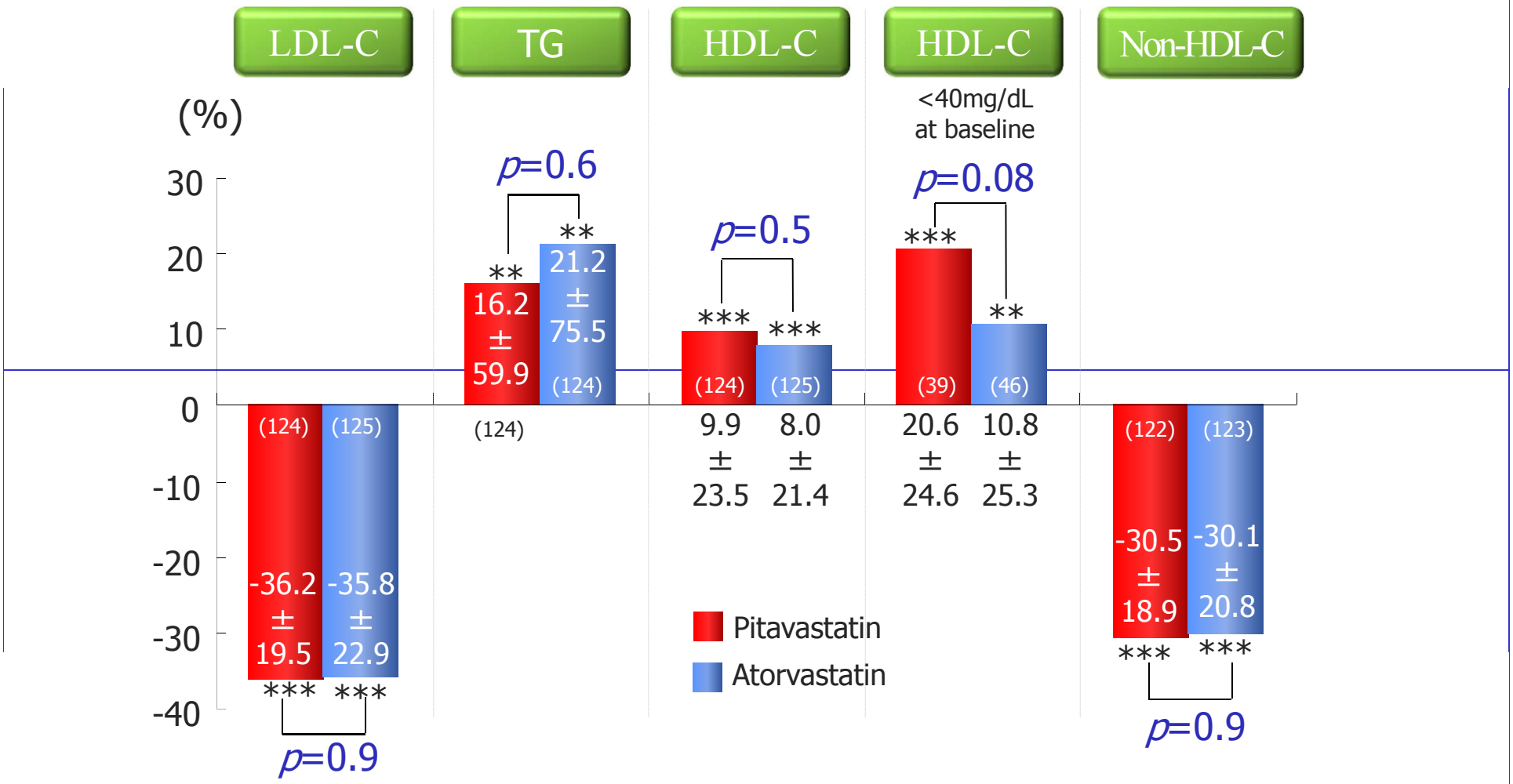
ID # 008
64y.o. male
Pitavastatin

Baseline (mm^3)
Plaque Volume=84.6
Vessel Volume=168.8
Lumen Volume=84.2
Follow Up (mm^3)
Plaque Volume=71.8
Vessel Volume=163.7
Lumen Volume=91.8
% Change
Plaque Volume=-15.1 %
Vessel Volume=-3.0%
Lumen Volume=+9.0%

Takafumi Hiro, J Am Coll Cardiol. 2009 Jul 21;54(4):293-302.

JAPAN-ACS
Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome

% Change in Lipid Parameters



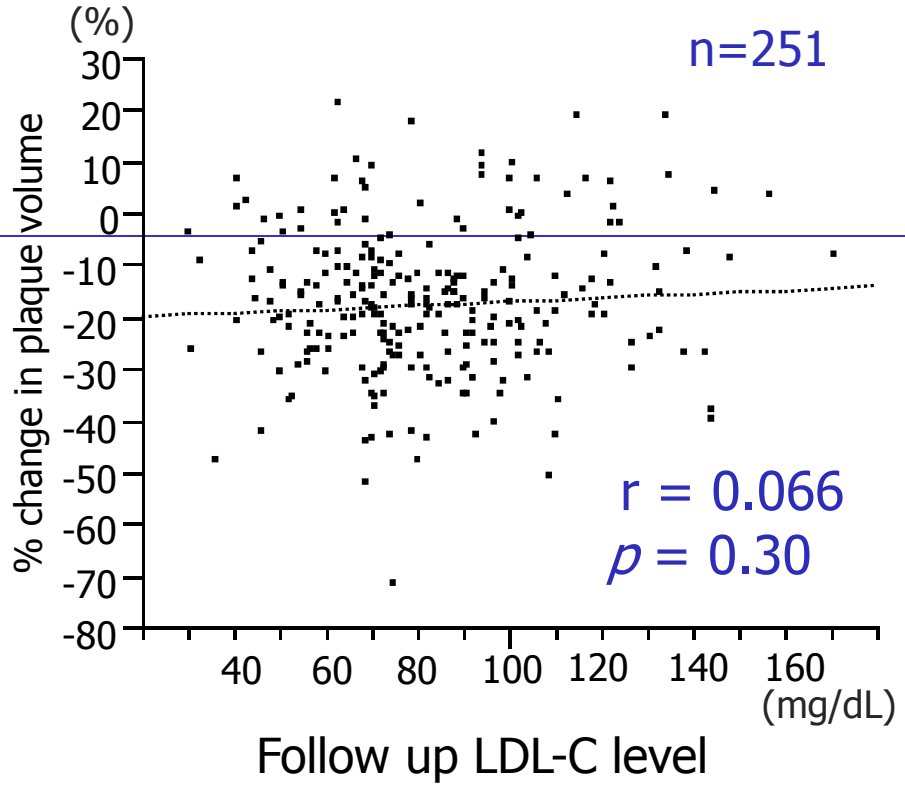
( ): number of patients, mean±SD
2 sample *t*-test (between groups), 1 sample *t*-test (each group)
** : p < 0.01, *** : p < 0.001

Takafumi Hiro, J Am Coll Cardiol. 2009 Jul 21;54(4):293-302.

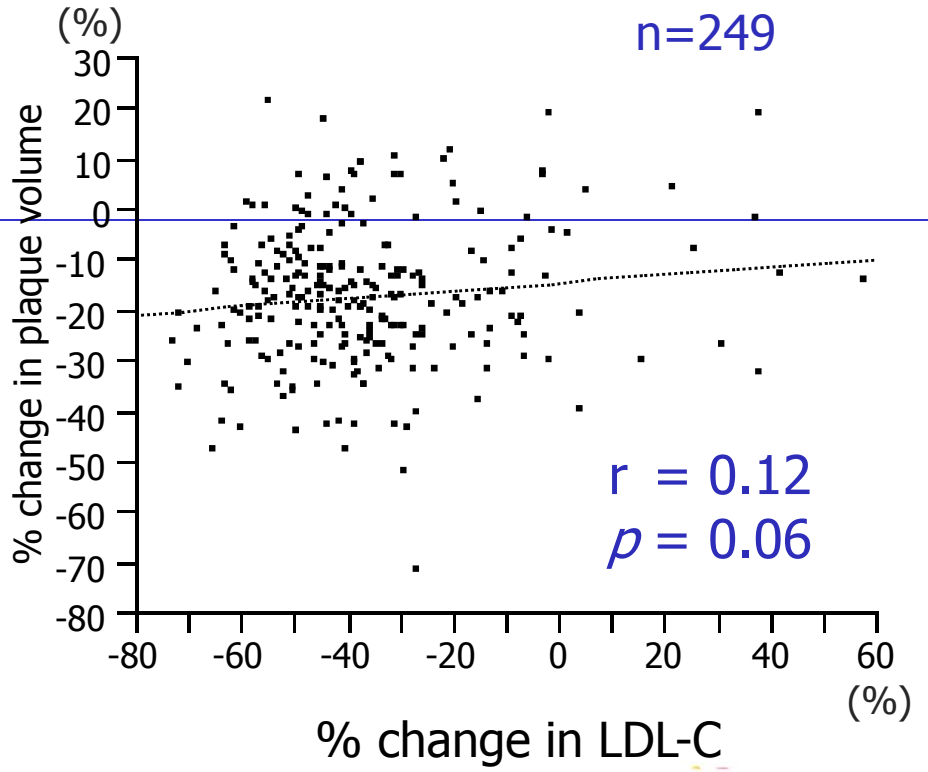
Relationship Between LDL-C and % Change in Plaque Volume

JAPAN-ACS
Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome

Follow up LDL-C level



% change in LDL-C



Takafumi Hiro, J Am Coll Cardiol. 2009 Jul 21;54(4):293-302.

MACE (major adverse cardiac events)

	Pitavastatin (n= 147)	Atorvastatin (n= 149)	*p*
MACE	**30(20.4)**	**34(22.8)**	**0.6**
Myocardial Infarction	**0**	**3(2.0)**	**0.2**
Coronary revascularization	**30(20.4)**	**31(20.8)**	**0.9**
TLR	**16(10.9)**	**19(12.8)**	**0.6**
TVR	**9(6.1)**	**8(5.4)**	**0.8**
Other Vessel Revascularization	**8(5.4)**	**9(6.0)**	**0.8**
Death from any cause	**0**	**0**	**-**

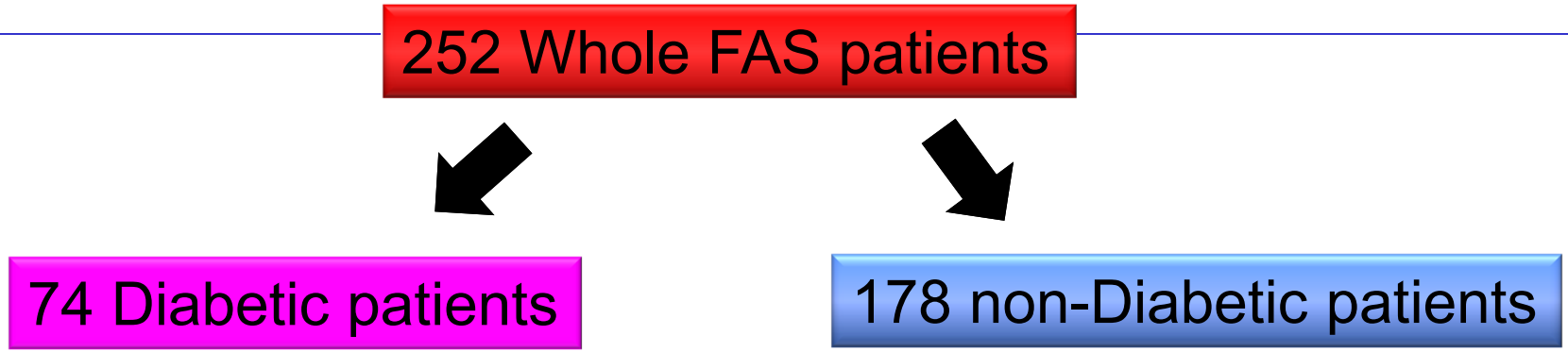
( ): % of patients, χ^2 test

MI: Stent thrombosis in 1 patient
Procedural complication in 1 patient
Spontaneous MI in 1 patient

Takafumi Hiro, J Am Coll Cardiol. 2009 Jul 21;54(4):293-302.

JAPAN-ACS
- Sub-Analysis of DM Patients -

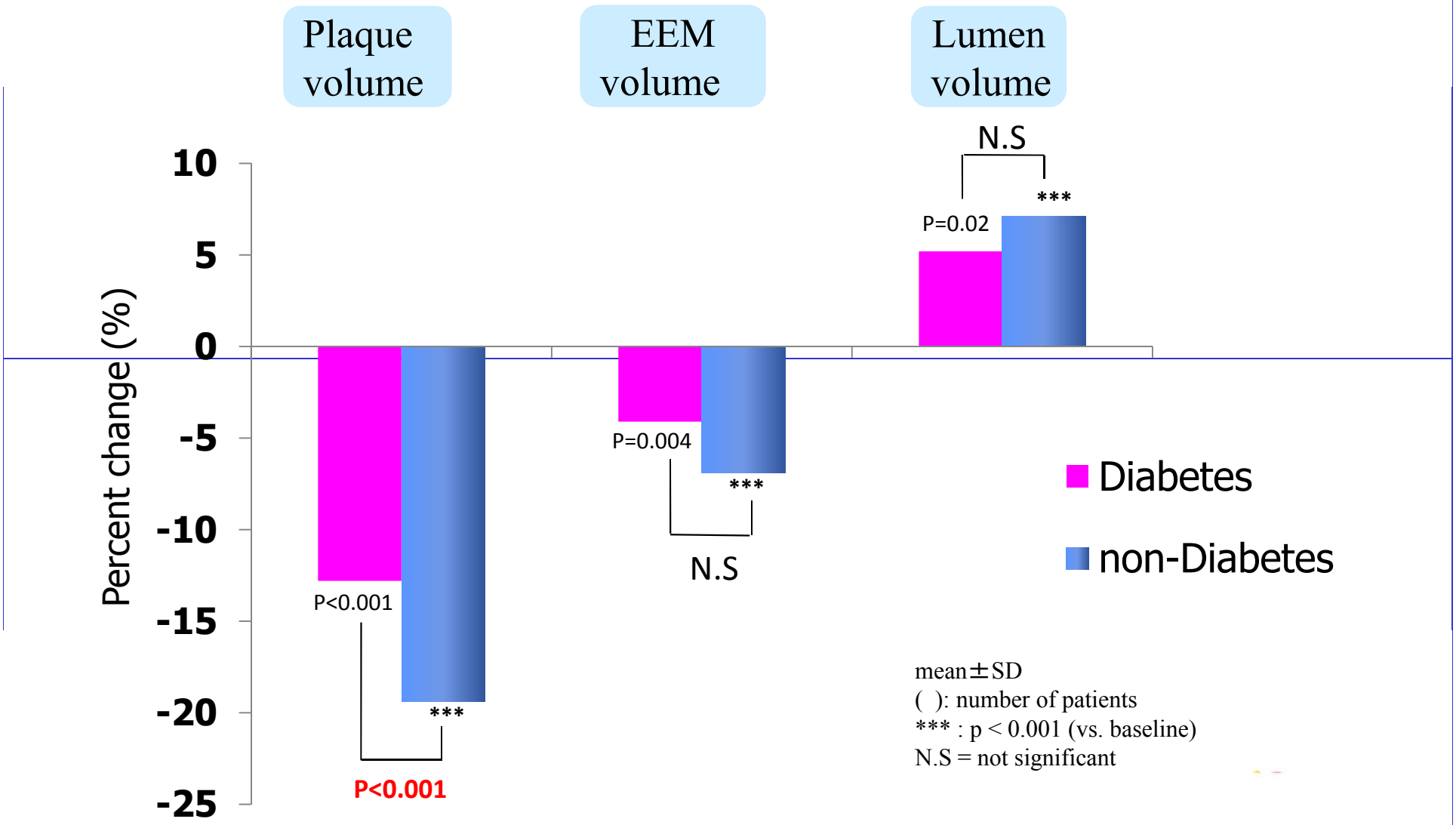
Since there was no significant difference in % change
in plaque volume between pitavastatin and atorvastatin groups,
the following analyses were evaluated in the whole FAS patients.



*FAS: Full Analysis Set

Hiro T et al. Circ J 2010;74;1165-74

IVUS Parameters Change
in Patients with or without DM



mean±SD
( ): number of patients
*** : p < 0.001 (vs. baseline)
N.S = not significant

Hiro T et al. Circ J 2010;74;1165-74.

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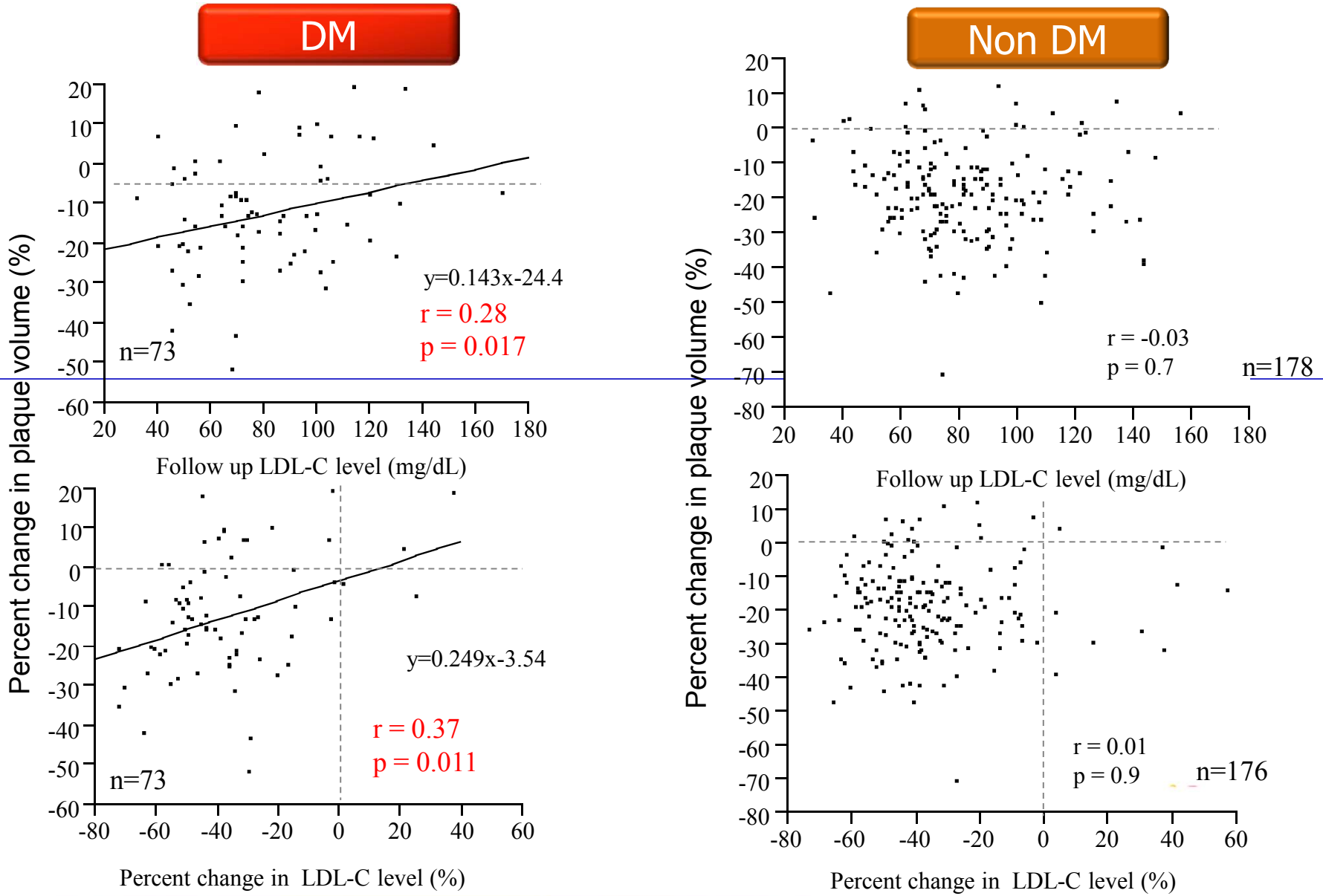
Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome

Relationship between LDL-C and Percent Change in Plaque Volume in Patients with DM or without DM



Clinical benefits of Pitavastatin in T2DM

4. Effects on the prevention of CV events

LIVES study Extension

- Patients

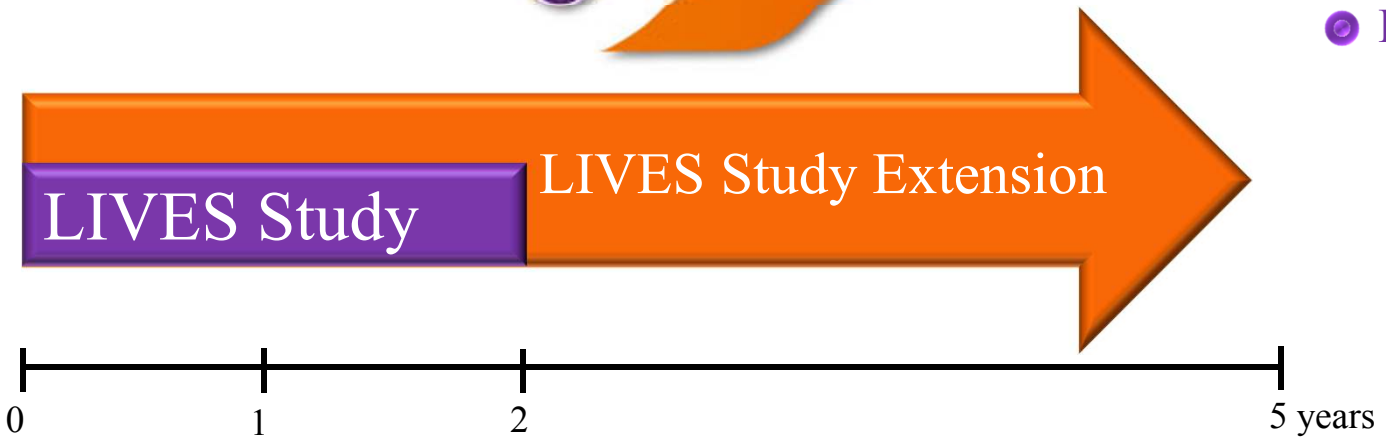
  Hypercholesterolemia patients (n=6,582)

- Drugs

  Pitavastatin
  1, 2, or 4mg/day

- Endpoint

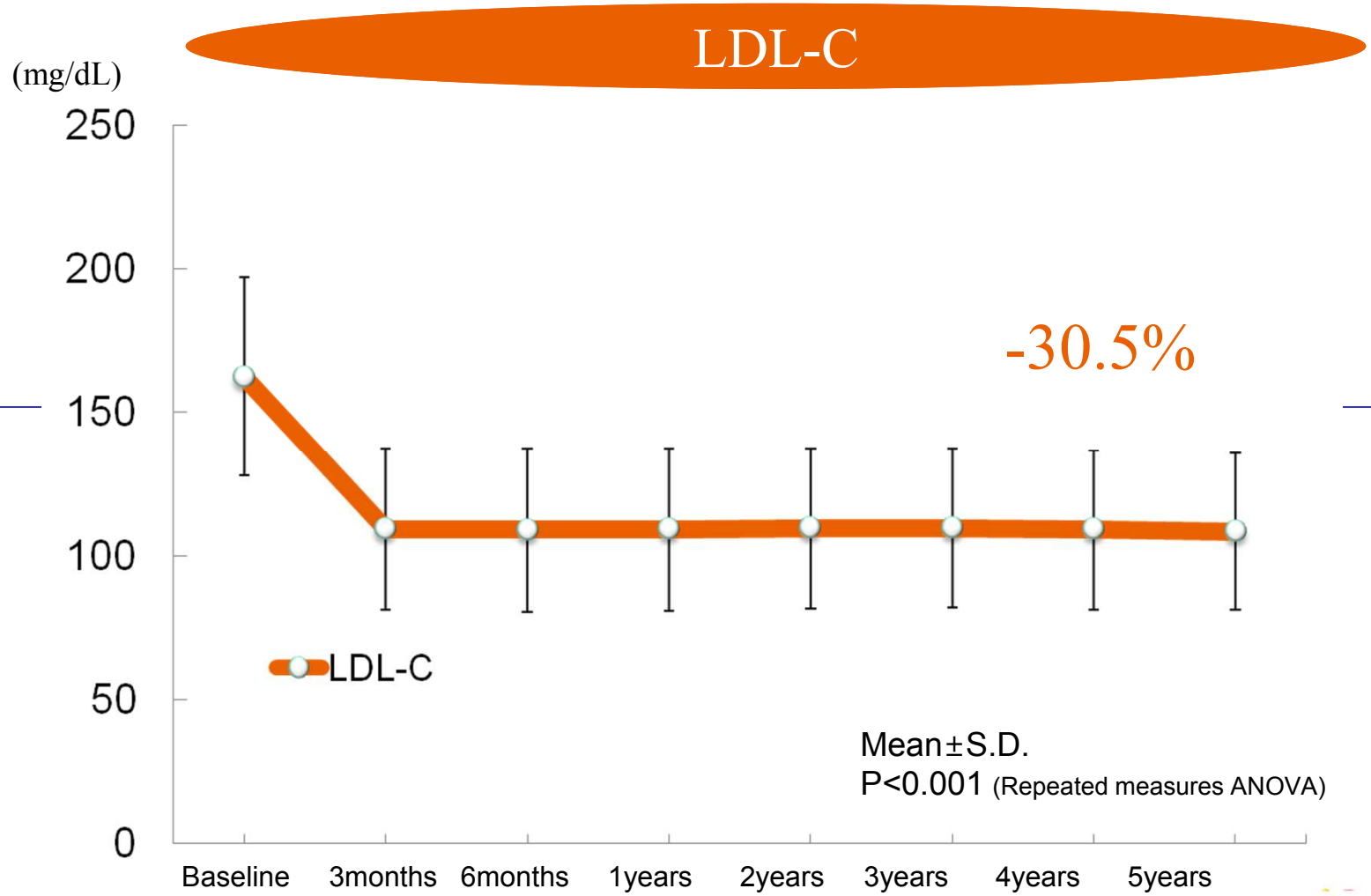
  Cardiovascular events, Cerebrovascular events, and sudden death



Jpn Pharmacol Ther 2011;39:789-803.

LIVES study Extension

Effects of pitavastatin on lipid parameters

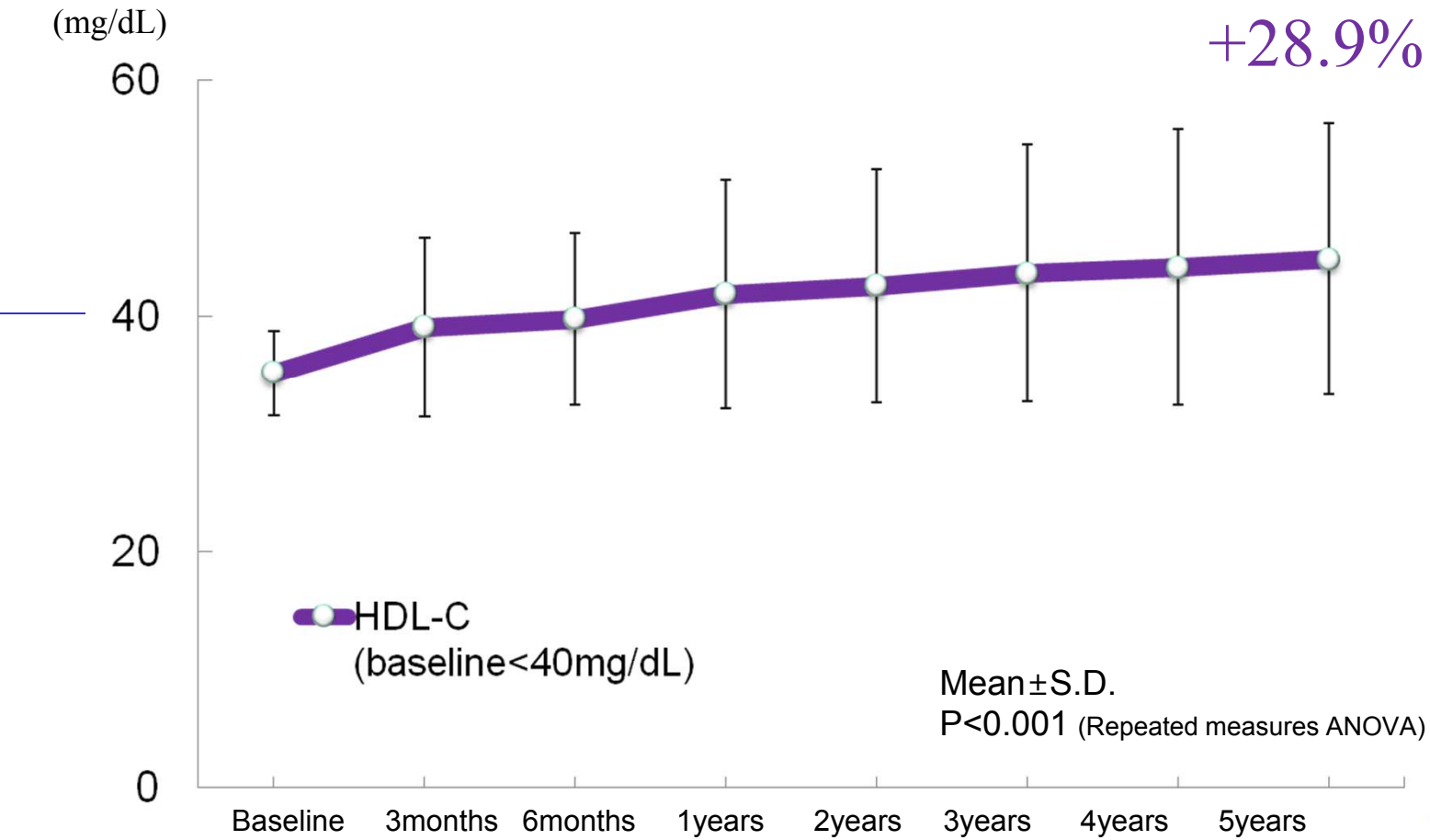


No. of Pts.	4530	3499	3550	4228	4987	5115	5339	5464

LIVES study Extension

Effects of pitavastatin on lipid parameters

HDL-C (baseline<40mg/dL)



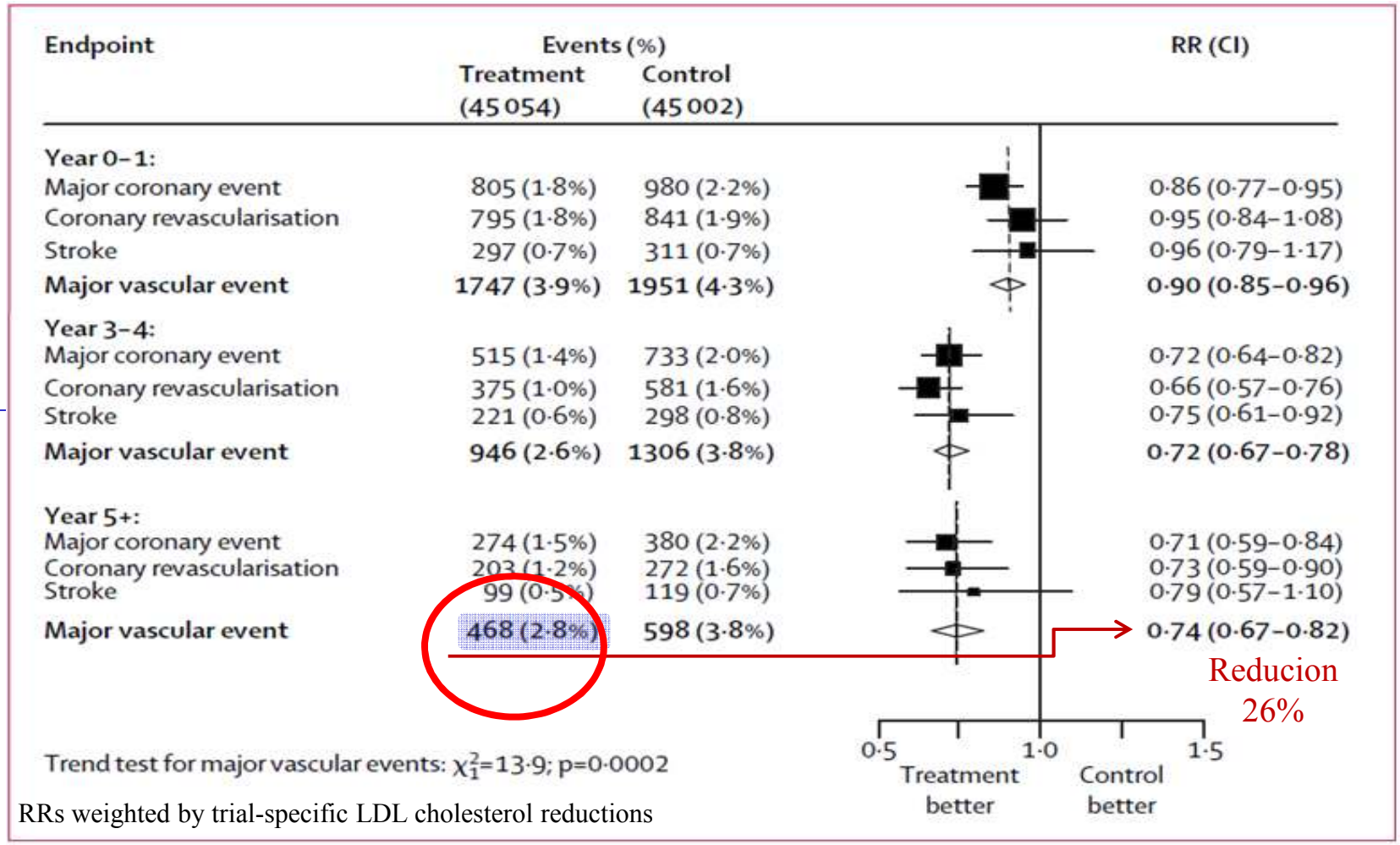
No. of Pts.	483	359	348	414	463	448	425	419

LIVES study Extension
on Cardio-Cerebrovascular Events

	No. of patients (%)		
	Total patients (n=6580)	Without history of ischemic heart disease (n=6155)	With history of ischemic heart disease (n=425)
Total events	**184 (2.8)**	124 (2.0)	60 (14.1)
Cardiovascular events	117 (1.8)	65 (1.1)	52 (12.2)
- Myocardial infarction	27 (0.4)	20 (0.3)	7 (1.6)
- Angina pectoris	90 (1.4)	45 (0.7)	45 (10.6)
Cerebrovascular events	61 (0.9)	52 (0.8)	9 (2.1)
- Cerebral infarction	44 (0.7)	37 (0.6)	7 (1.6)
- Cerebral hemorrhage	15 (0.2)	14 (0.2)	1 (0.2)
Sudden death	8 (0.1)	7 (0.1)	1 (0.2)

Follow－up period, 5.31 years (median)

The effects of statins on major vascular events

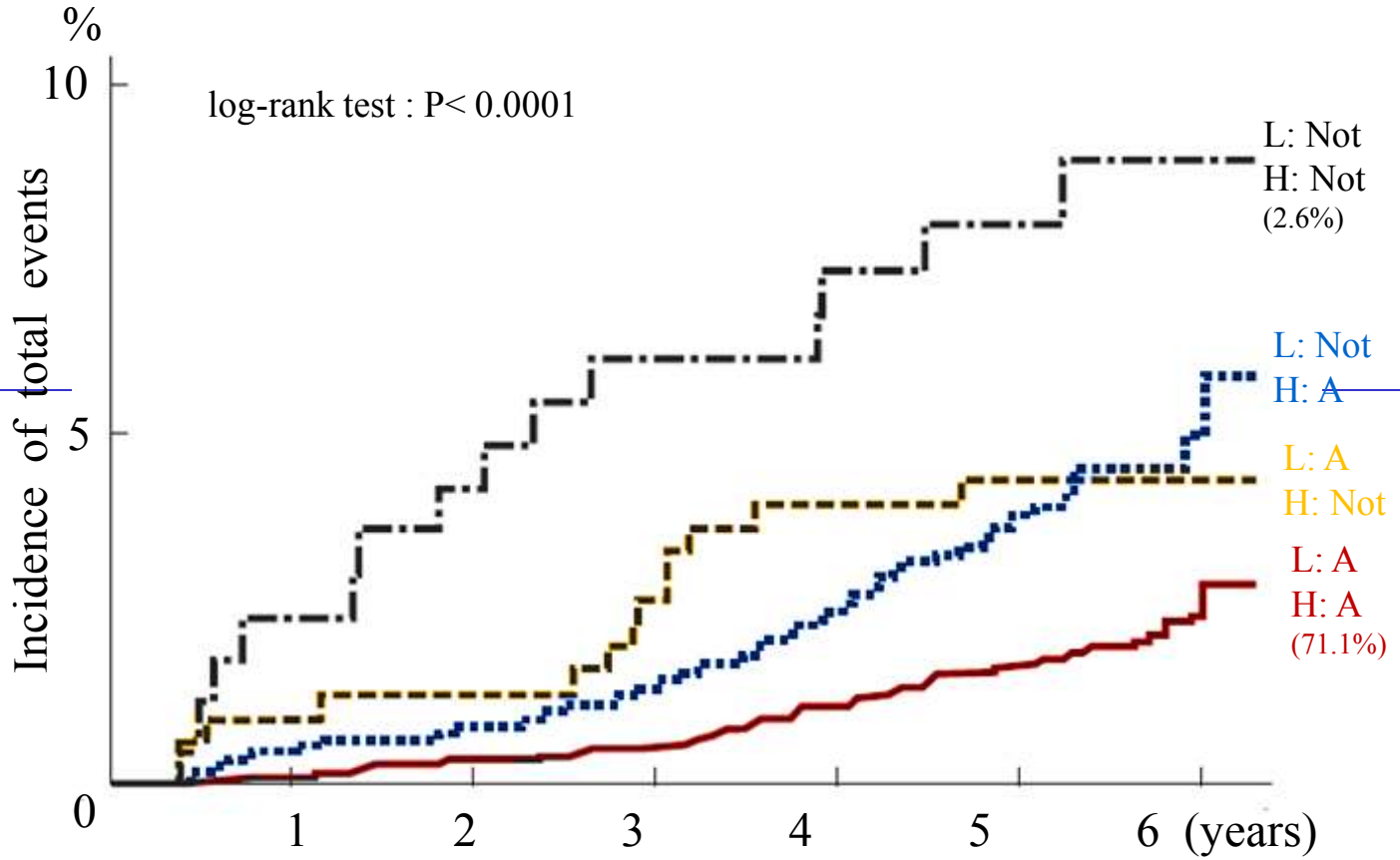


Major coronary events: non-fatal myocardial infarction [MI] or coronary heart disease [CHD] death
Major vascular events: The combined outcome of major coronary event,
non-fatal or fatal stroke, or coronary revascularisation

Lancet 2005; 366: 1267–78

LIVES study Extension
on Cardio-Cerebrovascular Events

Association of lipid treatment goal achievement



LDL-C treatment goal: L, HDL-C treatment goal : H, Achieved: A, Not achieved: Not

Patients: Hypercholesterolemia patients (n=6,582) were enrolled in the LIVALO Effectiveness andSafety Study (LIVES Study)
Method: Pitavastatin 1, 2, or 4mg/day, Follow－up period, 5.31 years (median)

LAMIS (Livalo® in Acute Myocardial Infarction Study)

Study population	**AMI patients as a substudy of KAMIR (Korea Acute Myocardial Infarction Registry)**
Primary endpoints	**All cause mortality at 12 months after the index PCI.**
	• Individual hard endpoints **• The cumulative major adverse cardiac events (MACEs) at 12 months.**
Study drug	**Pitavastatin 2mg/day**
Target No. of patients	**1,200**

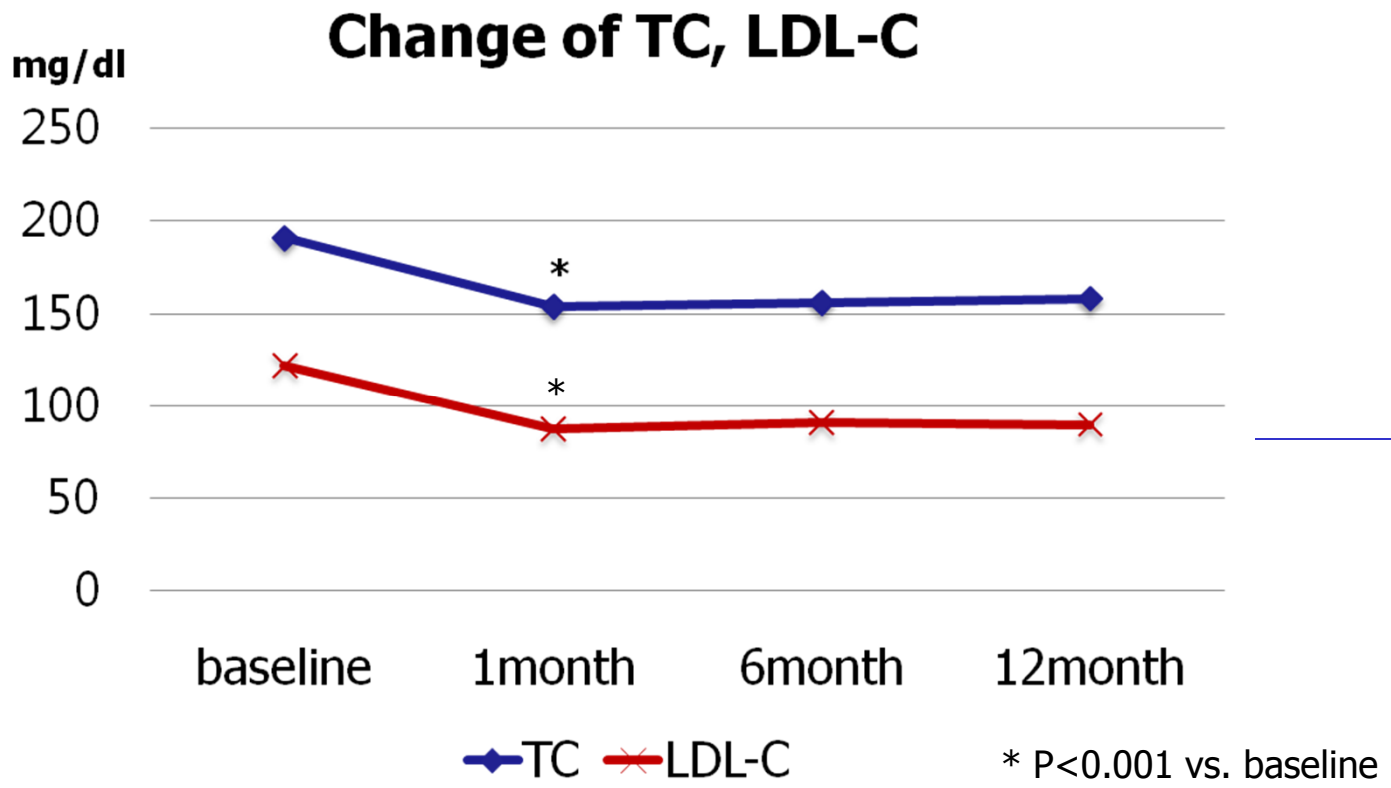
12month, a large long-term **prospective observational study**

If the target LDL level was not achieved during the follow up period, dose escalation to 4 mg daily was strongly recommended.

Suh SY et al. Am J Cardiol. 2011;108(11):1530-5.

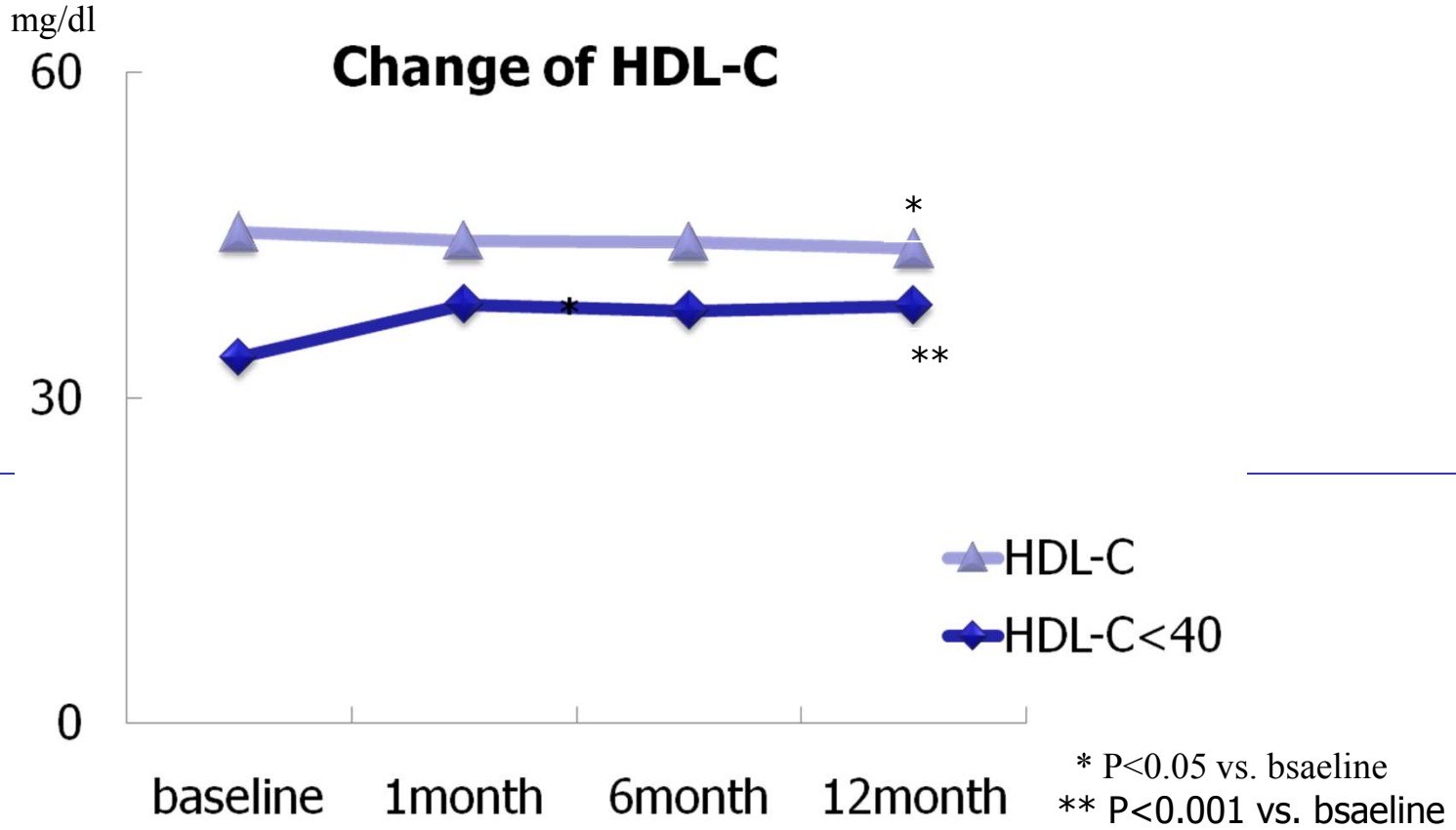
* MACE: Total death, Nonfatal MI, Repeated PCI or CABG(coronary artery bypass grafting)

Changes in Lipid Profile (1)



TC and LDL-C were decreased significantly during the first 1 month of pitavastatin treatment and sustained throughout the 12-month follow up.

Changes in Lipid Profile (2)



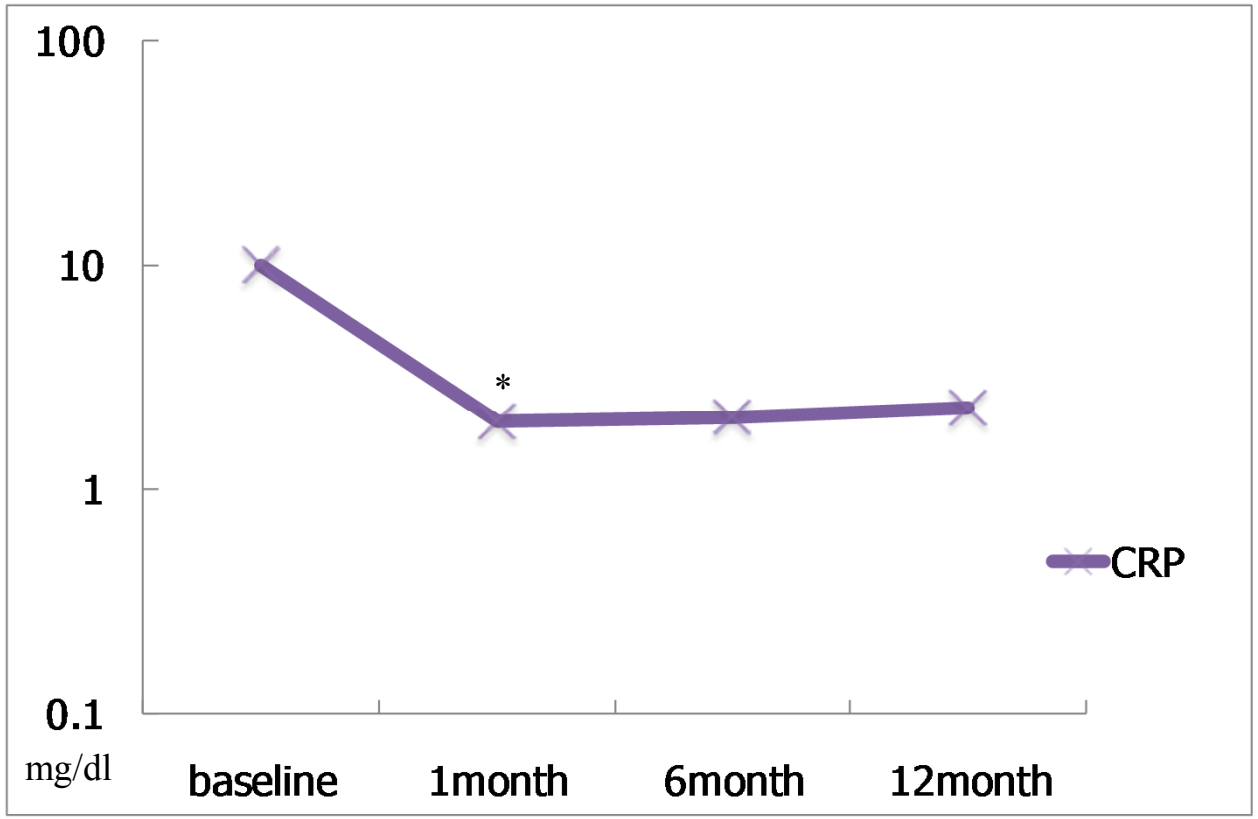
Mean HDL-C was decreased 2.4% from baseline to 12-month in all patients. Interestingly, for the low HDL group (HDL-C < 40 mg/dl, N=99 patients), HDL-C was **increased by 13.5%** change

LDL-C target attainment

	Pre discharge (N=1007)	1-month (N=540)	6-month (N=438)	12-month (N=319)
LDL-C attainment (N, %)	274 (27.2%)	378 (70.0%)	293 (66.9%)	**225 (70.5%)**
Diabetic patients (24% of total subjects)	78 (31.7%)	96 (74.4%)	62 (69.7%)	**45 (67.2%)**
Non diabetic patients	196 (25.9%)	281 (68.7%)	231 (66.6%)	**180 (71.7%)**

70.5% patients had achieved the LDL-C target defined by the NCEP criteria and LDL-C target attainment for diabetic patients was 67.2%

Changes in hs-CRP



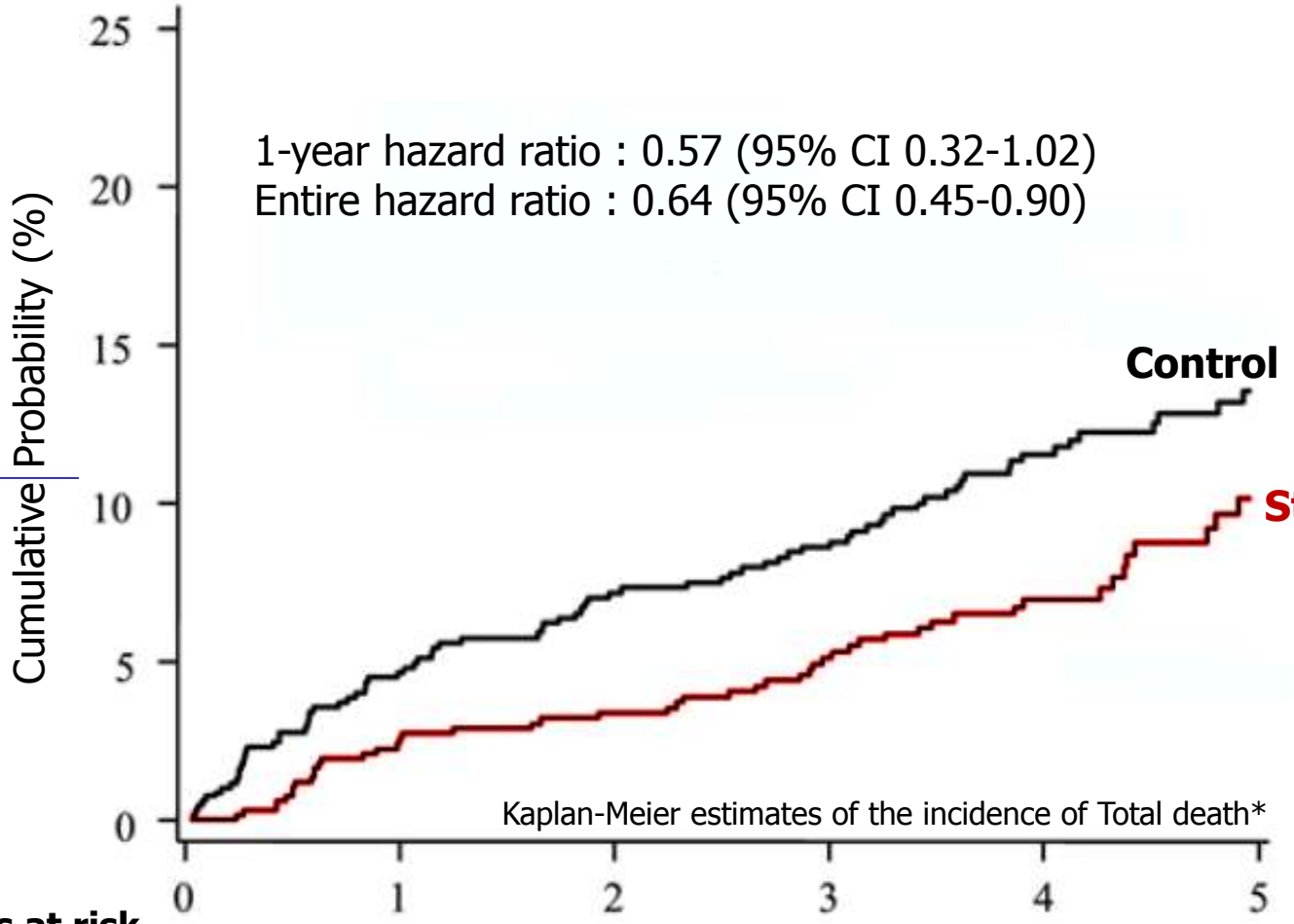
* P<0.05 vs. bsaeline

hs-CRP, was remarkably high at baseline but normalized during the first 1 month and sustained up to 12-month follow up

Cumulative Clinical Outcomes

Variables	1-month (N = 1039)	6-month (N = 963)	12-month (N = 901)
Total death	8 (0.8%)	20 (2.1%)	**32 (3.6%)**
Cardiac death	6 (0.6%)	13 (1.4%)	19 (2.1%)
Non cardiac death	2 (0.2%)	7 (0.7%)	13 (1.4%)
Recurrent Myocardial infarction			
STEMI	1 (0.1%)	5 (0.5%)	8 (0.9%)
NSTEMI	1 (0.1%)	5 (0.5%)	6 (0.7%)
Repeat PCI			
Target lesion revascularization	1 (0.1%)	18 (1.8%)	42 (4.7%)
Target vessel revascularization	2 (0.1%)	26 (2.7%)	59 (6.5%)
Coronary bypass graft	0	0	2 (0.2%)
Total major adverse cardiac event	8 (0.8%)	34 (3.5%)	**66 (7.3%)**

The association
between statin administration and the total death



Patients at risk

Control	702	606	583	542	409	225
Statins	702	622	592	521	353	168

*** Total death:** AMI, heart failure, sudden death, cerebrovascular disease, other cardiovascular cause, or noncardiovascular cause

Patients: 1404 patients after acute myocardial infarction

Method: Statins(n=702), Control(n=702) For a median 4.1 years

Michitaka N et al, Am J Cardiol 2007;99:1523–2

On-going clinical study

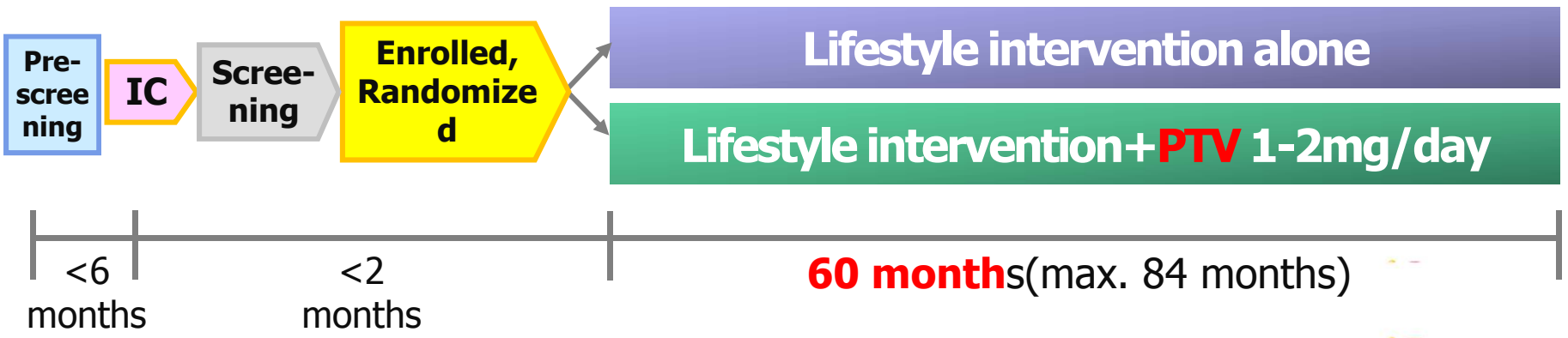
J-PREDICT

Pitavastatin, the Balanced Statin

Japan PREvention Trial of Diabetes by pitavastatin in Patients With Impaired GluCose Tolerance

Subject	**IGT**
Primary outcome	**Cumulative incidence of diabetes**
Secondary outcome	**Incidence of any cardiovascular diseases, etc**
Study drug	**Pitavastatin 1-2mg/day vs. control group**
Sample size	**1,240**
Study period	**Apr. 1, 2006 to Mar. 31, 2015 (recruitment closure Mar. 31,2010)**
Principal investigator	**Takashi Kadowaki (the university of Tokyo)**

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



NCT00301392, UMIN ID:C000000394

LIVALO TAB. 2mg

J-DOIT3

Pitavastatin, the Balanced Statin

Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases

Study population	**Type-2 DM patients with hypertension or abnormal lipid metabolism (age 45-70, HbA_{1c}≧6.5%)**
Sample size	**3,000**
Primary outcomes	**Death, MI or stroke (study goal: 30% decrease in incidence within 3 years)**
Secondary outcomes	**Onset or aggravation of nephropathy or retinopathy, CABG, PCI, lower limb amputation**
Study period	**Registration: ~ Dec.2008, follow-up: ~ Mar.2013**

Treatment goal	Intensive treatment	Conventional treatment
Blood glucose	**HbA_{1c}<6.2% (pioglitazone)**	**Behavioral and Drug** - The physician in charge is to administer appropriate therapy in accordance with the Guidelines.
Blood pressure	**<120 / 75mmHg (ARB/ACEI)**	
Lipids	**LDL-C<80mg/dL (non-HDL-C*<110)** **【IHD : LDL-C<70mg/dL(non-HDL-C*<100)】** **HDL-C≧40mg/dL TG<120mg/dL** **(pitavastatin, atorvastatin, rosuvastatin)**	

ClinicalTrials.gov Identifier: NCT00300976

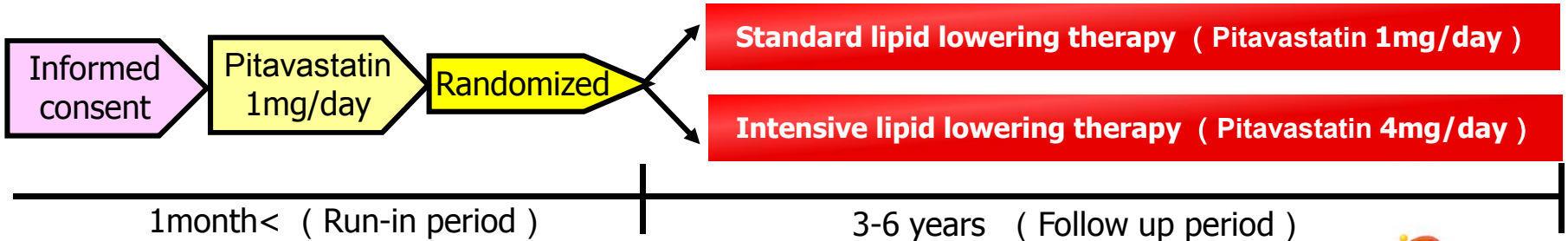
REAL-CAD

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

Pitavastatin, the Balanced Statin

Objectives	**To evaluate the effects of aggressive lipid-lowering therapy on coronary artery disease (CAD)**
Study Population	**CAD patients (Hypercholesterol Patients)**
Primary Endpoint	**Onset of one of following events** **・ CHD death** **・ Fatal or nonfatal stroke** **・ Nonfatal AMI** **・ Unstable Angina requiring hospitalizations**
Study Drugs	**Pitavastatin 1mg/day vs Pitavastatin 4mg/day**
Estimated Event Rate	**16% (Primary Events 1,033)**
Estimated Event per year	**2.5%**
Target Number of Subjects	**12,600 (6,300 in each group)**
Study Period	**Jan. 2010 –Dec. 2014 (Registration 2 years)**

Open-label, randomized, parallel-group comparison study



ClinicalTrials.gov Identifier: NCT01042730

HMG-CoA Reductase Inhibitor LIVALO TAB. 2mg

POET

The Prevention Of cardiovascular Events with piTavastatin in patients with clustering cardiovascular risk factors

Study population	Patients with cardiovascular risk factors or DM
Primary outcomes	Cardiac death or hospitalization
Study drug	pitavastatin vs. pitavastatin -free
Sample size	2,000
Study period	5 years (registration until May 2015)
Sponsor	Korea Centers for Disease Control and Prevention (CDC)

Conclusion

- Pitavastatin, the newest addition to the statin family,

  - has a favorable pharmacokinetic profile.

  - produces potent and beneficial effects on lipids (total and LDL cholesterol ↓, HDL cholesterol ↑) in hyperlipidemic patients with or without T2DM.

  - showed beneficial effects on metabolic syndrome and also did not deteriorate glucose metabolism in obese Korean adults with metabolic syndrome.

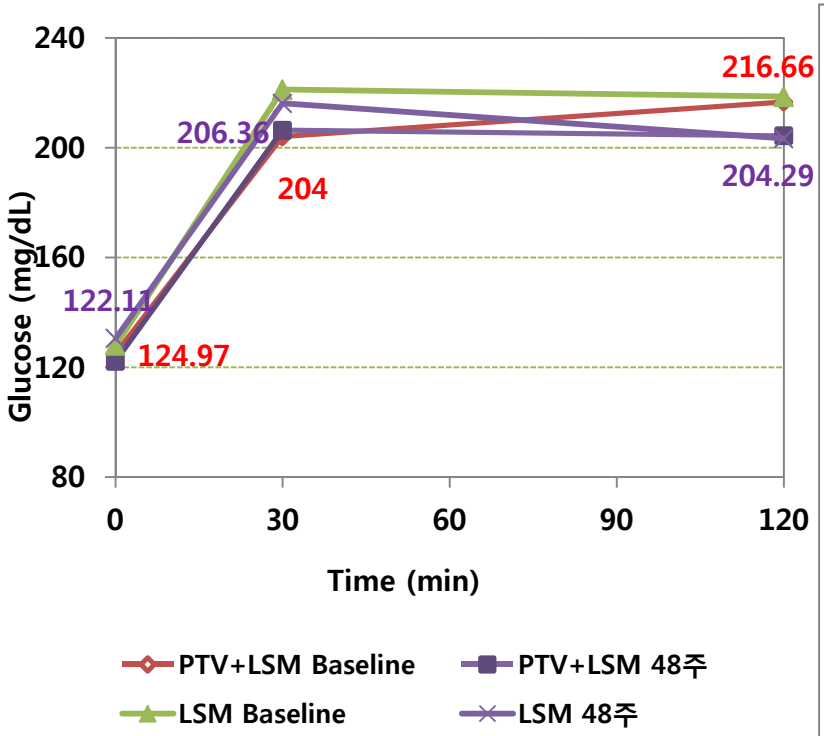
  - was non-inferior to atorvastatin at reducing plaque volume in patients with acute coronary syndome.

- On-going prospective trials can clarify the expected effects of pitavastatin on reducing mortality and morbidity in pts. with high risk of CVD.

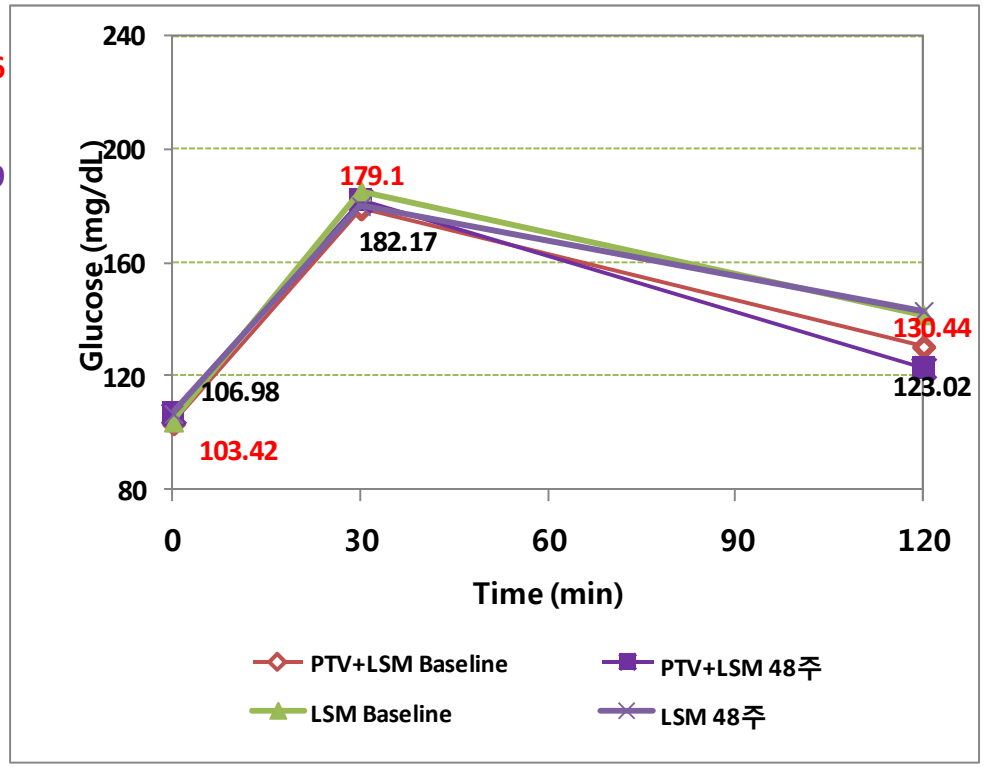

Thank you
for your attention!!

당뇨 유무에 따른 glucose의 변화

당뇨군

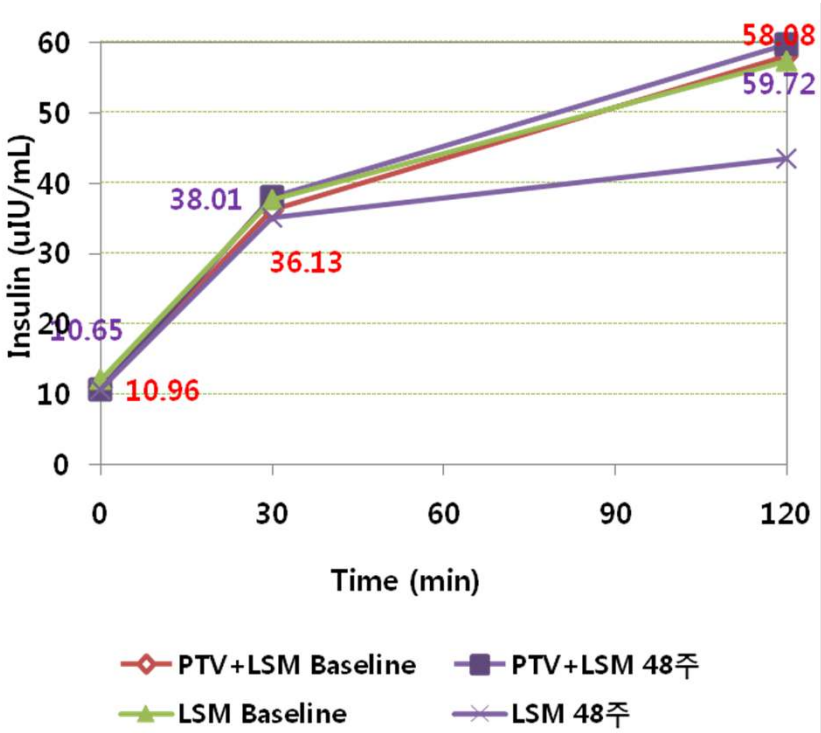


비 당뇨군



당뇨 유무에 따른 insulin의 변화

당뇨군



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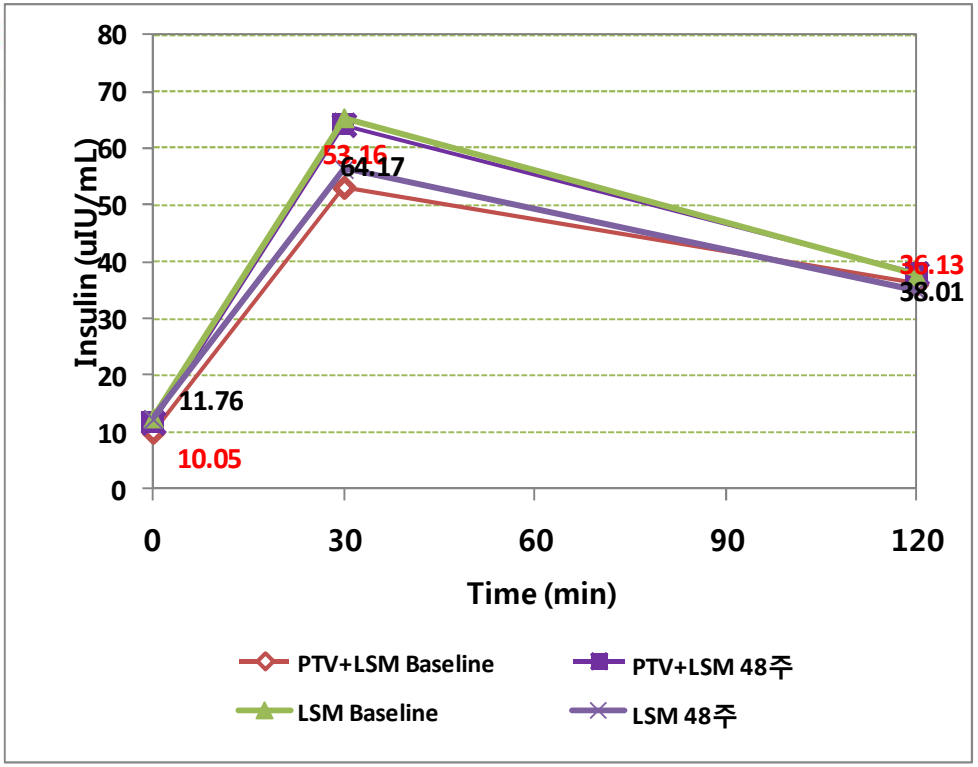
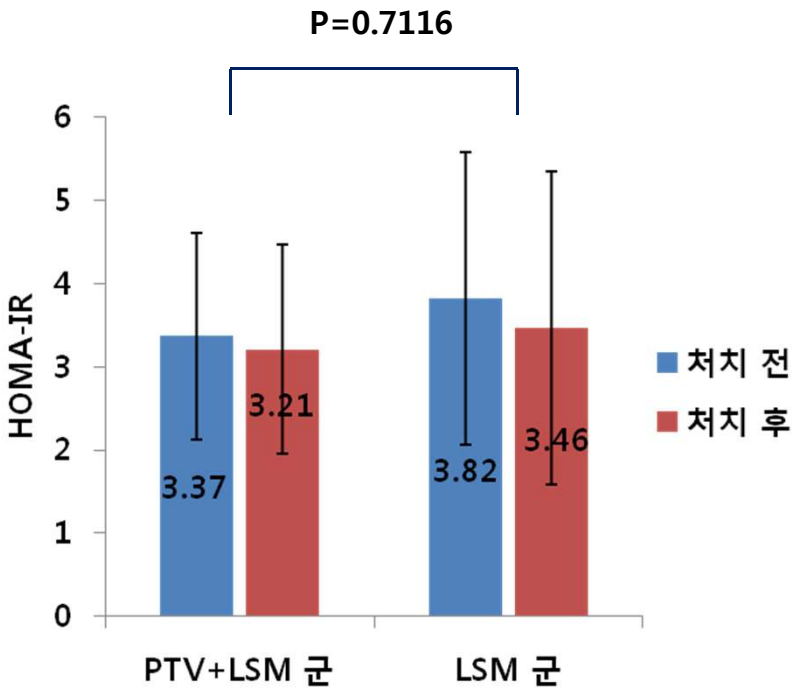


당뇨 유무에 따른 HOMA-IR의 변화

당뇨군



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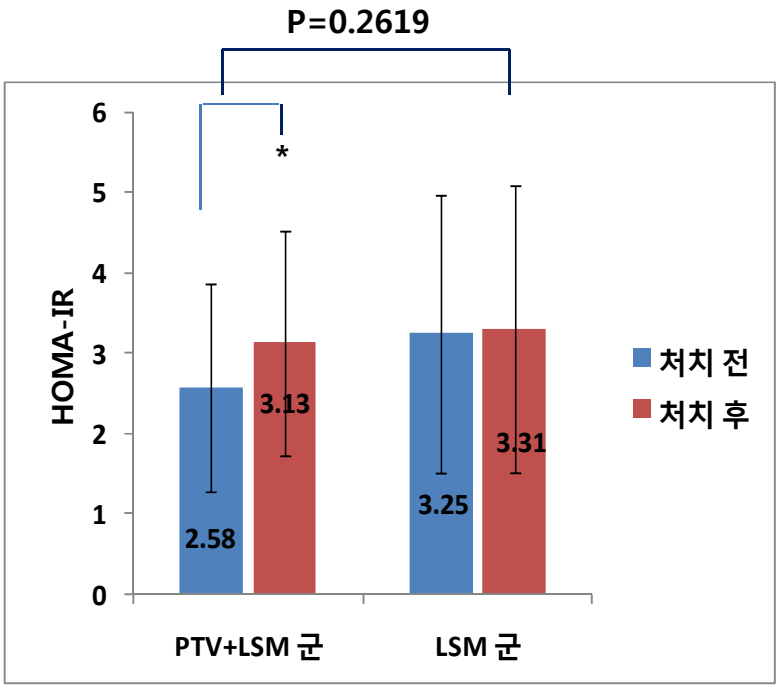

* p=0.0161 vs. baseline