Novel Statin Strategy to Prevent Atherosclerotic Cardiovascular Disease in Diabetic Patients-Curtailing Heart Attack

: Korean Data and JUPITER again in spotlight

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# Statin Revolution, "Lower is Better" to curtail heart attack

4S trial started the revolution of statin

30%
risk reduction
p = 0.0003

Proportion of patients dead

Placebo

Simvastatin

Years since randomization

Lancet 1994;344:1383
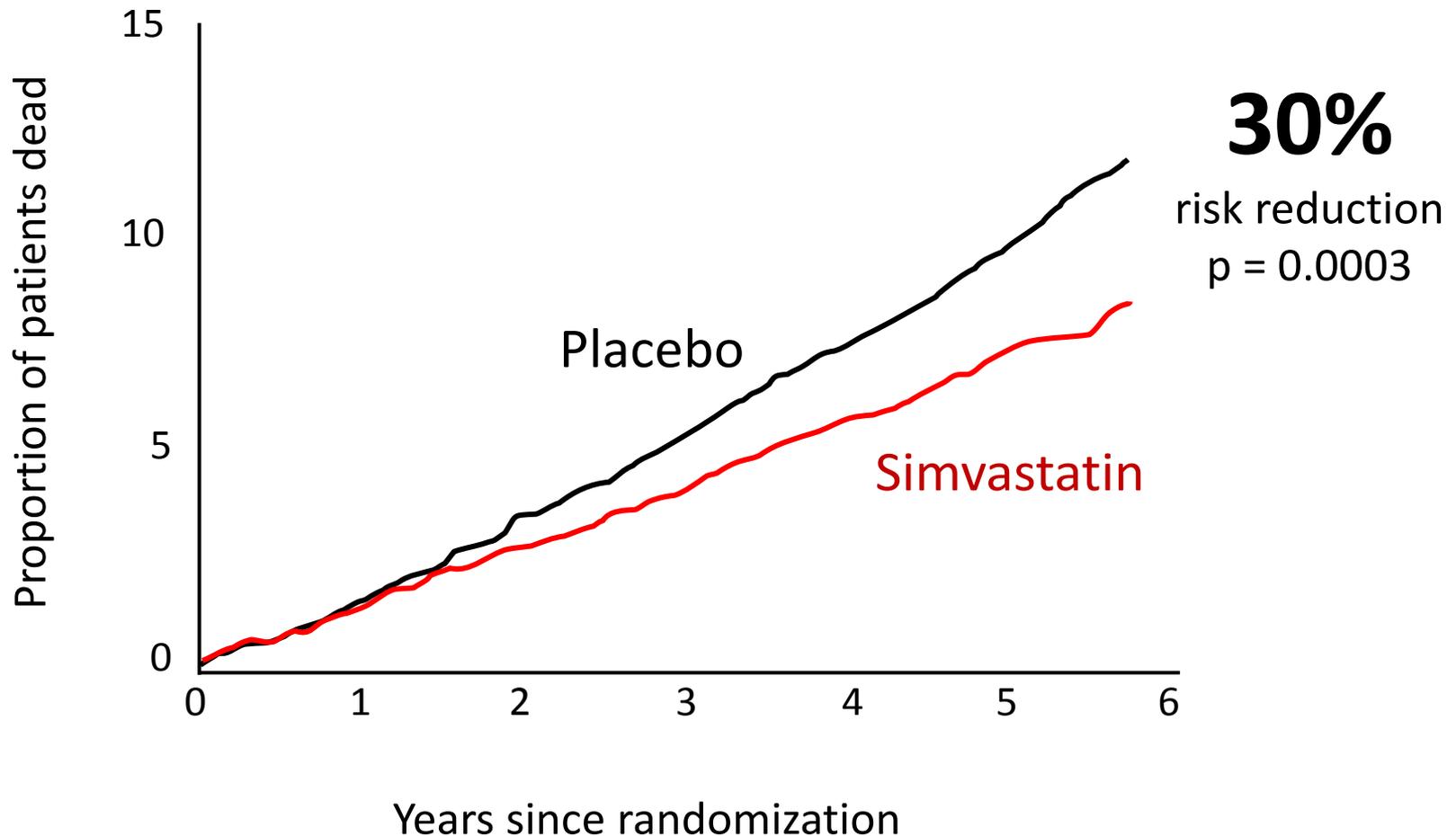
LDL-C target has been lowered

ATP I 1988	ATP II 1993	ATP III 2001	ATP III Update 2004
Exclusive focus on LDL-C	Risk assessment guides therapy	Lower LDL-C threshold for therapy initiation in high-risk patients	Lower LDL-C threshold for therapy initiation in very-high-risk patients

100

70

Where did the target come from?

Percent with CHD event (%) vs End of study LDL-C (mg/dL)

- 4S-PI
- 4S-Rx
- Lipid-PI
- CARE-PI
- HPS-PI
- CARE-Rx
- LIPID-Rx
- HPS-Rx

Rx - Drug group
PI - Placebo group

TARGET 100 mg/dL (2.5)

100
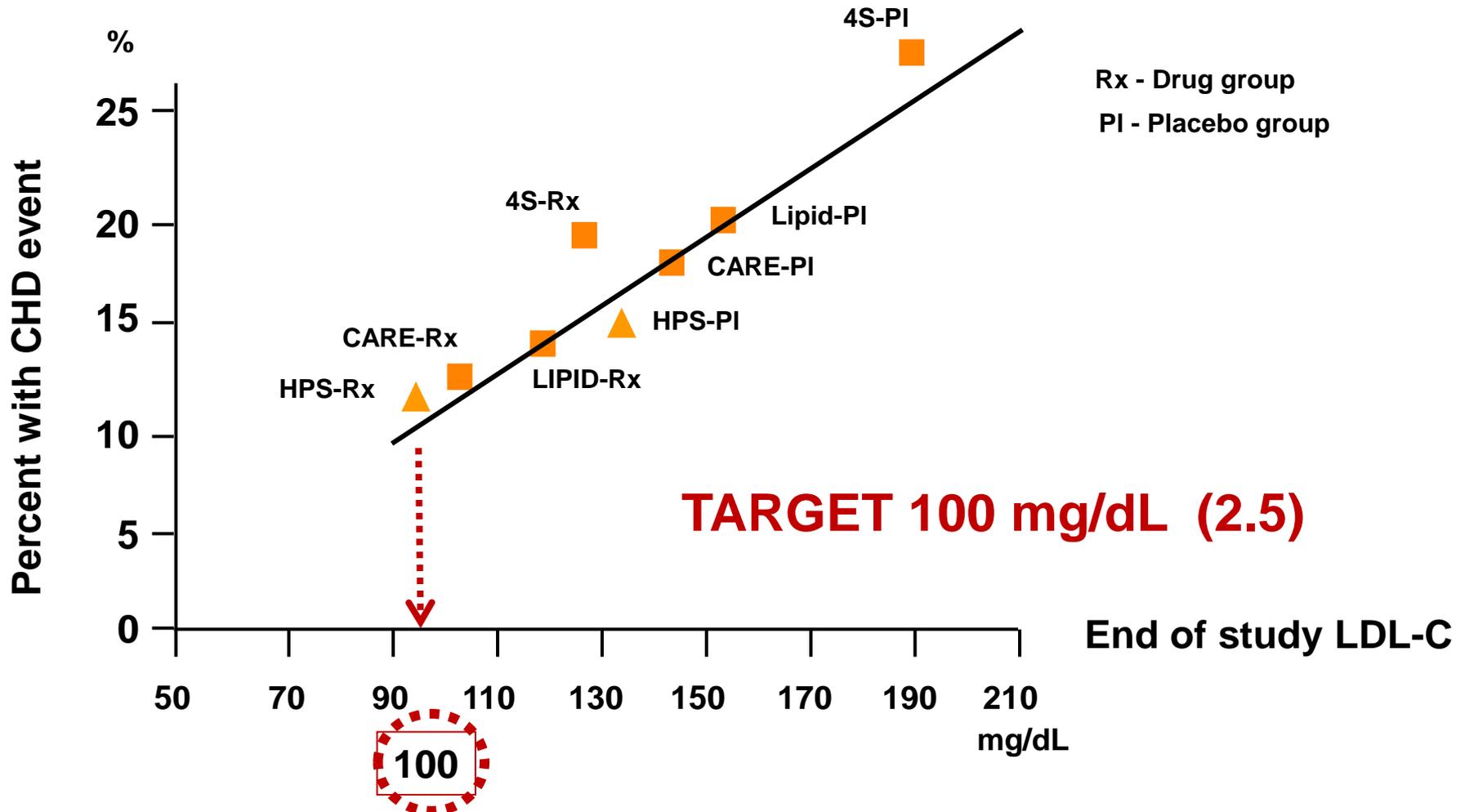
Where did target come from?

Adapted from Kastelein JJ. Atherosclerosis 1999;143(Suppl 1):S17–S21
Heart Protection Study Collaborative Group. Lancet 2002;360:7–22
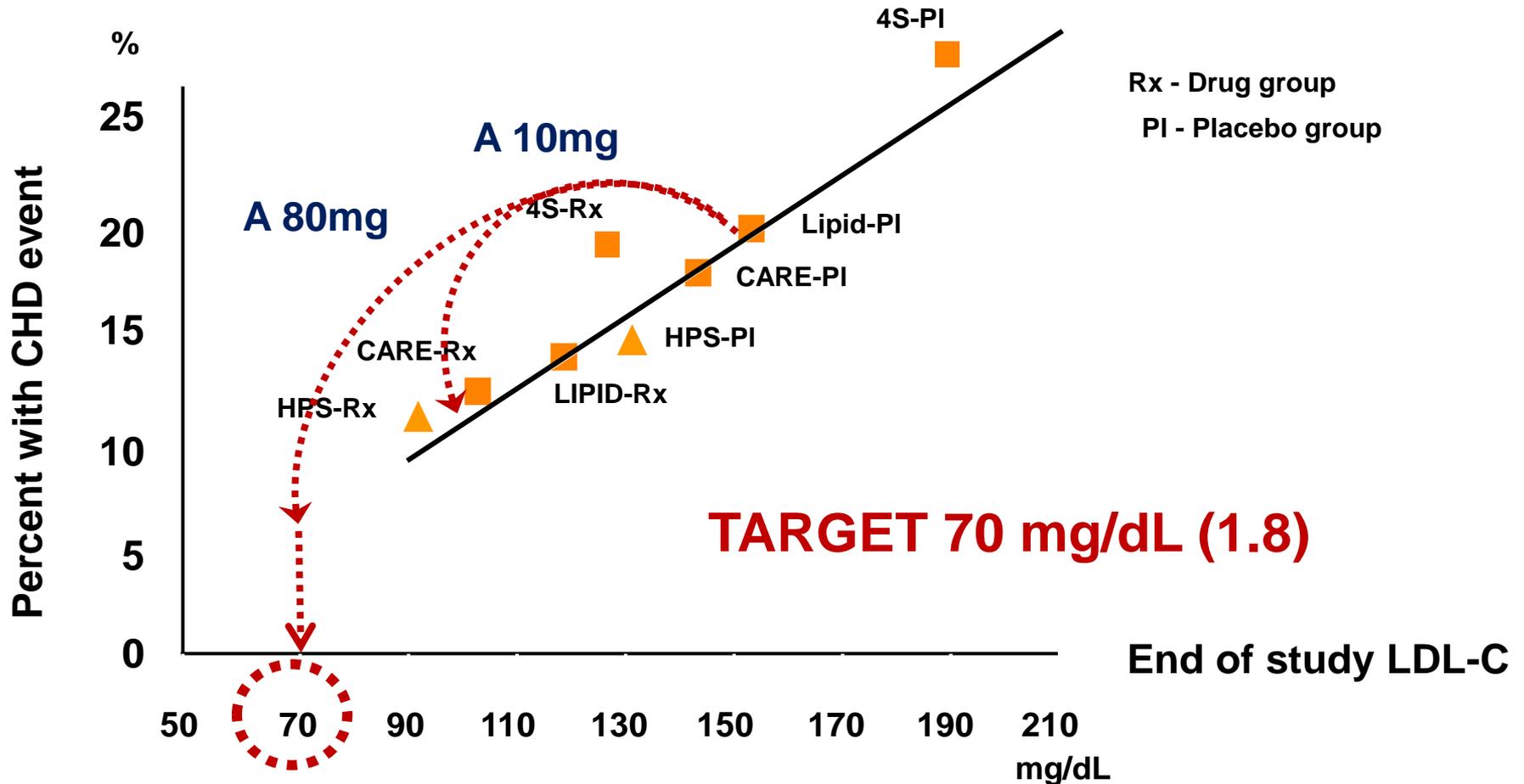
The problem of LDL–C target

Target is 70 mg/dl

Would you treat LDL 70 mg/dl or 73 or 68?

Would you cut back dose if LDL 60 mg/dL?

Lower LDL-C makes better outcome

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

Median Time avg
69.5 vs. 53.7 mg/dL

HR 0.936 CI (0.887, 0.988)
p=0.016

Number at risk:
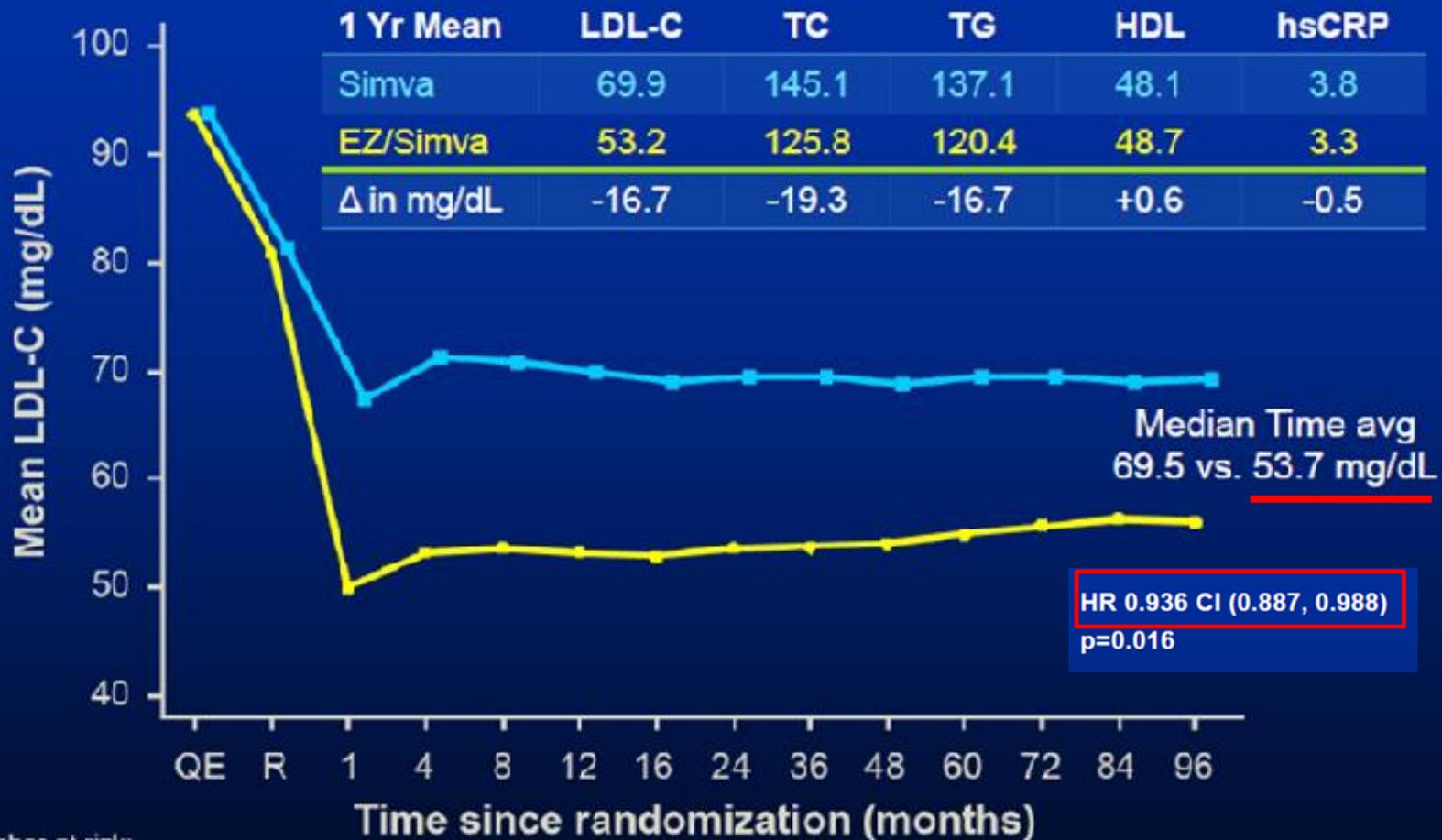
	QE	R	1	4	8	12	16	24	36	48	60	72	84	96
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

2013 ACC/AHA Cholesterol Guideline

PRACTICE GUIDELINE

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

CrossMark

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

Who benefits from Statins?

✓ 4 Statin Benefit Group

01	02	03	04
Clinical ASCVD* 환자	LDL-C 190mg/dl 이상인 환자	당뇨병 환자-Type1 or 2 (40-75y, LDL-C 70~189 mg/dL)	10년 내 추산된 ASCVD 발생위험이 7.5% 이상인 환자 (40-75y, LDL-C 70~189 mg/dL)

* indicates 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).**
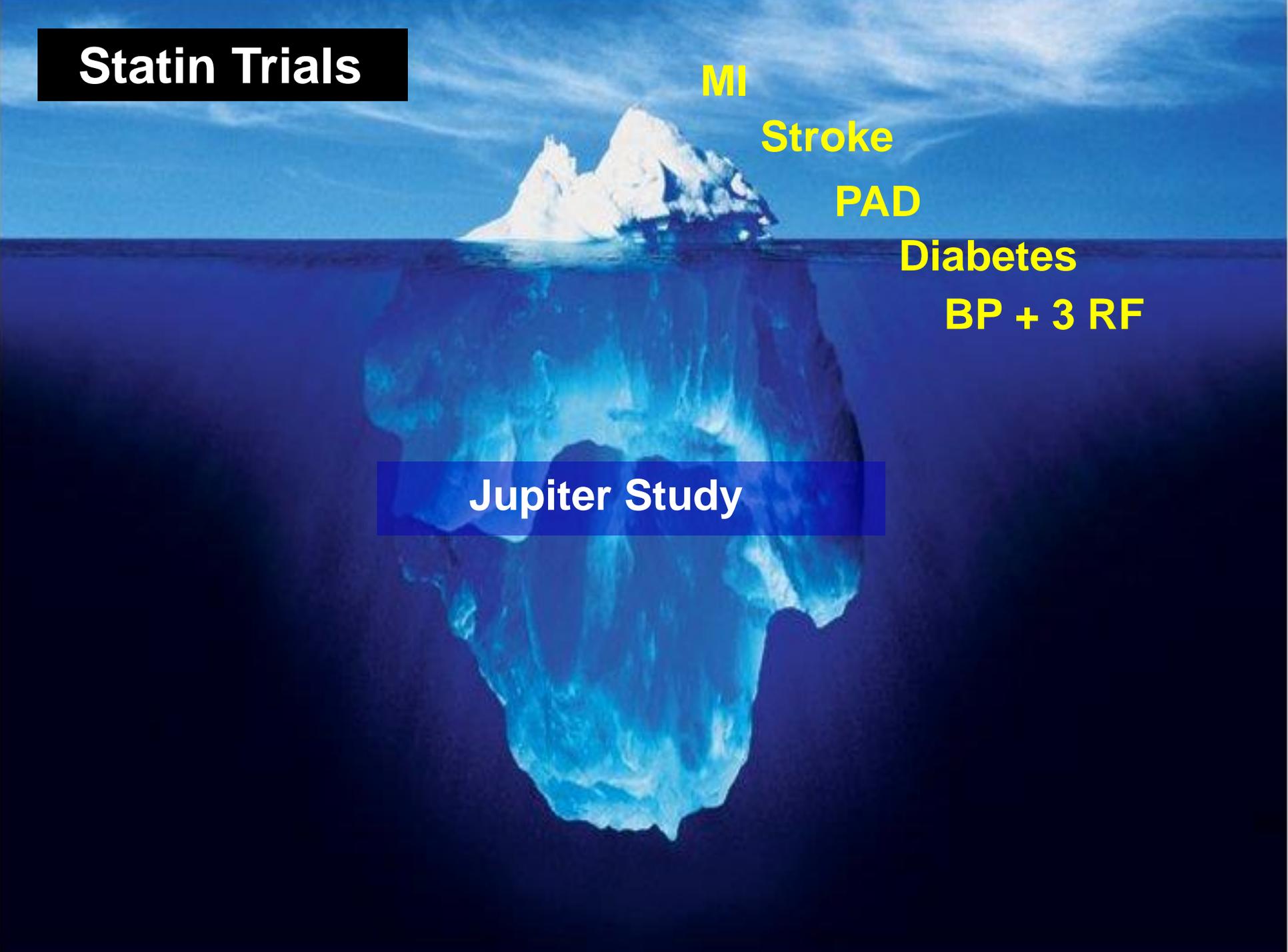
JUPITER Study

Average LDL 108 mg/dL -> 54 mg/dL (-50%) / 2 yrs

Patients (n=17,802)

Men ≥50 years
Women ≥60 years

No history of CVD

**LDL-C< 130 mg/dL**

TG < 500 mg/dL
hsCRP ≥ 0.2 mg/dL

Rosuvastatin 20 mg (n=8,901)

Placebo (n=8,901)

Death, MI, Stroke, Revasc.

Ridker PM et al. *NEJM* 2008; 359: 2195–2207

JUPITER trial results

Relative risk reduction (%)

Primary: -44% P<0.00001
MI: -54% P=0.0002
Stroke: -48% P=0.002
Revasc*: -46% P<0.0001
Angina: -41% P=0.09
Death: -20% P=0.02

STOP
1.9 yrs

* Revascularization

Adapted from Ridker PM et al. N Engl J Med 2008;359:2195–207
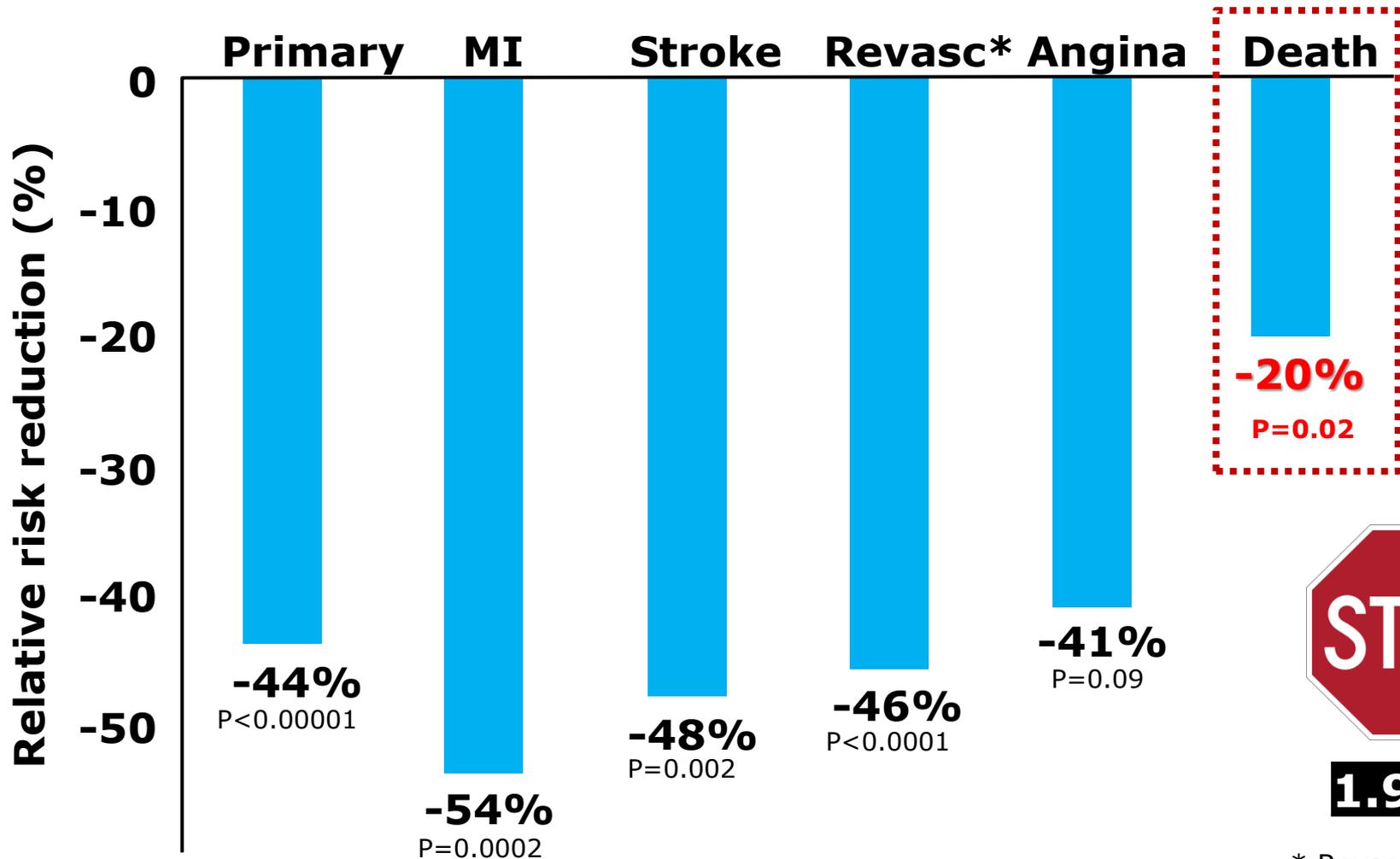
JUPITER sub-analysis : high risk vs. low risk

Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
Sex			0.80
Male	11,001		
Female	6,801		
Age			0.32
≤65 yr	8,541		
>65 yr	9,261		
Smoker			0.63
Yes	2,820		
No	14,975		
Race or ethnic group			0.57
White	12,683		

Framingham risk score

≤10%	8,882	
>10%	8,895	

ATP-III risk factor

0	6,375	
≥1	11,399	

Framingham risk score			0.99
≤10%	8,882		
>10%	8,895		
ATP-III risk factor			0.43
0	6,375		
≥1	11,399		
Time of event			0.56
≤24 mo	17,802		
>24 mo	7,765		
All participants	17,802		

0.25 0.50 1.00 2.00 4.00

Rosuvastatin Better ← → Placebo Better

Established evidence of "Lower is Better"

Rx - Statin therapy
Pl – Placebo
Pra – pravastatin
Atv – atorvastatin
Sim - simvastatin

Secondary Prevention

Primary Prevention

4S - Pl
4S - Rx
LIPID - Pl
CARE - Pl
LIPID - Rx
CARE - Rx
IDEAL-Sim
HPS - Rx
TNT – Atv10
HPS - Pl
PROVE-IT - Pra
TNT – Atv80
IDEAL-Atv
PROVE-IT – Atv
WOSCOPS – Pl
AFCAPS - Pl
AFCAPS - Rx
WOSCOPS - Rx
MEGA-Pl
ASCOT-PL
MEGA-Rx
JUPITER-Rosu
ASCOT - Rx
JUPITER-Pl

Event rate (%)

LDL-C achieved mg/dL (mmol/L)

40 (1.0) 60 (1.6) 80 (2.1) 100 (2.6) 120 (3.1) 140 (3.6) 160 (4.1) 180 (4.7) 200 (5.2)

Exp Opin Emerg Drugs 2004;9(2):269–279, *N Engl J Med* 2005;352:1425–1435. *JAMA* 2005;294:2437; *Lancet* 2006;368:1155

Use the strength of Statin by RCTs

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% to <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*

Pleiotropic effect of statin
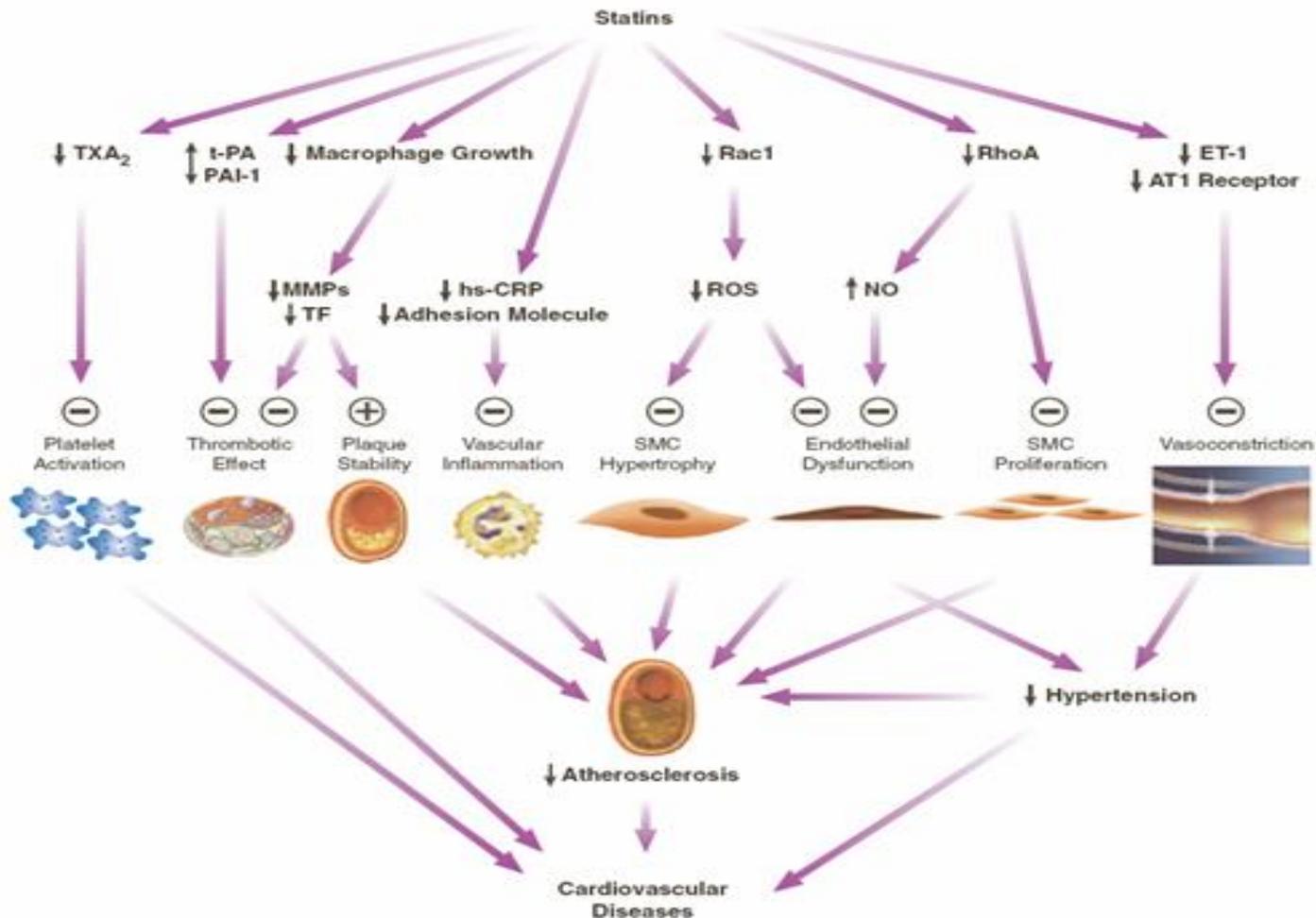
Effects of statins on glucose homeostasis & NODM

Safety profile of statins

Generally well-tolerated[1]

Low incidence of side-effects, such as muscle aches and increase in liver enzymes[1]

Linked to the development of incident diabetes[1], but the risk is small and of no clear practical evidence[2]

1. Bhatia L, et al. *Evidence-Based Med.* 2010;15(3):84–85.
2. Sampson UK, et al. *Curr Opin Cardiol.* 2011;26(4):342–347.

Statin safety – News clipping

New concern for Statins

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

1. Removal of the recommendation for routine monitoring of liver enzymes

2. Reports of increased blood glucose and glycosylated hemoglobin (HbA1c) levels

New contraindications and dose limitations

All statins could induce New-Onset DM

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 Events	Statin Rate	Placebo or control Events	Placebo or control Rate	OR (95% CI)	Weight (%)
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%

0·5   1·0   2·0

Naveed Sattar et al., Lancet 2010;375:735-42

Baseline fasting glucose levels to be assessed before using statins

- Statins have individual effects on glycemic control[1]

- Statins can increase FPG in both diabetes and non-diabetes patients[2]

- Only atorvastatin and not pravastatin or pitavastatin have negative effect on glycemic control[1]

- Baseline fasting glucose levels are to be assessed before using statins[2]

Pitavastatin 2 mg/day   Pravastatin 10 mg/day
Atorvastatin 10 mg/day

Fasting Plasma Glucose

NS

*

NS

mg/dL

300
250
200
150
100
50
0

0   3 months

Mean ± SD
*P < .001
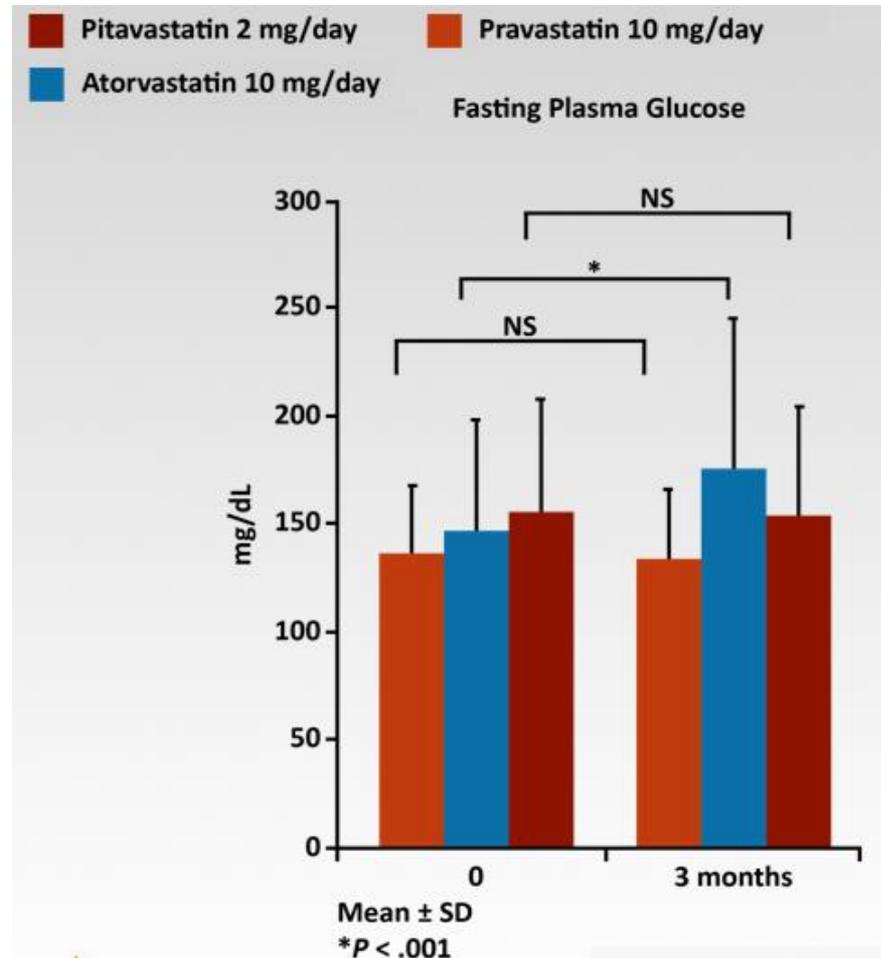
1. Yamakawa T, et al. J Atheroscler Thromb. 2008;15:269–275.
2. Sukhija R, et al. J Investigative Med. 2009;57(3):495–499.

Age, independent risk factor for statin-induced New-Onset DM

Age

BMI
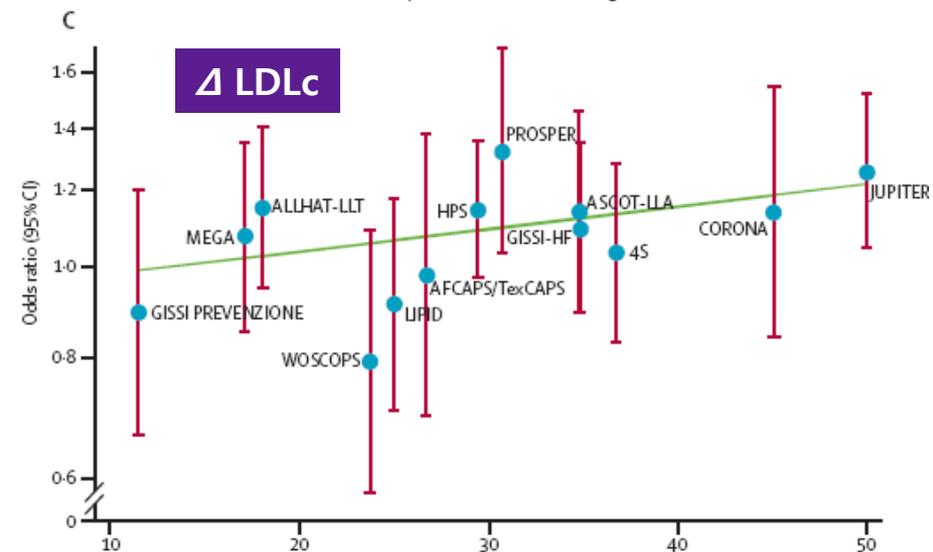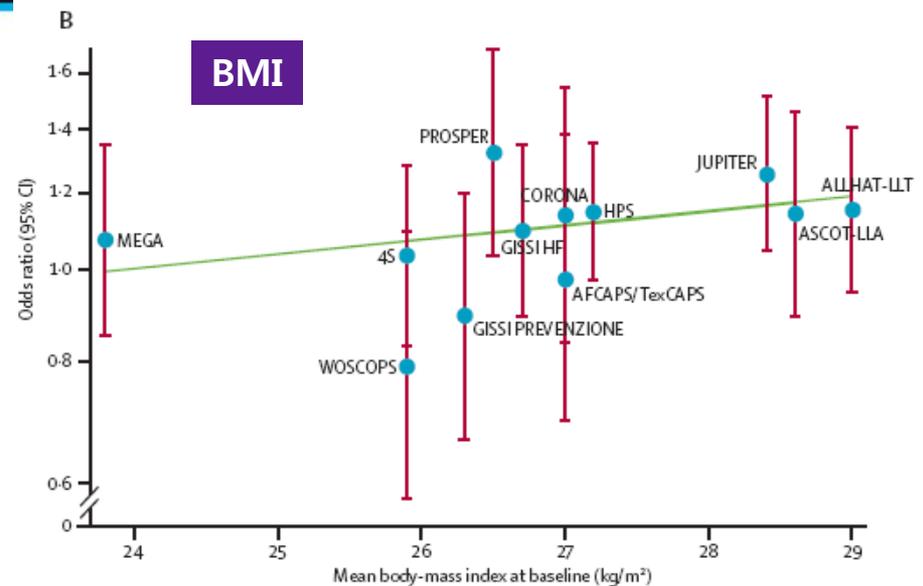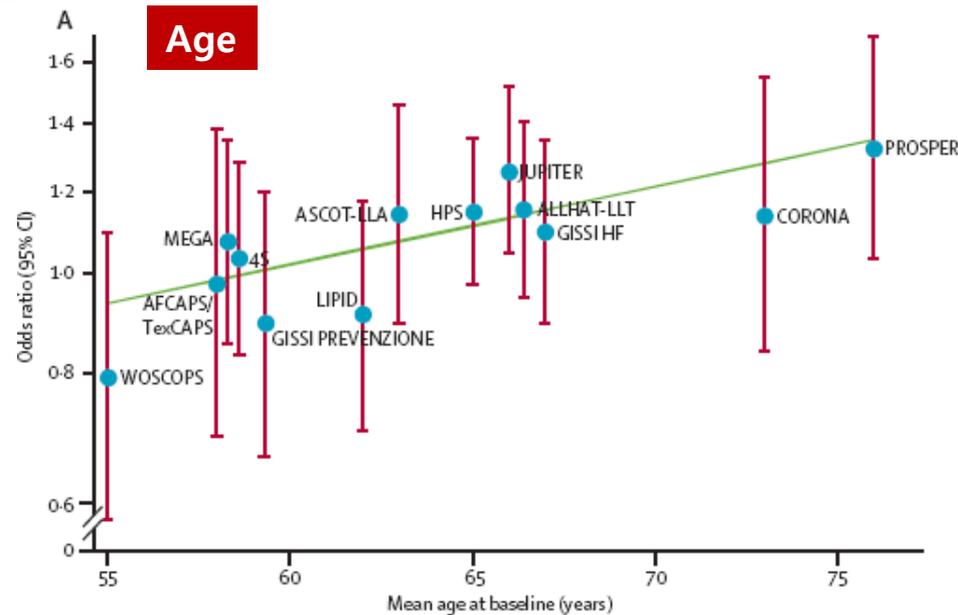
Δ LDLc

Meta-regression
Age, *p* = 0.019
BMI, *p* = 0.177
ΔLDL-C, *p* = 0.102

Naveed Sattar et al., Lancet 2010;375:735-42

Intensive-dose vs. moderate-dose statin Tx

INCIDENT DIABETES

Statin type	Intensive Cases / n (%)	Standard dose Cases / n (%)		OR (95% CI)
Atorvastatin 80 mg				
PROVE IT-TIMI 22 (18)	101/1707 (5.9%)	99/1688 (5.9%)		1.01 (0.76, 1.34)
TNT (15)	418/3798 (11.0%)	358/3797 (9.4%)		1.19 (1.02, 1.38)
IDEAL (16)	240/3737 (6.4%)	209/3724 (5.6%)		1.15 (0.95, 1.40)
Subtotal pooled odds ratio				1.15 (1.03, 1.28)
Simvastatin 80 mg				
A to Z (17)	65/1768 (3.7%)	47/1736 (2.7%)		1.37 (0.94, 2.01)
SEARCH (5)	625/5398 (11.6%)	587/5399 (10.9%)		1.07 (0.95, 1.21)
Subtotal pooled odds ratio				1.13 (0.93, 1.38)
Overall pooled odds ratio p-value for heterogeneity = 0.562				1.12 (1.04, 1.22)

INCIDENT CVD

	Intensive Cases / n (%)	Standard dose Cases / n (%)		OR (95% CI)
Atorvastatin 80 mg				
	315/1707 (18.4%)	355/1688 (21.0%)		0.85 (0.72, 1.01)
	647/3798 (17.0%)	830/3797 (21.9%)		0.73 (0.65, 0.82)
	776/3737 (20.8%)	917/3724 (24.6%)		0.80 (0.72, 0.89)
Subtotal pooled odds ratio				0.78 (0.73, 0.85)
Simvastatin 80 mg				
	212/1768 (12.0%)	234/1736 (13.5%)		0.87 (0.72, 1.07)
	1184/5398 (21.9%)	1214/5399 (22.5%)		0.97 (0.88, 1.06)
Subtotal pooled odds ratio				0.95 (0.88, 1.03)
Overall pooled odds ratio p-value for heterogeneity < 0.001				0.84 (0.75, 0.94)

Preiss et al. JAMA 2011;305:2556-64

High-risk subgroups are more prone to new-onset T2DM

High-risk group of patients

- Old age
- Baseline fasting glucose >100 mg/dL
- Fasting triglycerides >150 mg/dL
- BMI >30 kg/m^2
- History of hypertension

Number of risk factors=risk severity

1. Waters DD, et al. JACC. 2011;57:1535–1545.

Statins, Risk of Diabetes, and Implications on Outcomes in the General Population

Kang-Ling Wang, MD,*†‡ Chia-Jen Liu, MD,† Tze-Fan Chao, MD,†‡ Chi-Ming Huang, MD,†‡
Cheng-Hsueh Wu, MD,†‡ Su-Jung Chen, MD,†‡ Tzeng-Ji Chen, MD, PHD,§‖
Shing-Jong Lin, MD, PHD,*†‡¶ Chern-En Chiang, MD, PHD*†‡¶#

Taipei, Taiwan

Diabetes

MACE

15%

9%

In-hospital death

39%
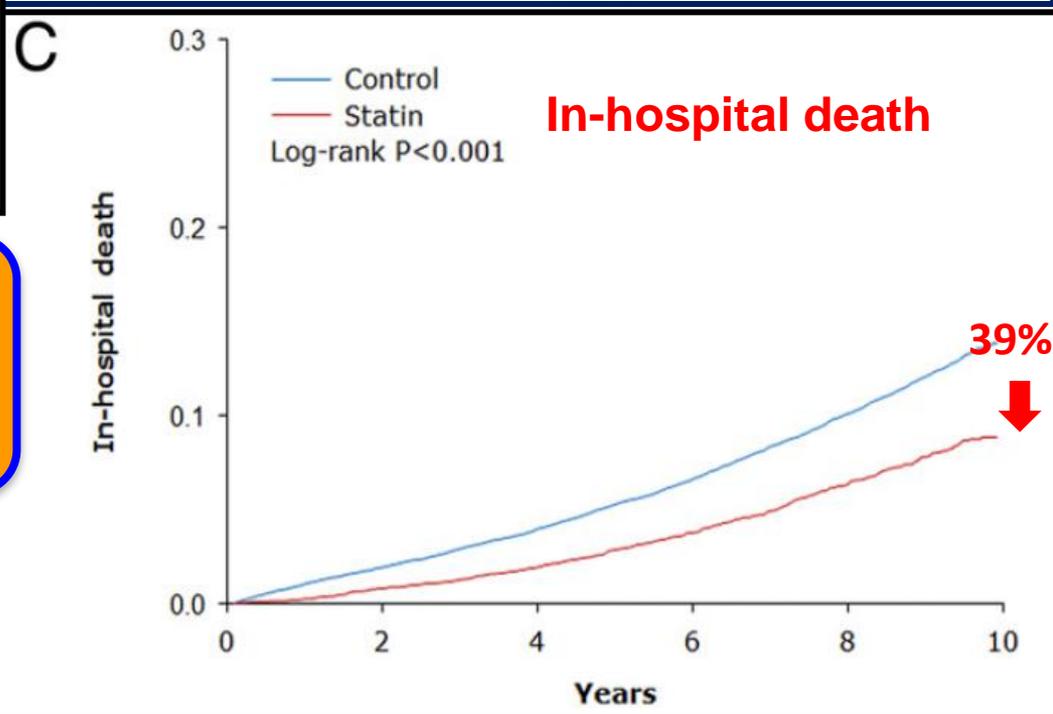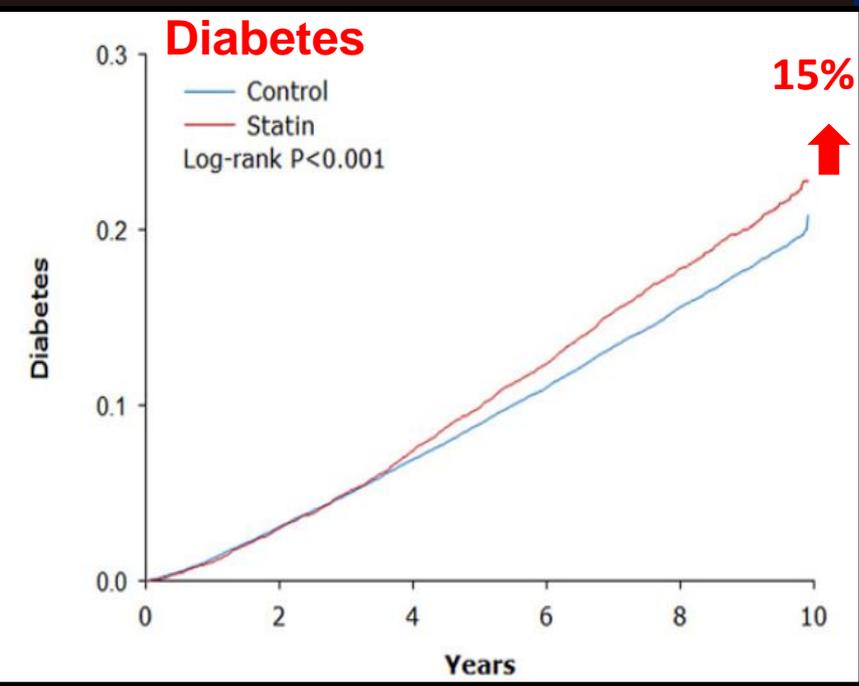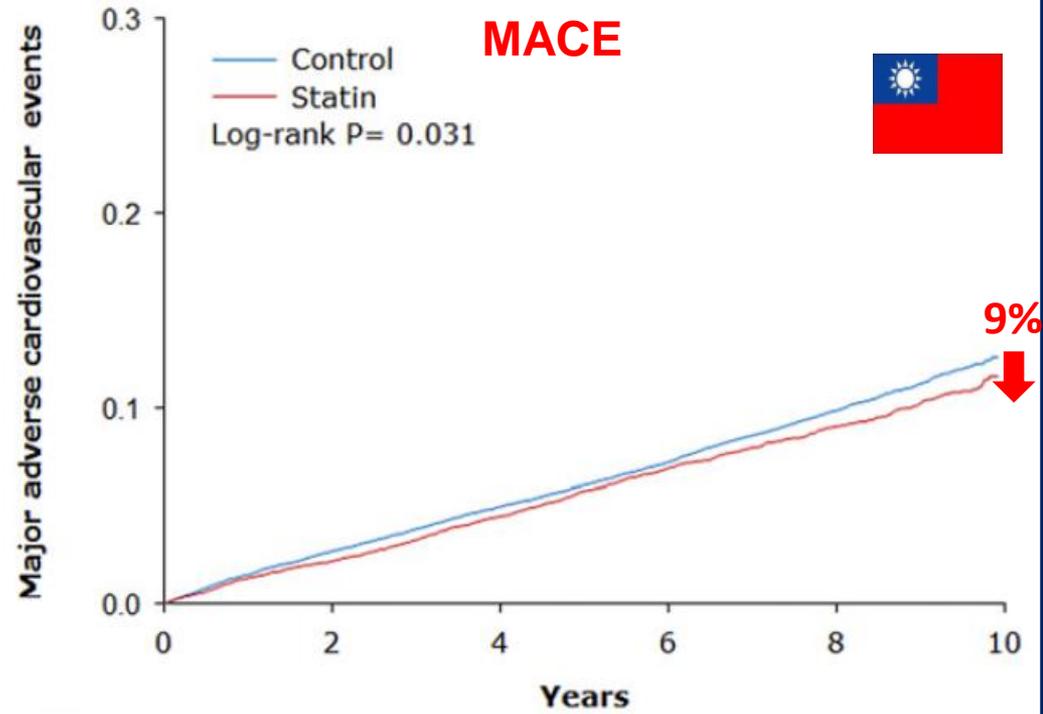
Risk of diabetes was increased after statins, but outcomes were favorable

Table 2	Univariate and Multivariate Analyses of In-Hospital Deaths According to Status of Diabetes and Prior Exposure of Statins			
	nonDM nonStatin	**DM nonStatin**	**DM Statin**	**nonDM Statin**
Overall cohort				
N	29,332	4,316	1,387	7,025
Crude	Reference	1.70 (1.51–1.91)	1.38 (1.10–1.73)	0.59 (0.54–0.66)
Adjusted*	Reference	1.91 (1.70–2.15)	1.54 (1.23–1.92)	0.58 (0.53–0.64)
High-risk cohort†				
N	15,481	2,206	728	3,720
Crude	Reference	1.45 (1.25–1.69)	1.11 (0.83–1.49)	0.61 (0.54–0.68)
Adjusted*	Reference	1.69 (1.45–1.96)	1.31 (0.98–1.75)	0.62 (0.55–0.70)
Secondary prevention cohort				
N	13,733	1,986	652	3,266
Crude	Reference	1.43 (1.22–1.67)	1.08 (0.79–1.47)	0.61 (0.53–0.69)
Adjusted*	Reference	1.68 (1.44–1.98)	1.28 (0.94–1.73)	0.62 (0.55–0.71)

High risk

Secondary prevention

Impact of low dose atorvastatin on development of new-onset diabetes mellitus in Asian population : Three-year clinical outcomes

Variables, n (%)	LDA (n=409)	Control (n=409)	P-value
Cumulative incidence of NODM	24 (5.9)	13 (3.2)	0.064
Follow up days,mean±SD	962 ± 291	956 ± 295	0.802
Clinical outcomes up to 3 years			
Mortality	3 (0.7)	4 (1.0)	1.000
Cardiac death	1 (0.2)	1 (0.2)	1.000
Myocardial infarction	1 (0.2)	1 (0.2)	1.000
Cerebrovascular accidents	1 (0.2)	4 (1.0)	0.373
MACCE	5 (1.2)	6 (1.5)	1.000

N=3566, PSM; 409 pairs
LDA; 10-20mg

Park JY, Rha SW et al. Int J Cardiol 2015

Kaplan-Meier curves for the cumulative probabilities of NODM

Park JY, Rha SW et al. Int J Cardiol 2015
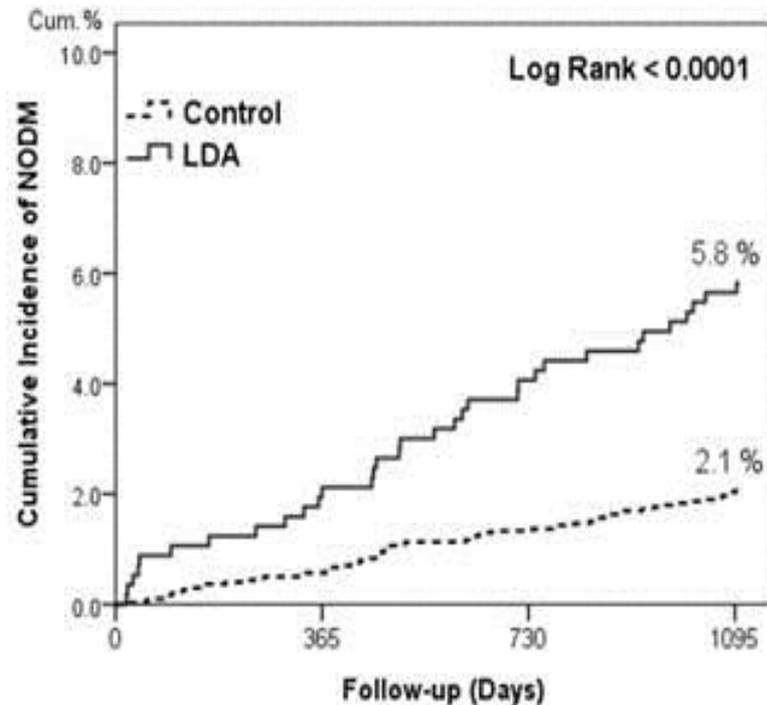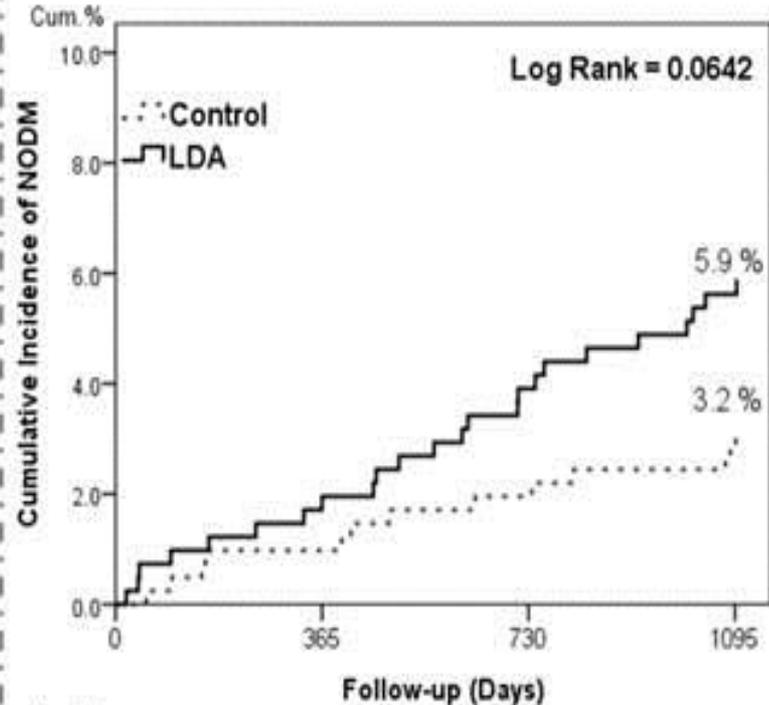
Impact of Statin Use on Development of New-onset Diabetes Mellitus in Asian Population

Cumulative Clinical Outcomes up to 3-year

Variable, N (%)	Overall Patients				After Propensity Score Matched			
	All Patients (n=10994)	Statin Use (n=2324)	No Use (n=8670)	P Value	All Patients (n=3398)	Statin Use (n=1699)	No Use (n=1699)	P Value
New-onset diabetes	227 (2•0)	116 (4•9)	111 (1•2)	< 0•001	121 (3•5)	80 (4•7)	41 (2•4)	< 0•001
Mortality	66 (0•6)	18 (0•7)	48 (0•5)	0•221	31 (0•9)	8 (0•4)	23 (1•3)	0•007
Cardiac death	21 (0•1)	10 (0•4)	11 (0•1)	0•006	10 (0•2)	3 (0•1)	7 (0•4)	0•205
Myocardial infarction	22 (0•3)	14 (1•0)	8 (0•1)	< 0•001	10 (0•5)	4 (0•4)	6 (0•6)	0•755
Cerebrovascular accidents	37 (0•3)	11 (0•4)	26 (0•2)	0•200	21 (0•6)	6 (0•3)	15 (0•8)	0•049
MACCEs	98 (0•8)	34 (1•4)	64 (0•7)	0•001	46 (1•3)	15 (0•8)	31 (1•8)	0•018

Rha SW et al.

Risk of NODM and MACCEs by Statin Use

Description	Patients. No.	NODM		MACCEs	
		HR (95% CI)	P Value	HR (95% CI)	P Value
Unadjusted HR	10 994	4•05 (3•10-5•27)	< 0•001	1•99 (1•31-3•03)	0•001
Adjusted HR (95% CI)					
Multivariate	10 994	2•70 (1•99-3•67)	< 0•001	0•70 (0•42-1•18)	0•191
Propensity score	10 994	2•71 (1•94-3•79)	< 0•001	0•50 (0•29-0•87)	0•015
Propensity score matched	3 398	1•99 (1•36-2•92)	< 0•001	0•47 (0•25-0•89)	0•020

Rha SW et al.

Cumulative Incidence of NODM, MACCEs and NODM related MACCEs up to 3-year.

Rha SW et al.
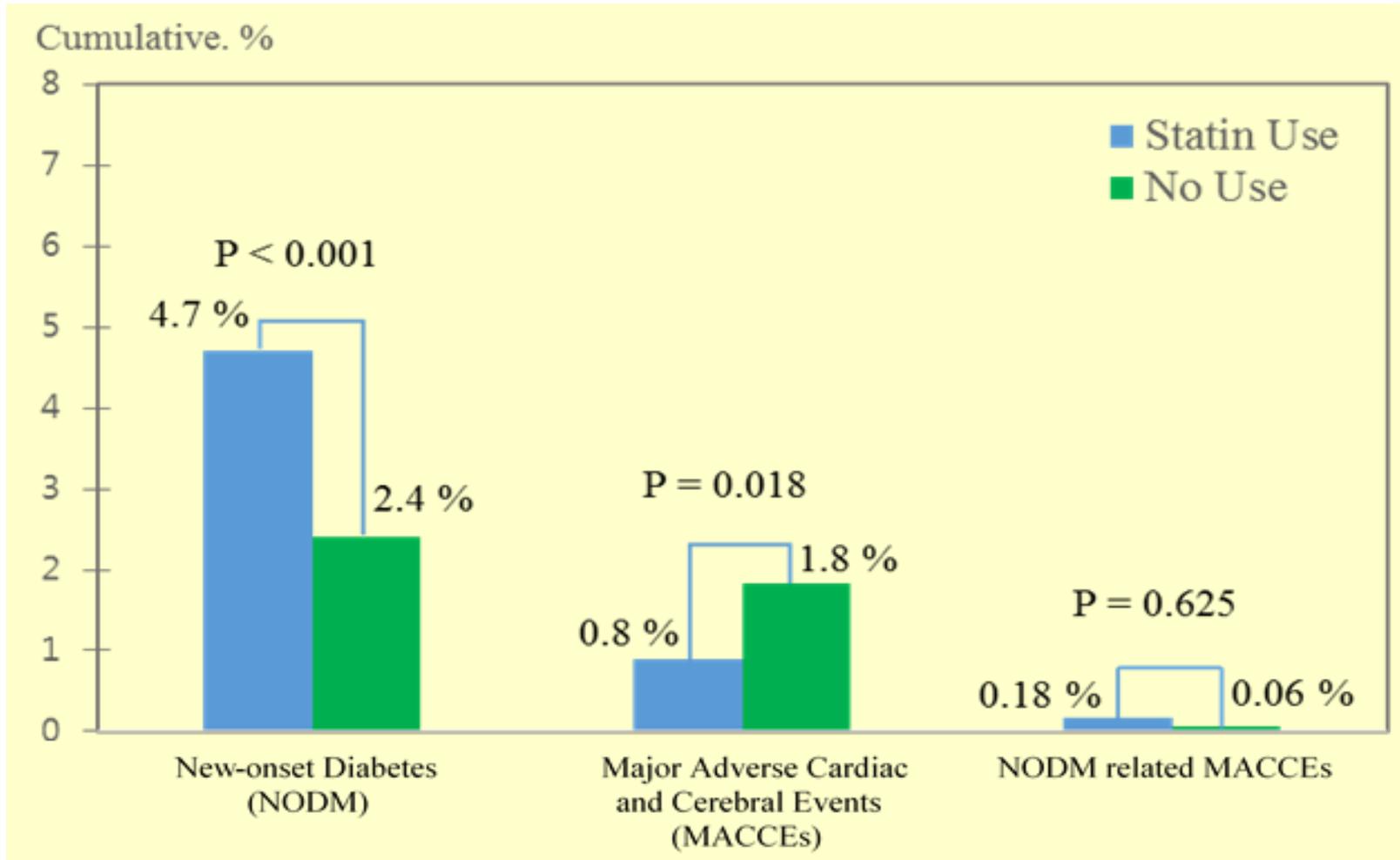
CV benefit of intensive-dose therapy outweigh moderate-dose therapy

	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: $I^2=74\%$; $P=.004$			
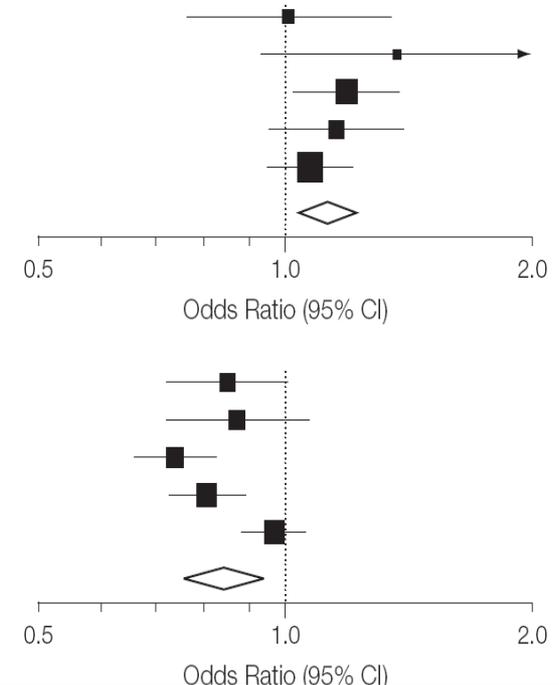
Intensive-dose statin therapy increases risk for incident diabetes mellitus but reduces cardiovascular events compared with moderate-dose therapy

Preiss et al. JAMA 2011;305:2556-2564

Statin risk summary
: CV benefits outweigh risk

Risk of development of incident diabetes

CV benefits outweigh risks

- **8 times more likely to prevent CV events than cause one case of diabetes[1]**
- **34% CV risk reduction in patients with IFG[2]**

Statin use is encouraged but with vigilance, particularly in high-risk patients

1. Bhatia L, et al. *Evidence-Based Med.* 2010;15(3):84–85.
2. Sampson UK, et al. *Curr Opin Cardiol.* 2011;26(4):342–347.

Statins are all the same?
: Efficacy & Safety profile on NODM

Statins are all the same?

Fungal Statins

Lovastatin

Simvastatin

Pravastatin

Synthetic Statins

Rosuvastatin
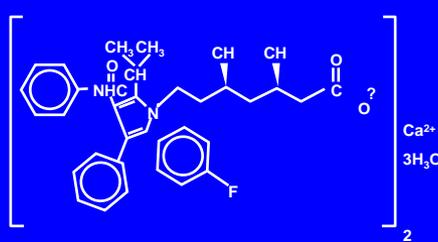
Atorvastatin

Fluvastatin

Cerivastatin

Furberg CD. Circulation. 1999;99:185-188.

Good efficacy & Safety profile on Rosuvastatin

의약품의 안전성프로파일과 관련한 상세한 정보는 각 의약품 국내 허가사항을 참고하시기 바랍니다.
크레스토의 국내 최고 허가용량은 20 mg이며 한국아스트라제네카는 40 mg 처방을 권장하지 않습니다.

H. Bryan Brewer, Jr., MD. Am J Cardiol 2003;92(suppl):23K-29K

Hydrophilic statins are preferred over lipophilic statins

Adversely affect carbohydrate metabolism
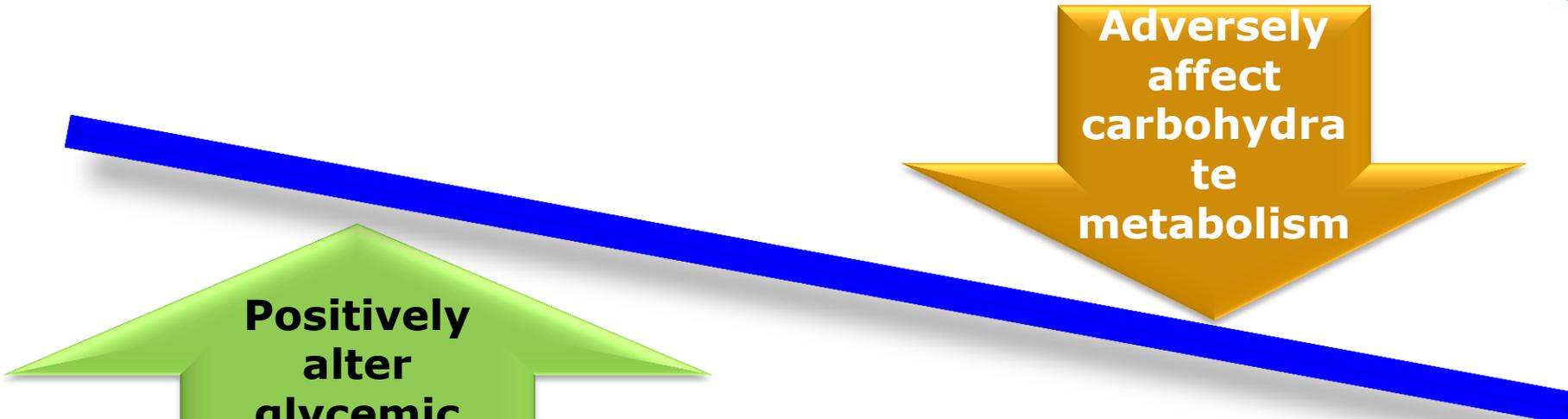
Positively alter glycemic control with traits such as

- **Hypotriglyceridemic capacity**
- **Endothelial-dependent increase in pancreatic islet blood flow**
- **Anti-inflammatory properties**
- **Capacity to alter circulating levels of adipokines**

Hydrophilic statins (such as rosuvastatin, pravastatin and pitavastatin) have preferable effect over lipophilic statins (such as atorvastatin and simvastatin).

1. Kostapanos MS, et al. Curr Vasc Pharmacol. 2010;8(5):612–631.

Proposed Mechanism of NODM by Statins

1. *Statins inhibited glucose induced calcium (Ca^{2+}) signaling in pancreatic islet β-cells* by directly blocking L-type Ca^{2+} channels, result in impaired insulin secretion.

2. *Within the cell, insulin signaling and via glucose transporter 4 (GLUT4) transport can be altered by changes in IRS-1, Akt, Rab4, Ras, phosphorylation of the IR β-subunit, or membrane fraction of RhoA,* all of which have been shown to be inhibited by statin therapy.

3. *The lipophilic statins inhibit the synthesis of isoprenoid and suppressing ubiquinone (CoQ10) biosynthesis* and thus delaying formation of ATP by pancreatic β-cells leading to impaired insulin secretion, inhibiting glucose-induced insulin secretion from pancreatic islets, reducing sensitivity to insulin, altering glycemic control by decreasing various isoprenoids that enhance glucose uptake via GLUT4 in adipocytes.

4. *Activation of the NOD-like receptor family, pyrin domain containing (NLRP)3/caspase-1 inflammasome* promotes insulin resistance, and statins activate the NLRP3 inflammasome in various immune and metabolic cells of adipose tissue, independently of potency or lipophilic properties.

5. *Other mechanisms* exists for decreased adipocyte differentiation, dolichol reductions, adiponectin and leptin decreases, as well as new avenues, such as UCP3 changes and miRNA inhibition.

Brault M et al. Metabolism: clinical and experimental 2014.
Koh KK. et al. Circulation 2013;127:e837.
Henriksbo BD et al. Diabetes, 2014;63:3742-7.

SUBARU Study - Japan
(Atorvastatin 10mg Vs Switching to Rosuvastatin 5mg)

314   *Journal of Atherosclerosis and Thrombosis*   Vol.15, No.6

Original Article

Superior Benefit of Aggressive Lipid-Lowering Therapy for High-Risk Patients Using Statins: the SUBARU Study

—More Hypercholesterolemic Patients Achieve Japan Atherosclerosis Society LDL-C Goals with Rosuvastatin Therapy than with Atorvastatin Therapy

Masahiko Kurabayashi[1], Tsutomu Yamazaki[2], and the SUBARU Study Group

[1]Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, Maebashi, Japan
[2]Department of Clinical Epidemiology & Systems, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Study Design

At least 4weeks

Atorvastatin 10mg/day

Atorvastatin 10mg/day

Rosuvastatin 5mg/day

Eligibility assessment
Informed consent

0 week
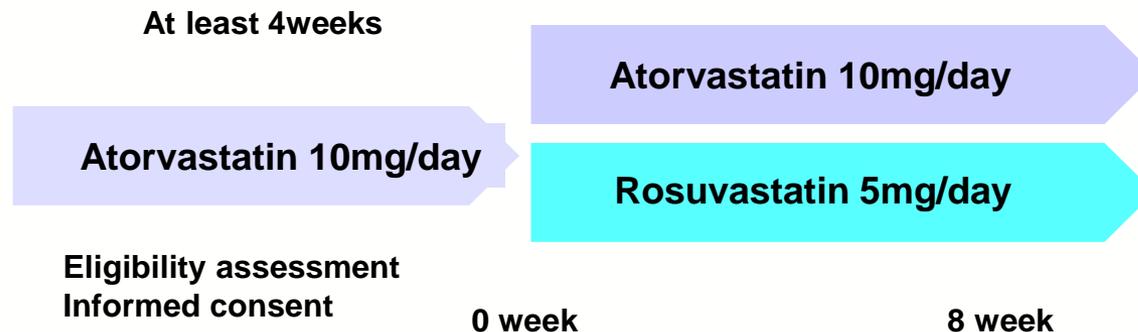
8 week

LDL–C Reduction Efficacy
(Atorvastatin 10mg Vs Switching to Rosuvastatin 5mg)
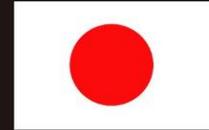
Achievement of JAS2002 GL LDL-C goals at 8 weeks

Achieving the LDL-C Goals(%)

100

P<0.01
80.3

67.3

50

0

n

Atorvastatin 10mg
205

Rosuvastatin 5mg
108
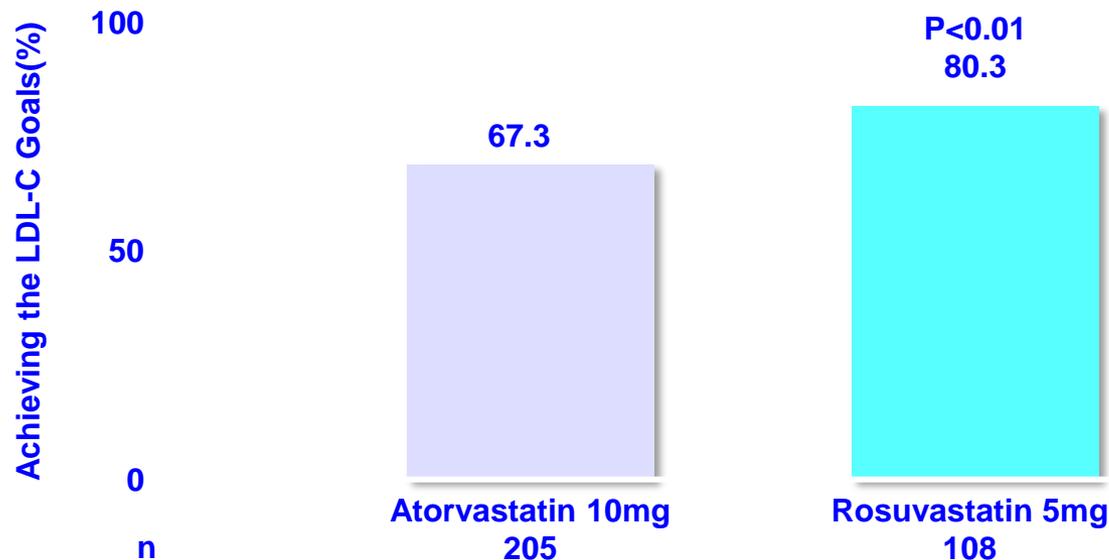
LDL-C goal: Category B3(<120mg/dL): B4(<120mg/dL);C(<100mg/Dl)
Fisher's exact test
P values show differences between the rosuvastatin and atorvastatin groups

Kurabayashi et al. J Atherosler Thromb, 2008; 15:314-323.

Percent Change of Lipid Parameter & Fasting Plasma Glucose Level
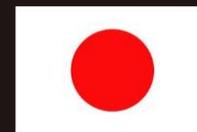
Percent changes of lipids and other parameters from baseline to 8 weeks

	Atorvastatin 10 mg (mean ± SD)			Rosuvastatin 5 mg (mean ± SD)		
	Baseline $n=207$	8 weeks $n=205$	% change from baseline $n=205$	Baseline $n=207$	8 weeks $n=198$	% change from baseline $n=198$
LDL-C (mg/dL)	109.3 ± 30.6	106.7 ± 28.7	− 1.2 ± 14.7	102.9 ± 25.1	95.3 ± 24.2	− 6.0 ± 17.0 [**]
TC (mg/dL)	192.3 ± 34.8	187.4 ± 32.9	− 2.2 ± 10.3	186.1 ± 28.8	178.5 ± 28.5	− 3.3 ± 11.6
HDL-C (mg/dL)	60.1 ± 15.3	58.8 ± 14.6	− 1.7 ± 11.7	60.9 ± 17.6	60.7 ± 17.7	0.1 ± 12.2
TG (mg/dL)	130.9 ± 72.2	129.7 ± 89.5	5.2 ± 43.5	128.5 ± 67.4	136.7 ± 80.4	12.9 ± 48.2
LDL-C/HDL-C ratio	1.94 ± 0.74	1.94 ± 0.75	1.4 ± 16.7	1.84 ± 0.71	1.70 ± 0.64	− 5.0 ± 20.3 [**]
Adiponectin (μg/mL)	12.3 ± 8.3	11.8 ± 7.1	− 2.3 ± 18.5	12.1 ± 7.4	11.3 ± 7.8	− 3.3 ± 20.7
sd-LDL	0.33 ± 0.03	0.35 ± 0.04	4.5 ± 8.6	0.33 ± 0.03	0.35 ± 0.03	4.6 ± 9.0
hs-CRP (mg/L)	1.59 ± 6.31	1.23 ± 3.34	0.13 ± 0.91	0.95 ± 1.47	1.10 ± 2.43	0.14 ± 0.81
Fasting plasma glucose (mg/dL)	119.0 ± 32.7	121.4 ± 35.1	3.3 ± 20.4	124.4 ± 41.4	120.6 ± 38.8	− 2.2 ± 16.2 [**]

SD: standard deviation
P values show differences between the rosuvastatin and atorvastatin groups.
t-test, [**]: $p < 0.01$

Kurabayashi et al. J Atherosler Thromb, 2008; 15:314-323.

JUPITER design

Average LDL 108 mg/dL

Patients (n=17,802
Men ≥50 years
Women ≥60 years
No history of CVD
**LDL-C< 130 mg/dL**
TG < 500 mg/dL
hsCRP ≥2 mg/L

Rosuvastatin 20 mg (n=8,901)

Placebo (n=8,901)

Death, MI, Stroke, Bypass

Ridker PM et al. *NEJM* 2008; 359: 2195–2207

JUPITER : Primary CV outcome benefit

**JUPITER study –
Primary Endpoint**

HR 0.56, 95%CI 0.46-0.69
P < 0.00001

Placebo

Relative risk reduction **44%**

Rosuvastatin 20mg

Cumulative Incidence

Follow-up (years)

**JUPITER study –
Any death**

HR 0.80, 95%CI 0.67-0.97
P = 0.02

Placebo

Relative risk reduction **20%**

Rosuvastatin 20mg

Follow-up (years)

Ridker P et al. N Eng J Med 2008;359: 2195-2207
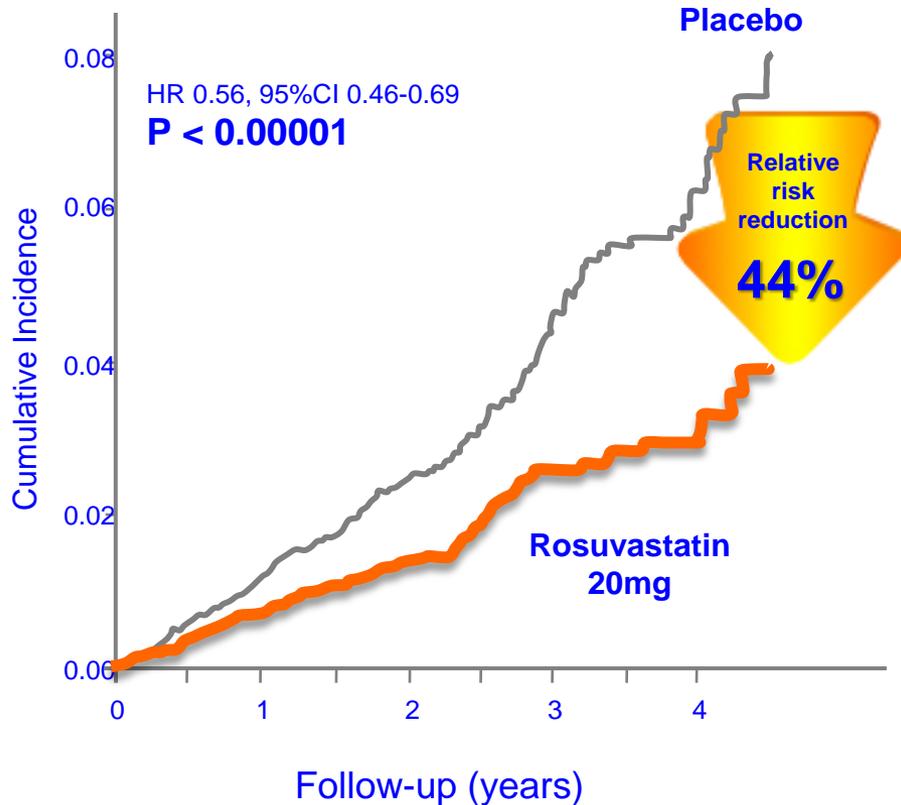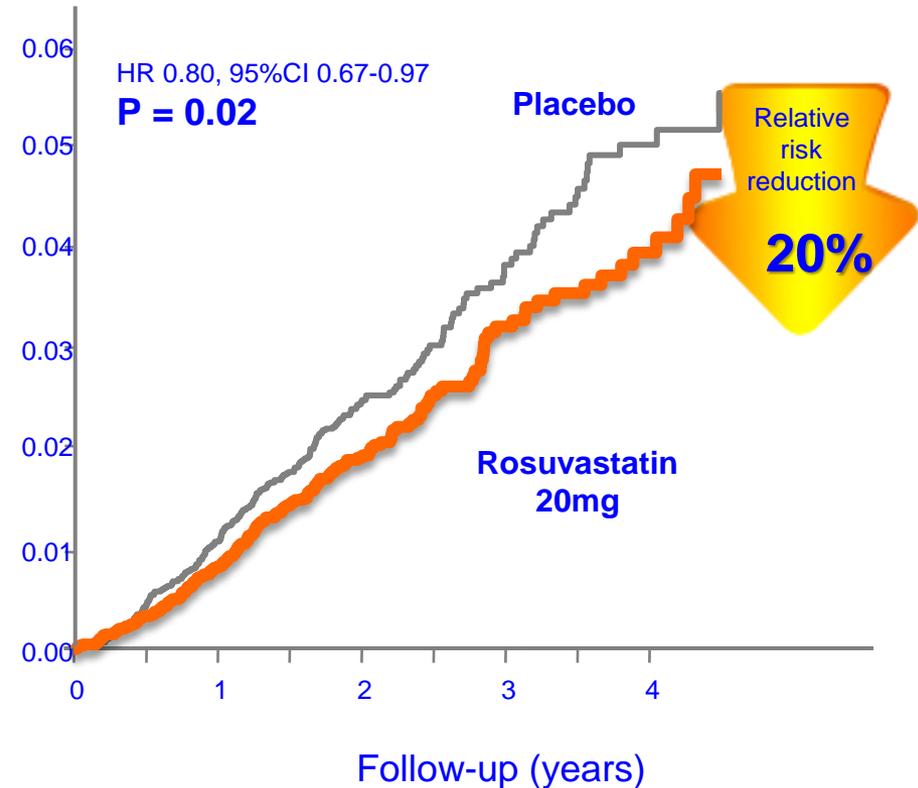
JUPITER
Tolerability and safety data

	Placebo	Rosuvastatin	p-value
[n=8901] [n=8901]			
Adverse Events, (%)			
Any serious adverse event	15.5	15.2	0.60
Muscle weakness, stiffness, pain	15.4	16.0	0.34
Myopathy	0.1	0.1	0.82
Rhabdomyolysis	0.0	<0.1*	----
Newly diagnosed cancer	3.5	3.4	0.51
Death from cancer	0.7	0.4	0.02
Gastrointestinal disorders	19.2	19.7	0.43
Renal disorders	5.4	6.0	0.08
Bleeding	3.1	2.9	0.45
Hepatic disorders	2.1	2.4	0.13
Other events, (%)			
Newly diagnosed diabetes**	2.4	3.0	0.01
Haemorrhagic stroke	0.1	0.1	0.44

*Occurred after trial completion; **physician reported newly diagnosed diabetes

# CV benefit of Rosuvastatin exceeds the diabetes risk
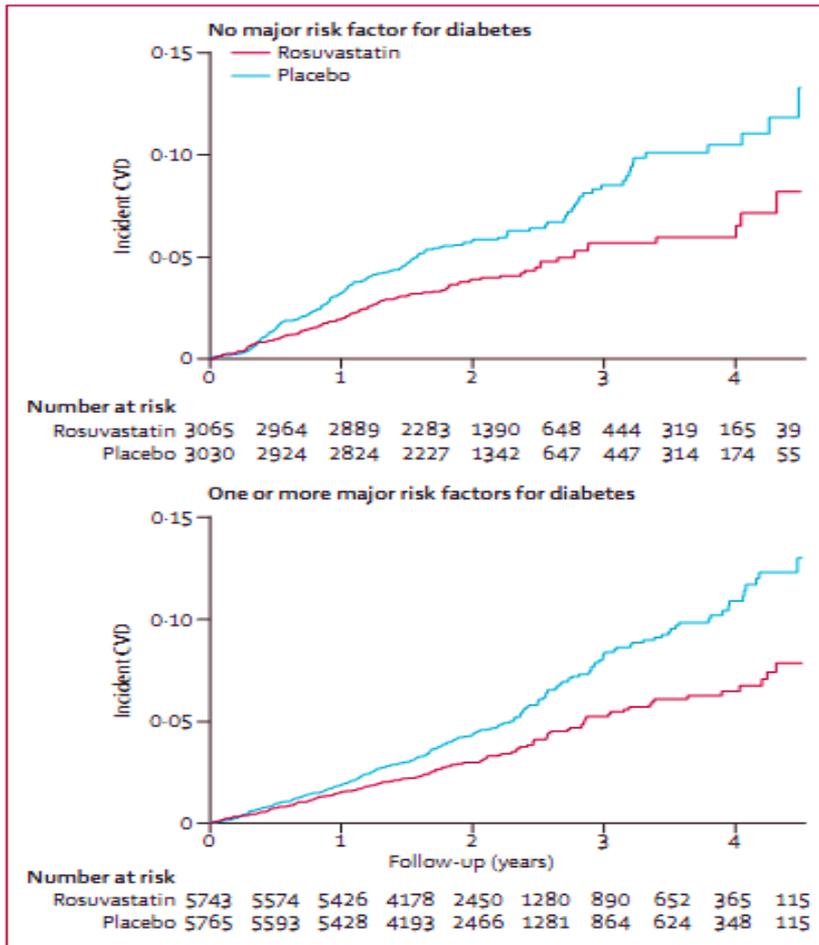
Figure 2: Cumulative incidence of cardiovascular events and total mortality in participants with and without major risk factors for diabetes
CVD=cardiovascular disease.
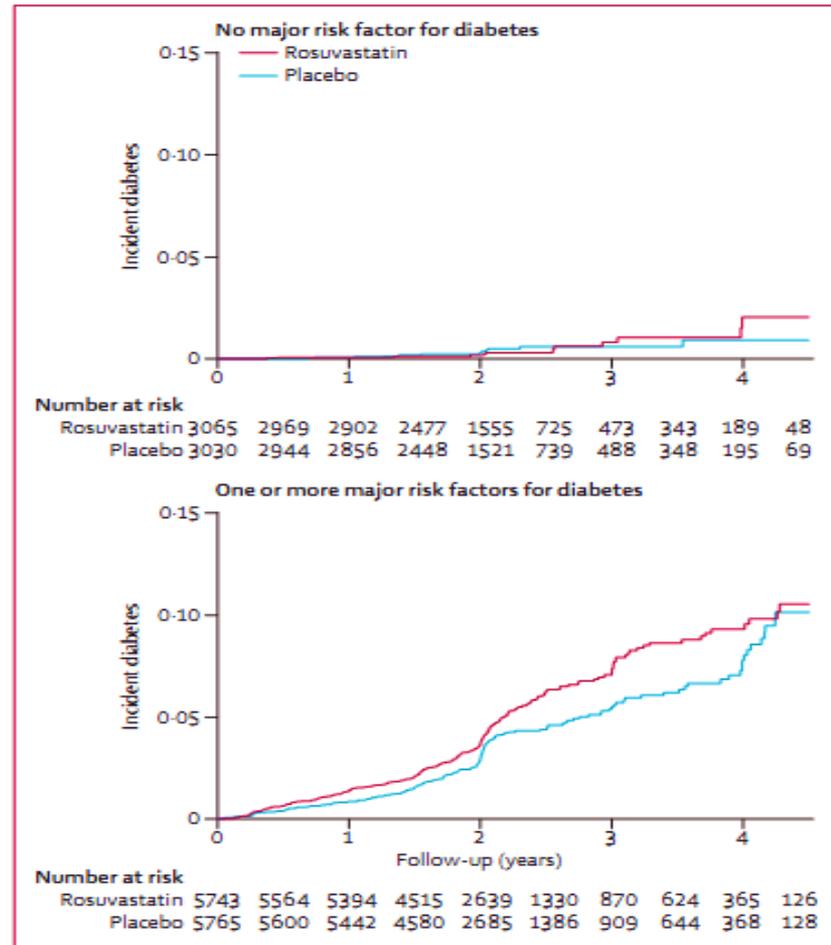
Figure 3: Cumulative incidence of diabetes in participants with and without major risk factors for diabetes

Ridker et al. Lancet. 2012;380:565–571.

Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial

Paul M Ridker, Aruna Pradhan, Jean G MacFadyen, Peter Libby, Robert J Glynn

Findings Trial participants with one or more major diabetes risk factor (n=11 508) were at higher risk of developing diabetes than were those without a major risk factor (n=6095). In individuals with one or more risk factors, statin allocation was associated with a 39% reduction in the primary endpoint (hazard ratio [HR] 0·61, 95% CI 0·47–0·79, p=0·0001), a 36% reduction in venous thromboembolism (0·64, 0·39–1·06, p=0·08), a 17% reduction in total mortality (0·83, 0·64–1·07, p=0·15), and a 28% increase in diabetes (1·28, 1·07–1·54, p=0·01). Thus, for those with diabetes risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. For trial participants with no major diabetes risk factors, statin allocation was associated with a 52% reduction in the primary endpoint (HR 0·48, 95% CI 0·33–0·68, p=0·0001), a 53% reduction in venous thromboembolism (0·47, 0·21–1·03, p=0·05), a 22% reduction in total mortality (0·78, 0·59–1·03, p=0·08), and no increase in diabetes (0·99, 0·45–2·21, p=0·99). For such individuals, a total of 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed. In analysis limited to the 486 participants who developed diabetes during follow-up (270 on rosuvastatin vs 216 on placebo; HR 1·25, 95% CI 1·05–1·49, p=0·01), the point estimate of cardiovascular risk reduction associated with statin therapy (HR 0·63, 95% CI 0·25–1·60) was consistent with that for the trial as a whole (0·56, 0·46–0·69). By comparison with placebo, statins accelerated the average time to diagnosis of diabetes by 5·4 weeks (84·3 [SD 47·8] weeks on rosuvastatin vs 89·7 [50·4] weeks on placebo).

Interpretation In the JUPITER primary prevention trial, the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including in participants at high risk of developing diabetes.

Diabetes risk by different statins - 6 years METSIM cohort study in Finland

Table 3 The association of simvastatin and atorvastatin treatment at baseline and their doses with insulin sensitivity (Matsuda ISI) and insulin secretion (DI) in non-diabetic participants in the cross-sectional METSIM study

Treatment/dose	Matsuda ISI					DI				
	n	Mean	SD	% change	p value (vs no statin)	n	Mean	SD	% change	p value (vs no statin)
No statin	6,569	7.31	4.3		-	6,569	166.5	73.3		-
Simvastatin	1,397	5.71	3.48	−21.9	<0.001***	1,397	153.8	66.4	−7.6	<0.001***
Atorvastatin	388	5.53	3.21	−24.4	<0.001***	388	154.1	71	−7.4	<0.001***
Simvastatin dose (mg/day)										
Low dose (10 or 20)	960	5.79	3.49	−20.8	<0.001***	960	155.5	66.8	−6.6	<0.001***
High dose (40 or 80)	384	5.45	3.35	−25.4	<0.001***	384	150.1	67.0	−9.8	<0.001***
Atorvastatin dose (mg/day)										
Low dose (10)	175	6.10	3.46	−16.6	0.001***	175	160.9	72.4	−3.4	0.580
High dose (20 or 40)	197	5.10	2.95	−30.2	<0.001***	197	149.1	71.5	−10.5	<0.001***

The reference group in each analysis is the group without statin treatment at baseline

***$p<0.004$

Diabetes risk by different statins
- 6 years METSIM cohort study in Finland

Henna et al. Diabetologia DOI 10.1007/s00125-015-3528-5
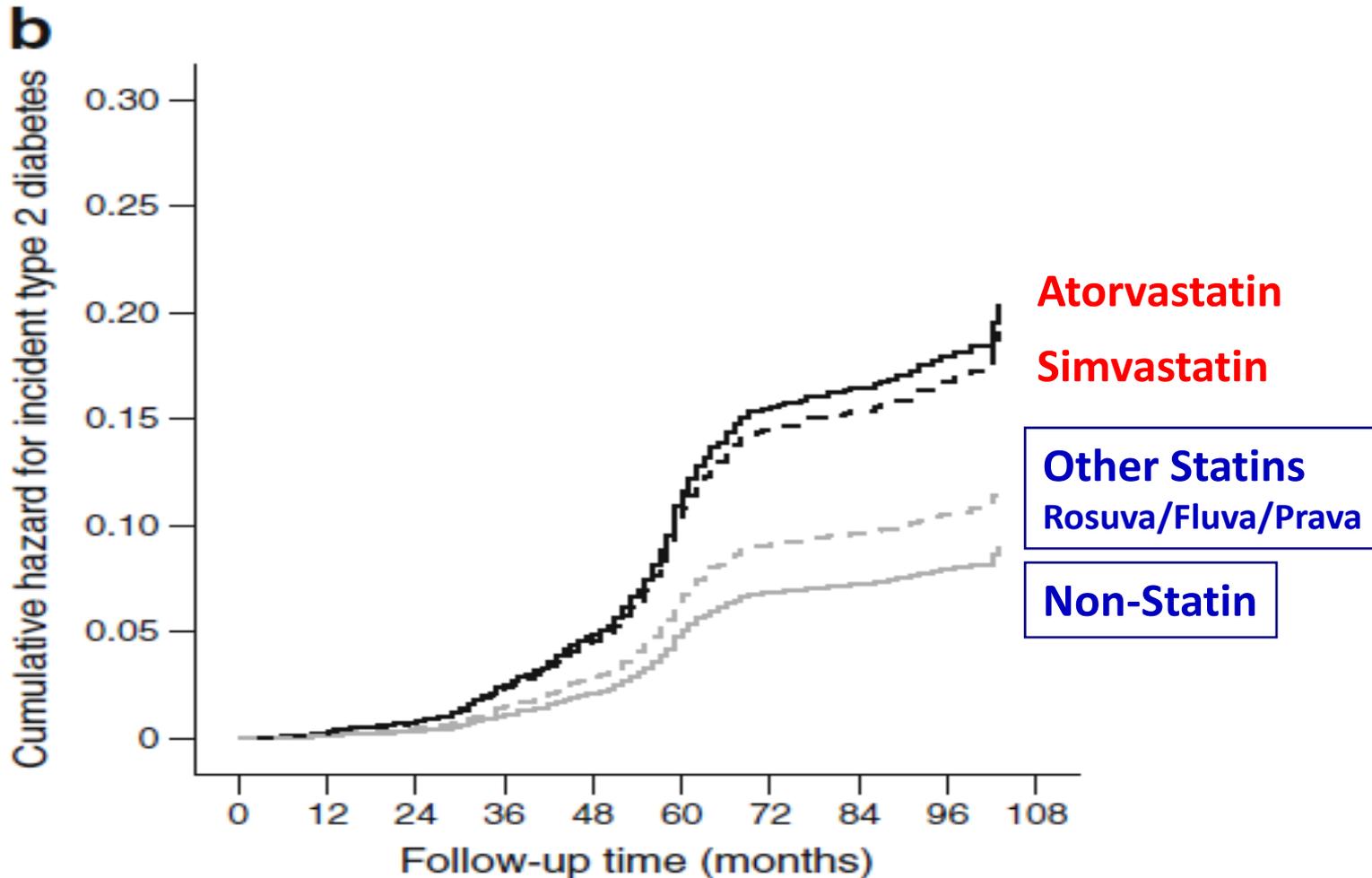
Risk of diabetes with Rosuvastatin in Koreans

- **Study Groups**

  **a total of 3,260 consecutive patients
  who did not have DM were enrolled**

  Rosuvastatin = 260 pts

  No Rosuvastatin = 3,000 pts

- **Study Endpoint**

  The primary end-point was the cumulative incidence of

 new-onset DM (HbA1C level > 6.5% or fasting glucose level >

  126 mg/dL)

Rha SW et al. Circulation. 2013; 128: A13425
Korean Cardiology Related-Societies Joint Scientific Congress 2014 Presentation

Risk of diabetes with Rosuvastatin in Koreans

Rha SW et al. Circulation. 2013; 128: A13425
Korean Cardiology Related-Societies Joint Scientific Congress 2014 Presentation
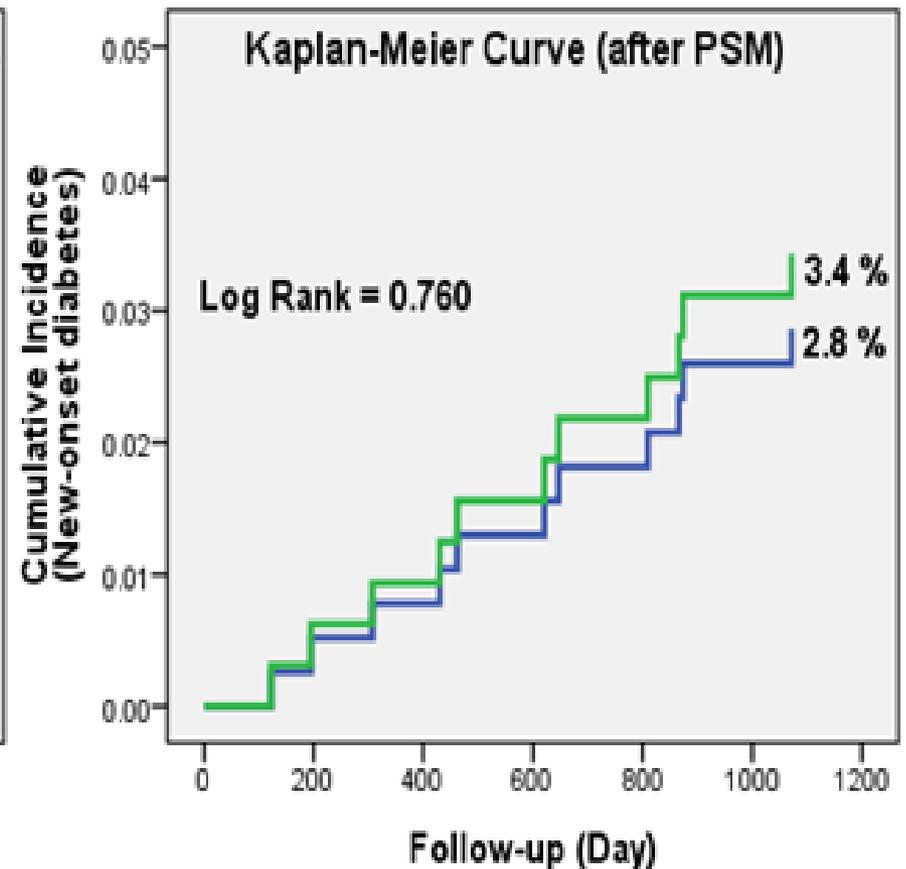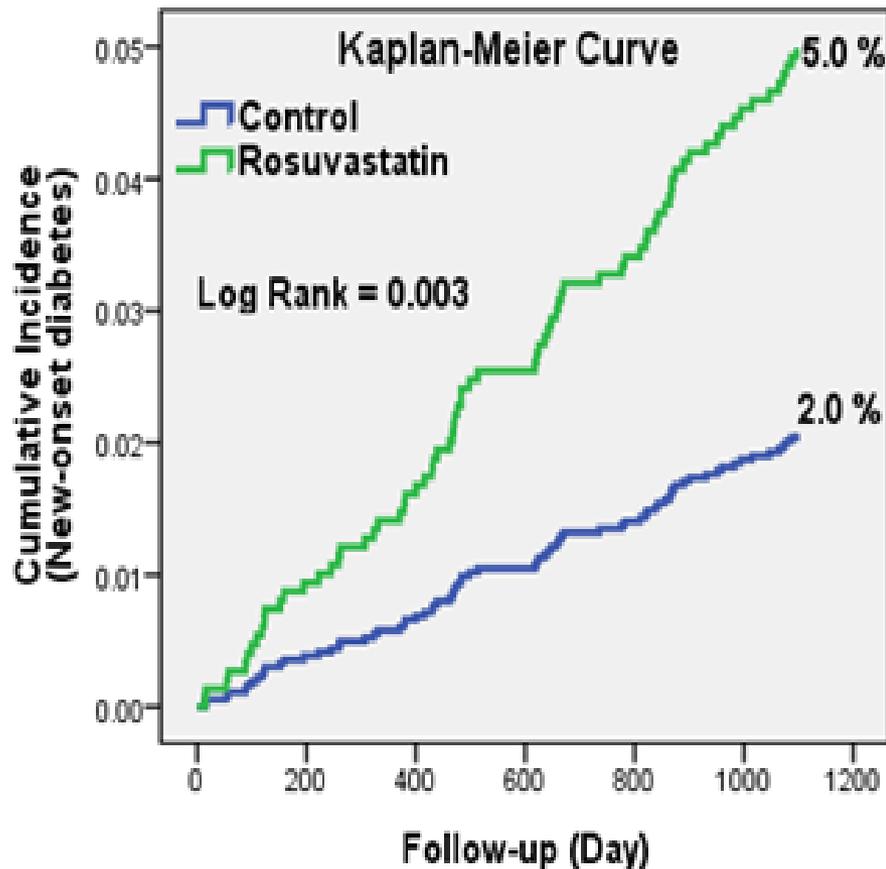
Competitive price for patients

	CRESTOR®[1]	LIPITOR®[2]	LIPINON®[2]
High-Intensity Statin therapy [3]	20 mg/686원	80mg/1,591원 40mg/1,391원	80mg/1,352원 40mg/1,261원
Moderate -Intensity Statin therapy [3]	10 mg/612원 5 mg/346원	20mg/712원 10mg/663원	20mg/712원 10mg/663원

Ref) 1. 보건복지부 고시 제2014-33호, 약제 급여 목록 및 급여 상한금액표 일부 개정(크레스토 10. 20mg).
       보건복지부 고시 제2014-42호, 약제 급여 목록 및 급여 상한금액표 일부 개정(크레스토 5mg)
2. 2015년 3월 1일 현재 약제 급여목록 기준
3. Stone NJ, et al. J Am Coll Cardiol. 2013: 가이드라인 기반으로 스타틴을 분류하였습니다.

Conclusion

1. Statin revolution has been on the progress to define how much we lower LDL-C to curtail more heat attack.

2. JUPITER shows that usual dosage of Rosuvastatin could be a treatment option for patients to curtail heart attack(48%) by lowering 50% LDL-C.

3. Statins are not all the same based on pharmacokinetics which could reflect efficacy and safety profile on each statin.

4. When it comes to New Onset DM induced by statin, statins might be different based on some cohort trials. However, CV benefit of statin treatment outweighs the diabetes risk.

Thank you for your attention

Korea University Guro Hospital