Statin Use and DM

Seung Hwan Han, MD, PhD

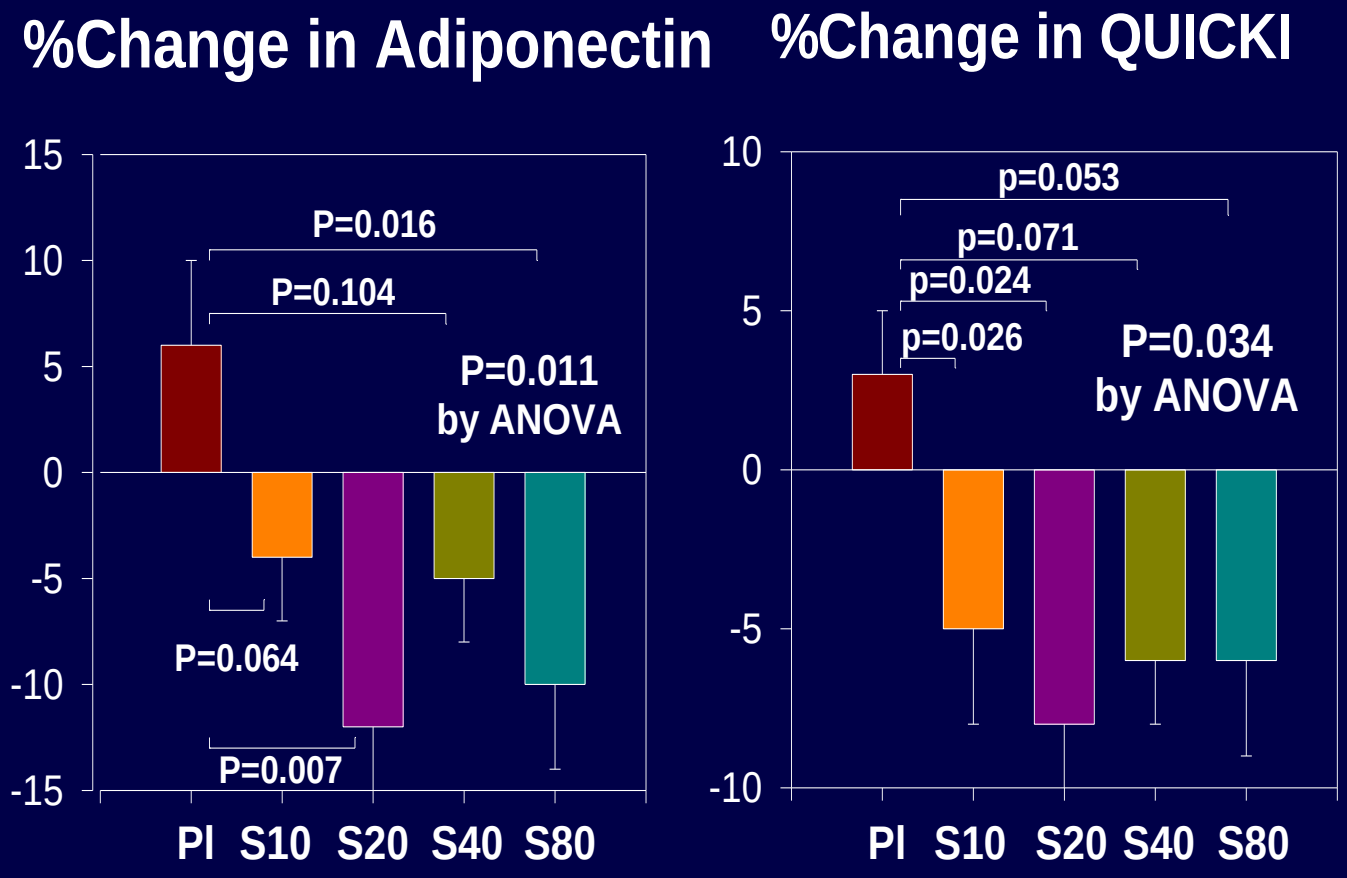
Cardiology,
Gachon University Gil Hospital
Incheon, Korea

Gachon University
Gil Medical Center

Contents

- Introduction
- Statin use and diabetes: Evidence
- Risk factors for new onset diabetes on statin treatment
- The incidence of new onset diabetes differ in statins?
- Suggested mechanism
- How to minimize the risk of new onset diabetes on statin treatment

Simvastatin Dose-Dependently Reduces Adiponectin and Insulin Sensitivity In HC Patients



*QUICKI=Quantitative Insulin-Sensitivity Check Index, a surrogate index of insulin sensitivity, QUICKI = 1/[log(insulin)+log(glucose)]

Koh KK, Han SH, et al. Diabetes Care 2008;31:176

JUPITOR trial
: Rosuvastatin and Newly Diagnosed Diabetes

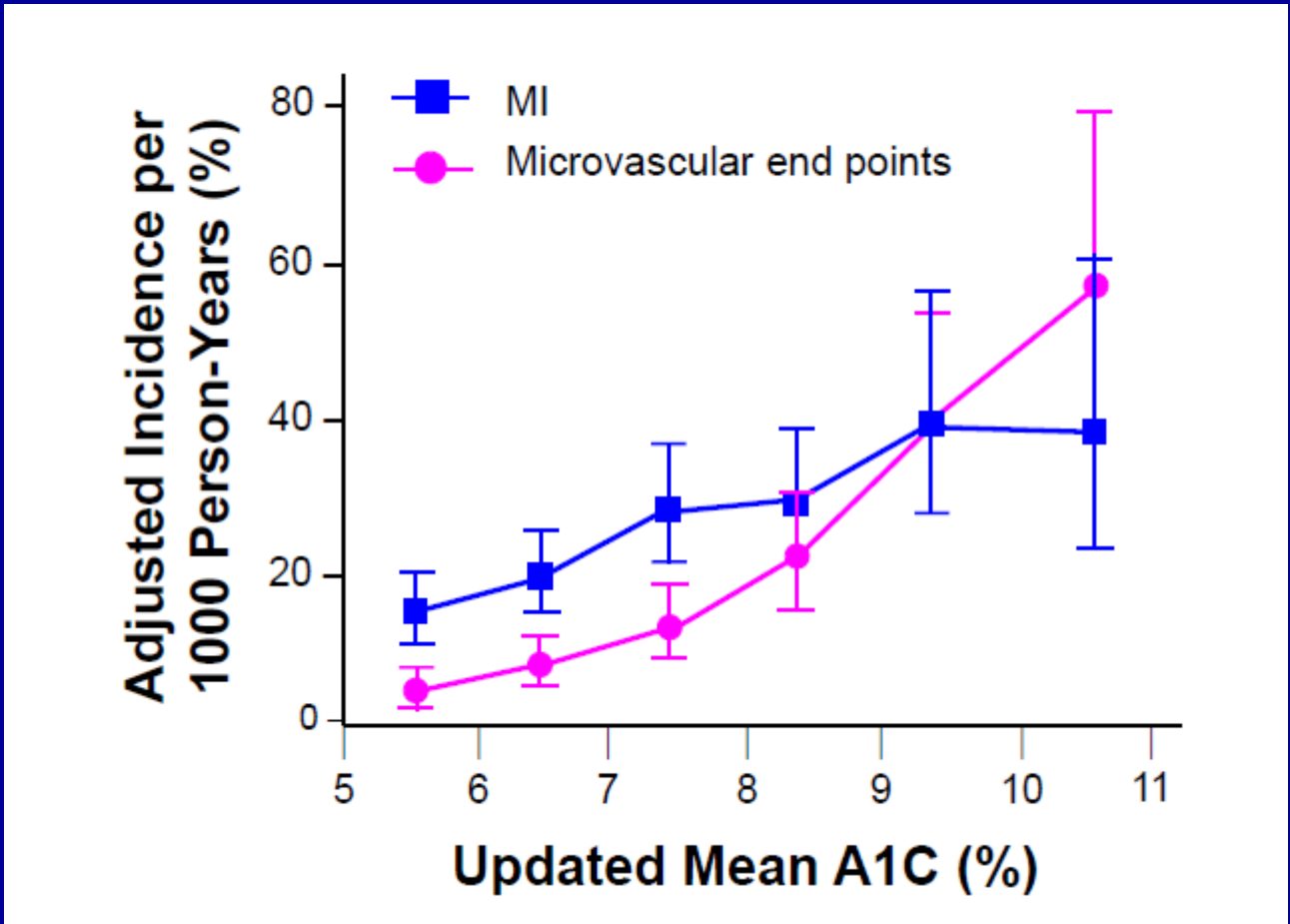
- 17802 healthy men and women with LDL-C <130 mg/dL & hs-CRP ≥ 2 mg/L
- Median F/U period: 1.9 years

	Rosuvastatin (n=8901)	Placebo (n=8901)	HR (95% CI)	p value
Newly diagnosed diabetes, n (%)	270 (3.0)	216 (2.4)	1.25 (1.05-1.49)	0.001

Ridker PM, et al. N Engl J med 2008;359:2195

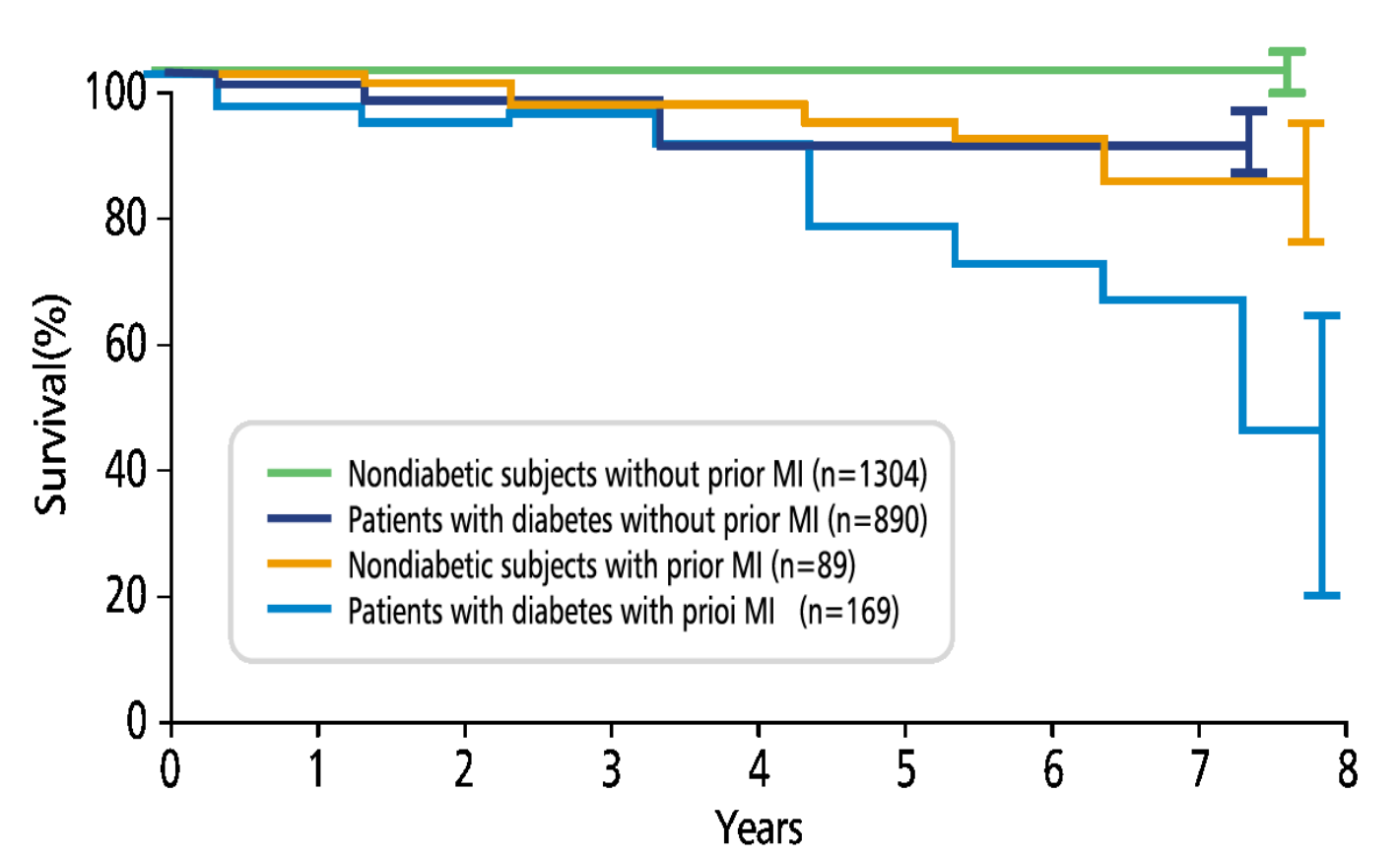
Gachon University Gil Medical Center

UKPDS: Glycemia & Micro, Macrovascular Complications



Stratton IM, et al. BMJ 2000;321:405-12.

Comparison with risk of DM & MI

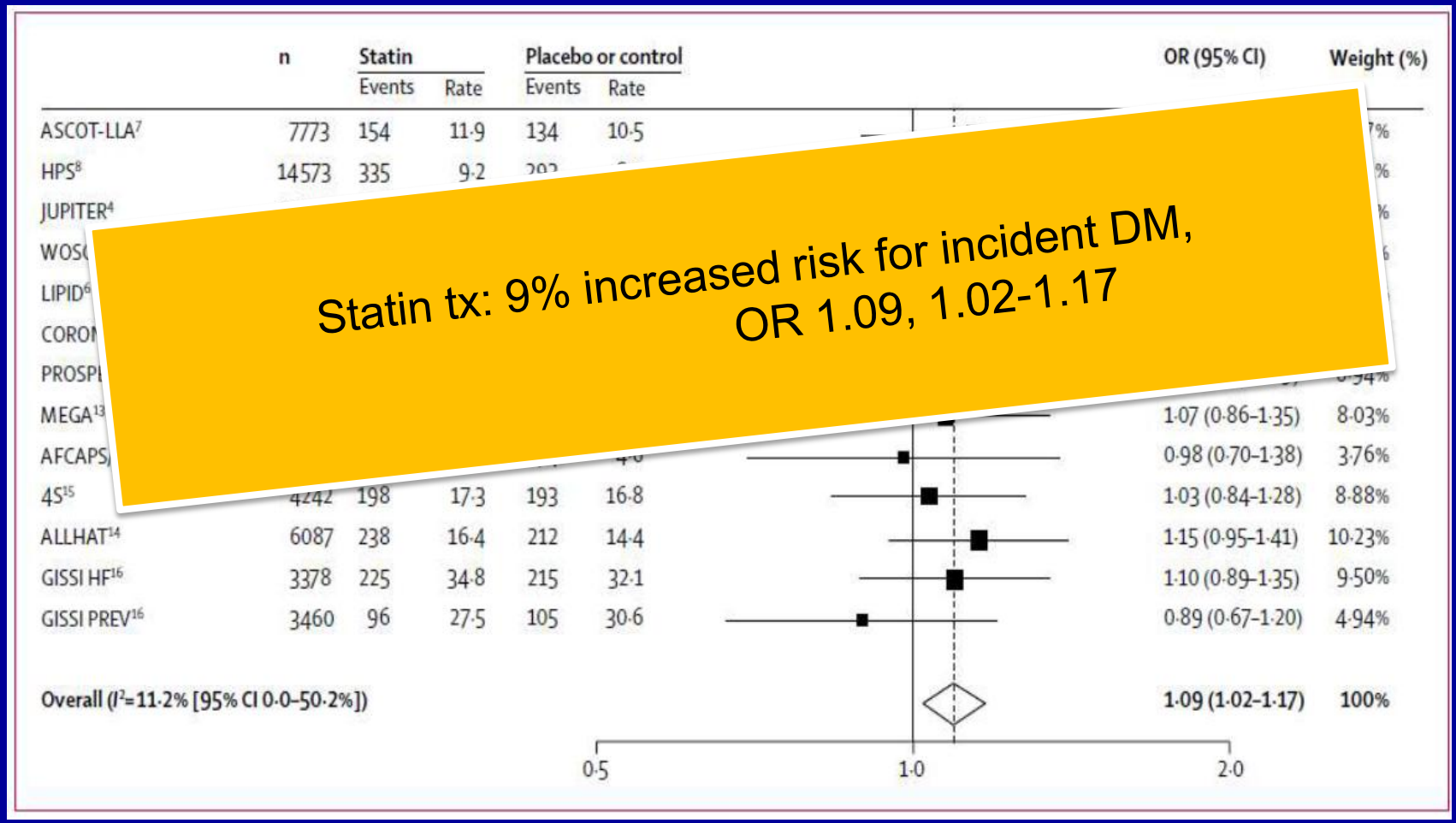


Diabetes is equivalent to CHD risks

Contents

- Introduction
- Statin use and diabetes: Evidence
- Risk factors for new onset diabetes on statin treatment
- The incidence of new onset diabetes differ in statins?
- Suggested mechanism
- How to minimize the risk of new onset diabetes on statin treatment

Statin and New Onset DM



	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		
HPS[8]	14573	335	9·2				
JUPITER[4]							
WOS(							
LIPID[6]							
CORON							
PROSPI							
MEGA[13]						1·07 (0·86–1·35)	8·03%
AFCAPS/						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%

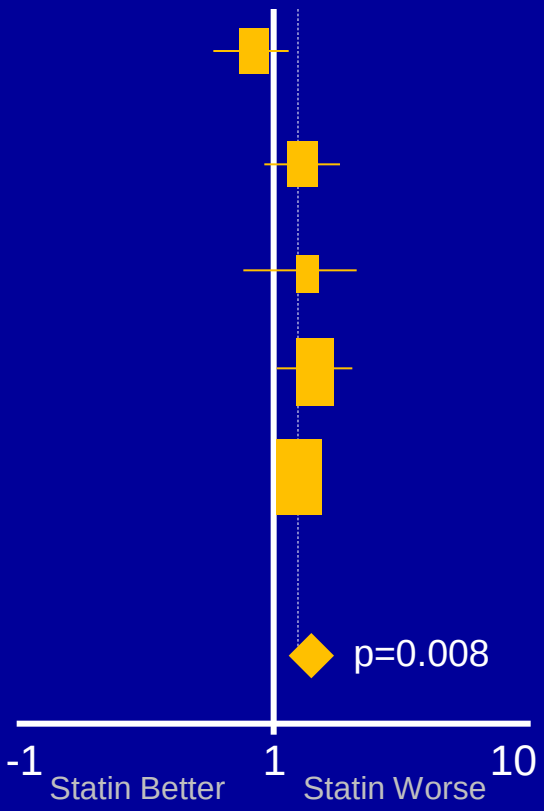
0·5 1·0 2·0

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

Gachon University Gil Medical Center

Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis

	No. statins/ Total(%)	No. Placebo/ Total(%)	Excluding WOSCOPS (n=5)	95% CI
LIPID	172/3970(4.3)	181/3967(4.6)		**0.95** (0.77, 1.16)
ASCOT	154/3910(3.9)	134/3863(3.5)		1.14 (0.90, 1.43)
CORONA	100/1771(5.6)	88/1763(5.0)		1.13 (0.86, 1.49)
JUPITER	270/8901(3.0)	216/8901(2.4)		1.25 (1.05, 1.49)
HPS	335/7291(4.6)	293/7252(4.0)		1.14 (0.98, 1.33)
Combined	1088/28842(3.8)	994/28751(3.5)	p=0.008	**RR=1.13 (1.03, 1.23)**



- 6 randomized controlled statin trials
- 57,593 patients & 2,082 incident diabetes cases
- Mean follow-up: 3.9 years

Diabetes Care 2009; 32:1924-1929

Gachon University Gil Medical Center

NAVIGATOR study

Abstract

Objective To examine the degree to which use of β blockers, statins, and diuretics in patients with impaired glucose tolerance and other cardiovascular risk factors is associated with new onset diabetes.

Design Reanalysis of data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.

Setting NAVIGATOR trial.

Participants Patients who at baseline (enrolment) were treatment naïve to β blockers (n=5640), diuretics (n=6346), statins (n=6146), and calcium channel blockers (n=6294). Use of calcium channel blocker was used as a metabolically neutral control.

Main outcome measures Development of new onset diabetes diagnosed by standard plasma glucose level in all participants and confirmed with glucose tolerance testing within 12 weeks after the increased glucose value was recorded. The relation between each treatment and new onset diabetes was evaluated using marginal structural models for causal inference, to account for time dependent confounding in treatment assignment.

Results During the median five years of follow-up, β blockers were started in 915 (16.2%) patients, diuretics in 1316 (20.7%), statins in 1353 (22.0%), and calcium channel blockers in 1171 (18.6%). After adjusting for baseline characteristics and time varying confounders, diuretics and statins were both associated with an increased risk of new onset diabetes (hazard ratio 1.23, 95% confidence interval 1.06 to 1.44, and 1.32, 1.14 to 1.48, respectively), whereas β blockers and calcium channel blockers were not associated with new onset diabetes (1.10, 0.92 to 1.31, and 0.95, 0.79 to 1.13, respectively).

Conclusions Among people with impaired glucose tolerance and other cardiovascular risk factors and with serial glucose measurements, diuretics and statins were associated with an increased risk of new onset diabetes, whereas the effect of β blockers was non-significant.

Trial registration ClinicalTrials.gov NCT00097786.

Shen L, et al. BMJ 2013;347:f6745

Gachon University Gil Medical Center

NAVIGATOR study

Table 3| **Effect of time dependent drugs on progression to diabetes**

Drugs	Unadjusted hazard ratio (95% CI)	Baseline adjusted* hazard ratio (95% CI)	MSM adjusted† hazard ratio (95% CI)	Absolute excess risk† (95% CI) at 5 years (%)
β blocker	1.25 (1.07 to 1.46)	1.23 (1.05 to 1.44)	1.10 (0.92 to 1.31)	2.6 (–2.3 to 8.0)
Diuretics	1.36 (1.20 to 1.55)	1.36 (1.19 to 1.55)	1.23 (1.06 to 1.44)	5.9 (1.5 to 10.7)
Statins	1.30 (1.14 to 1.48)	1.30 (1.13 to 1.49)	1.32 (1.14 to 1.48)	8.1 (3.5 to 13.0)
Calcium channel blocker	1.01 (0.87 to 1.18)	0.98 (0.84 to 1.14)	0.95 (0.79 to 1.13)	–1.5 (–5.8 to 3.4)

MSM=marginal structural model.

*Standard Cox proportional hazard model with regression adjustment for baseline variables, and treatment included as a time dependent covariate.

†MSM with regression adjustment for baseline variables and inverse probability of treatment weighting for time dependent confounders; truncation of extreme weights applied at 0.25th centile and 99.75th centile.

Shen L, et al. BMJ 2013;347:f6745

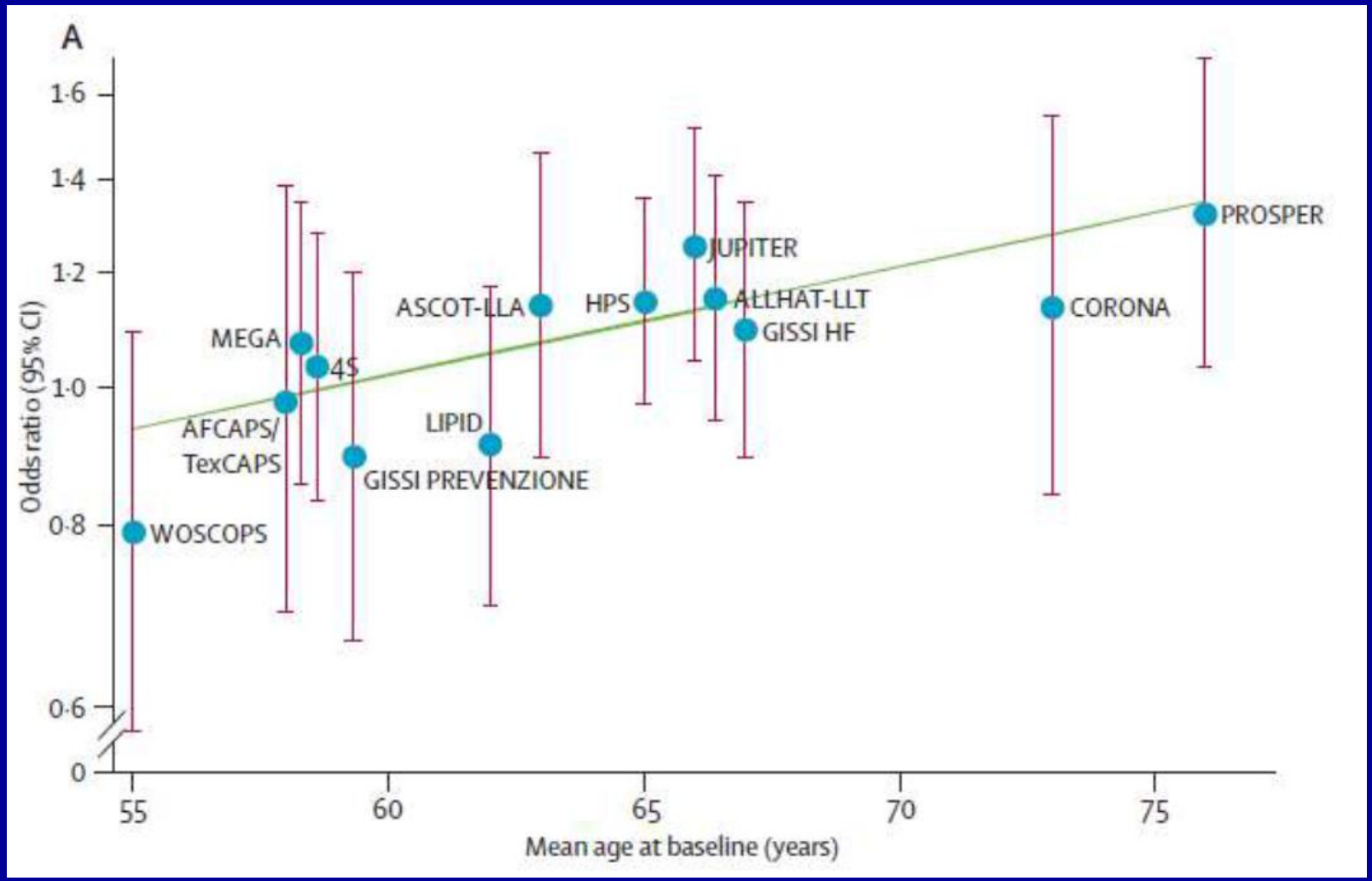
FDA Expands Advice on **STATIN RISKS**

- People being treated with statins may have an increased risk of raised blood sugar levels and the development of Type 2 diabetes.

Contents

- Introduction
- Statin use and diabetes: Evidence
- Risk factors for new onset diabetes on statin treatment
- The incidence of new onset diabetes differ in statins?
- Suggested mechanism
- How to minimize the risk of new onset diabetes on statin treatment

Greater Risk at Increasing Age



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

Gachon University
Gil Medical Center

JUPITER
Adverse Events and Measured Safety Parameters

Event	Rosuvastatin	Placebo	P
Any SAE	1,352 (15.2)	1,337 (15.5)	0.60
Muscle weakness	1,421 (16.0)	1,375 (15.4)	0.34
Myopathy	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis	1 (0.01)*	0 (0.0)	—
Incident Cancer	298 (3.4)		
Cancer Deaths			
	98 (91–107)	98 (90–106)	0.12
HbA1c (% at 24 mth)	**5.9** (5.7–6.1)	**5.8** (5.6–6.1)	**0.01**
Glucosuria (12 mth)	36 (0.5)	32 (0.4)	0.64
Incident Diabetes**	270 **(3.0)**	216 **(2.4)**	**0.01**

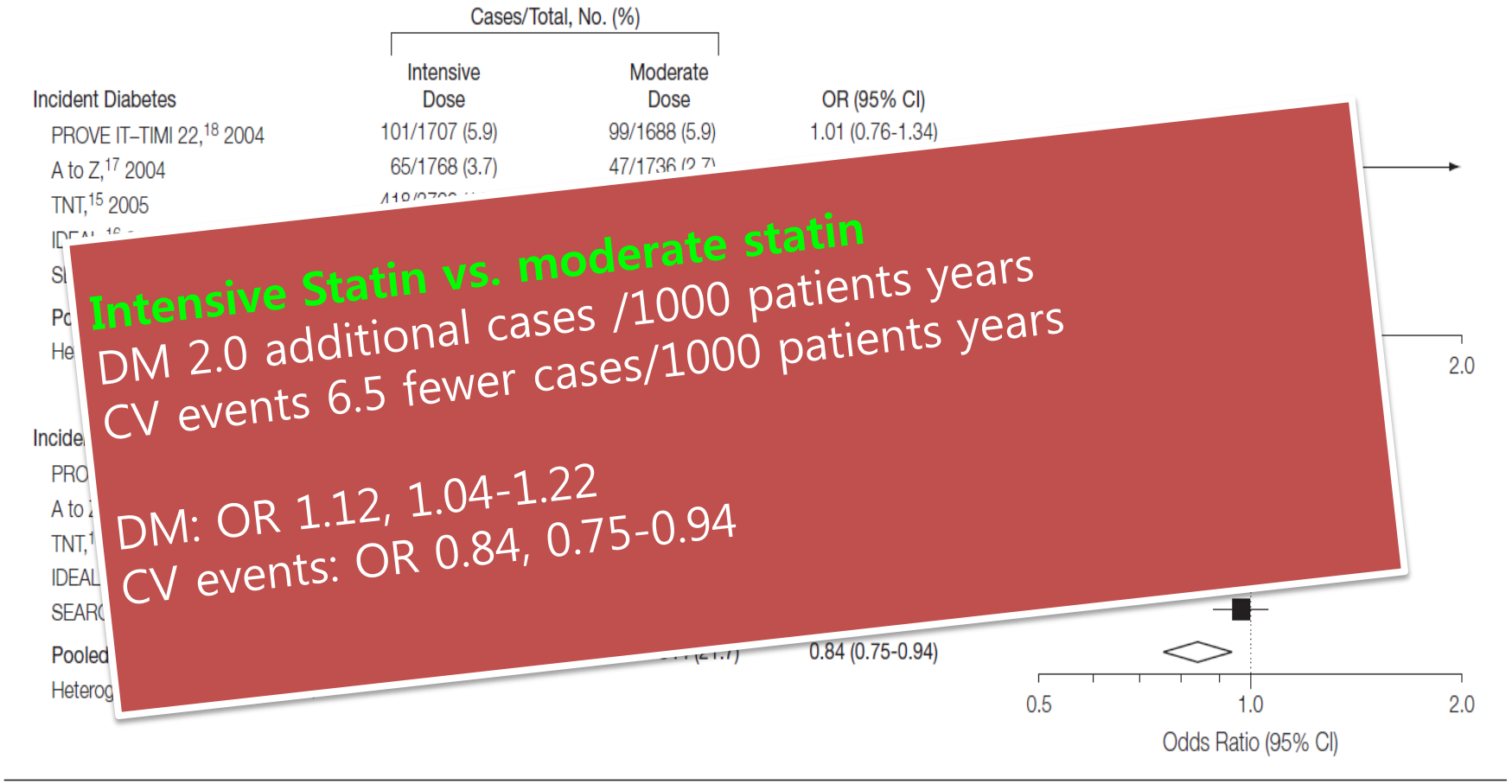
4 Major risk factors for DM
Metabolic syndrome, BMI >30
FBS, glycated Hb >6%

*Occurred after trial completion, trauma induced.
**Physician reported

All values are median (interquartile range) or N (%)

Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy

A Meta-analysis



Intensive Statin vs. moderate statin

DM 2.0 additional cases /1000 patients years

CV events 6.5 fewer cases/1000 patients years

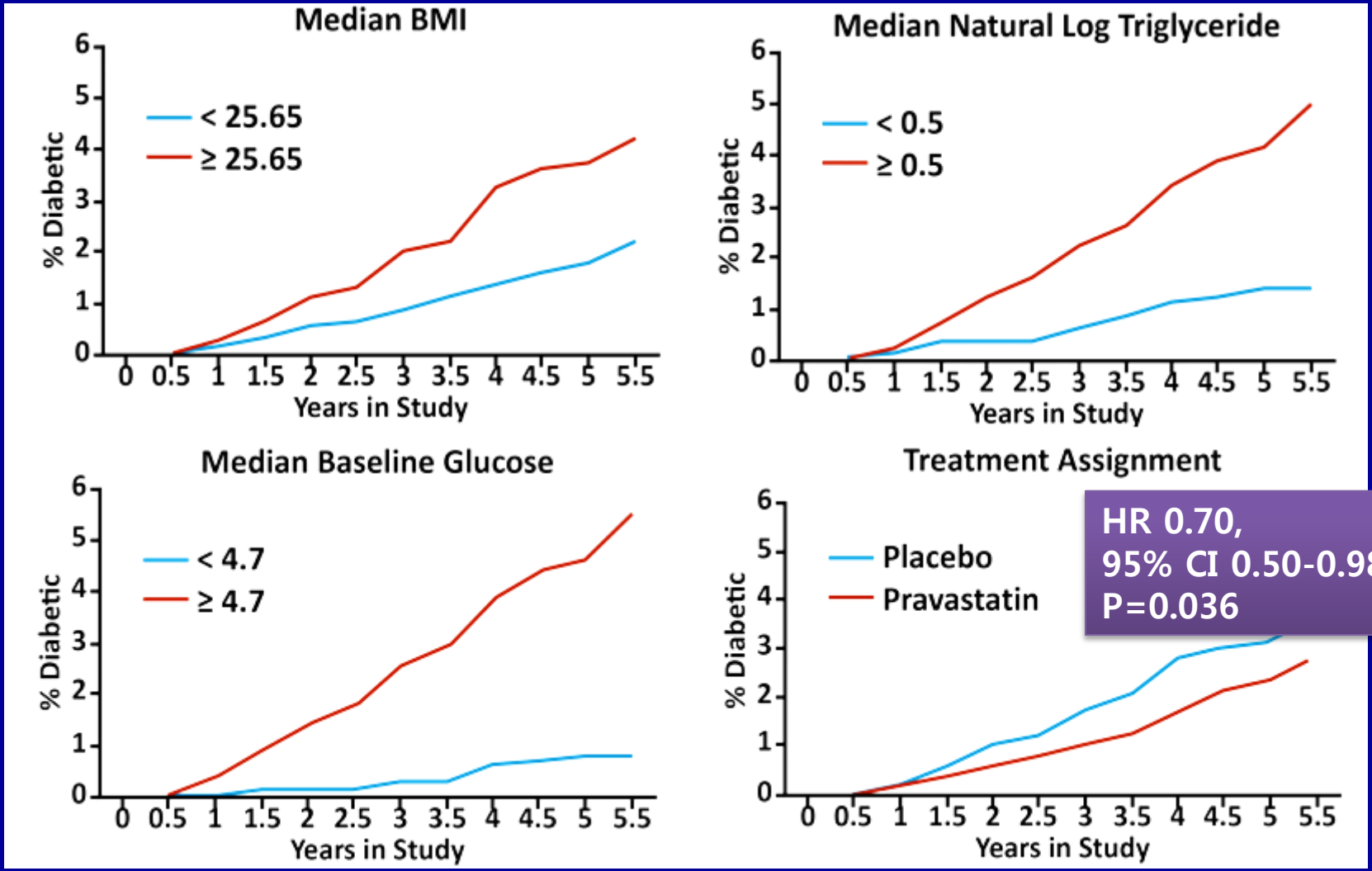
DM: OR 1.12, 1.04-1.22

CV events: OR 0.84, 0.75-0.94

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

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

WOSCOPS: Pravastatin and Reductions in Newly Diagnosed Diabetes



Freeman DJ, et al. Circulation 2001;103:357

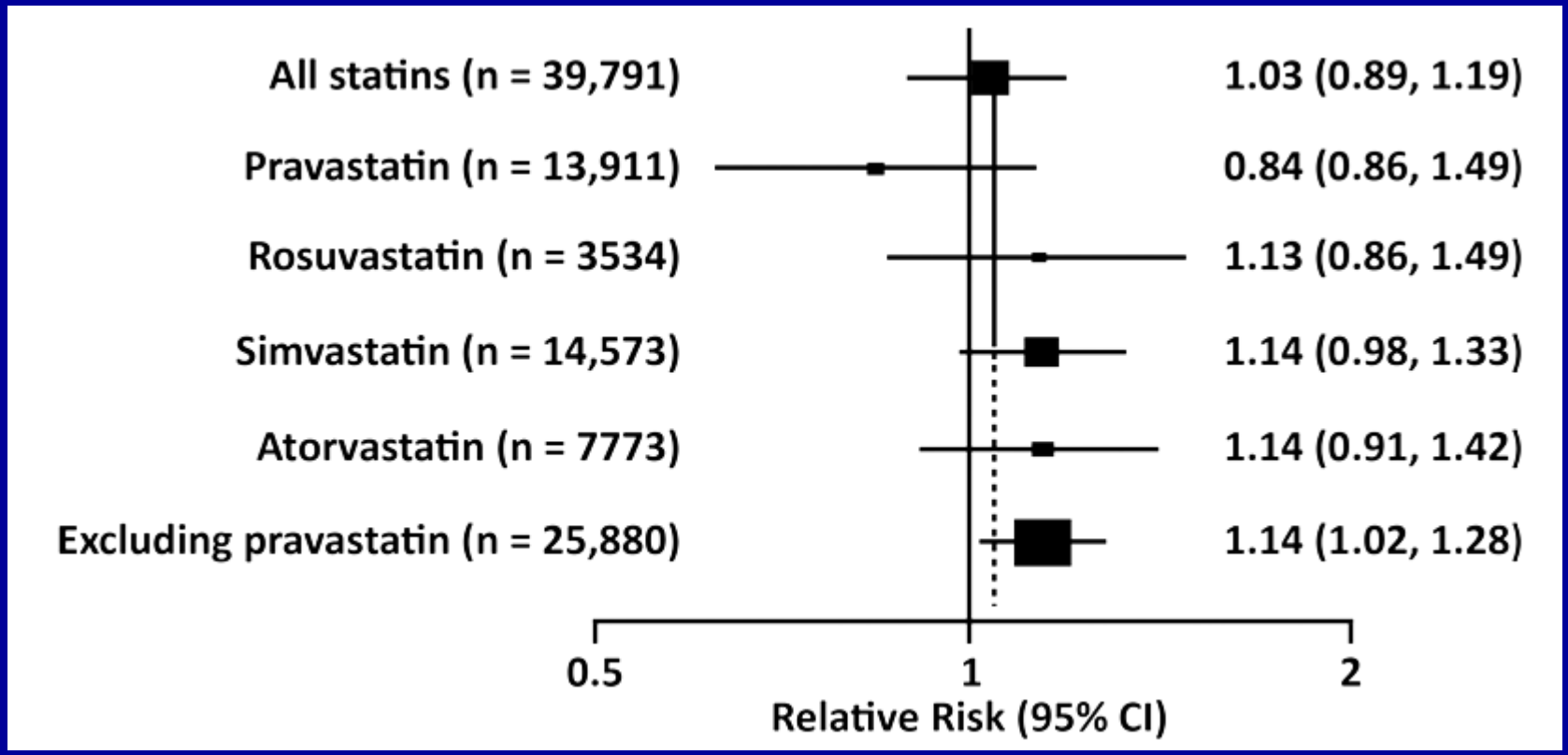
Gachon University Gil Medical Center

Contents

- Introduction
- Statin use and diabetes: Evidence
- Risk factors for new onset diabetes on statin treatment
- The incidence of new onset diabetes differ in statins?
- Suggested mechanism
- How to minimize the risk of new onset diabetes on statin treatment

Meta-analysis of Statin Trial for New-Onset Type 2 Diabetes

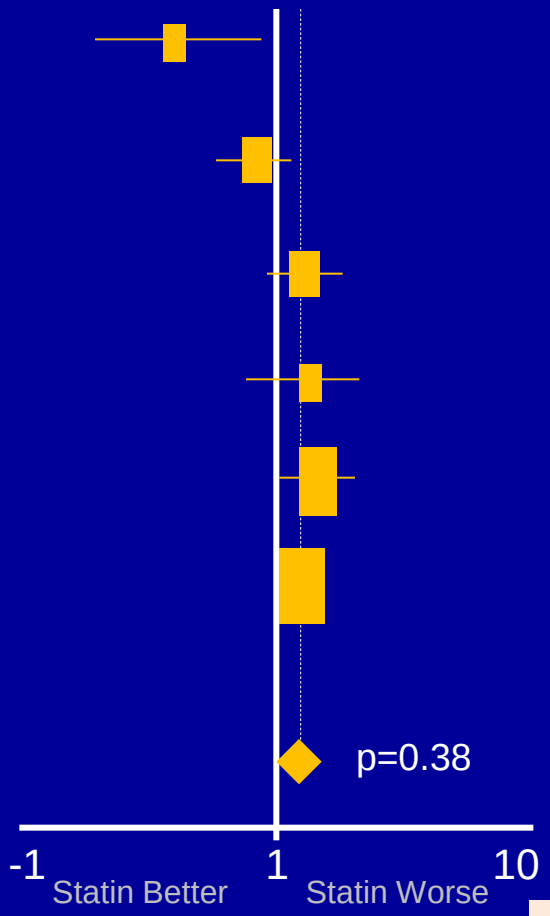
- 5 RCTs, 39791 subjects



Coleman CI, et al. Curr Med Res Opin 2008;24:1359

Effect of Different Statins on Diabetes Risk

	No. statins/ Total(%)	No. Placebo/ Total(%)	All studies (n=6)	95% CI
WOSCOPS	57/2999(1.9)	82/2975(2.8)		**0.69** (0.49, 0.96)
LIPID	172/3970(4.3)	181/3967(4.6)		**0.95** (0.77, 1.16)
ASCOT	154/3910(3.9)	134/3863(3.5)		1.14 (0.90, 1.43)
CORONA	100/1771(5.6)	88/1763(5.0)		1.13 (0.86, 1.49)
JUPITER	270/8901(3.0)	216/8901(2.4)		1.25 (1.05, 1.49)
HPS	335/7291(4.6)	293/7252(4.0)		1.14 (0.98, 1.33)
Combined	1088/28842(3.8)	994/28751(3.5)	p=0.38	RR=1.06 (0.93, 1.22)



Diabetes Care 2009; 32:1924-1929

Gachon University Gil Medical Center

BMJ 2013;346:f2610 doi: 10.1136/bmj.f261

Risk of incident
statins: populati

OPEN ACCESS

Aleesa A Carter *pharmacist,*
Camacho *epidemiologist*[3], Da
associate professor[3 5 6 7], Muh

[1]Toronto General Hospital, Toronto, ON, Ca
Evaluative Sciences, Toronto, ON, Canada,
[5]Department of Medicine, Kings College Cir

Over the 14 year stu
with no history of di
no history of diabete
Of these, 227 994 (4
prevention, while 24
secondary preventio
was 73 (interquartile
women.

There was no significantly increased risk am
fluvastatin (0.95, 0.81 to 1.11) or lovastatin (
absolute risk for incident diabetes was about
person years for atorvastatin and rosuvastat
a slightly lower absolute risk with simvastati
person years) compared with pravastatin (23
years). Our findings were consistent regardl
used for primary or secondary prevention of
Although similar results were observed whe
potency, the risk of incident diabetes associa
became non-significant (adjusted hazard rat
dose was taken into account.

Abstract

Objective To examine the risk of new onset diabetes among patients treated with different HMG-CoA reductase inhibitors (statins).

Design Population based cohort study with time to event analyses to estimate the relation between use of particular statins and incident diabetes. Hazard ratios were calculated to determine the effect of dose and type of statin on the risk of incident diabetes.

Setting Ontario, Canada.

Participants All patients aged 66 or older without diabetes who started treatment with statins from 1 August 1997 to 31 March 2010. The analysis was restricted to new users who had not been prescribed a statin in at least the preceding year. Patients with established diabetes before the start of treatment were excluded.

Interventions Treatment with statins.

Main outcome measure Incident diabetes.

Results Compared with pravastatin (the reference drug in all analyses), there was an increased risk of incident diabetes with atorvastatin (adjusted hazard ratio 1.22, 95% confidence interval 1.15 to 1.29), rosuvastatin (1.18, 1.10 to 1.26), and simvastatin (1.10, 1.04 to 1.17). There was no significantly increased risk among people who received fluvastatin (0.95, 0.81 to 1.11) or lovastatin (0.99, 0.86 to 1.14). The absolute risk for incident diabetes was about 31 and 34 events per 1000 person years for atorvastatin and rosuvastatin, respectively. There was a slightly lower absolute risk with simvastatin (26 outcomes per 1000 person years) compared with pravastatin (23 outcomes per 1000 person years). Our findings were consistent regardless of whether statins were used for primary or secondary prevention of cardiovascular disease. Although similar results were observed when statins were grouped by potency, the risk of incident diabetes associated with use of rosuvastatin became non-significant (adjusted hazard ratio 1.01, 0.94 to 1.09) when dose was taken into account.

Contents

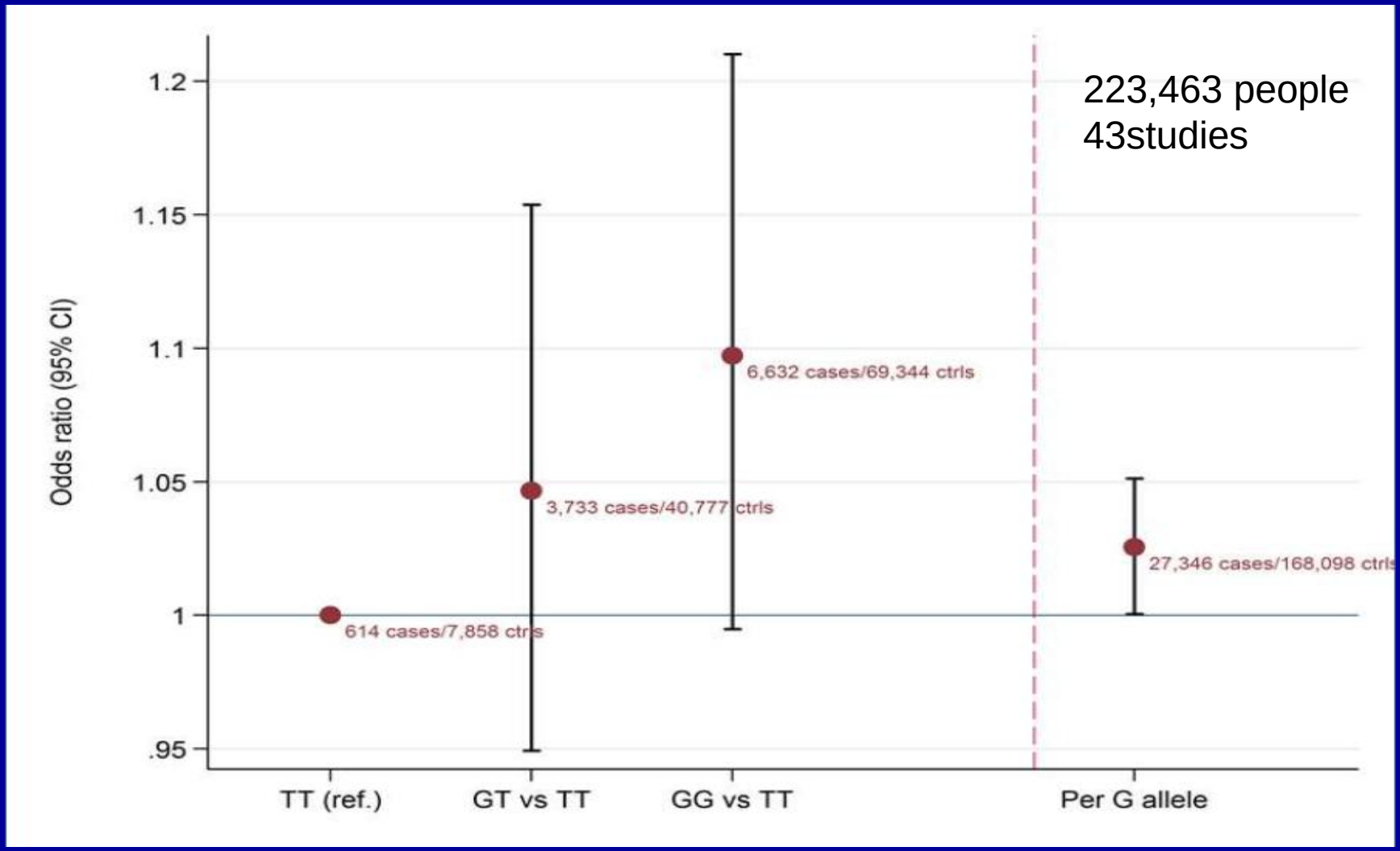
- Introduction
- Statin use and diabetes: Evidence
- Risk factors for new onset diabetes on statin treatment
- The incidence of new onset diabetes differ in statins?
- Suggested mechanism
- How to minimize the risk of new onset diabetes on statin treatment

Do Statins Alter Glucose/Insulin Metabolism?

1. Genetic association
2. Affect insulin secretion through direct, indirect or combined effects on calcium channels in pancreatic Beta-cells
3. Reduced translocation of glucose transporter 4
4. Decreases other important downstream products, such as coenzyme Q10, farnesyl pyrophosphate, geranylgeranyl pyrophosphate and dolichol
5. Interference with intracellular insulin signal transduction pathways via inhibition of necessary phosphorylation events and reduction of small GTPase action, inhibition of adipocyte differentiation leading to decreased PPAR gamma
6. Decrease Adiponetin, adiopocytokine

Brault M, et al. Metabolism 2014;63:735-45.

Association of Single Nucleotide Polymorphism in the HMGCR gene (rs 17238484) with risk of T2DM



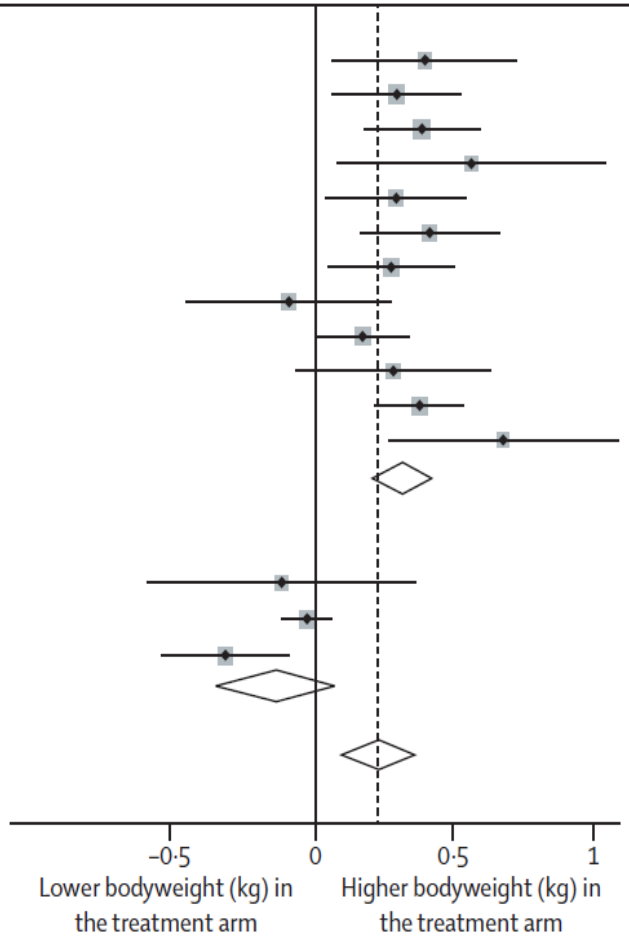
Swerdlow DI, et al. Lancet Sep 24, e-pub

Gachon University
Gil Medical Center

Statin tx increases Bwt

	Statin treatment	Control	Change in bodyweight (kg 95% CI)	Weight (%)
Placebo-controlled or standard care-controlled				
4S	2029	2026	0·42 (0·07 to 0·77)	5·94
WOSCOPS	2999	2975	0·31 (0·06 to 0·56)	7·34
AFCAPS TextCAPS	3220	3230	0·41 (0·19 to 0·63)	7·71
LIPID	4116	4116	0·60 (0·08 to 1·12)	4·16
GISSI-Prevenzione	1743	1717	0·31 (0·04 to 0·58)	7·06
PROSPER	2459	2475	0·44 (0·17 to 0·71)	7·08
ASCOT-LLA	3752	3660	0·29 (0·05 to 0·53)	7·43
SPARCL	1970	1967	−0·10 (−0·49 to 0·29)	5·43
MEGA	2867	2974	0·18 (0·00 to 0·36)	8·27
CORONA	1771	1763	0·30 (−0·07 to 0·67)	5·68
JUPITER	7437	7331	0·40 (0·23 to 0·57)	8·35
GISSI-HF	1660	1718	0·72 (0·28 to 1·16)	4·88
Subtotal (I^2=18·6%, p=0·261)	**36 023**	**35 952**	**0·33 (0·25 to 0·42)**	**79·32**
Intensive *vs* moderate dose				
PROVE-IT TIMI 22	1649	1626	−0·13 (−0·64 to 0·38)	4·18
TNT	4209	4225	−0·03 (−0·13 to 0·07)	9·13
IDEAL	3843	3866	−0·35 (−0·59 to −0·10)	7·37
Subtotal (I^2=63·2%, p=0·066)	**9701**	**9717**	**−0·15 (−0·39 to 0·08)**	**20·68**
Overall (I^2=78·6%, p<0·0001)	**45 724**	**45 669**	**0·24 (0·10 to 0·38)**	**100·00**

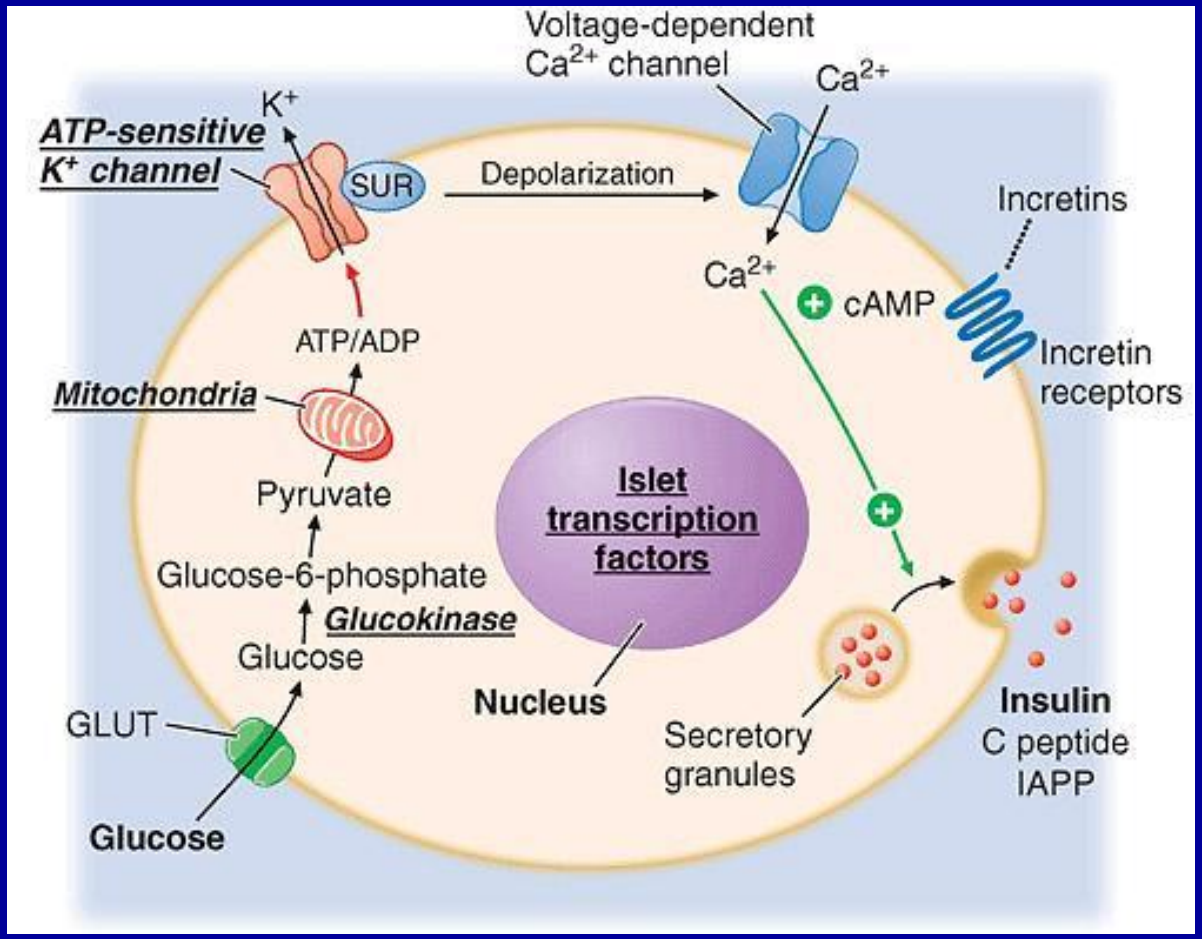
Note: weights are from random-effects analysis



Swerdlow DI, et al. Lancet Sep 24, e-pub

Gachon University Gil Medical Center

Mechanisms of Glucose-Mediated Insulin Secretion



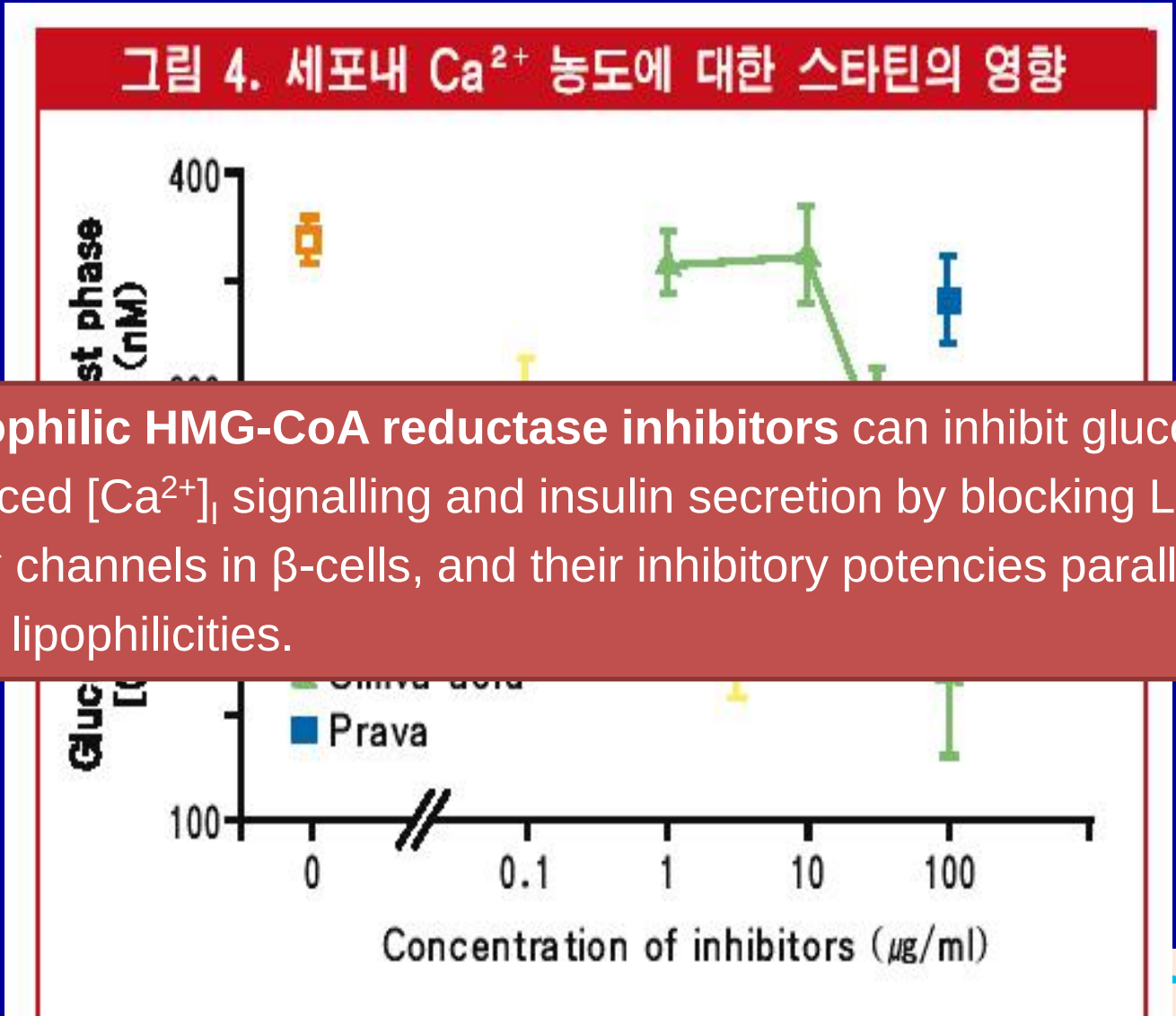
Panceratic beta cell

Harrison's principles of Internal Medicine, 18th edition

Gachon University
Gil Medical Center

Inhibition by simvastatin, but not pravastatin, of glucose-Induced Ca^{++} signaling in rat islet β-cells

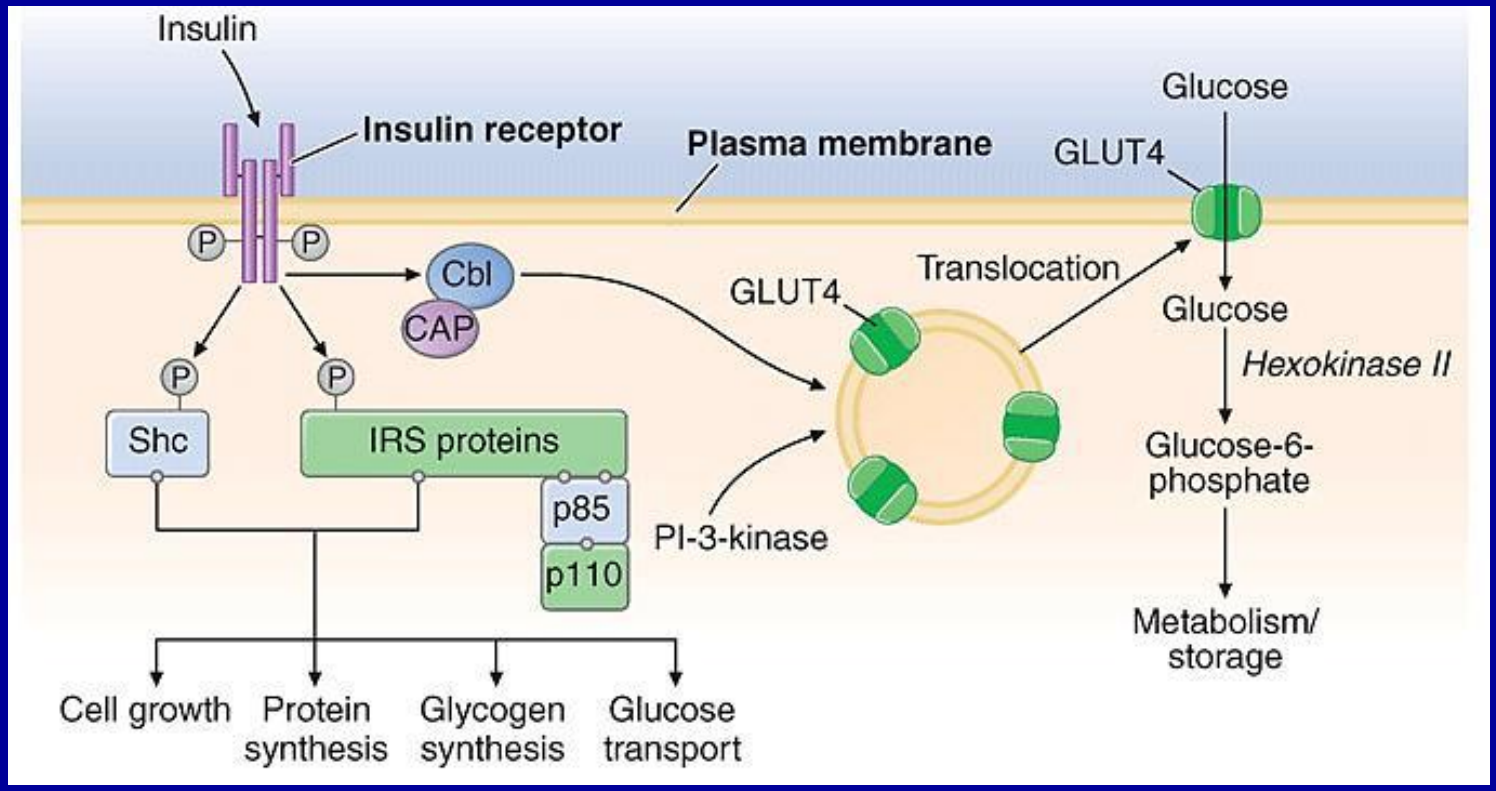
Yada T, et al. Br J Pharmacol 1999;126:1205



Lipophilic HMG-CoA reductase inhibitors can inhibit glucose-induced $[Ca^{2+}]_i$ signalling and insulin secretion by blocking L-type Ca^{2+} channels in β-cells, and their inhibitory potencies parallel their lipophilicities.

Gachon University
Gil Medical Center

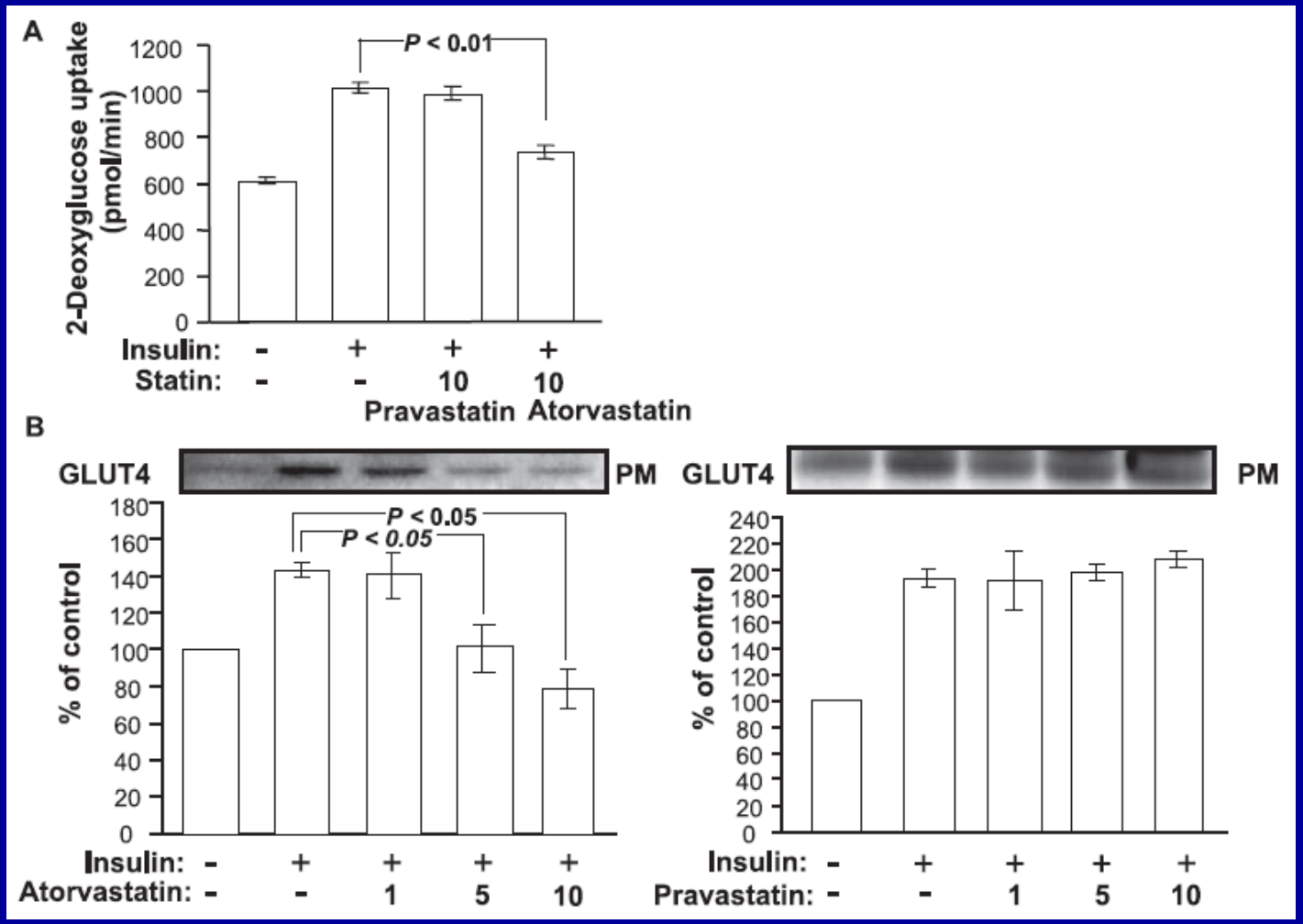
Insulin Signal Transduction Pathway



- **PI3K pathway (AKT→ Rab-family GTPase)**
- **Rho-family GTPase**
- **Ras-family GPTase**

Harrison's principles of Internal Medicine, 18th edition

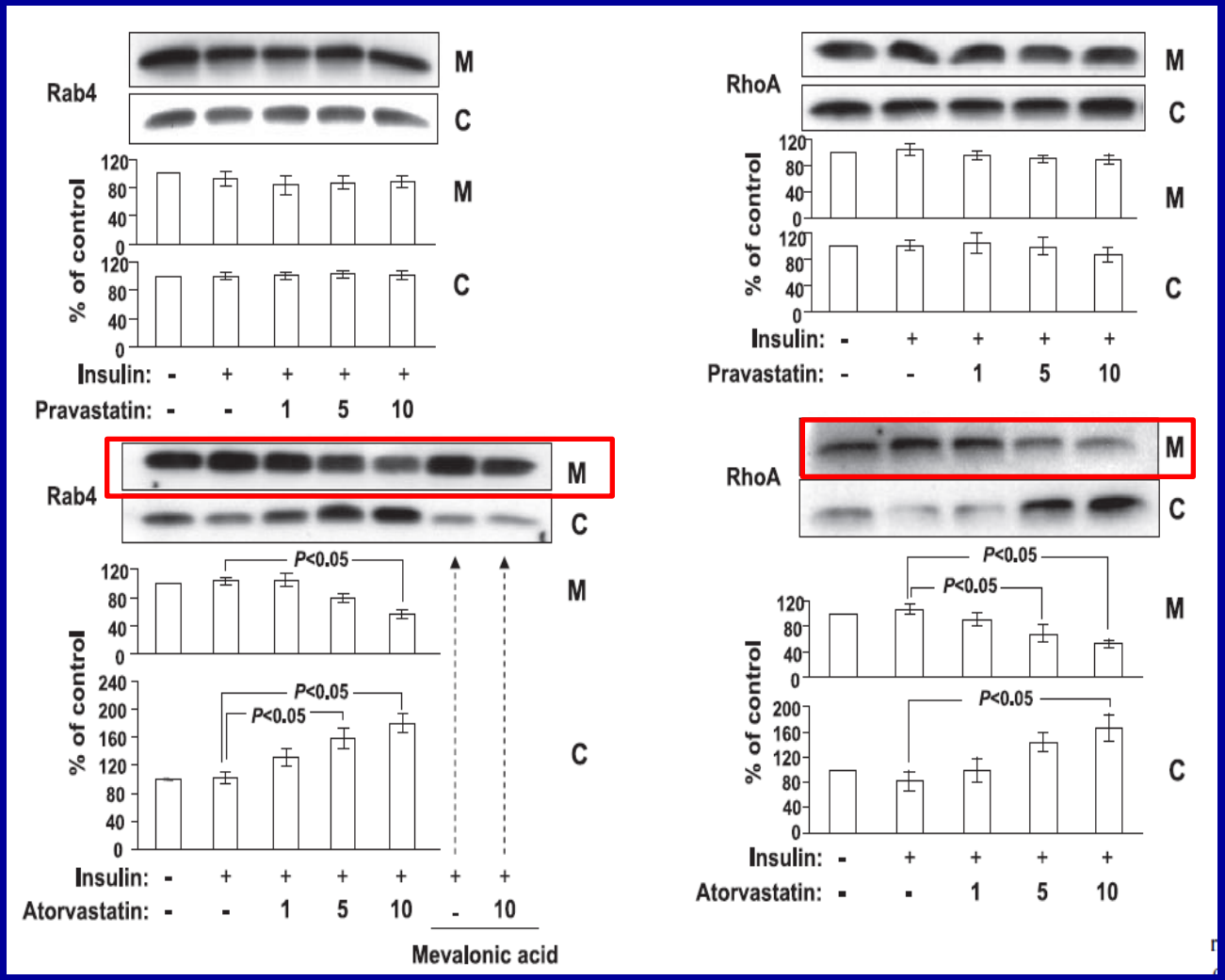
Effect of Statins on GLUT4 & Glucose Uptake in 3T3-L1 adipocyte



Takaguri A, et al. J Pharmacol Sci 2008;107:80

Gachon University Gil Medical Center

Effect of Statins on GLUT4 & Glucose Uptake in 3T3-L1 adipocyte

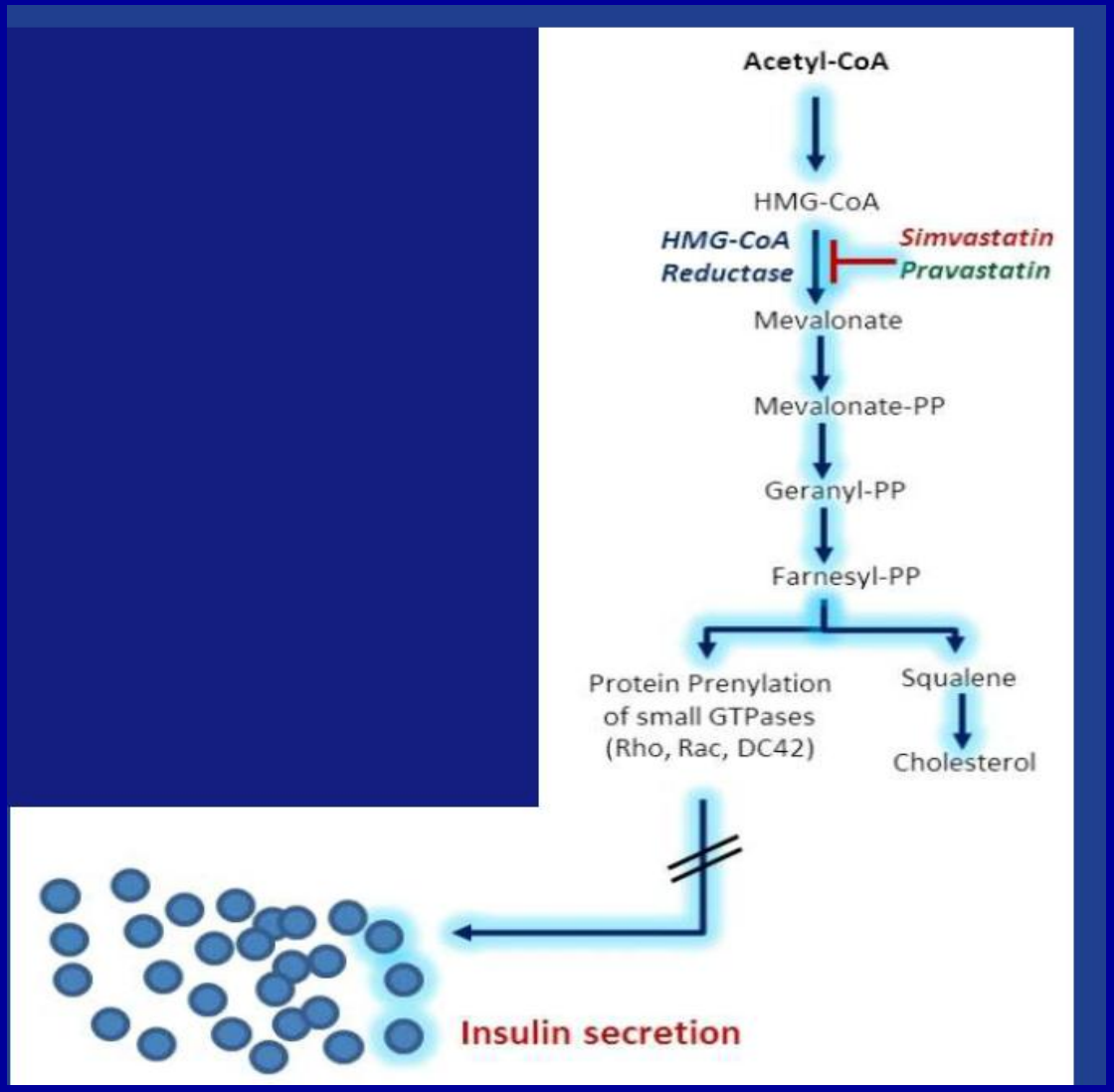


The amounts of Rab4 and RhoA that required lipid modification with farnesyl or geranylgeranyl pyrophosphate, in the membrane fraction were decreased by atorvastatin.

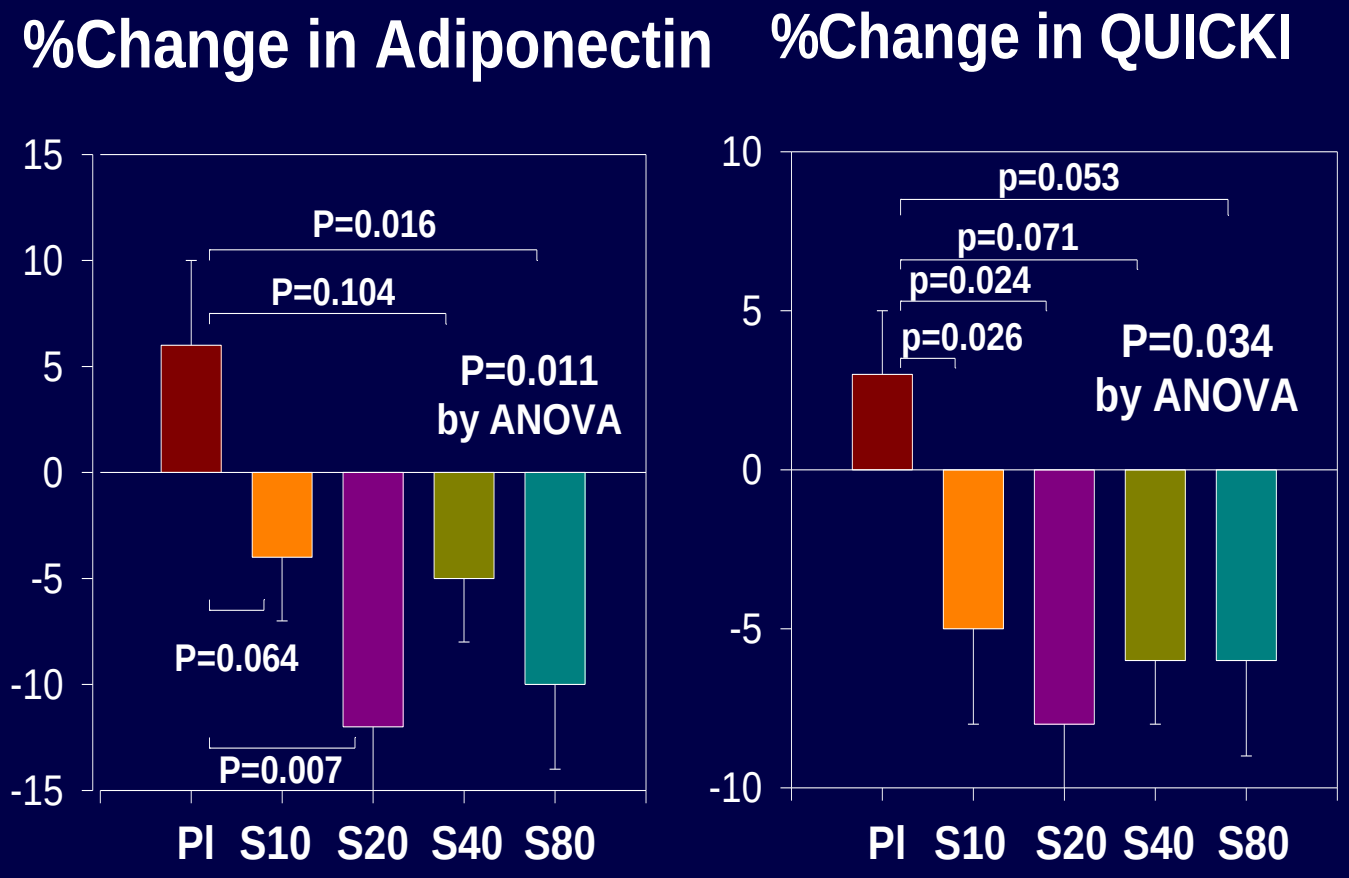
Takaguri A, et al. J Pharmacol Sci 2008;107:80

Gachon University Gil Medical Center

Inhibiting HMG-CoA may mediate glucose level via prenylation pathway



Simvastatin Dose-Dependently Reduces Adiponectin and Insulin Sensitivity In HC Patients

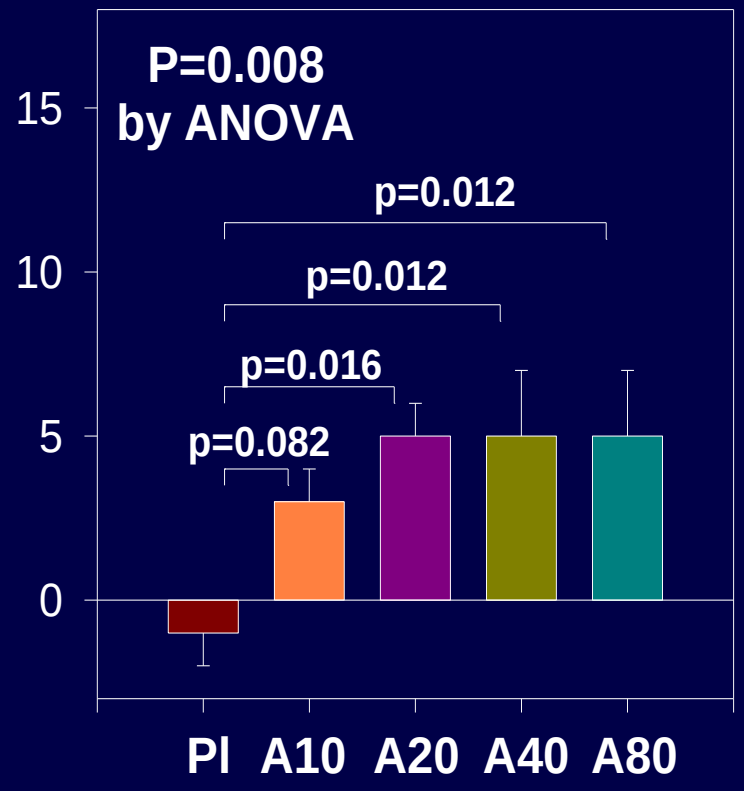


*QUICKI=Quantitative Insulin-Sensitivity Check Index, a surrogate index of insulin sensitivity, QUICKI = 1/[log(insulin)+log(glucose)]

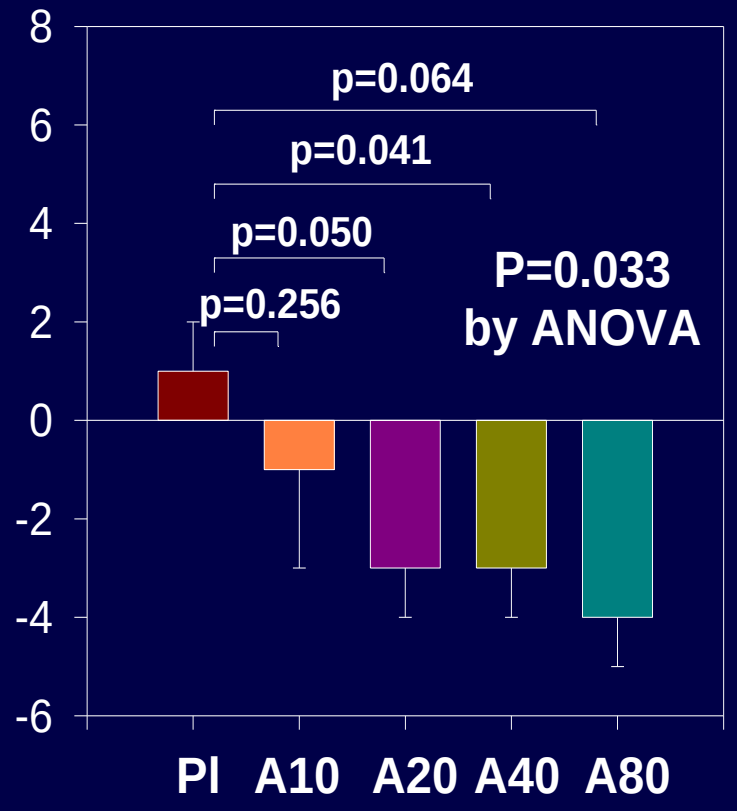
Koh KK, Han SH,et al. Diabetes Care 2008;31:176

Atorvastatin Dose-Dependently Increases Ambient Glycemia and Causes Insulin Resistance In HC Patients

%Change in HbA1C



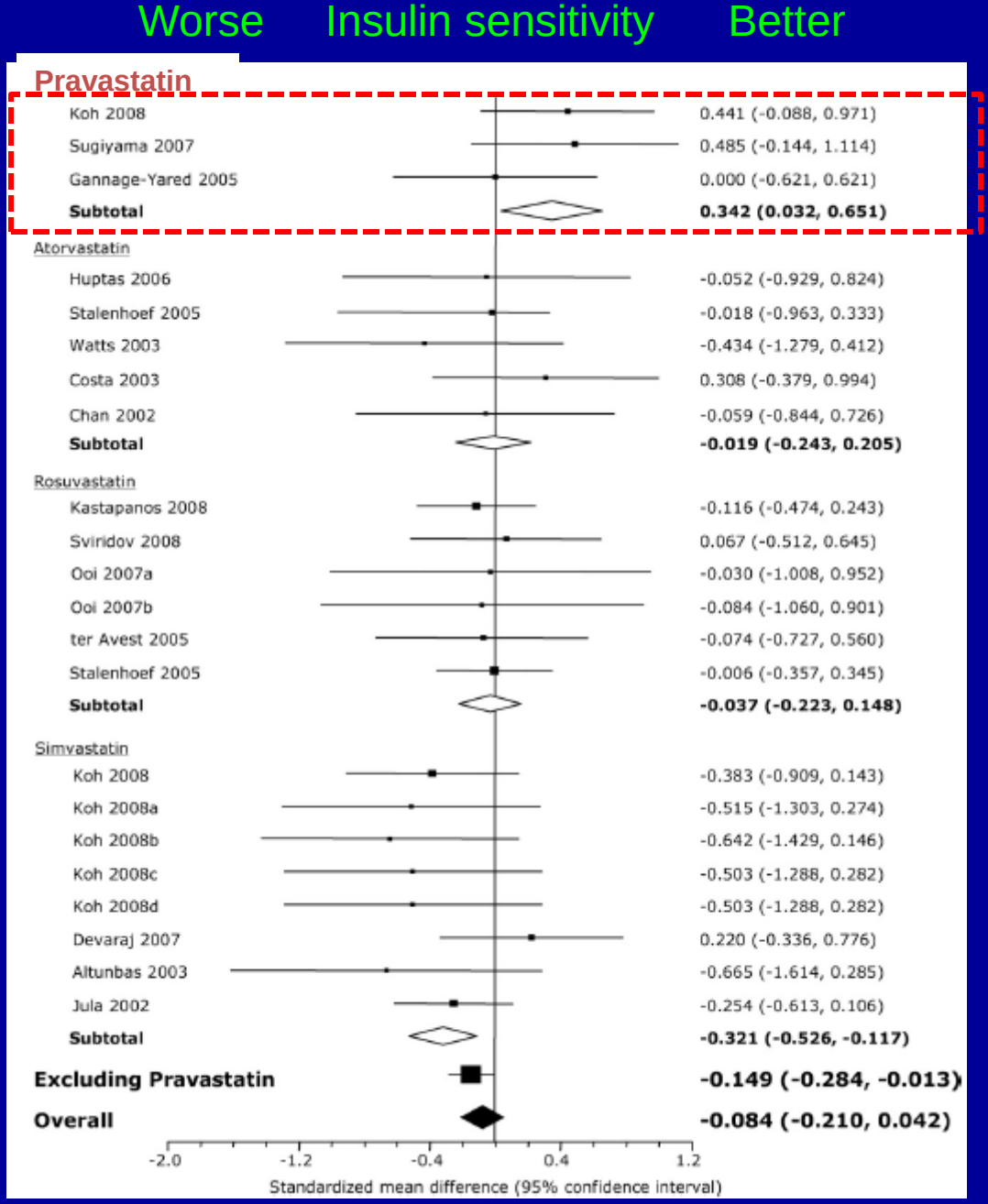
%Change in QUICKI



Koh KK, Han SH, et al. JACC 2010;55:1209

Meta-analysis: Statins and Insulin Resistance

- **16 RCTs (n=1146)**
- **Insulin sensitivity**
  - QUICKI
  - HOMA-IR
  - Euglycemic clamp



William L. Baker et al. Diabetes Res Clin Pract 2010;87(1):98-107

Gachon University Gil Medical Center

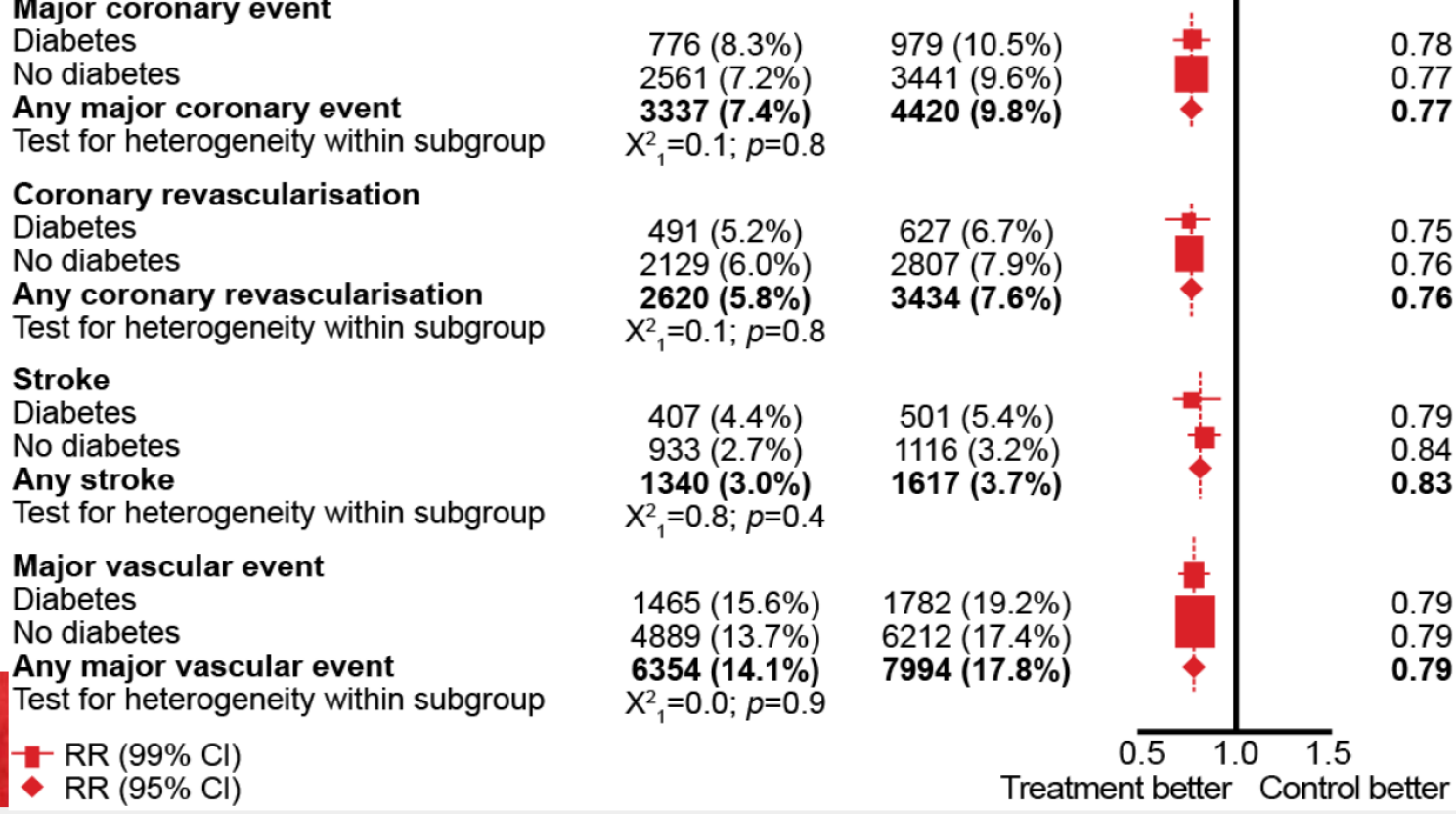
Contents

- Introduction
- Statin use and diabetes: Evidence
- Risk factors for new onset diabetes on statin treatment
- The incidence of new onset diabetes differ in statins?
- Suggested mechanism
- How to minimize the risk of new onset diabetes on statin treatment

Statin Effects on Major CV events are Similar Irrespective of DM

CTTC diabetes subanalysis: (n=18,686)

Major vascular event and prior diabetes	Events (%) Treatment	Control	RR (CI)
Major coronary event			
Diabetes	776 (8.3%)	979 (10.5%)	0.78 (0.69–0.87)
No diabetes	2561 (7.2%)	3441 (9.6%)	0.77 (0.73–0.81)
Any major coronary event	**3337 (7.4%)**	**4420 (9.8%)**	**0.77 (0.74–0.80)**
Test for heterogeneity within subgroup	X^2_1=0.1; p=0.8		
Coronary revascularisation			
Diabetes	491 (5.2%)	627 (6.7%)	0.75 (0.64–0.88)
No diabetes	2129 (6.0%)	2807 (7.9%)	0.76 (0.72–0.81)
Any coronary revascularisation	**2620 (5.8%)**	**3434 (7.6%)**	**0.76 (0.73–0.80)**
Test for heterogeneity within subgroup	X^2_1=0.1; p=0.8		
Stroke			
Diabetes	407 (4.4%)	501 (5.4%)	0.79 (0.67–0.93)
No diabetes	933 (2.7%)	1116 (3.2%)	0.84 (0.76–0.93)
Any stroke	**1340 (3.0%)**	**1617 (3.7%)**	**0.83 (0.77–0.88)**
Test for heterogeneity within subgroup	X^2_1=0.8; p=0.4		
Major vascular event			
Diabetes	1465 (15.6%)	1782 (19.2%)	0.79 (0.72–0.86)
No diabetes	4889 (13.7%)	6212 (17.4%)	0.79 (0.76–0.82)
Any major vascular event	**6354 (14.1%)**	**7994 (17.8%)**	**0.79 (0.77–0.81)**
Test for heterogeneity within subgroup	X^2_1=0.0; p=0.9		



CTTC. Lancet 2008;371:117-25.

Gachon University Gil Medical Center

Risk and Benefits of Statin Tx

- **Statin tx vs placebo:**

New onset DM---

+1, NNH=1,002/yr

Major CVD ---

- 5.4, NNT=185/yr

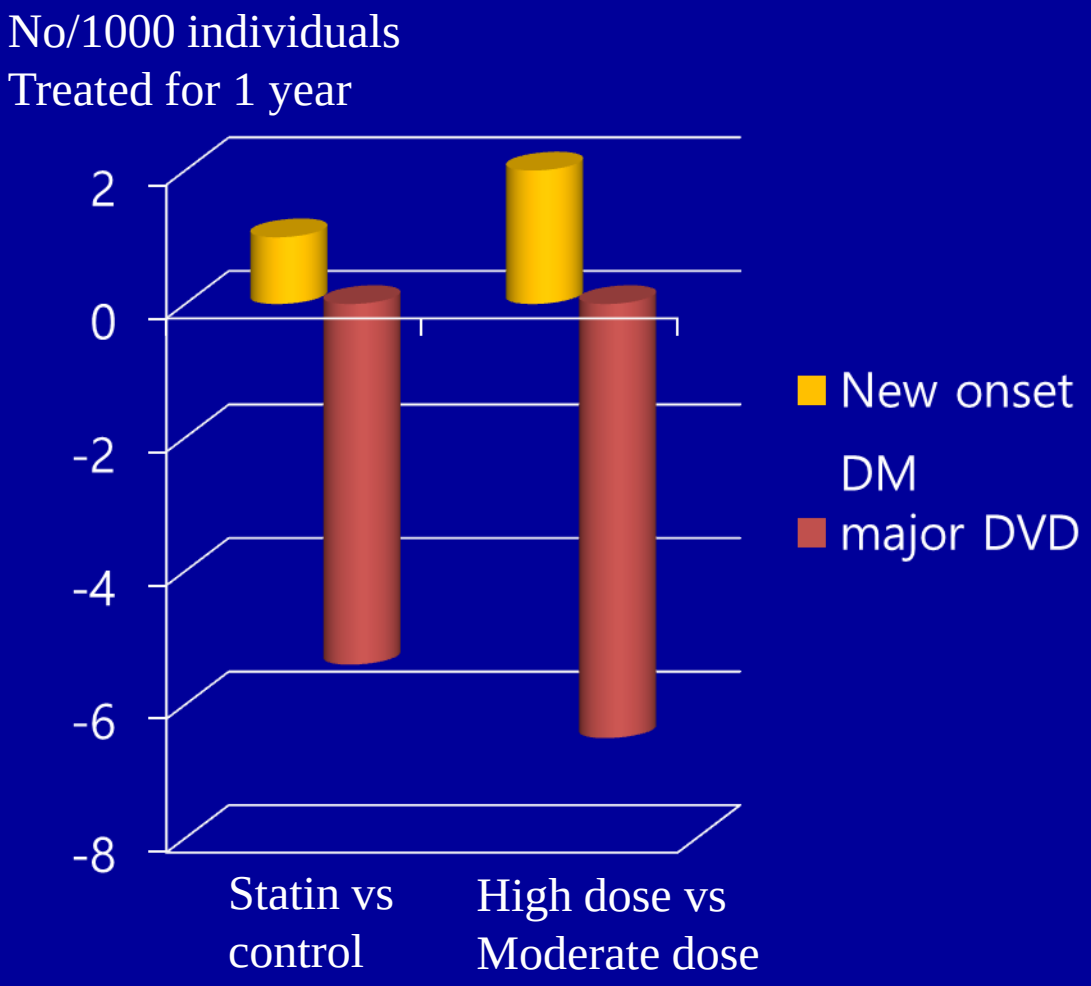
- **High intensity statin vs. moderate intensity statin**

New onset DM---

+ 2, NNH=498/yr

Major CVD ---

- 6.5, NNT=1555/yr



Sattar 2010, Preiss, PROVE-IT, A=Z, TNT, IDEAL, SEARCH, JUPITER

Guidelines

6. Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines (93). Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.	B (Moderate)	44	I‡	B

Gachon University
Gil Medical Center

Guidelines

- The absolute reduction in the risk of CVD in high risk patients outweighs the possible adverse effects of a small increase in the indicence of diabetes.

ESC/EAS guidelines for the management of dyslipidaemias
Atherosclerosis 2011;217:3-46

T2DM and Excess Risk of CVD

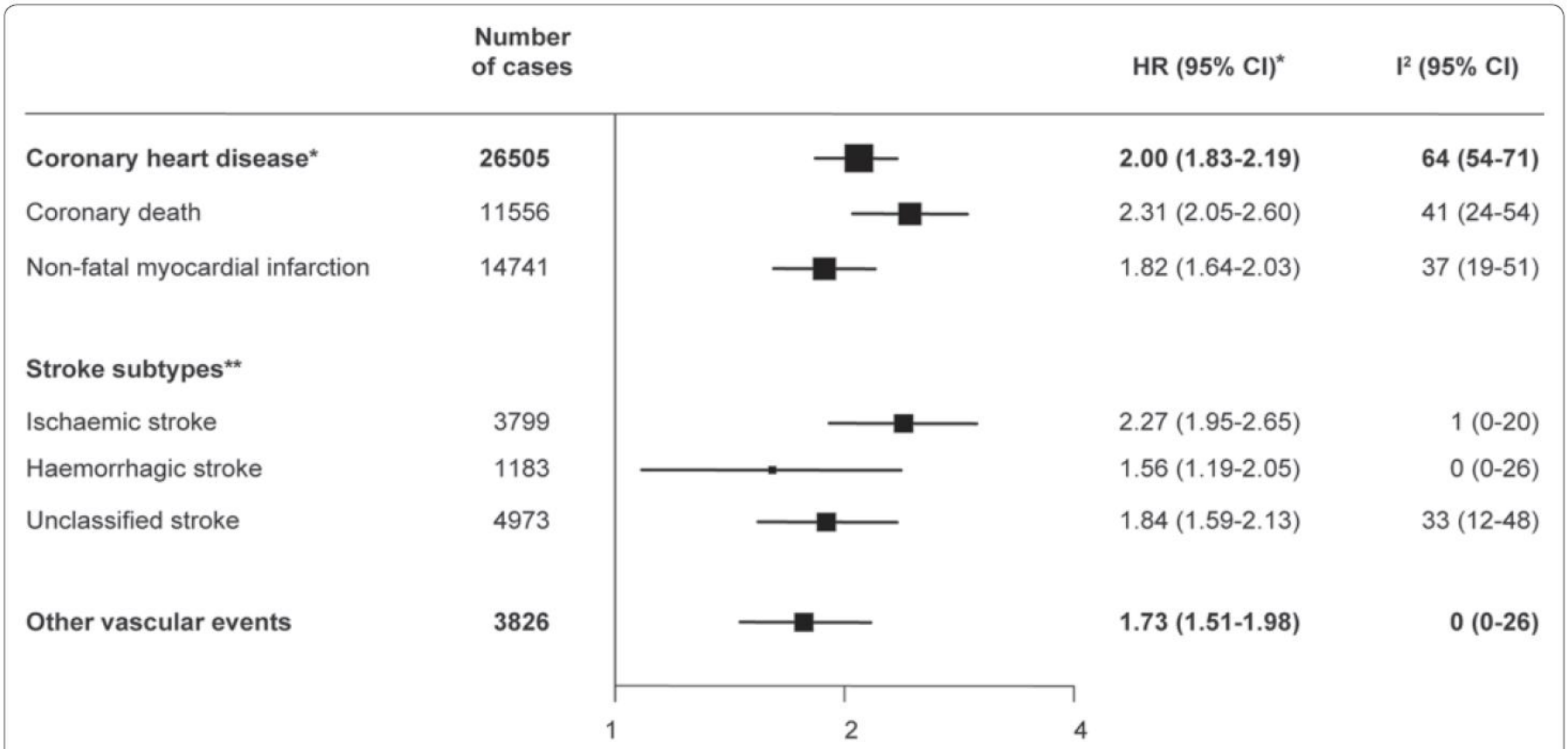


Figure 1. Type 2 diabetes confers excess risk for a wide range of vascular diseases. *Adjusted for age, smoking, BMI, systolic blood pressure and stratified by sex and trial arm (where appropriate). **Includes fatal and nonfatal events.

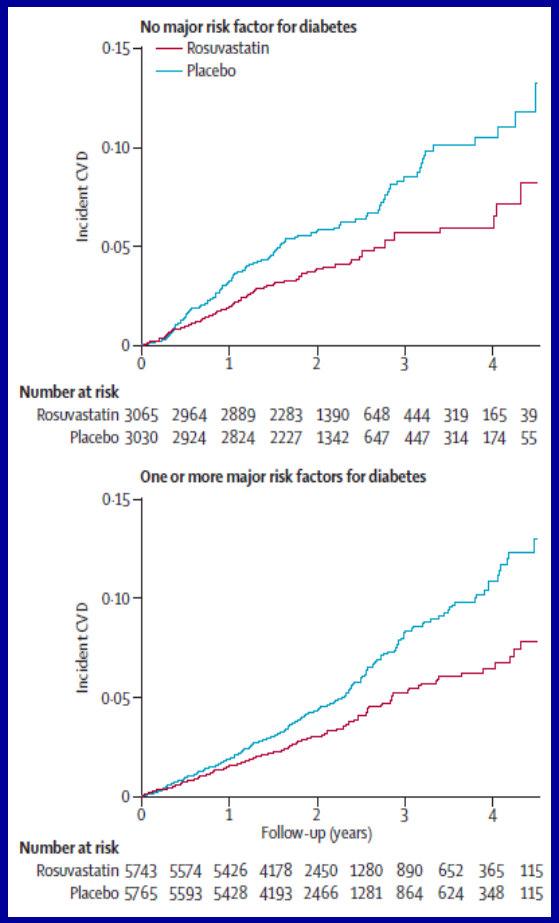
Ray K. Cariovascular Diabetology 2013;12(suppl1) S3

Gachon University Gil Medical Center

CV Benefits and Diabetes Risks of Rosuvastatin In Primary Prevention: JUPITER trial

Lancet 2012;380:581

CV events and total mortality in Pts c/s RFs* for DM

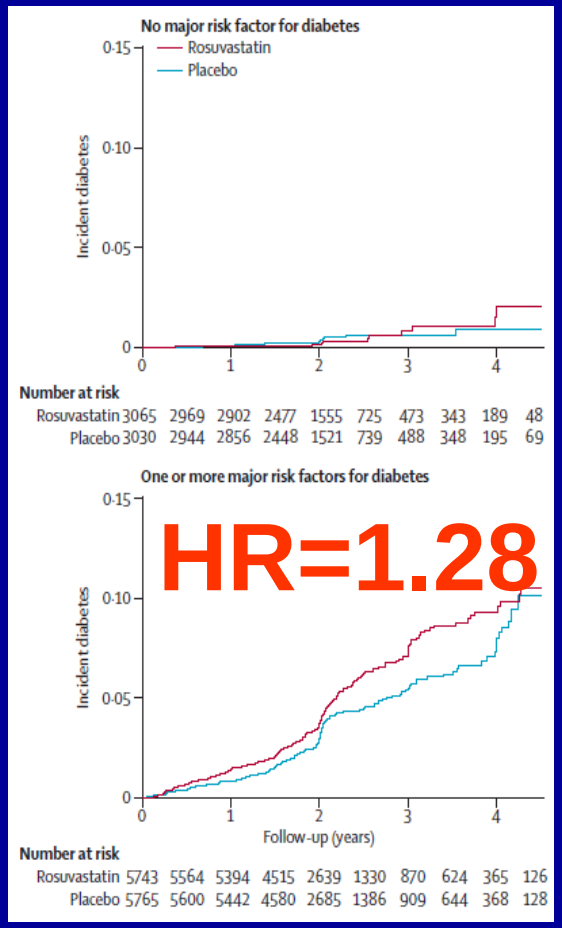


HR=0.48

-13%

HR=0.61

Diabetes in Pts c/s RFs* for DM



*MetS, IGT (101-125 mg/dL), BMI>30 kg/m2, or HbA1c> 6%

Gachon University Gil Medical Center

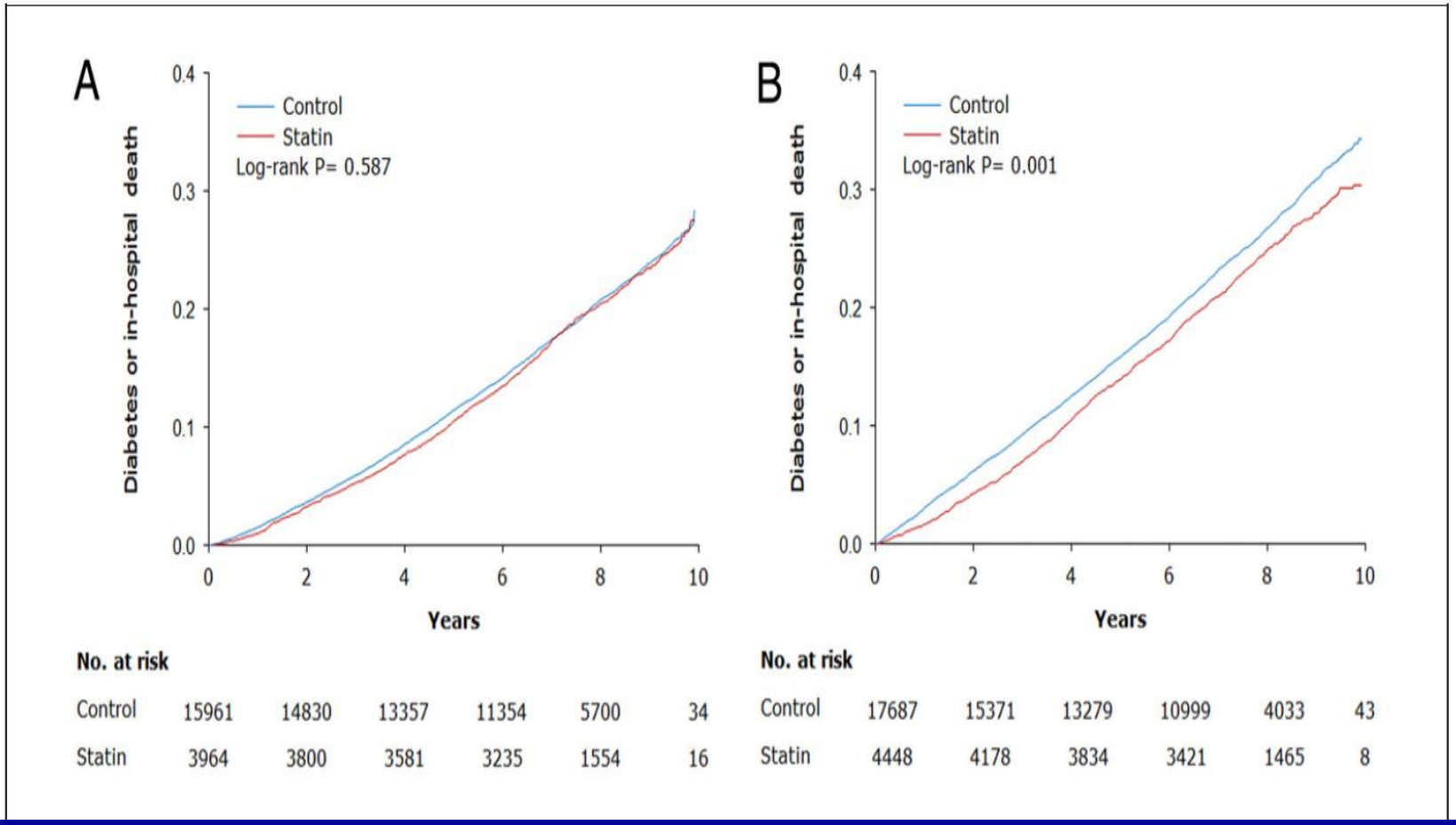
Statins increase the risk of dysglycemia and or DM in a dose dependent fasion

- Absolute terms at **low dose** prevent 5-7 CVD events for every 1 new case of DM over 1000 person years of treatment
- Fro **intensive statin therapy** this is 3 CVD cases prevented per 1 extra case of DM

Statin, Risk of DM, and Outcomes in the General Population (Taiwan National Health Insurance)

Low CV risk subjects

High CV risk subjects

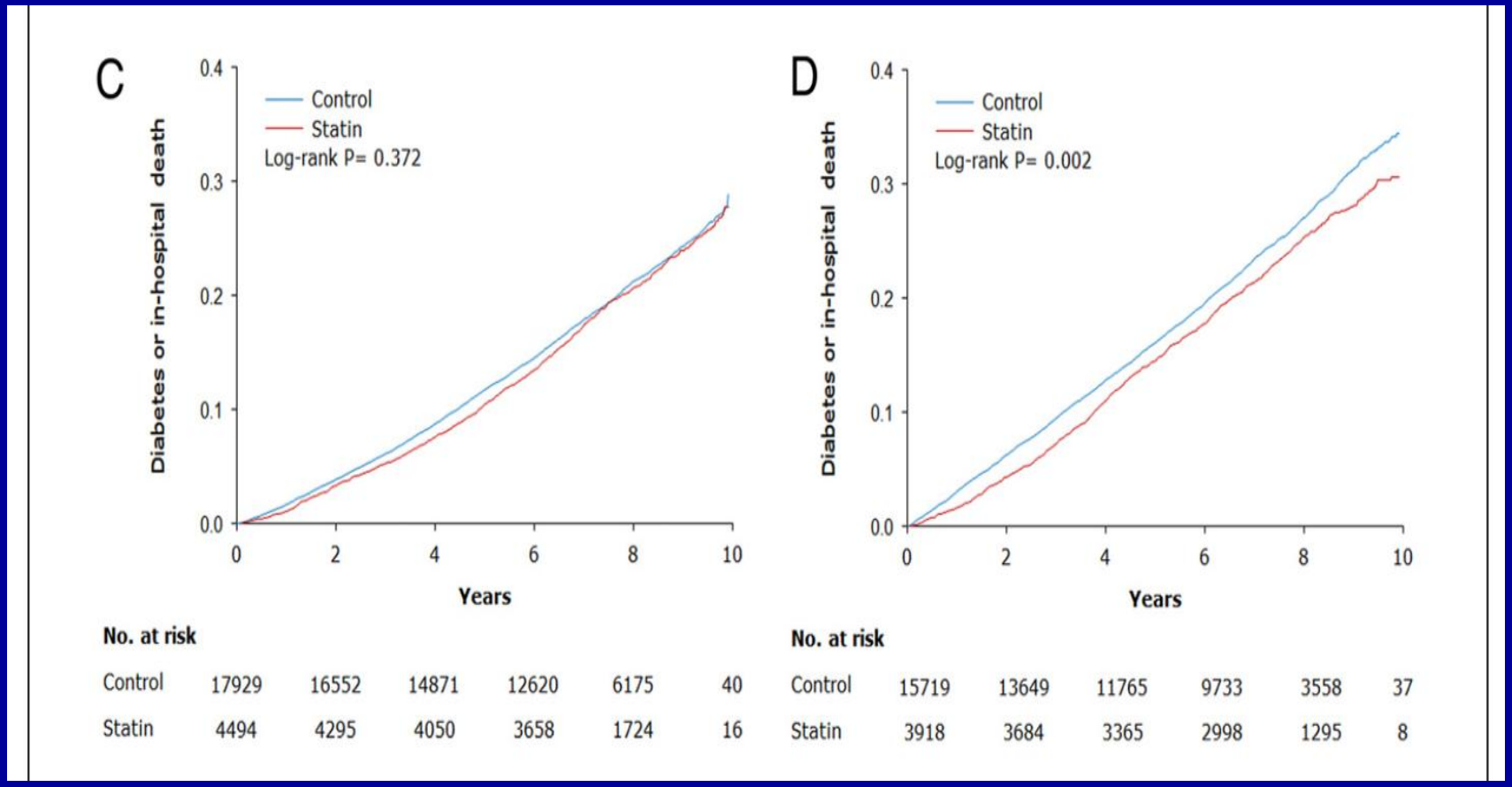


Wang KL, et al. JACC 2012;60:1231-8.

Statin, Risk of DM, and Outcomes in the General Population (Taiwan National Health Insurance)

Primary CV prevention

2ndary CV prevention



Gachon University Gil Medical Center

Summary & Conclusions (I)

- Diabetes is a major risk factor for macrovascular including CVD and microvascular disease.

- Statin increases the *incidence of new onset diabetes.*

- The **beneficial effects of statins** including high dose statins **outweigh the risk of statin for new onset diabetes, therefore, statin should be continued in high CV risk patients.**

Summary & Conclusions (II)

- **Differential effects** on insulin sensitivity and incidence of new onset diabetes **among statins** have been noted.

- **Dose reduction and careful selection of statin** should be considered by the risk benefit assessment for reduction of CVD and risk of DM in patients with *high risk for developing diabetes*, especially *in East-Asian population and low cardiovascular risk*.

- Further researches for this topic are warranted in the future.


Thank you for
your attention!!!

Intracellular Actions of Statins

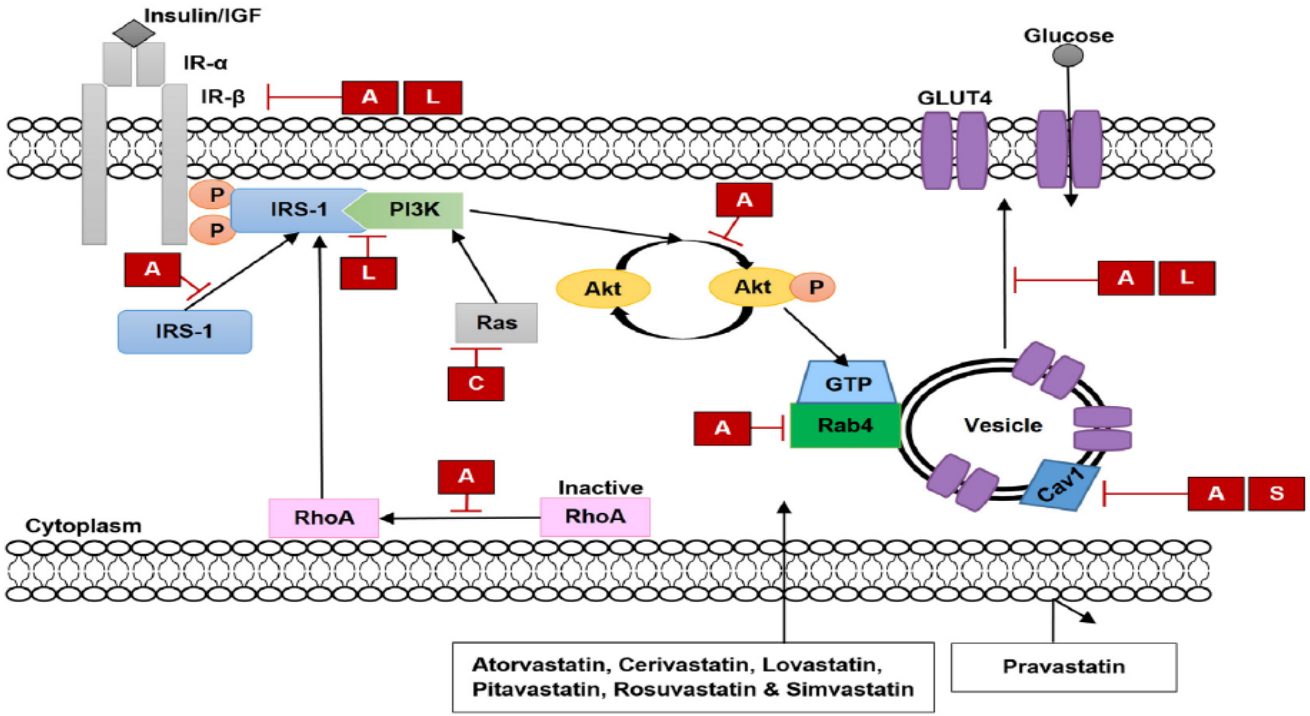


Fig. 2 – Intracellular actions of statins. Lipophilic statins penetrate the cell membrane easier those which are hydrophilic, and therefore are likely to have more extrahepatic effects. Statins have been shown to reduce membrane IR phosphorylation or expression, resulting in insulin resistance. Within the cell, insulin signalling and GLUT4 transport can be altered by changes in IRS-1, Akt, Rab4, Ras, IR-β, or membrane fraction of RhoA, all of which have been shown to be inhibited by statin therapy. Individual statins have been shown to affect different factors, as illustrated in this figure. A, atorvastatin; C, cerivastatin; L, lovastatin; Cav1, caveolin-1; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; GLUT4, glucose transporter; GTP, guanosine triphosphate; IGF, insulin like growth factor; IR, insulin receptor; IRS-1, Insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; S, simvastatin.

Brault M, et al. Metabolism 2014;63:735-45.

Mevalonate Pathway and Statin Mechanisms

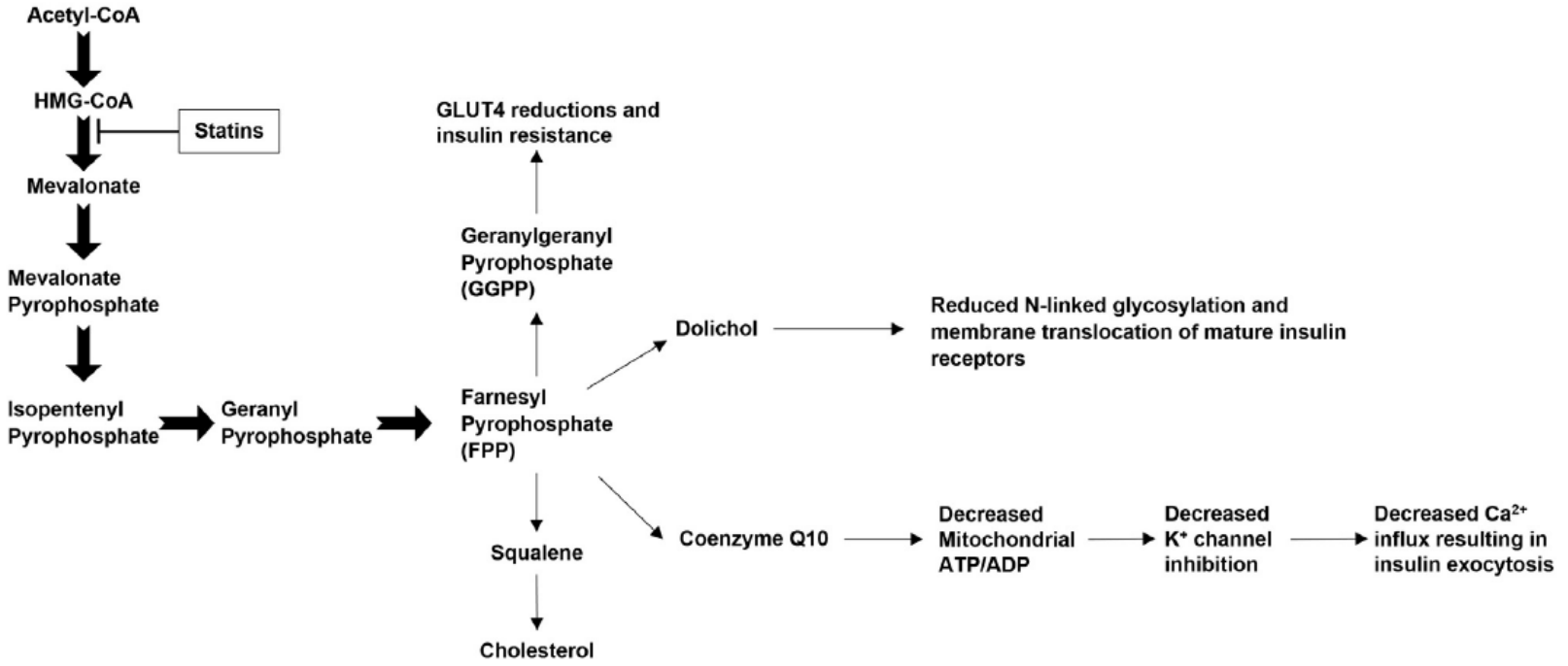
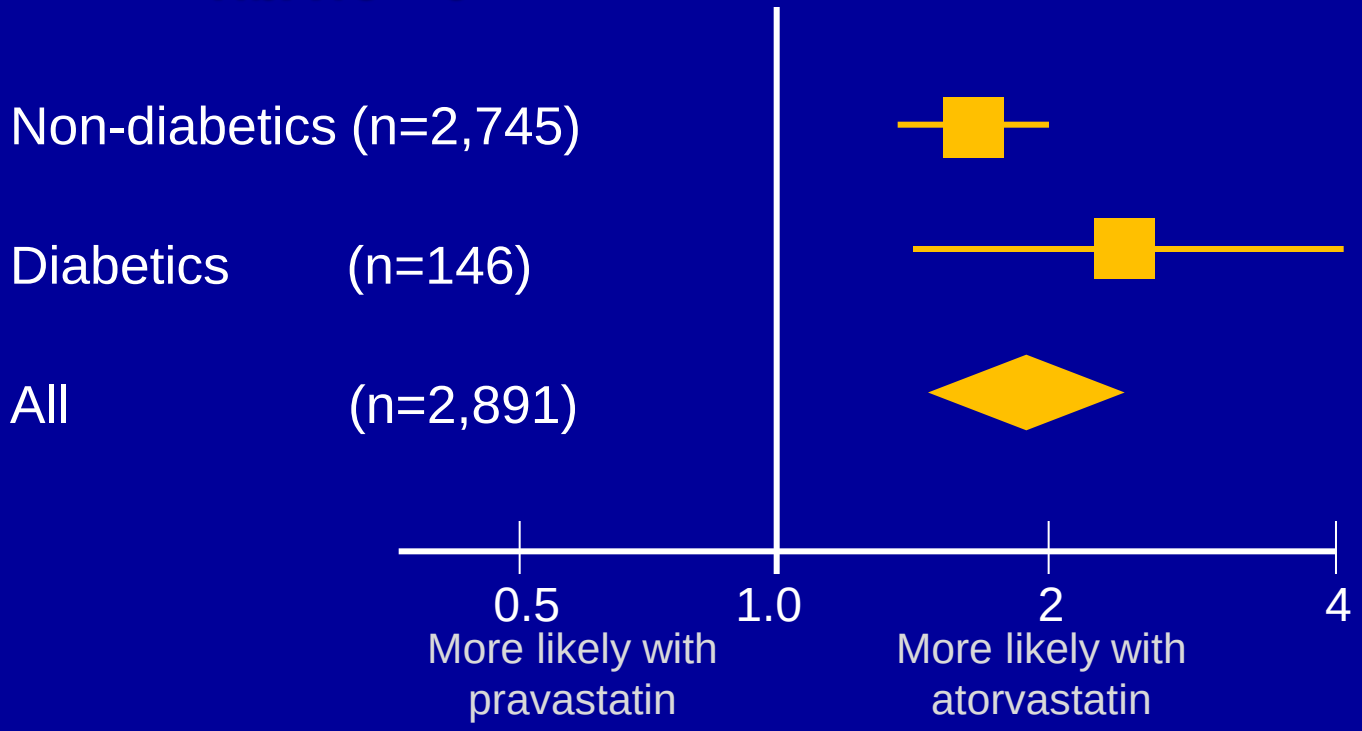


Fig. 1 – Mevalonate pathway and statin mechanisms.Mevalonate pathway inhibition by statins causes reductions in other downstream products. The major components which may be involved in new-onset diabetes are GGPP, FPP, dolichol and coenzyme Q10. Decreases in isoprenoids FPP and GGPP result in decreased GLUT4 glucose uptake and decreased Ras activity. Reduced dolichol results in reduced IR membrane levels. CoQ10 is necessary to produce mitochondrial ATP to stimulate insulin secretion via calcium influx in β-cells.ADP, adenosine diphosphate; ATP, adenosine triphosphate; Ca^{2+}, Calcium ions; CoQ10, coenzyme Q10; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; GLUT4, glucose transporter 4; IR, insulin receptor; K^{+}, potassium ions.

Brault M, et al. Metabolism 2014;63:735-45.

High-Dose Atorvastatin Associated with Worse Glycemic Control: A PROVE-IT TIMI-22 Substudy

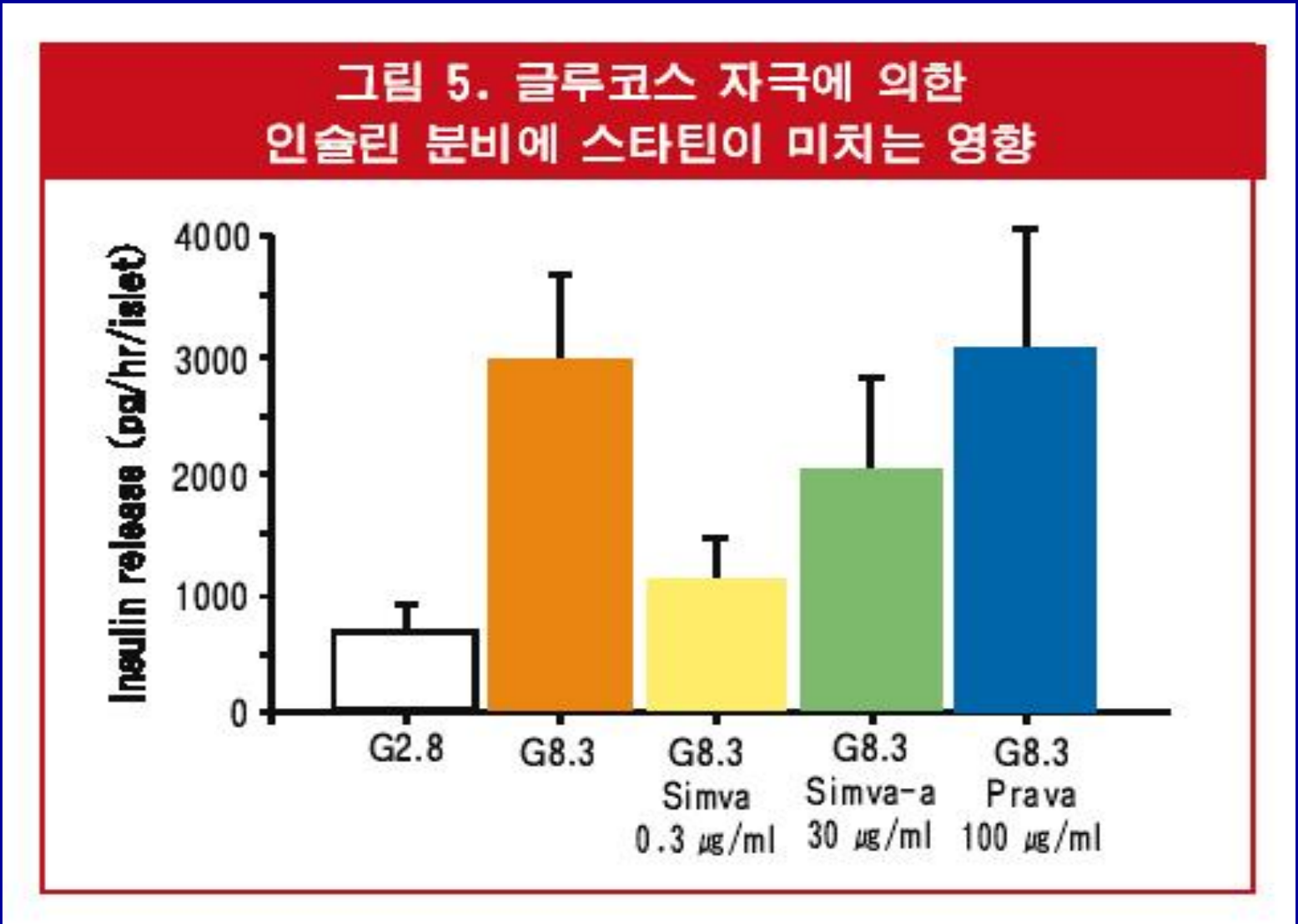
Adjusted HR & 95% CI for developing **HbA1c > 6** in those with baseline **HbA1c < 6**



Marc S. Sabatine, st al. Circulation 2004;110, III-834

Gachon University Gil Medical Center

Effects of Statins on Glucose-Stimulated Insulin Secretion

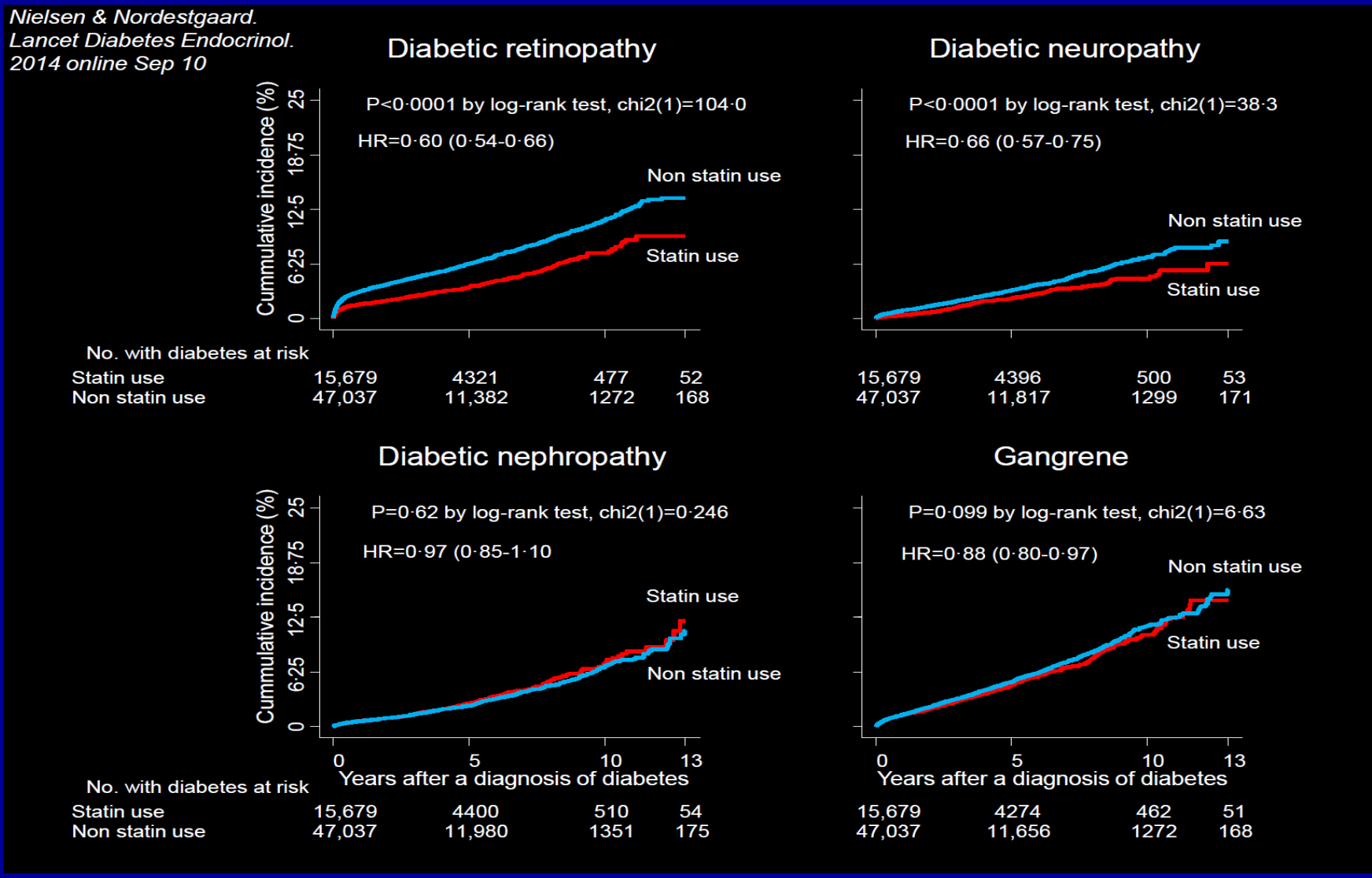


Yada T, et al. Br J Pharmacol 1999;126:1205

Gachon University
Gil Medical Center

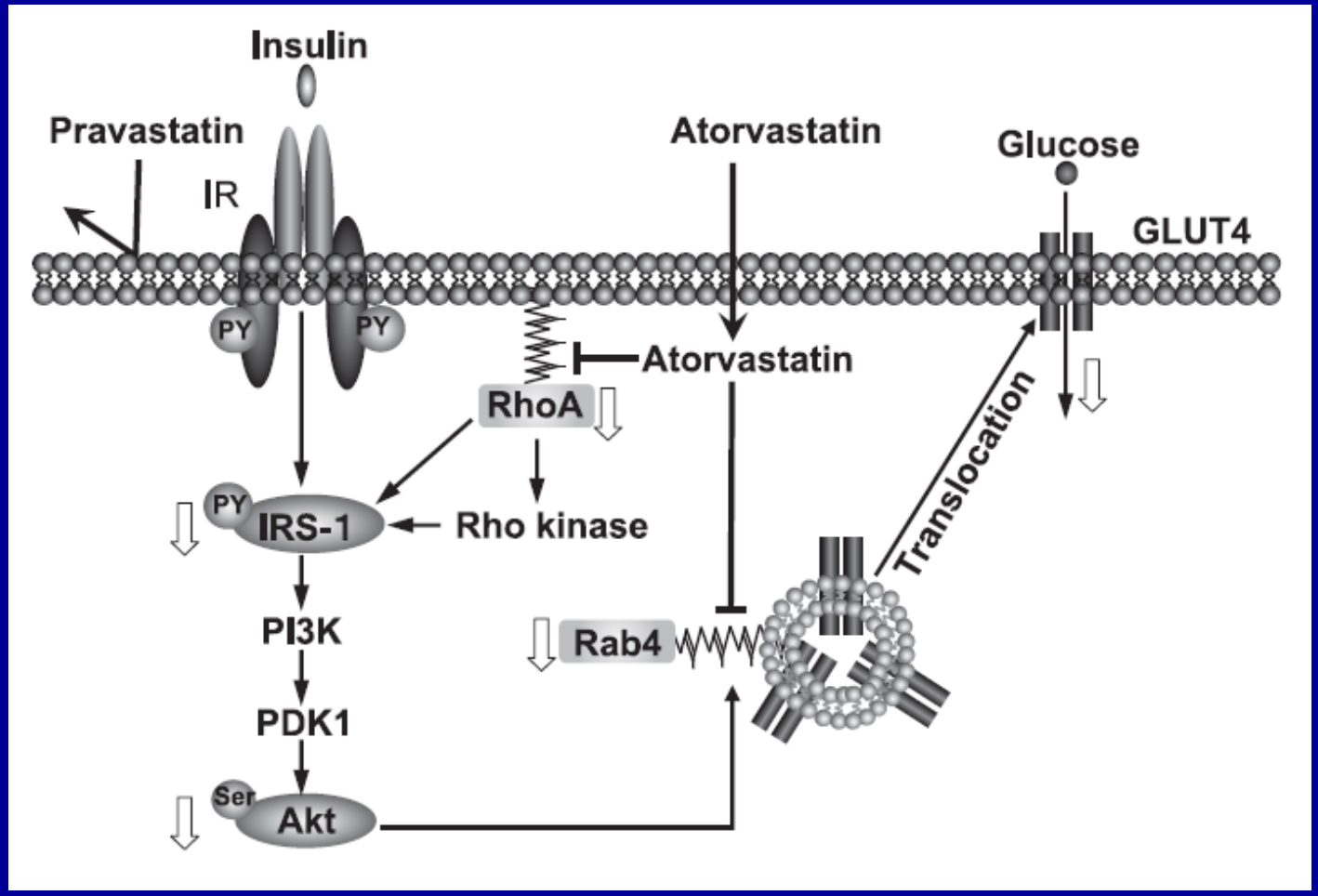
Statin and Microvascular Complications

Nielsen & Nordestgaard. Lancet Diabetes Endocrinol. 2014 online Sep 10



Gachon University Gil Medical Center

Impaired Insulin Signaling Pathway by Atrovastatin in 3T3L1 adipocyte



Takaguri A, et al. J Pharmacol Sci 2008;107:80

Gachon University Gil Medical Center