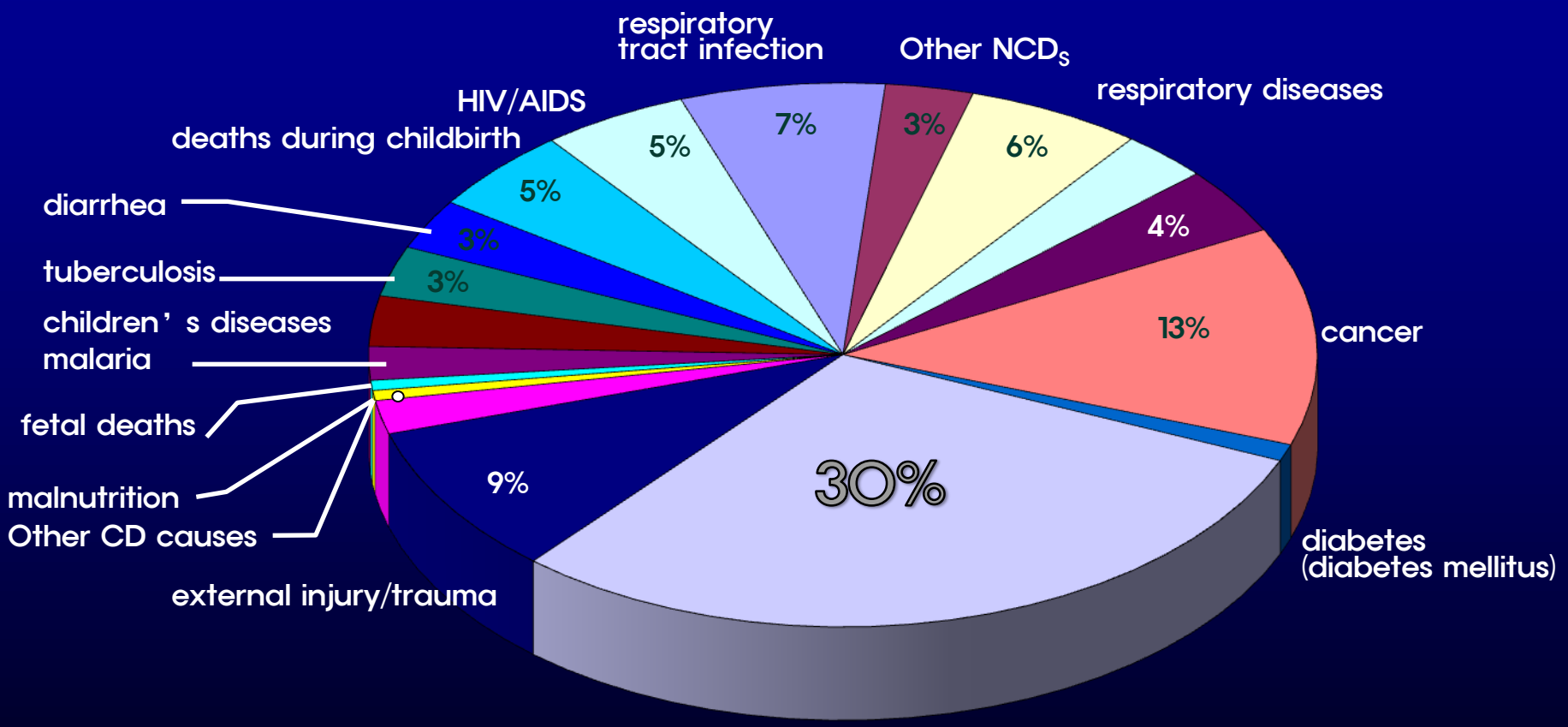
Tailored Statin Treatment for Type 2 Diabetes

Han, Ki Hoon
Asan Medical Center
University of Ulsan

Cardiovascular disease ; No1. death （2001）

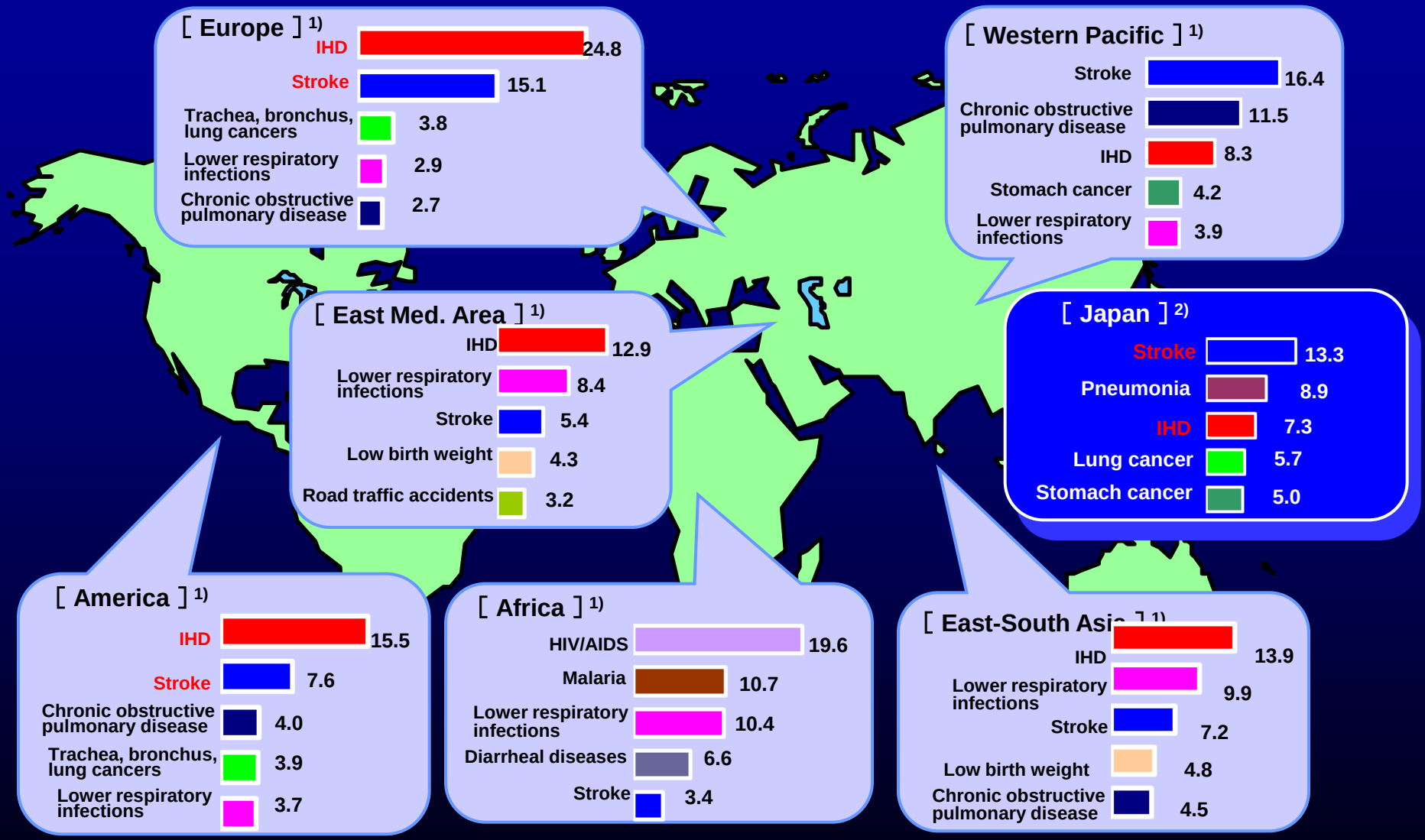


cardiovascular

Data from 56.5 million death

Main Causes of Death in the World, 2002

（Death Rate ％）



1) From WHO. The World Health Report 2004

2) From MHLW. Vital Statistics of Japan 2002

Difference between Korean and U.S. population

BMI

Unit: kg/m^2

	Men	Women
Korean	24.1	23.5
U.S.	26.6	26.5

*BMI (Body Mass Index)
Over weight: 〉25 / Obesity: 〉30

Prevalence

Unit: %

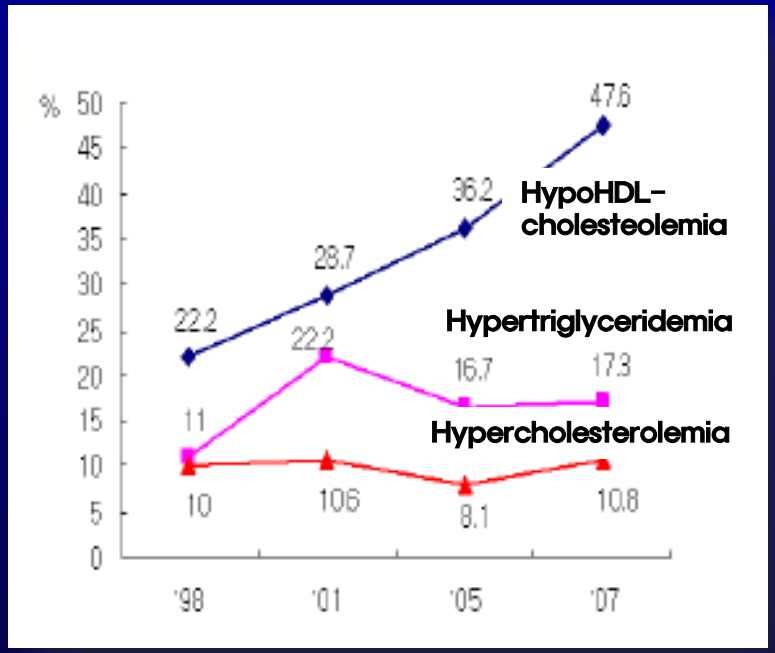
	IFG	DM
Korean (〉30yrs)	16.1	9.7
U.S. (〉20yrs)	35.4	10.7

*IFG (Impaired Fasting Glucose)/ DM (Diabetes Mellitus)

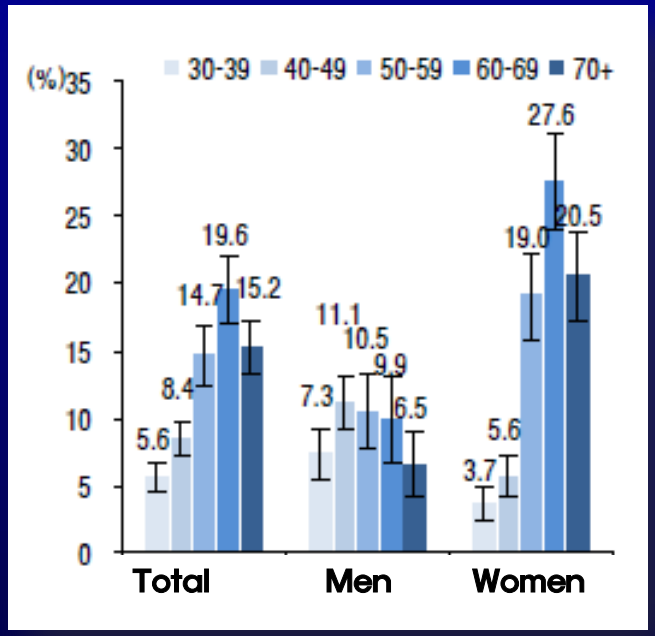
*Ref. 4th KNHANES(2007) *Korea National Health And Nutrition Examination Survey*
NHANES (1999-2000)
National Diabetes Fact Sheet, 2007

Prevalence of dyslipidemia

Dyslipidemia



Hyperlipidemia by aging



Prevalence of hypoHDL-cholesterolemia: HDL-cholesterol〈40mg/dL

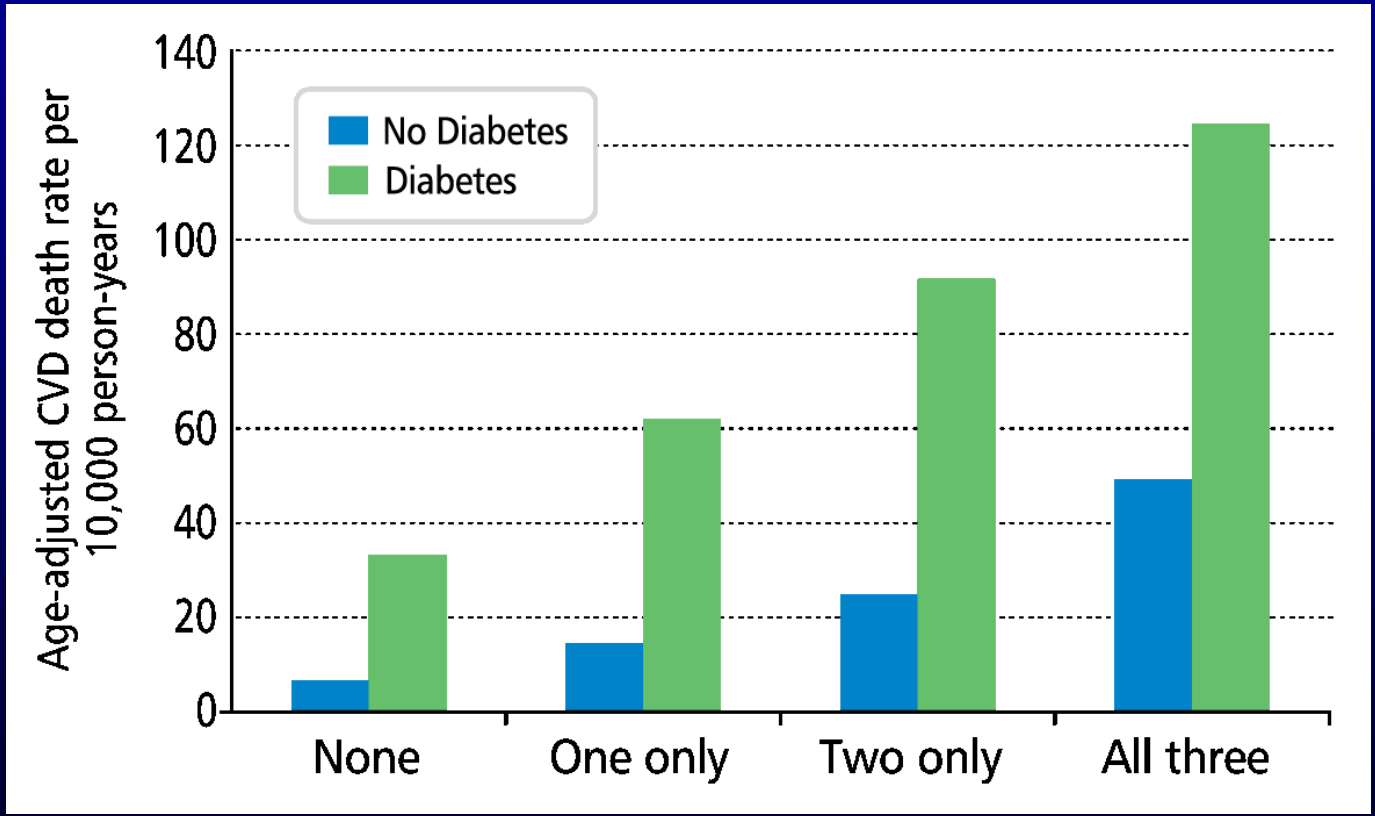
Prevalence of hypertriglyceridemia: triglyceride 〉200mg/dL

Prevalence of hypercholesterolemia: Total cholesterol 〉 240mg/dL or taking drug for cholesterol lowering

*30 years old, age standardization by estimated population on 2005

Ref. 4th KNHANES(2007) *Korea National Health And Nutrition Examination Survey

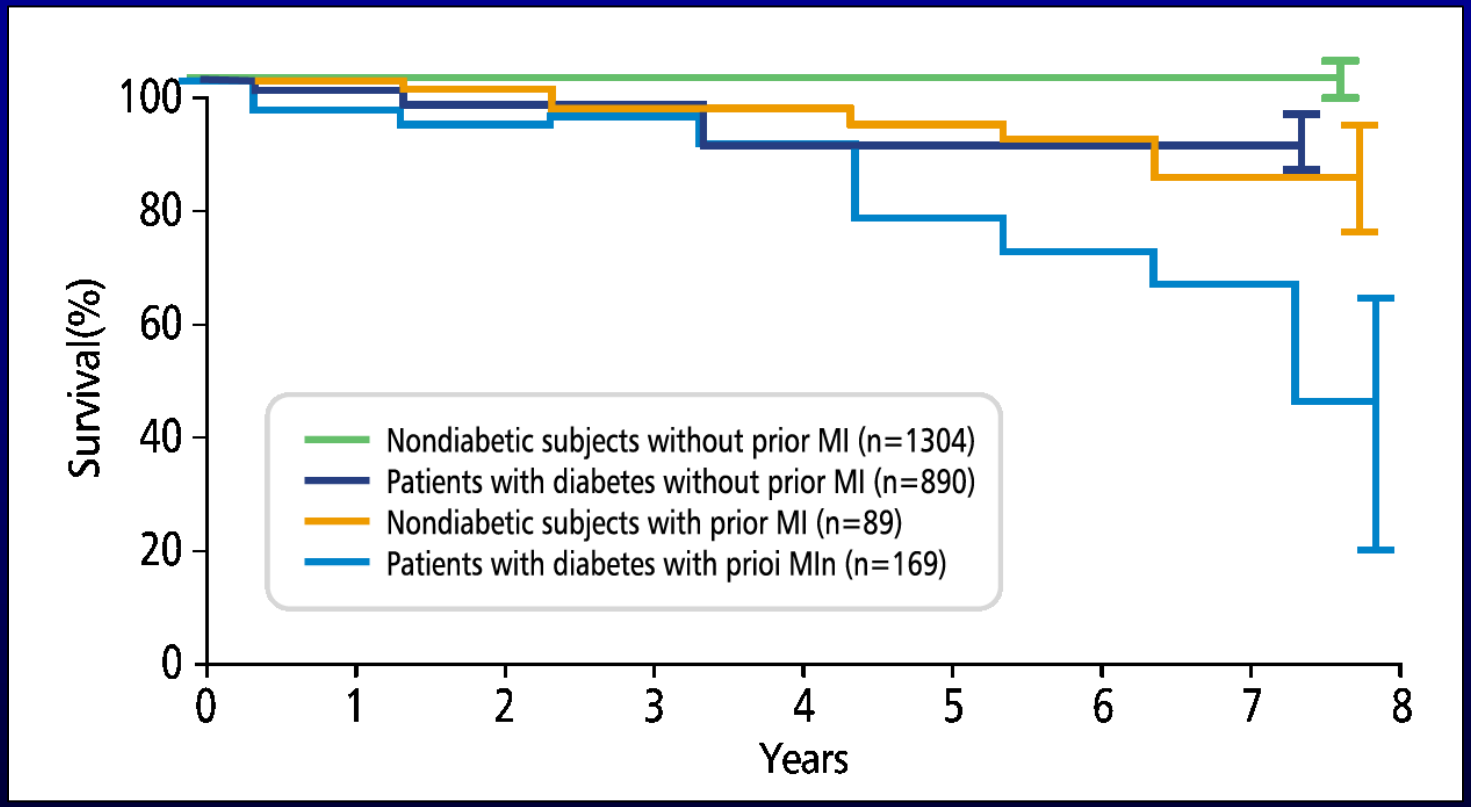
Influence of Multiple Risk Factors* on CVD Death Rates in Diabetic and Nondiabetic Men



*Serum cholesterol〉200mg/dL, Smoking, SBP〉120 mmHg

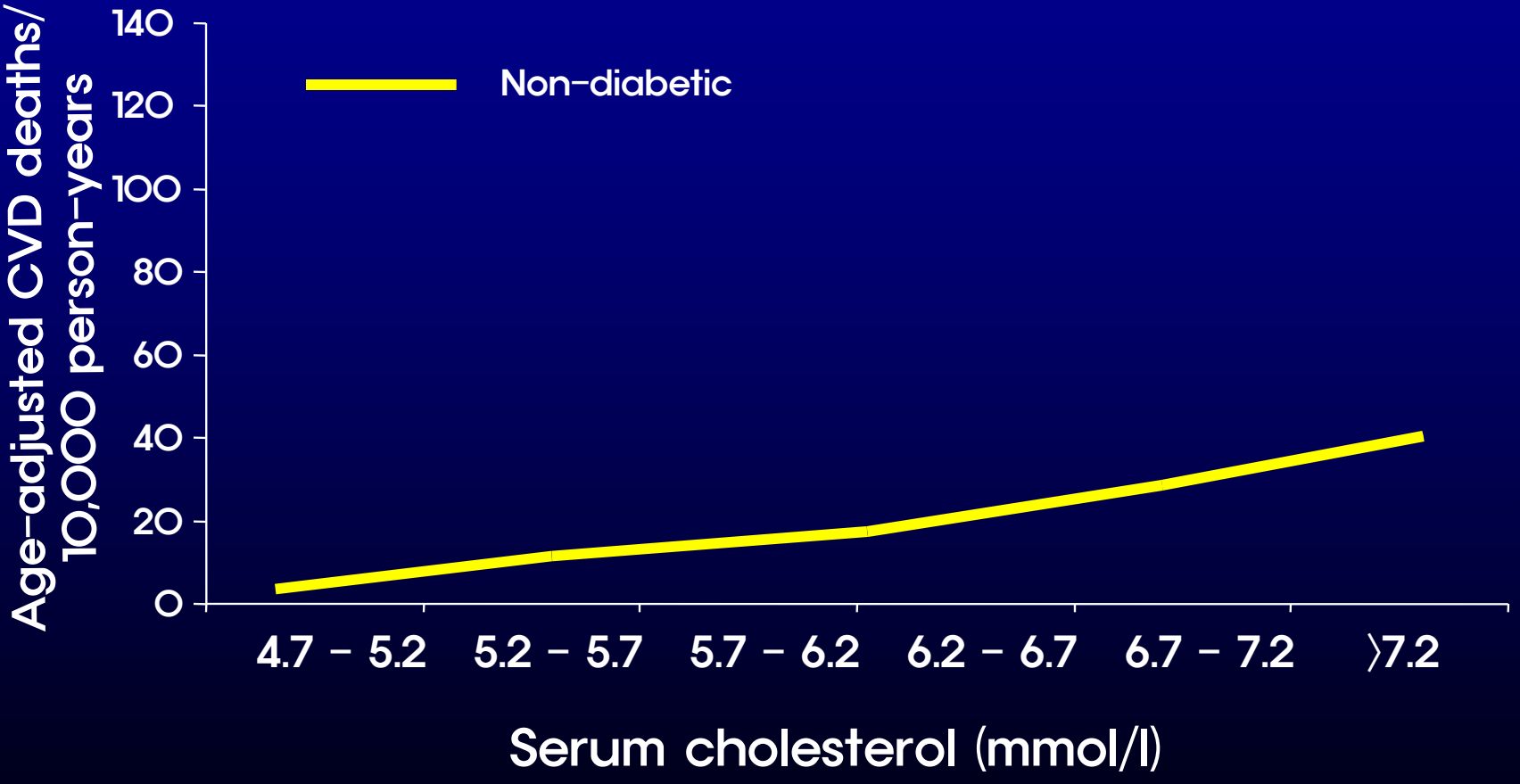
Diabetes Care. 1993;16(2):434-444

Comparison with Risk of DM and MI



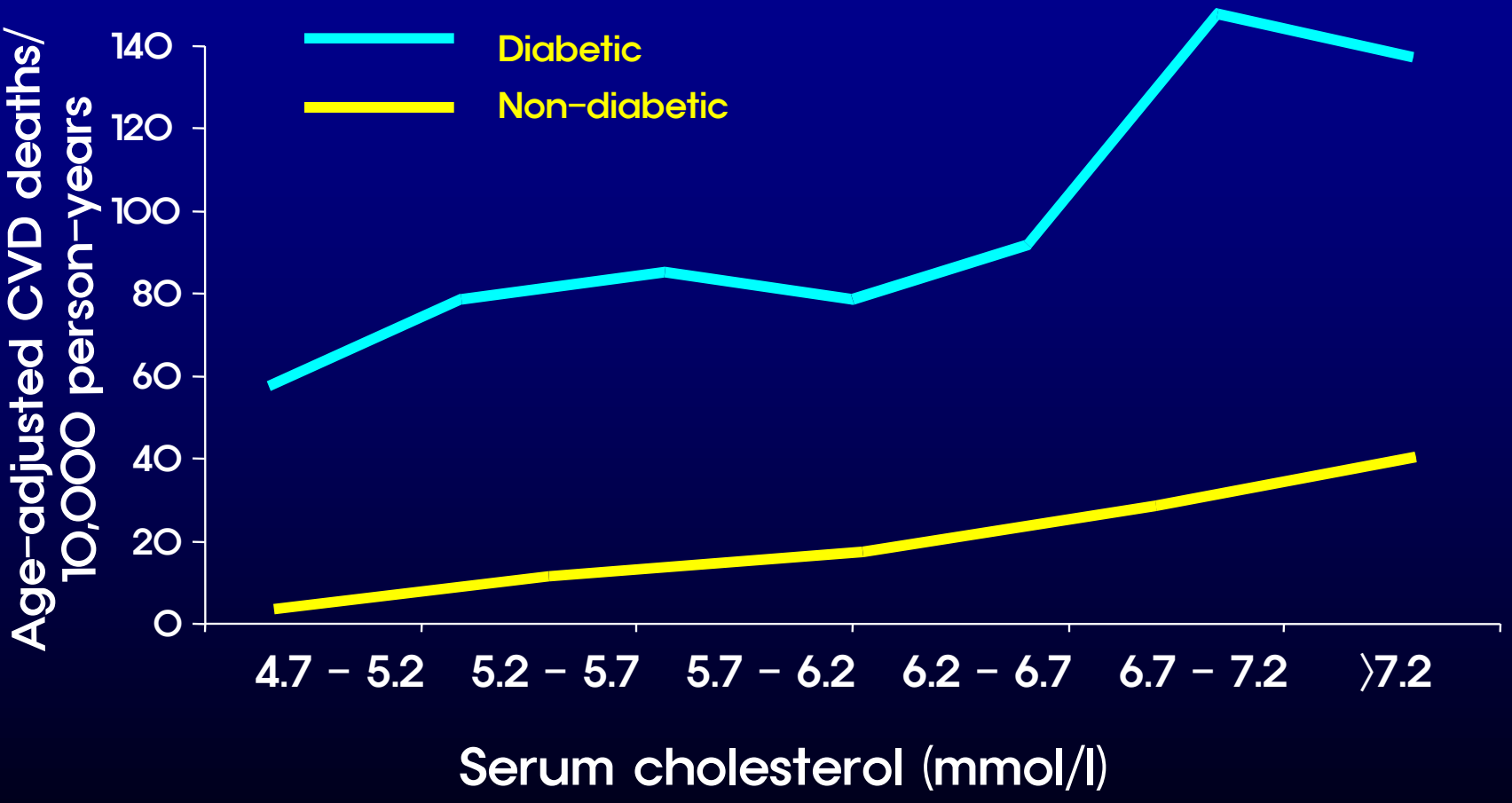
Diabetic risk is equivalent to CHD(Mycardial Infarction) risk

MRFIT: Diabetes, Other Risk Factors and 12-Year Cardiovascular Mortality



Stamler J, Vaccaro O, Neaton JD, et al, Diabetes Care (ii) 1993; 16/2: 434-444

MRFIT: Diabetes, Other Risk Factors and 12-Year Cardiovascular Mortality



Stamler J, Vaccaro O, Neaton JD, et al, Diabetes Care (ii) 1993; 16/2: 434-444

ATP III: Management of Diabetic Dyslipidemia

- Diabetes: CHD risk equivalent
- Primary target of therapy: LDL–C
- Therefore, goal for persons with diabetes: ⟨100 mg/dL
- Therapeutic options:
  - LDL–C 100–129 mg/dL: increase intensity of TLC; add drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid); intensify statin therapy
  - LDL–C ≥130 mg/dL: simultaneously initiate TLC and LDL–C–lowering drugs
- After LDL–C goal is met, if TG ≥200 mg/dL: non–HDL–C (⟨130 mg/dl) becomes secondary target

JAMA 2001; 285:2486–2497

LDL Cholesterol Goals ATP III Update, 2004

Risk Category	LDL-C Goal (mg/dL)
Very high: (NEW) CVD + multiple risk factors (especially diabetes), or severe/poorly controlled risk factors, or metabolic syndrome, or ACS	〈100 〈70 (optional goal)
High: CHD or CHD risk equivalents (10-year risk >20%)	〈100
Moderately high: 2+ risk factors (10-year risk 10%-20%)	〈130 〈100 (optional goal)
Moderate: 2+ risk factors (10-year risk 5%-10%)	〈130
Low: 0-1 risk factors	〈160

Grundy SM et al. *Circulation* 2004;110:227-239

Diabetes Mellitus or Lipidus ?

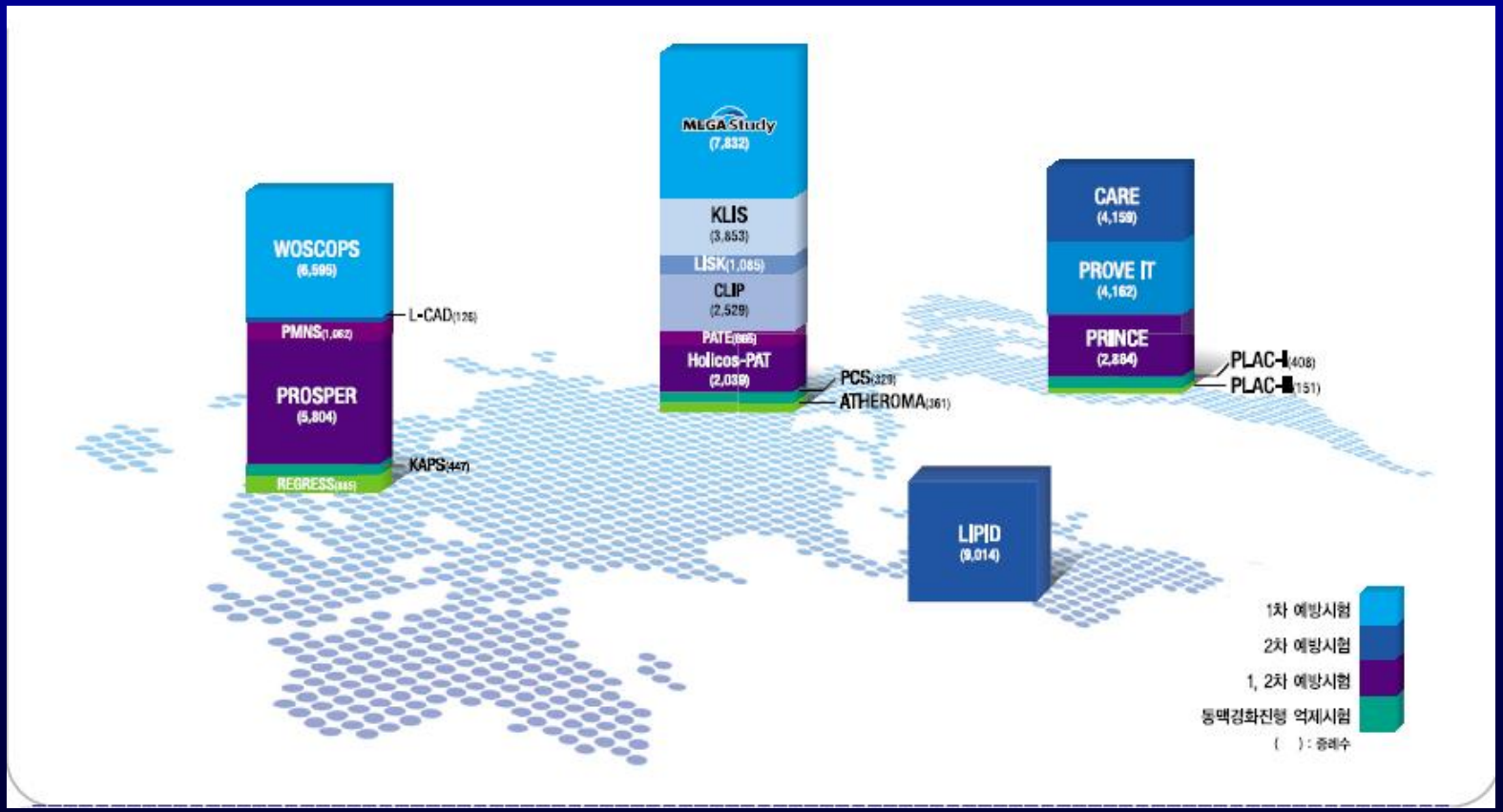
제2형 당뇨병 환자에게 발생한 관상동맥 질환의 위험인자 **(UKPDS: 23)**

Position in model	Coronary artery disease (n=280)		Fatal or non-fatal myocardial infarction (n=192)	
	Variable	p-value	Variable	p-value
1.	LDL chol	<0.001	LDL chol	0.0022
2.	HDL chol	0.001	Diastolic BP	0.0074
3.	HbA_{1c}	0.002	Smoking	0.025
4.	Systolic BP	0.0065	HDL chol	0.026
5.	Smoking	0.056	HbA_{1c}	0.053

2,693 white patients with type 2 diabetes mellitus
***Stepwise multivariate Cox models**

Turner RC et al. *BMJ* 1998;316:823–8

Pravastatin Trials in the world



Evidences of over 54,000 cases for 15 yrs

Pravastatin Pooling Project

WOSCOPS (1995)
6,595 Males
Age: mean 55(45–64)
TC: mean 272 mg/dL
F/U: 4.9 years

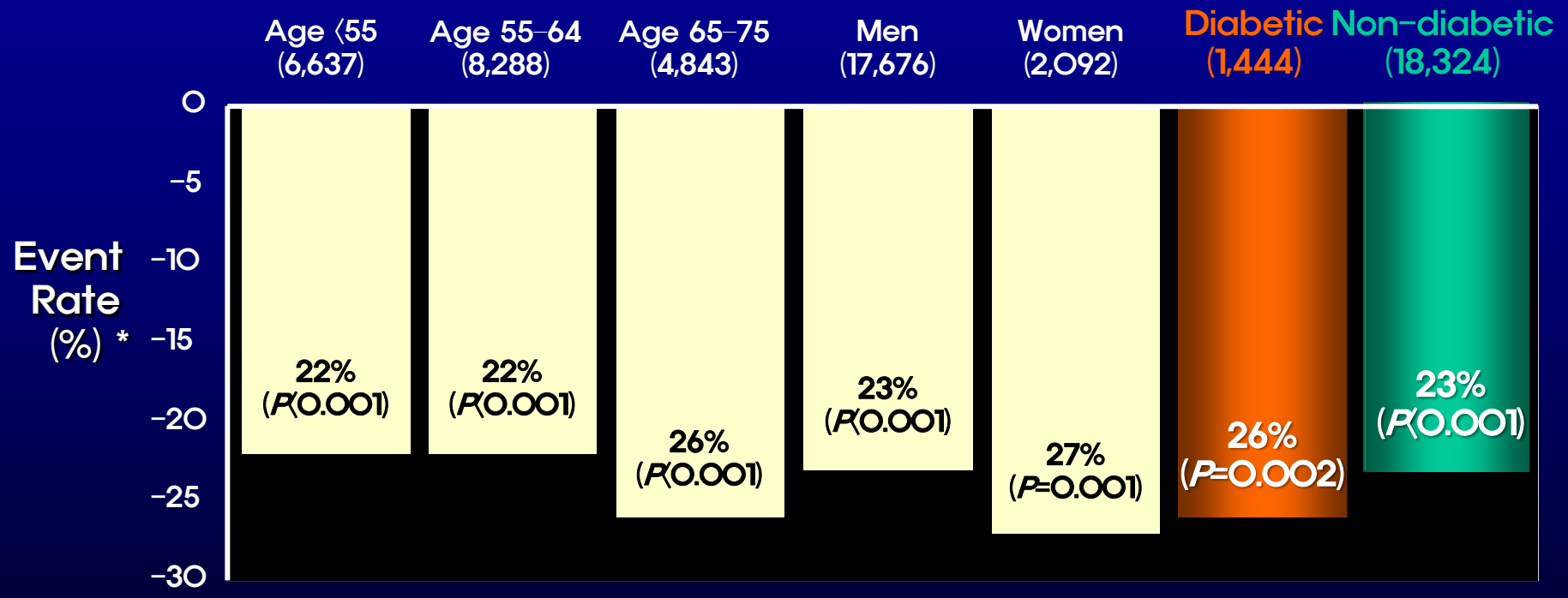
CARE (1996)
4,159 M(86%)
Age: mean 59(45–64)
TC: mean 209 mg/dL
F/U: 5 years

PPP
19,768 patients
Dosage: 40mg
F/U: 5–6years
Primary endpoint:
CHD death,
nonfatal MI

LIPID (1998)
9,014 M(83%)
Age: mean 62(31–75)
TC: mean 218 mg/dL
F/U: 6.1 years

Circulation 2000;102:1893–1900

PPP: Consistent Benefit Across All Subgroups



*CHD death and nonfatal MI, PTCA, CABG; 3,717 patients with events

Sacks FM *Circulation.* 2000:102;1893–1900

MANAGEMENT OF ELEVATED CHOLESTEROL IN THE PRIMARY PREVENTION GROUP OF ADULT JAPANESE

Primary prevention of cardiovascular disease in Japan.
Results of the randomized MEGA Study with pravastatin.

(MEGA Study Group.: Lancet.;368(9542):1155-63,2006.)

Result of MEGA study

1. 33% reduction in the incidence of coronary artery disease
2. 17% reduction in the incidence of stroke
3. 28% reduction in total mortality
4. Long-term safety

Background of the MEGA Study

- In Japan, compared to Western countries:

  A lower death rate from heart disease, but a higher death rate from stroke and cancer.

  A lower approved dose of pravastatin (10–20 mg daily).

  Lifestyle differences.

Patient Criteria

- **Inclusion Criteria:**

TC	220–270 mg/dL
Age	Men 40–70 yrs
	Women postmenopause–70 yrs
Weight	≥40 kg (88 pounds)

- **Major Exclusion Criteria:**

Familial hypercholesterolemia
History of CHD, stroke, TIA and ASO
History of cancer
History of serious liver or kidney disease
Secondary hypercholesterolemia

Study Design

Design: Prospective, Randomized, Open-labeled Blinded Endpoints (PROBE) study

Treatment: Diet* vs. Diet* + pravastatin (10-20 mg/day)

*NCEP step 1 diet.

Enrollment period: Feb 1994 to March 1999

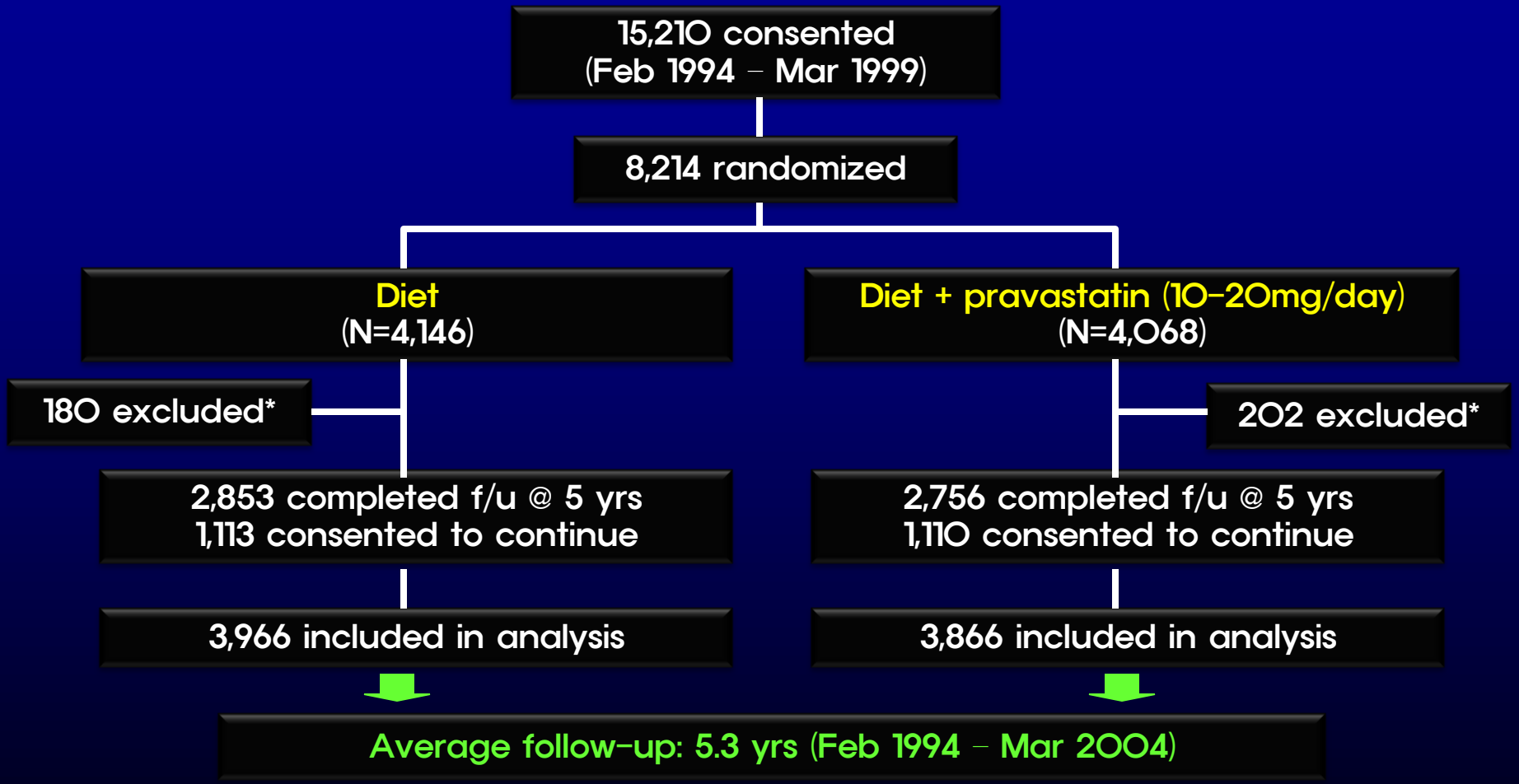
End of Follow-up: March 2004

Endpoints

- **Primary Endpoint:**
  - First occurrence of CHD
    - Fatal and Non-fatal MI
    - Angina
    - Cardiac/sudden death
    - Cardiac or vascular intervention

- **Major Secondary Endpoints:**
  - Stroke
    - Cerebral infarction
    - Intracranial hemorrhage
  - CHD + CI
  - All cardiovascular events
  - Total mortality

Study Flowchart



*Excluded patients were selected under blinding, based on information of pre-randomization by data reviewing committee before end of study.

Baseline Characteristics

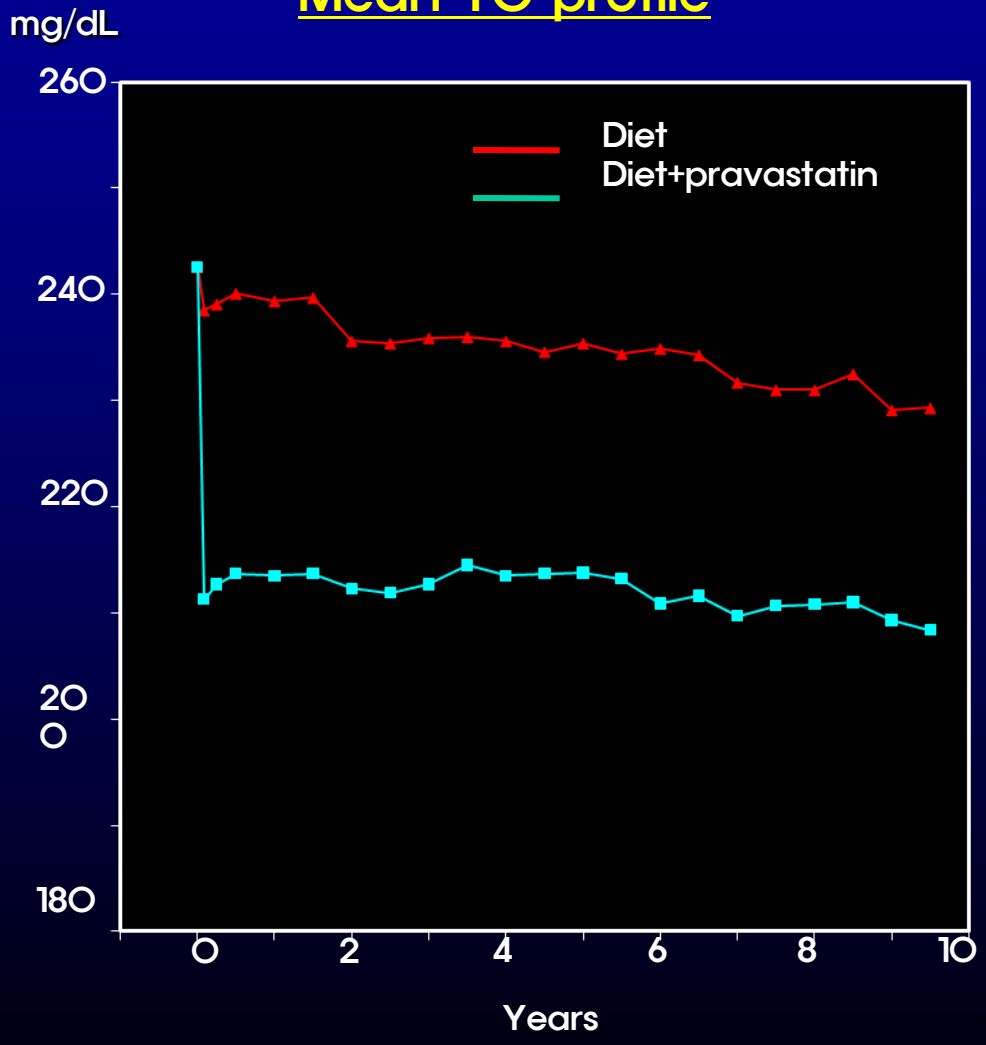
	Diet (N=3,966)	Diet+pravastatin (N=3,866)
Age, mean	58.4	58.2
Women, No.(%)	2,718 (68.5)	2,638 (68.2)
BMI, mean, kg/m^2	23.8	23.9
SBP/DBP, mean, mmHg	132.4/78.8	132.0/78.4
Hypertension, No.(%)	1,664 (42.0)	1,613 (41.7)
Diabetes, No.(%)	828 (20.9)	804 (20.8)
Current/past smoker, No.(%) Men Women	791 (19.9) 620 (15.6) 171 (4.3)	823 (21.3) 660 (17.1) 163 (4.2)

Baseline Lipid Levels

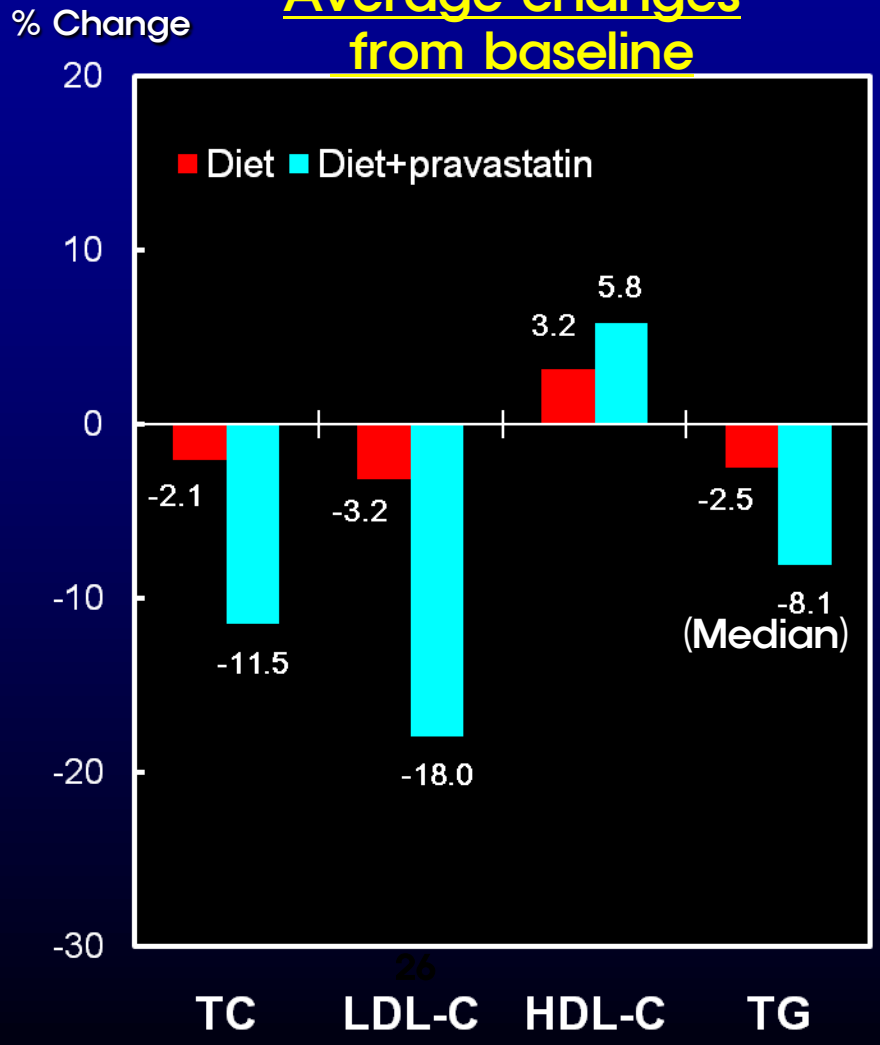
	Diet (N=3,966)	Diet+pravastatin (N=3,866)
TC, mean (mg/dL)	242.6	242.6
LDL-C, mean (mg/dL)	156.5	156.7
HDL-C, mean (mg/dL)	57.5	57.5
TG, median (mg/dL)	127.5	127.4
Lp(a), mean (mg/dL)	24.7	24.8

Average Lipid Changes

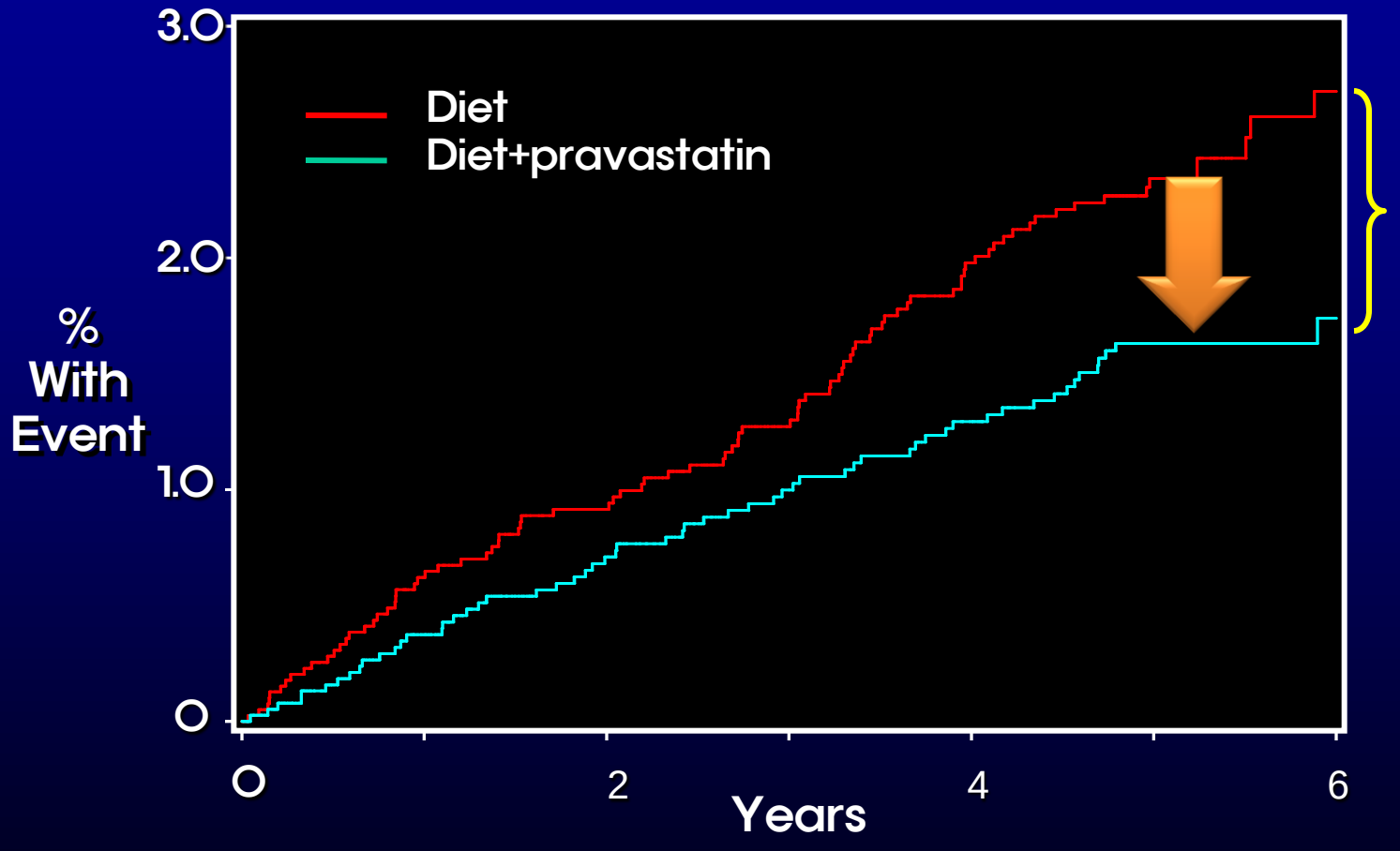
Mean TC profile



Average changes from baseline



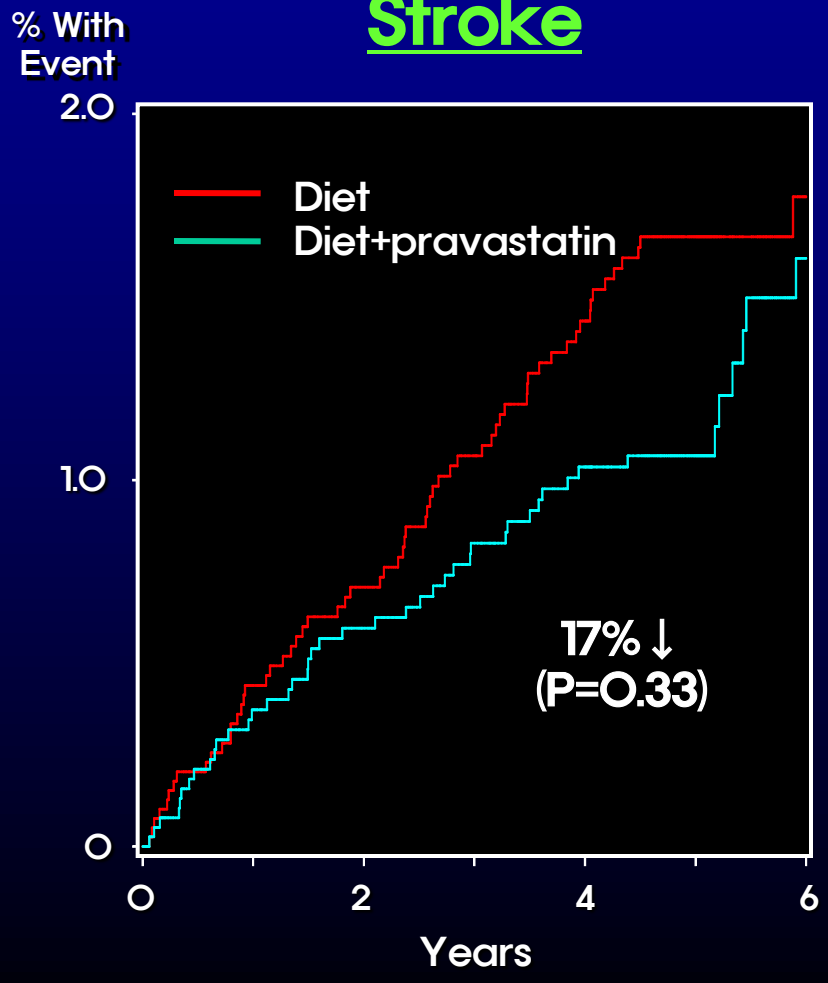
Primary Endpoint – CHD –

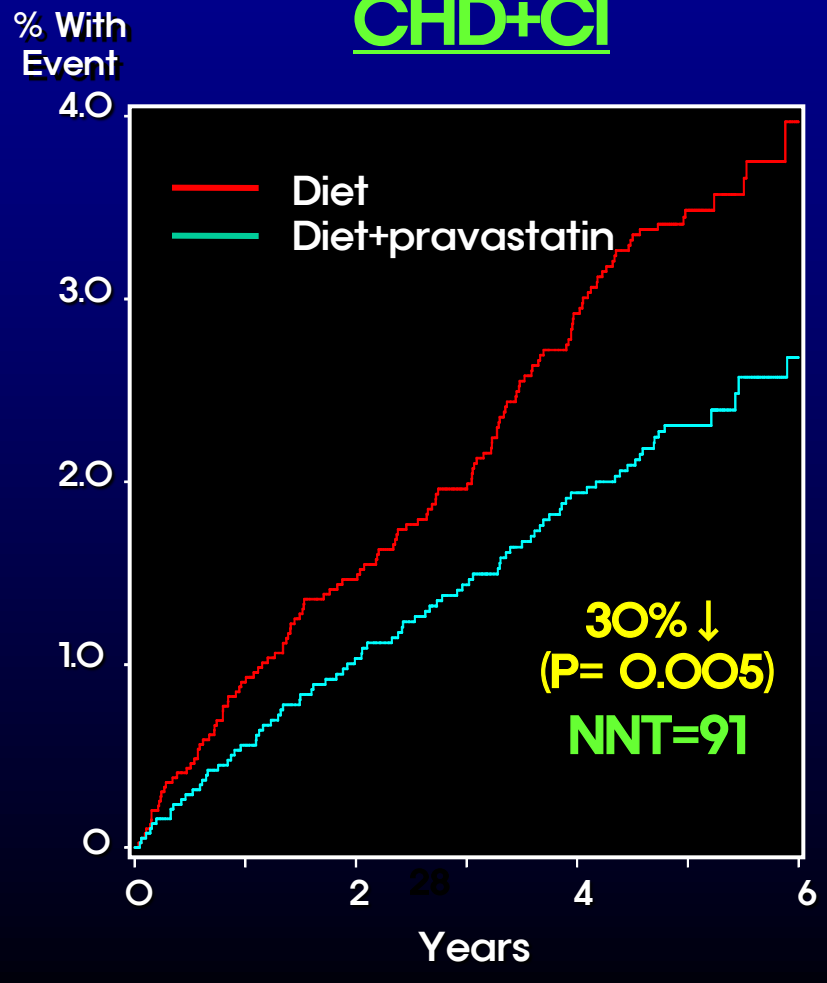


33% ↓
(P=0.010)

NNT=119

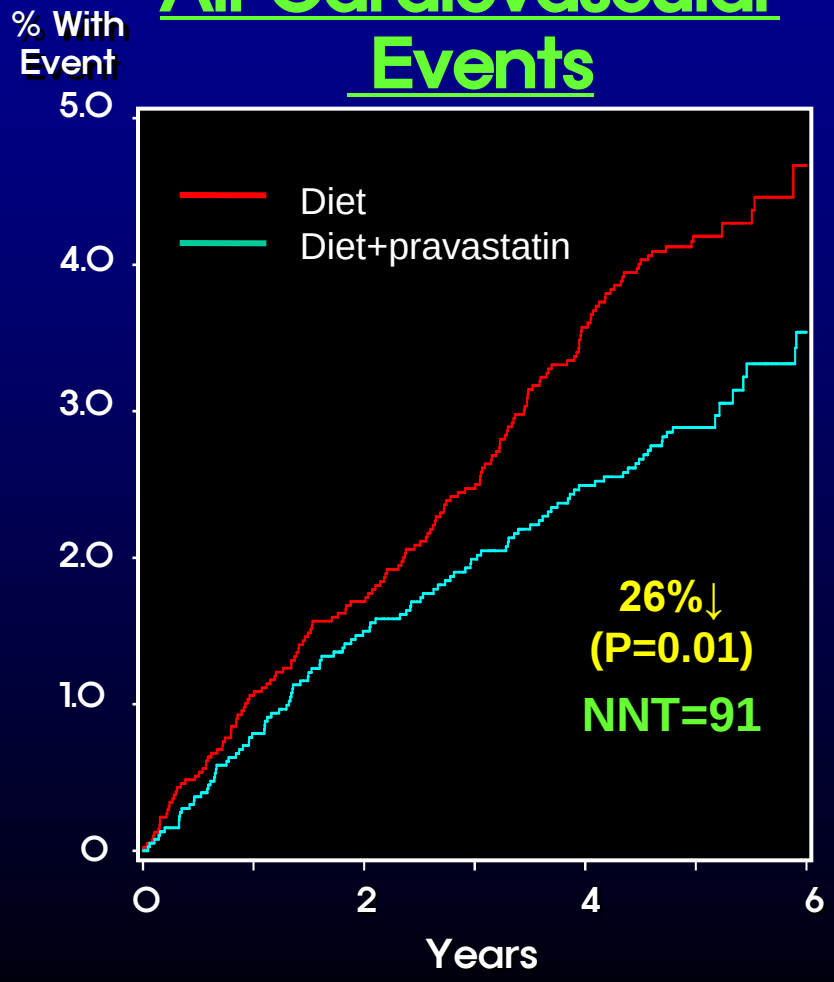
Secondary Endpoints
– Stroke, CHD+CI –



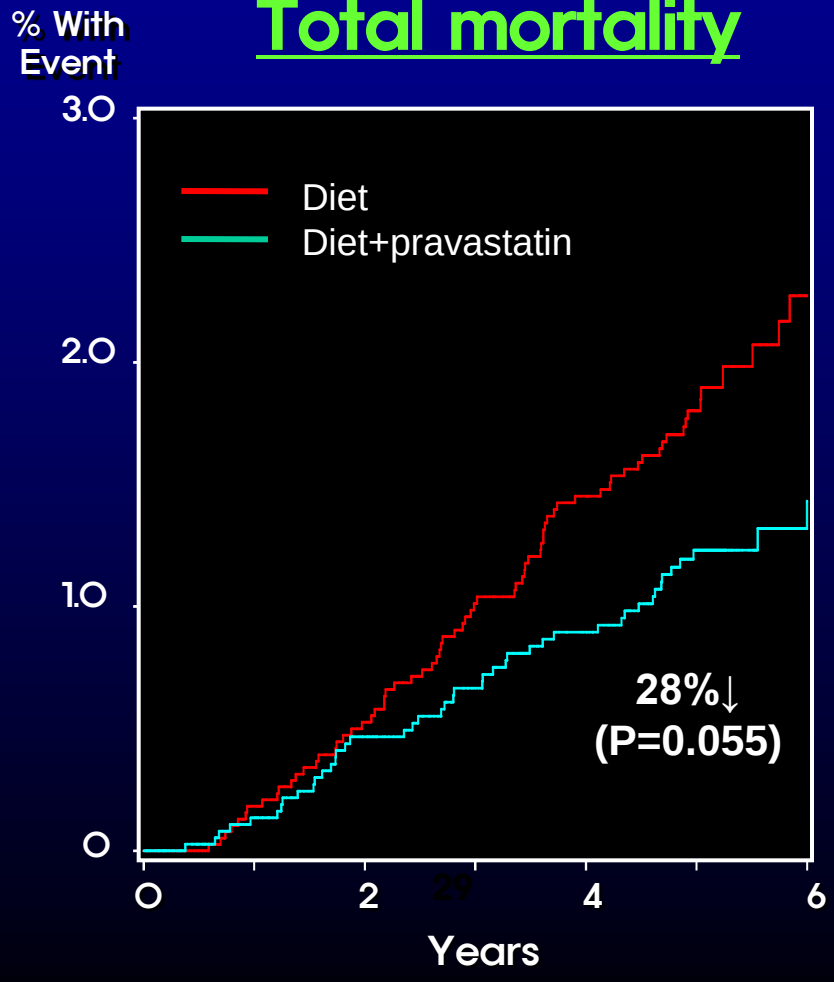


Secondary Endpoints
– All Cardiovascular Events,Total Mortality –

All Cardiovascular Events



Total mortality



Adverse Events and Laboratory Data

	Diet (N=3,966)	Diet+ pravastatin (N=3,866)
	No. (%)	
Serious Adverse Events	395 (10.0)	404 (10.5)
ALT 〉100 IU	107 (2.8)	104 (2.8)
CK 〉 500 IU	98 (2.6)	111 (3.1)
Rhabdomyolysis	0	0

Changes in LDL, HDL and CHD Risk in Primary Prevention Trials

Trials	LDL-C		HDL-C		CHD relative risk reduction	CHD RRR / LDL-C
	Pre	Post	Pre	Post		
	mg/dL, (% change)					
WOSCOPS*	192	142 (-26)	44	46 (+5)		1.2
AFCAPS/TexCAP	150	115 (-25)	36	39 (+6)	-37	1.5
ALLHAT-LLT	146	105 (-28)	48	49 (+2)	-9	0.3
ASCOT-LLA†	133	87 (-35)	51	50 (0)	-36	1.1
CARDS†	118	71 (-40)	54	55 (1)	-37	0.9
MEGA	157	128 (-18)	58	60 (+6)	-33	1.8

WOSCOPS, N Engl J Med 1995;333:1301-7.; AFCAPS/TexCAPS, JAMA 1998;279:1615-62.; ALLHAT-LLT, JAMA 2002;288:2998-3007.; ASCOT-LLA, Lancet 2003;363:1149-58.; CARDS, Lancet 2004;364685-96.

* Post /Pre LDL-C and HDL-C values was calculated by % change.
† To convert mmol/L into mg/dL , 38.7 was multiplied in LDL-C and HDL-C values.

Notable Features of the MEGA Results

- Despite less LDL-C reduction than in other trials, a similar reduction in CHD incidence.
- In this low risk population, a 33% reduction in CHD risk.
- Patients had higher HDL-C and lower triglyceride at baseline.
- Even though 68% of the patients were women, a significant risk reduction in CHD was observed.
- Diet may have added to the results.

Conclusions

- In MEGA patients (68% of whom were women), 10–20 mg pravastatin reduced the risk of CHD by 33%, the same as in primary prevention trials with 20–40 mg pravastatin in Europe and US.

- In low-risk populations, such as hypercholesterolemic Japanese patients with a high HDL-C level, less aggressive cholesterol lowering therapy may be sufficient to reduce CHD risk in primary prevention.

The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study

- Diabetic patients post-hoc analysis -

Hideaki Kurata[1],
Haruo Nakamura[2],
For the MEGA Study Group

1 Jikei University school of Medicine
2 Mitsukoshi Health and Welfare Foundation for the MEGA Study Group.

Definition of Subgroup according to Glucose Status

DM(Diabetes Mellitus)

Physician diagnosed diabetes or FPG ≥ 126mg/dl

IFG(Impaired Fasting Glucose)

Non-DM with FPG 110-〈126mg/dl

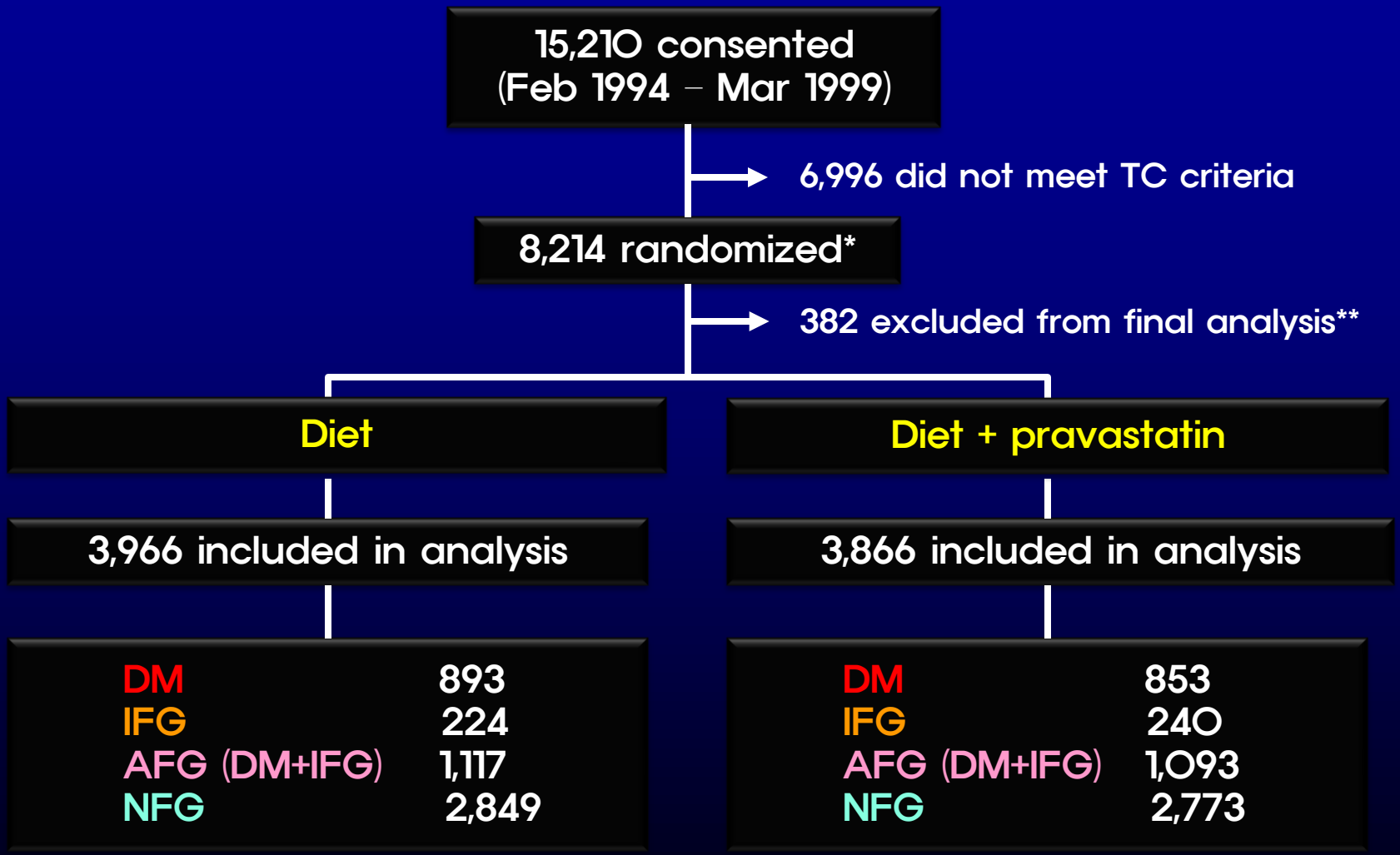
AFG(Abnormal Fasting Glucose)

DM + IFG

NFG(Normal Fasting Glucose)

Non-AFG

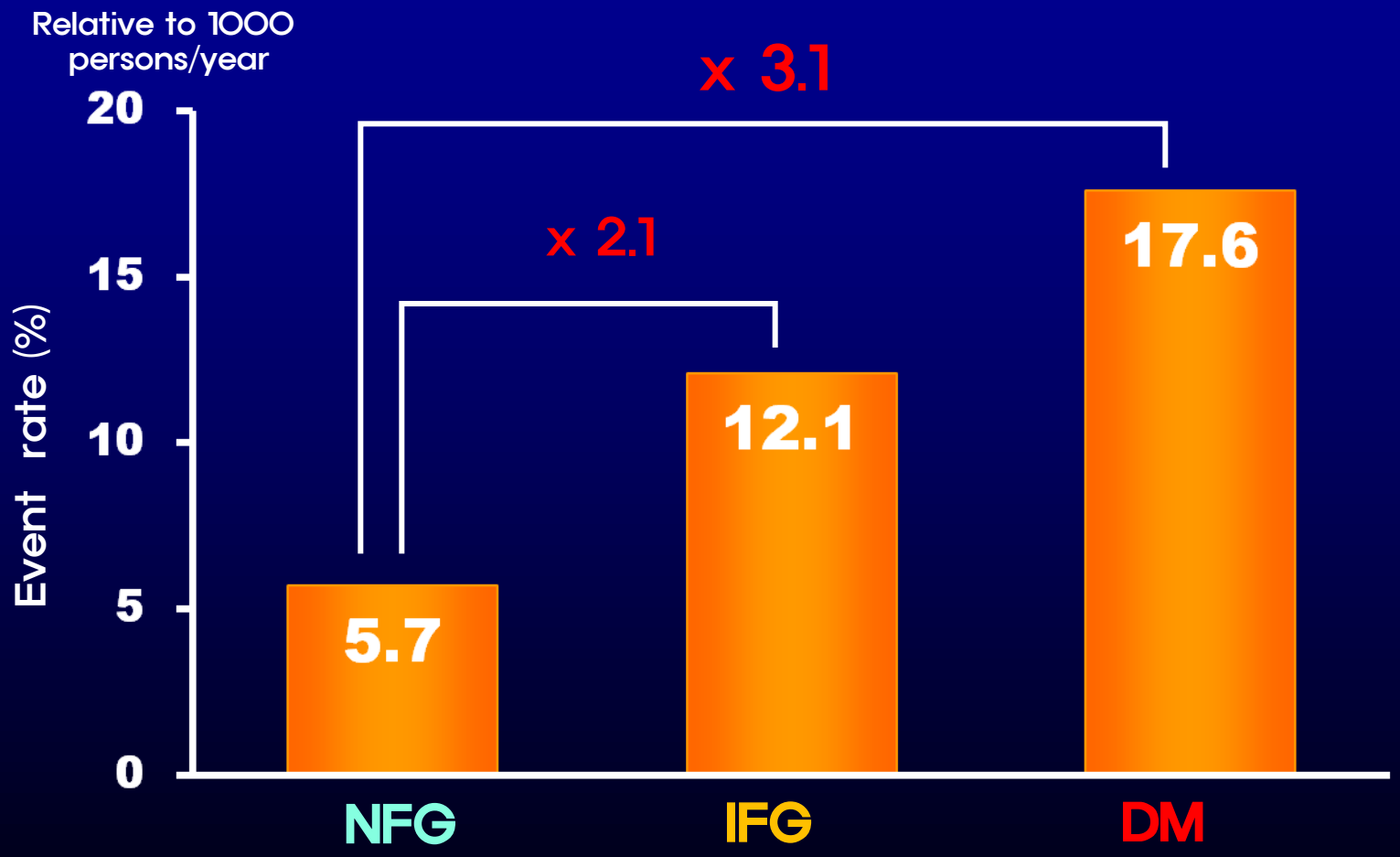
Study Flowchart



* stratified by gender, age and medical institution. **Patient exclusion was blinded, based on pre-randomization data reviewed by the monitoring committee.

Incidence rate of coronary vascular events in each subgroup

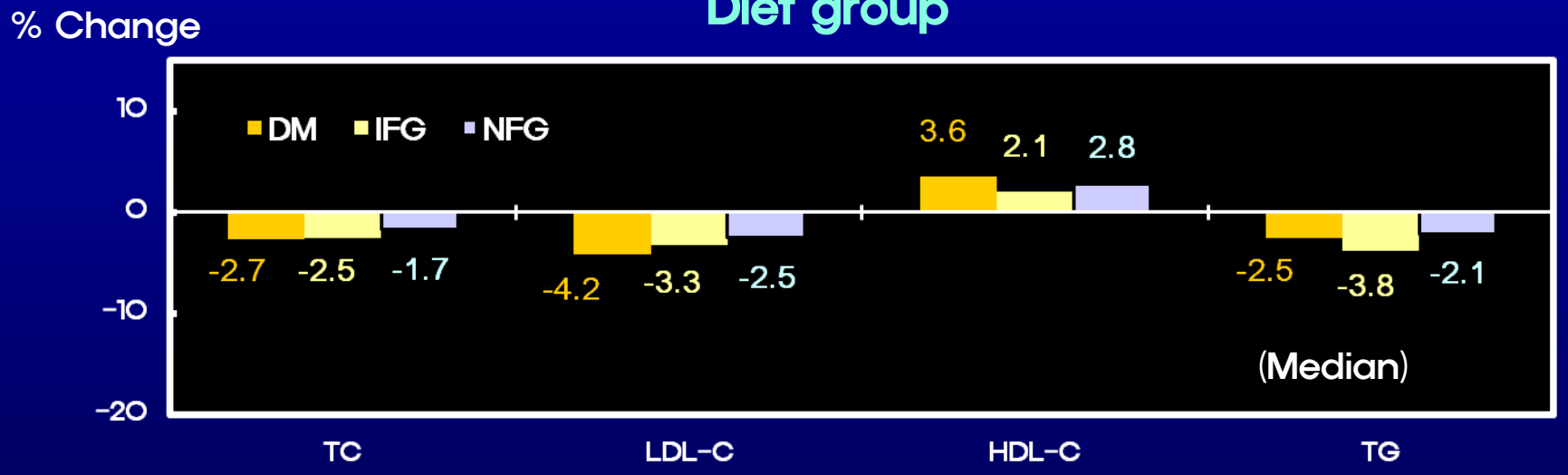
(diet group, before intervention)



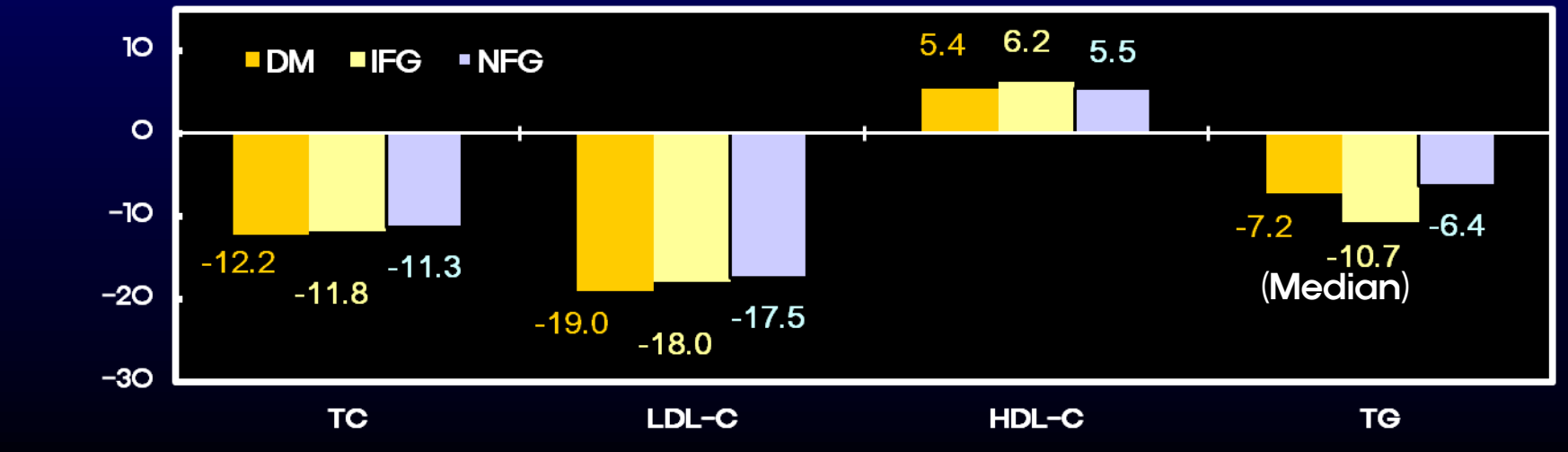
N. Tajima et al. Atherosclerosis 2008 ; 199 : 455-462

Changes in serum lipid levels

Diet group

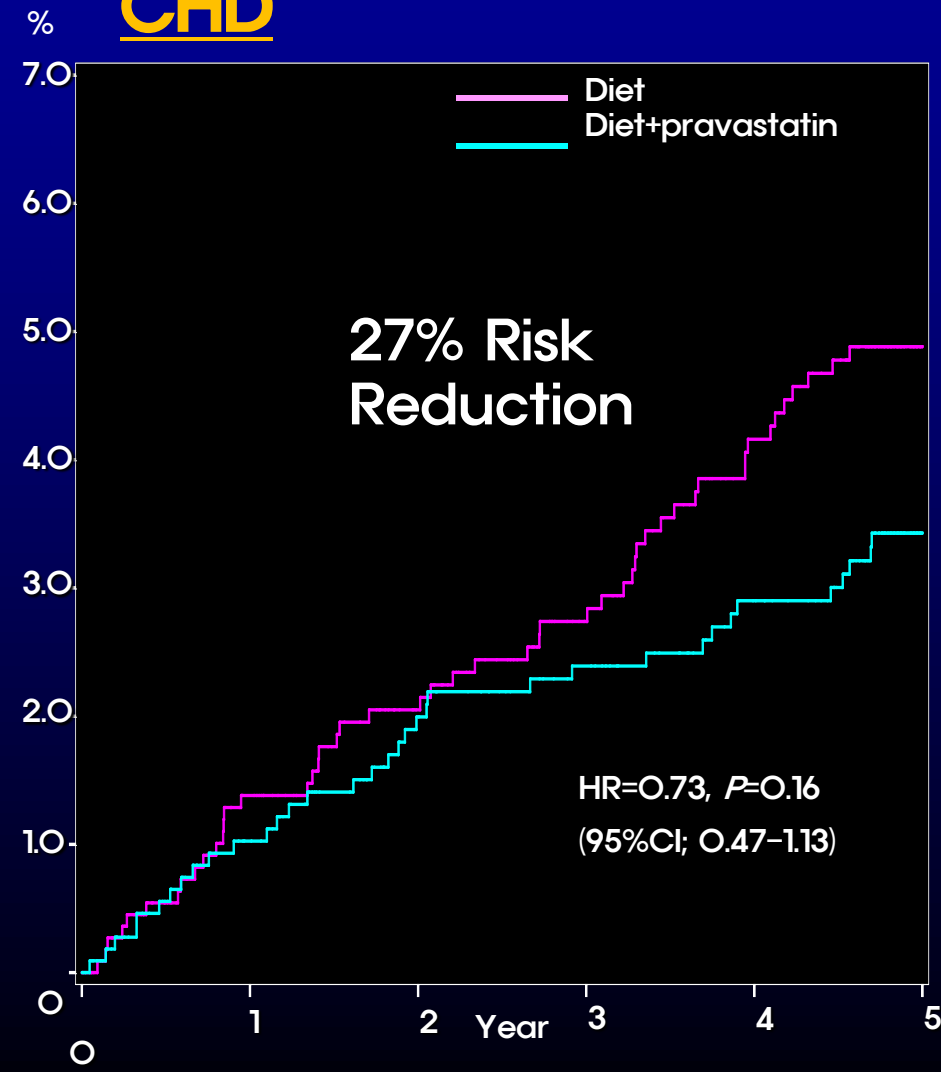


Diet + pravastatin group

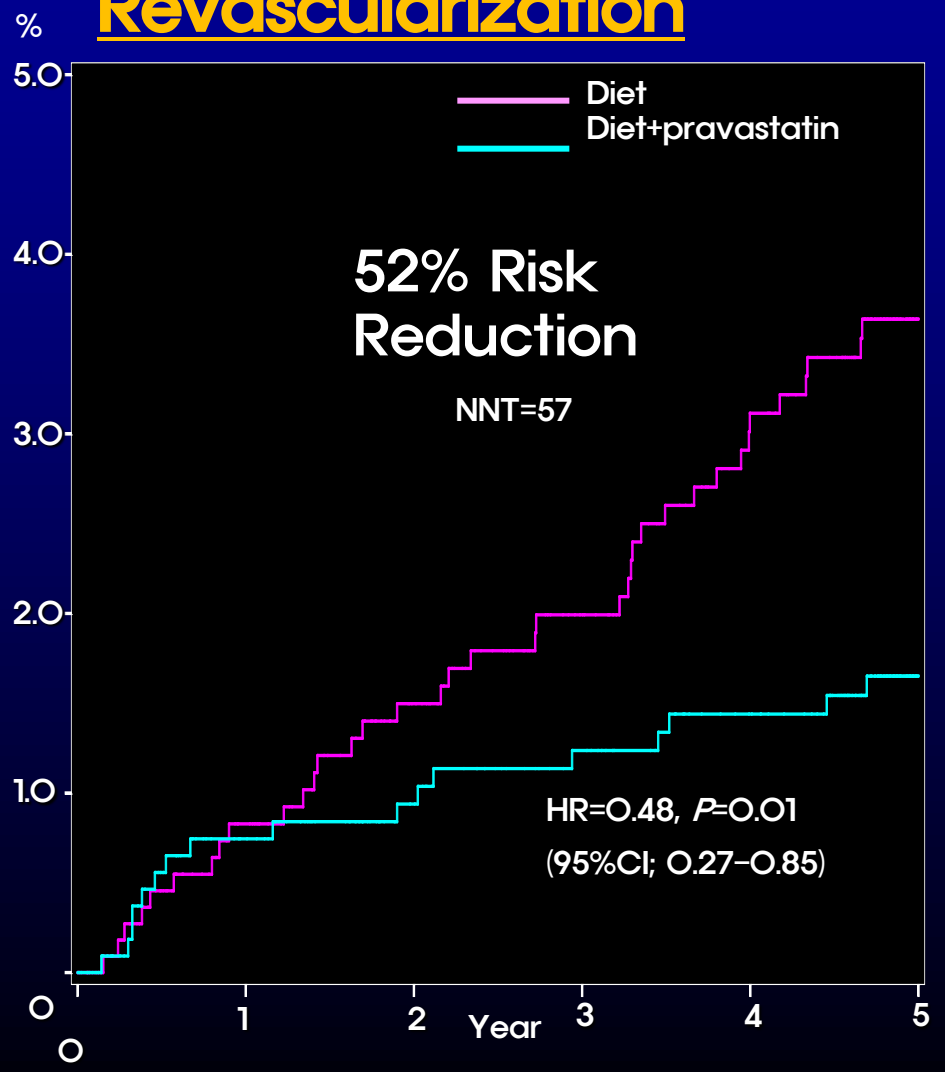


Kaplan–Meier plots showing the effects of pravastatin on events in AFG patients

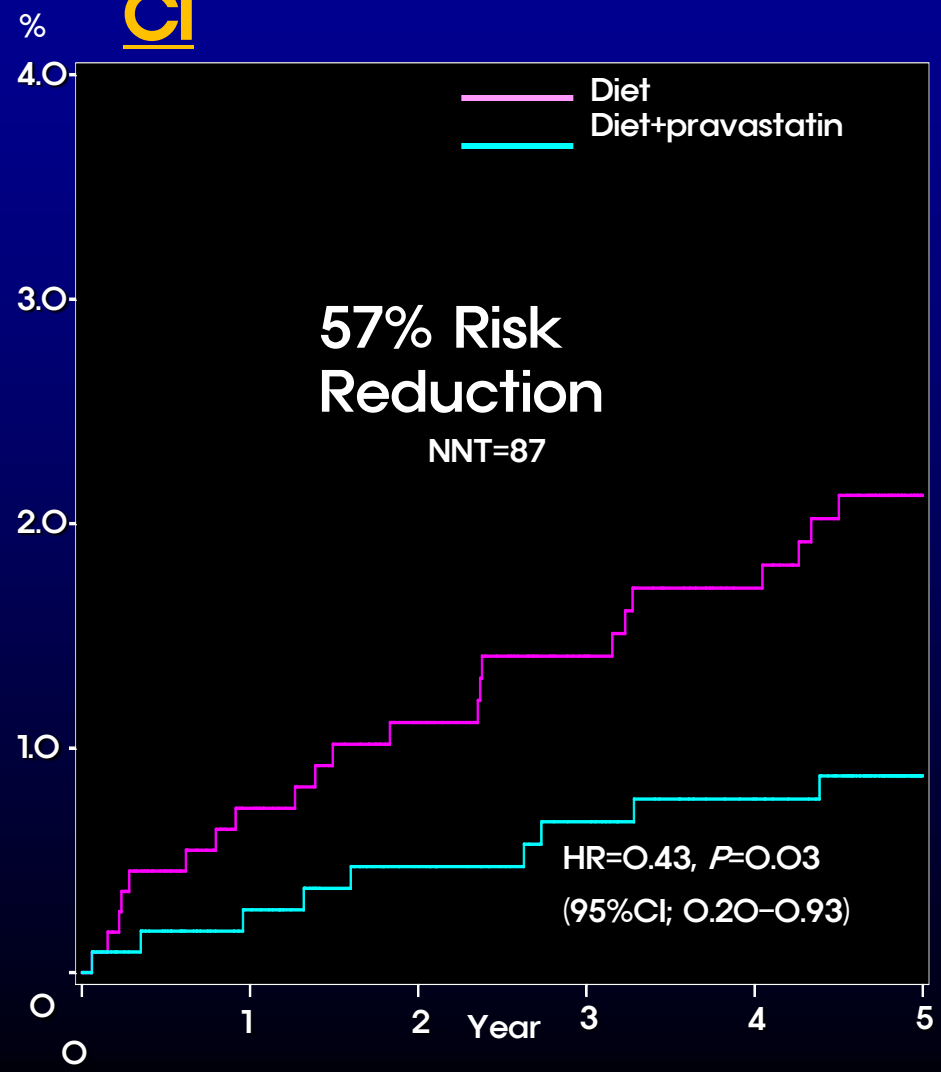
CHD

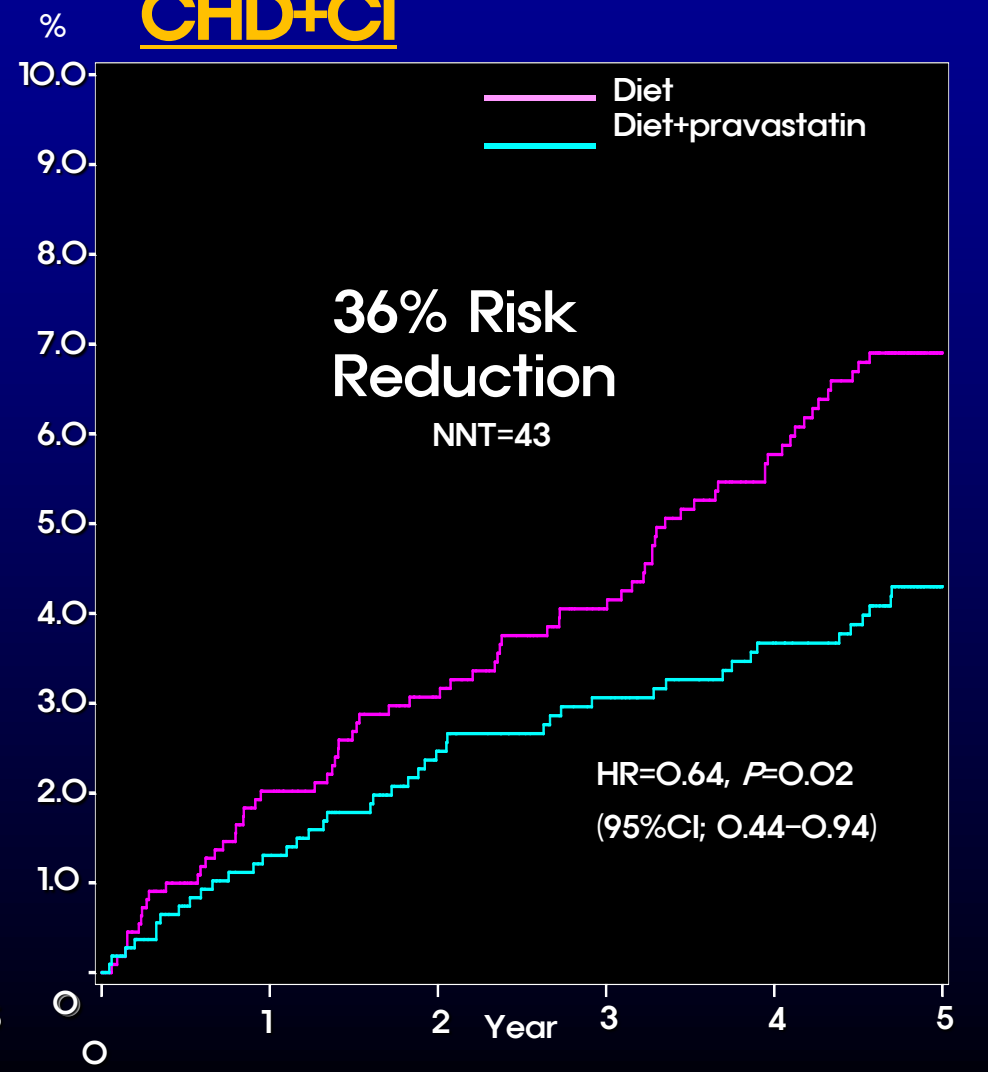


Revascularization



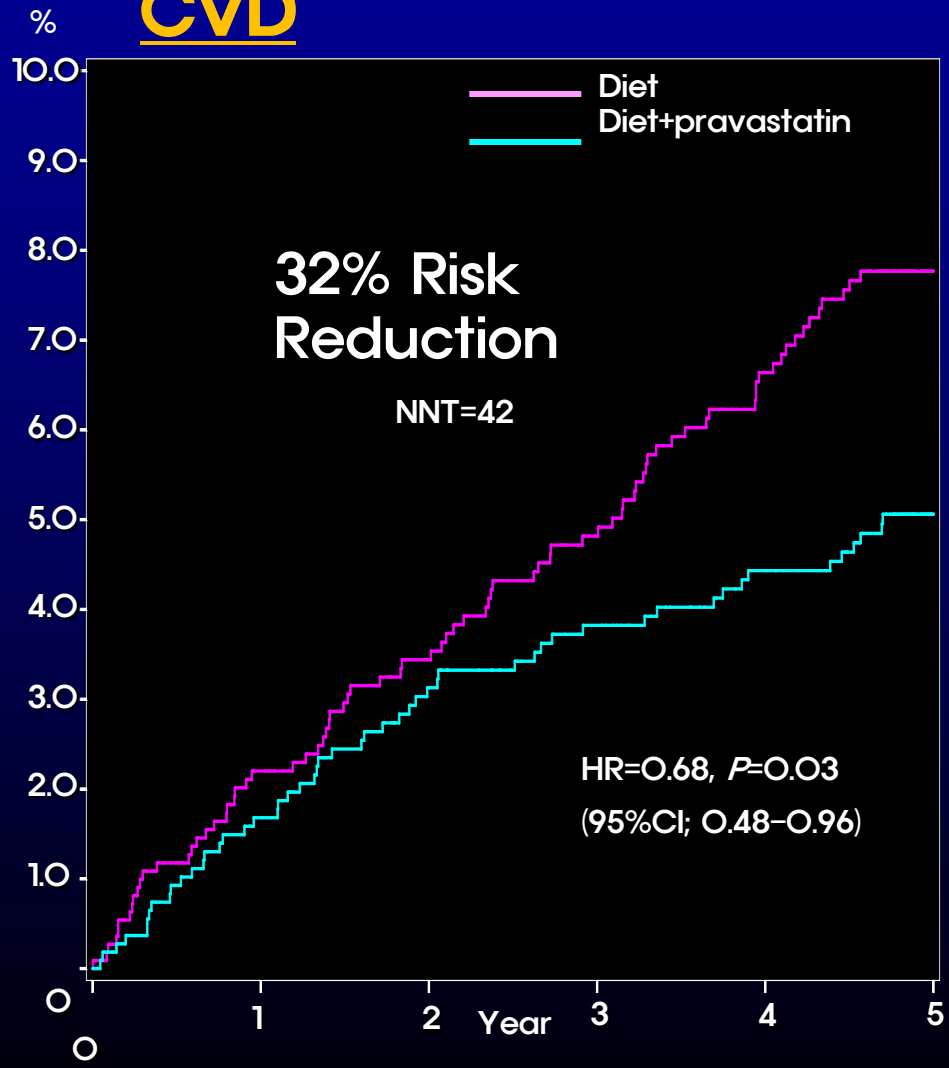
Kaplan–Meier plots showing the effects of pravastatin on events in AFG patients



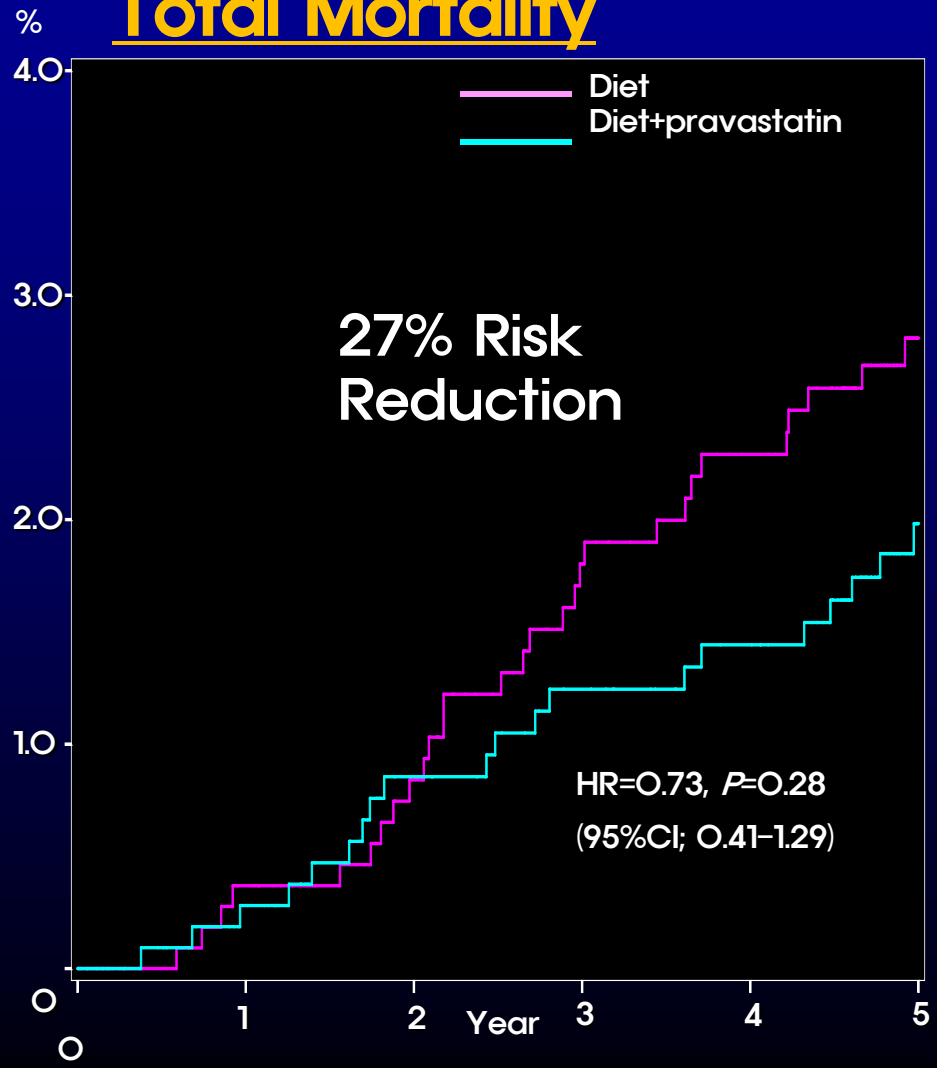


Kaplan-Meier plots showing the effects of pravastatin on events in AFG patients

CVD



Total Mortality



Adverse events and laboratory data in AFG patients

	Diet (N=1,117) No. (%)	Diet+ pravastatin (N=1,093) No. (%)	P-value
Serious Adverse Events	147 (13.2)	159 (14.5)	0.35
All Cancers	35 (3.1)	34 (3.1)	0.93
ALT 〉100 IU	33 (3.0)	39 (3.7)	0.42
CK 〉 500 IU	35 (3.3)	30 (2.9)	0.57
Rhabdomyolysis	0	0	-

Summary of Results 1

- The DM or IFG group included more men, greater history of smoking, higher prevalence of hypertension, and more obesity than patients with NFG.
- HDL-C was lower in the DM or IFG group, whereas triglycerides levels were higher than the NFG group.
- TC and LDL-C were reduced by 11.3 – 12.2% and 17.5 – 19.0%, respectively, in the glucose subgroups of the patients randomized to diet + pravastatin.
- The cardiovascular event rates were higher in the DM or IFG group than the NFG group.

Summary of Results 2

- Diet plus pravastatin reduced the risk of CHD, revascularization, CI, CHD+CI, and CVD by 27%, 52%, 57%, 36% and 32% in the AFG group, respectively, and reached statistical significance in nearly all events except CHD.
- No interactions of treatment effects were found in any events between AFG and NFG groups.
- The NNT of CHD+CI and CVD in the AFG group were lower than 50.
- No difference was found in the incidence of adverse events between diet and diet + pravastatin group in the AFG group.
- Sensitivity analysis found similar results as AFG group when the alternative definition of DM was applied.

Conclusions

- Diet plus pravastatin reduced all major cardiovascular events in patients with diabetes or IFG in this post-hoc analysis of the MEGA Study.

- Our results indicate that diet plus pravastatin treatment was effective to reduce cardiovascular events in Japanese patients with diabetes or IFG, similar to reductions in other large-scale clinical statin studies in Europe and the US.


Diabetes

Pravastatin & the Development of Diabetes Mellitus Evidence for a Protective Treatment Effect in the West of Scotland Coronary Prevention Study (WOSCOPS)

Freeman DJ, Norrie J, Sattar N, Neely DJ, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard C J, Shepherd J, Gaw A.

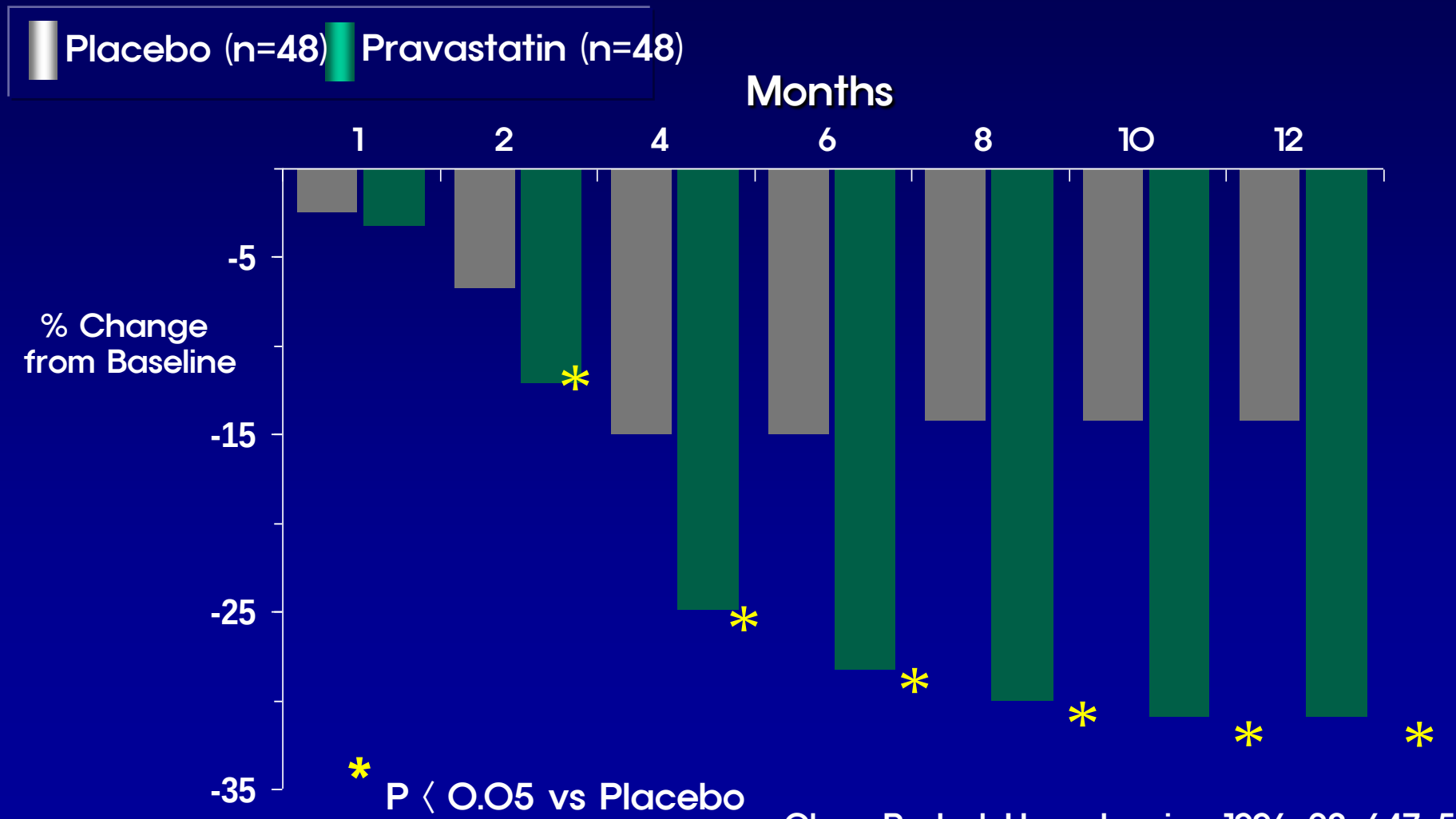
Circulation 2001; 103:357–362

Background

- **Lipids** & low-grade **inflammation** have been shown to predict new occurrence of type 2 diabetes [1,2]
- **Pravastatin** has demonstrated positive effects on lipids & inflammatory response
- The goal of this analysis was to determine the effect of pravastatin on the risk of developing type 2 diabetes

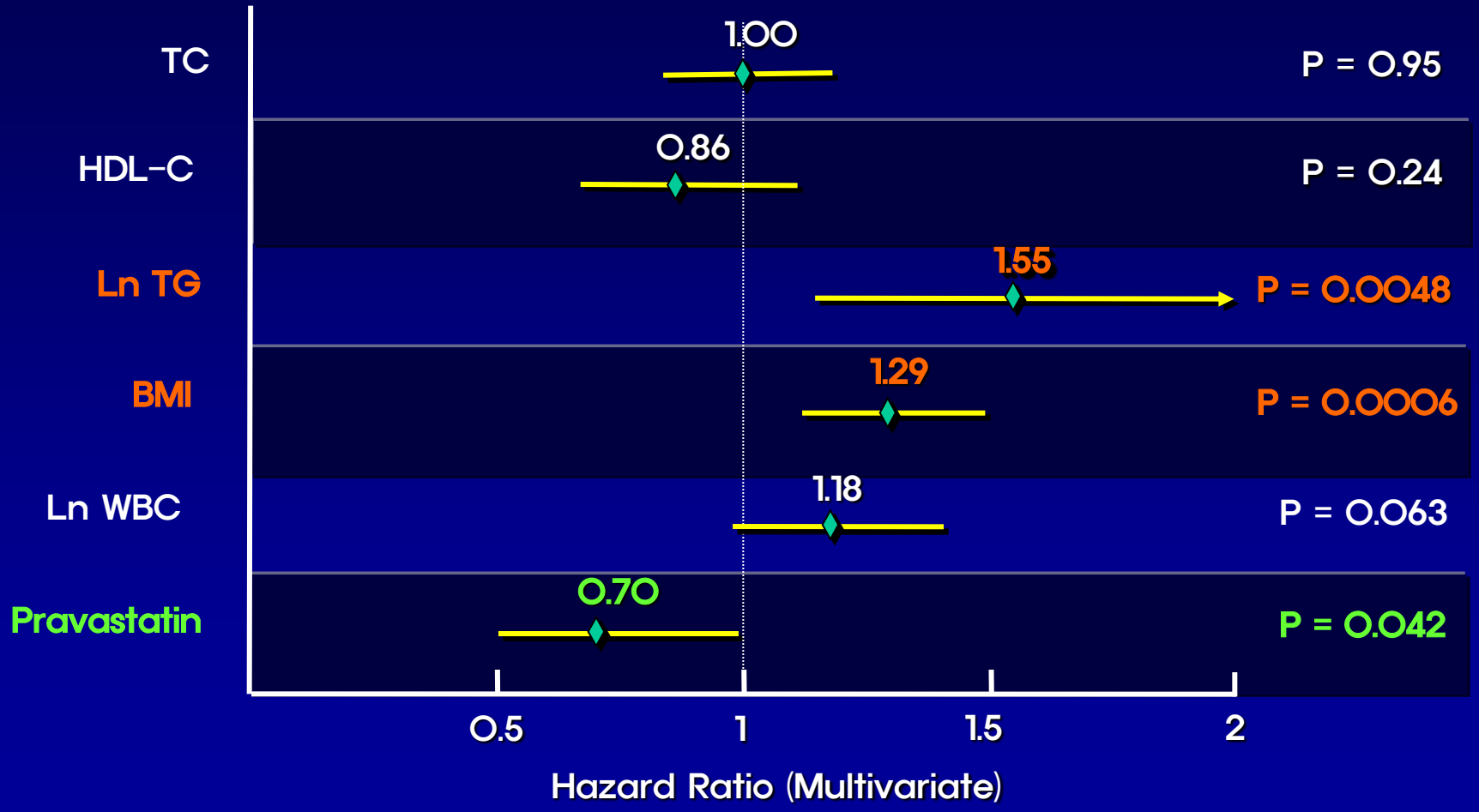
[1] Schmidt MI et al. Lancet 1999; 353:1649–52
[2] Haffner SM et al. JAMA 1990;263:2893–98
Freeman DJ et al. Circulation 2001;103;357–62

Pravastatin Induced Changes in Fasting Hyperinsulinemia



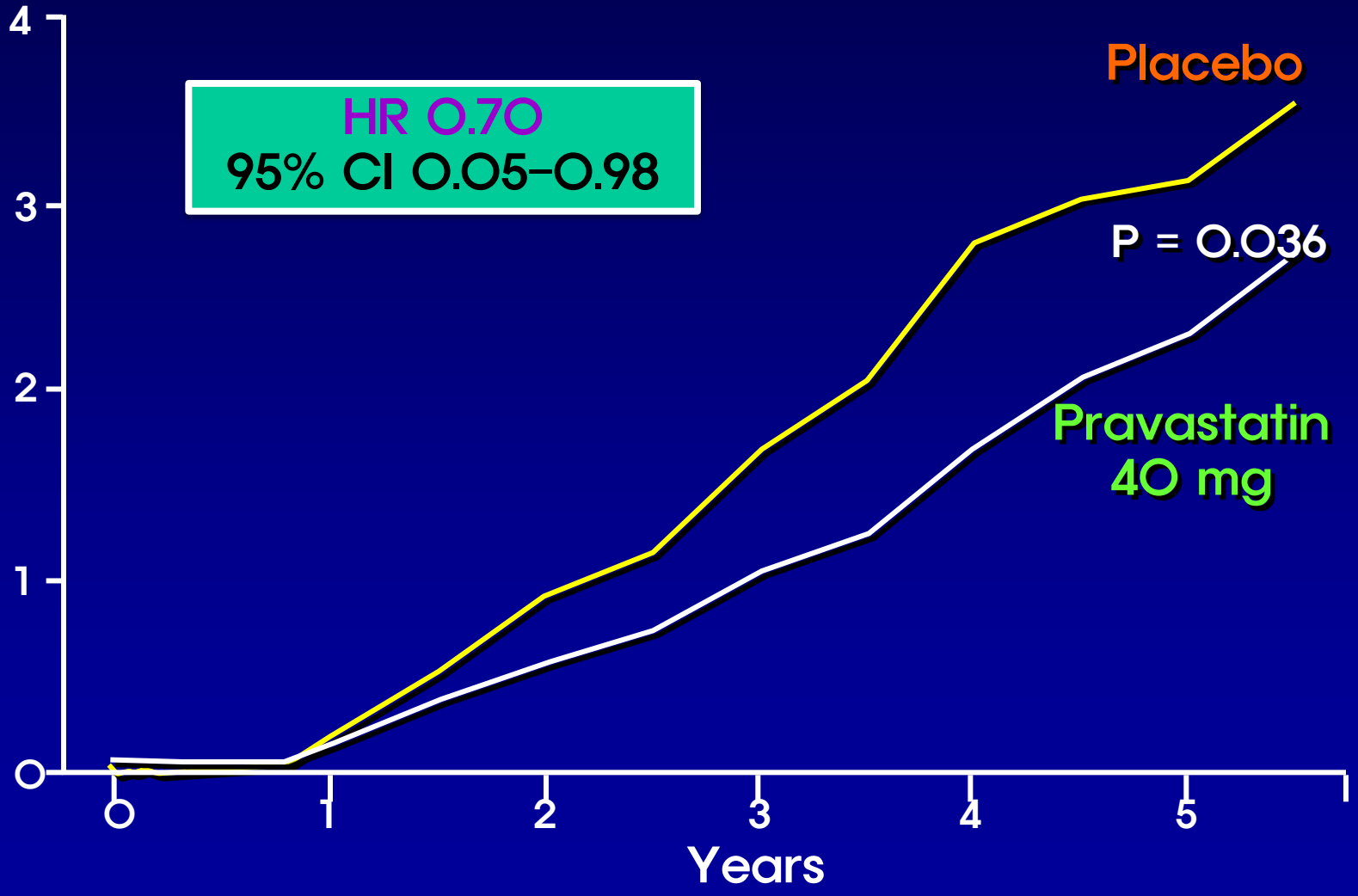
Chan P et al. Hypertension 1996; 28: 647–51

Multivariate Predictors of Diabetes



Freeman DJ et al. Circulation 2001; 103:357-362

Development of Diabetes According to Treatment Assignment



Conclusions

In WOSCOPS, pravastatin significantly reduced risk of developing type 2 diabetes in men with high cholesterol & no history of cardiac disease by 30%.

Freeman et al. Circulation 2001;103;346–7.

TIME

FEBRUARY 12, 2001

ADDED VALUE Are you on statin drugs to lower your cholesterol? Here are benefits you probably never counted on.
A Scottish study shows that Pravachol(pravastatin), one brand of statin, reduces the risk of developing diabetes 30%

…No, it' s not time to add statins to the drinking water.

The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials

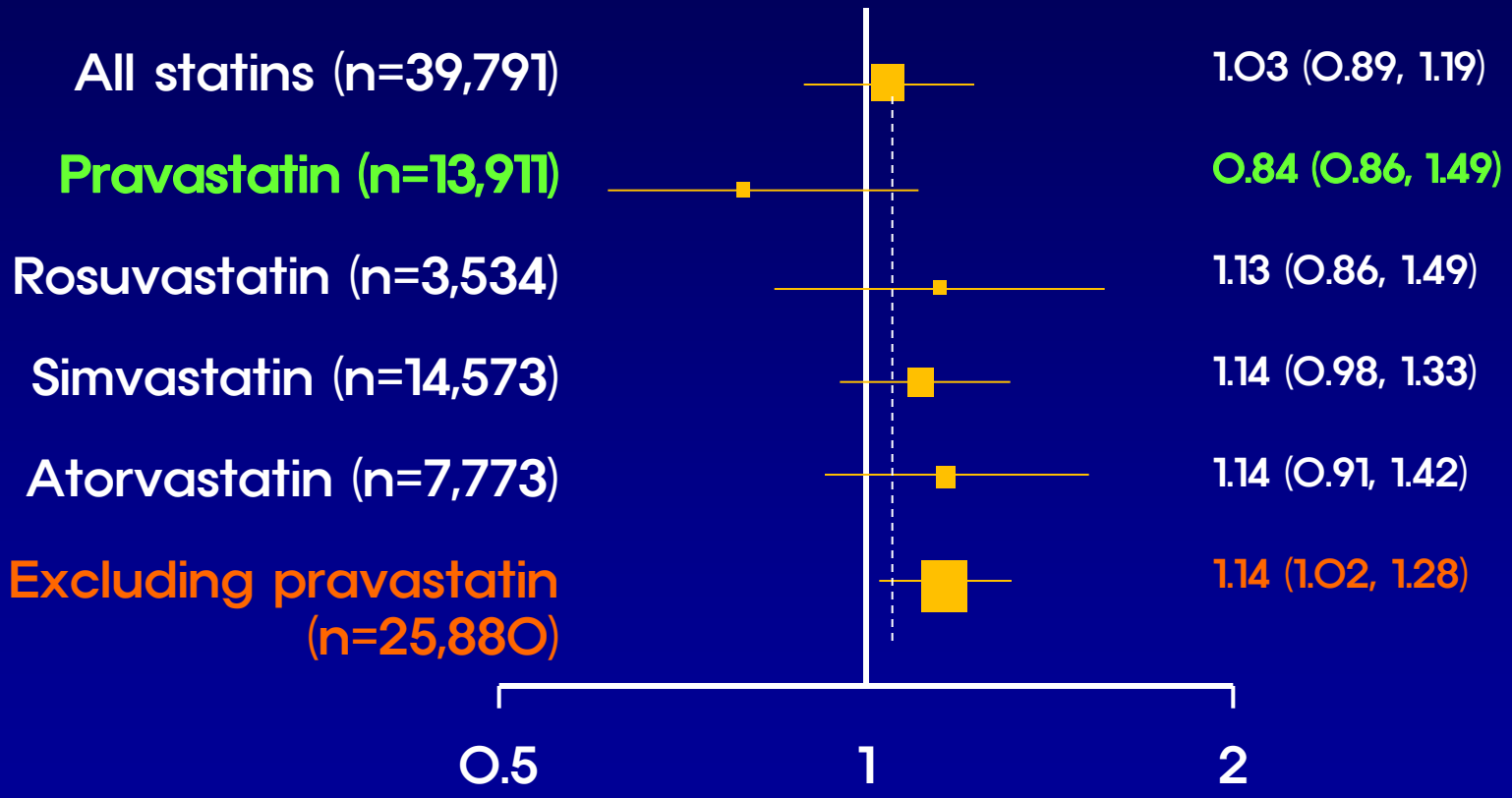
Coleman et al.
Curr Med Res Opin. 2008; 24(5):1359-62

Design

- To determine the ability of statins to prevent the development of new-onset type 2 diabetes mellitus
- 5 RCT (n = 39,791; new T2DM = 1,407)
- Follow-up range = 2.7–6.0 years

Statins	Dosage	Reference
Pravastatin	40 mg	Pravastaitn and the development of diabetes mellitus: (Circulation 2001; 103:357–62) Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: (Diabetes Care 2003; 26:2713–21)
Simvastatin	40 mg	Heart Protection Study Collaborative Group (Lancet 2003; 361:7–22)
Atorvastatin	10 mg	ASCOT-LLA (Lancet 2003; 361:1149–58)
Rosuvastatin	10 mg	Rosuvastatin in older patients with systolic heart failure. (New Engl J Med 2007; 357:10.1056)

Evaluating Statins Effect on New-onset type 2 Diabetes Mellitus



Conclusion

With the exception of Pravastaitn, the other statins (Rosuvastatin, Simvastatin, Atorvastaitn) were associated with a significantly increased risk of new-onset type 2 diabetes mellitus.

Curr Med Res Opin. 2008; 24(5):1359-62

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

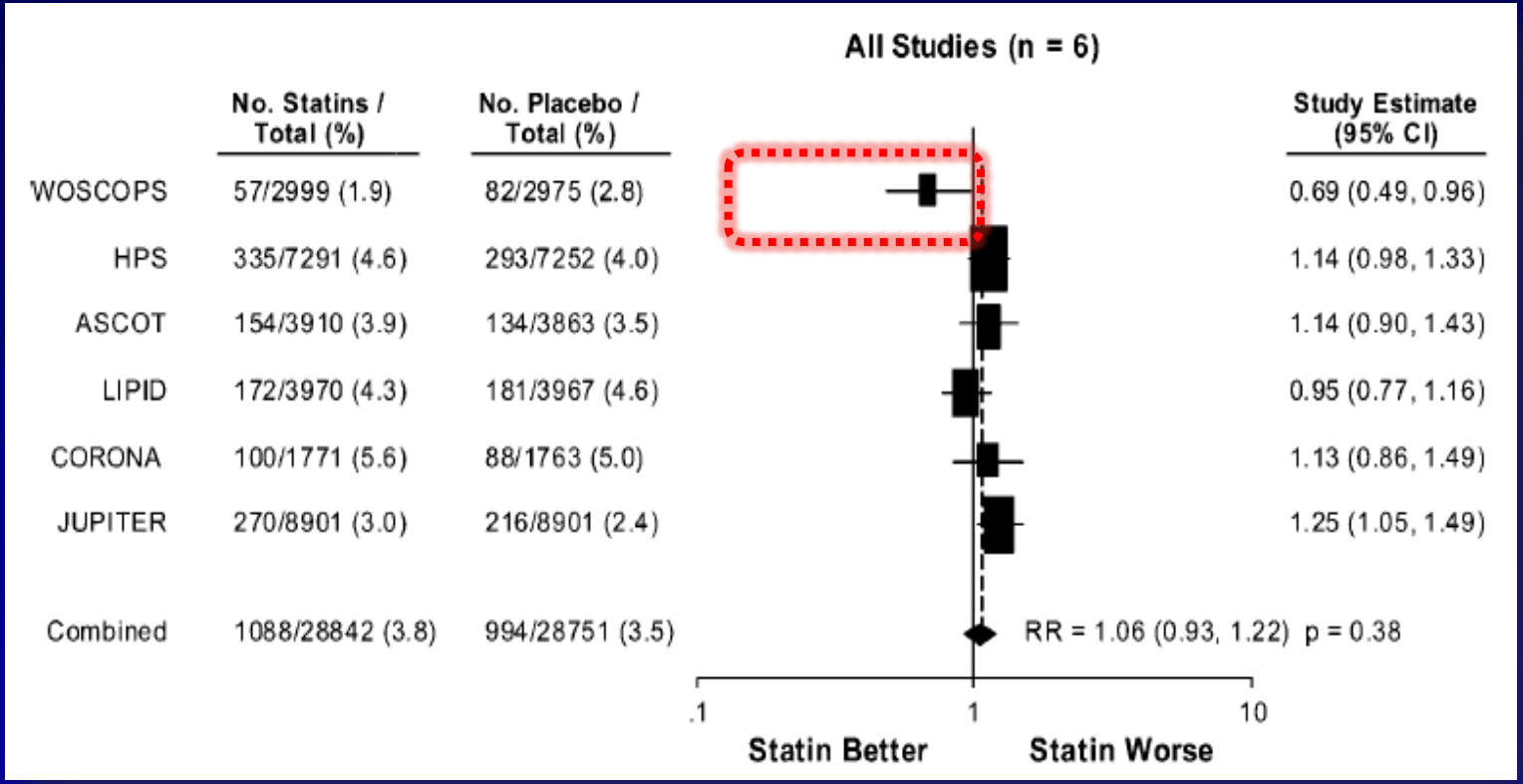
- 6 randomized controlled statin trials
- 57,593 patients & 2,082 incident diabetes cases
- Mean follow-up: 3.9 years

Rajpathak et al.
Diabetes Care 2009; 32:1924-1929

Effect of Statin Use on Risk of incident Type 2 Diabetes

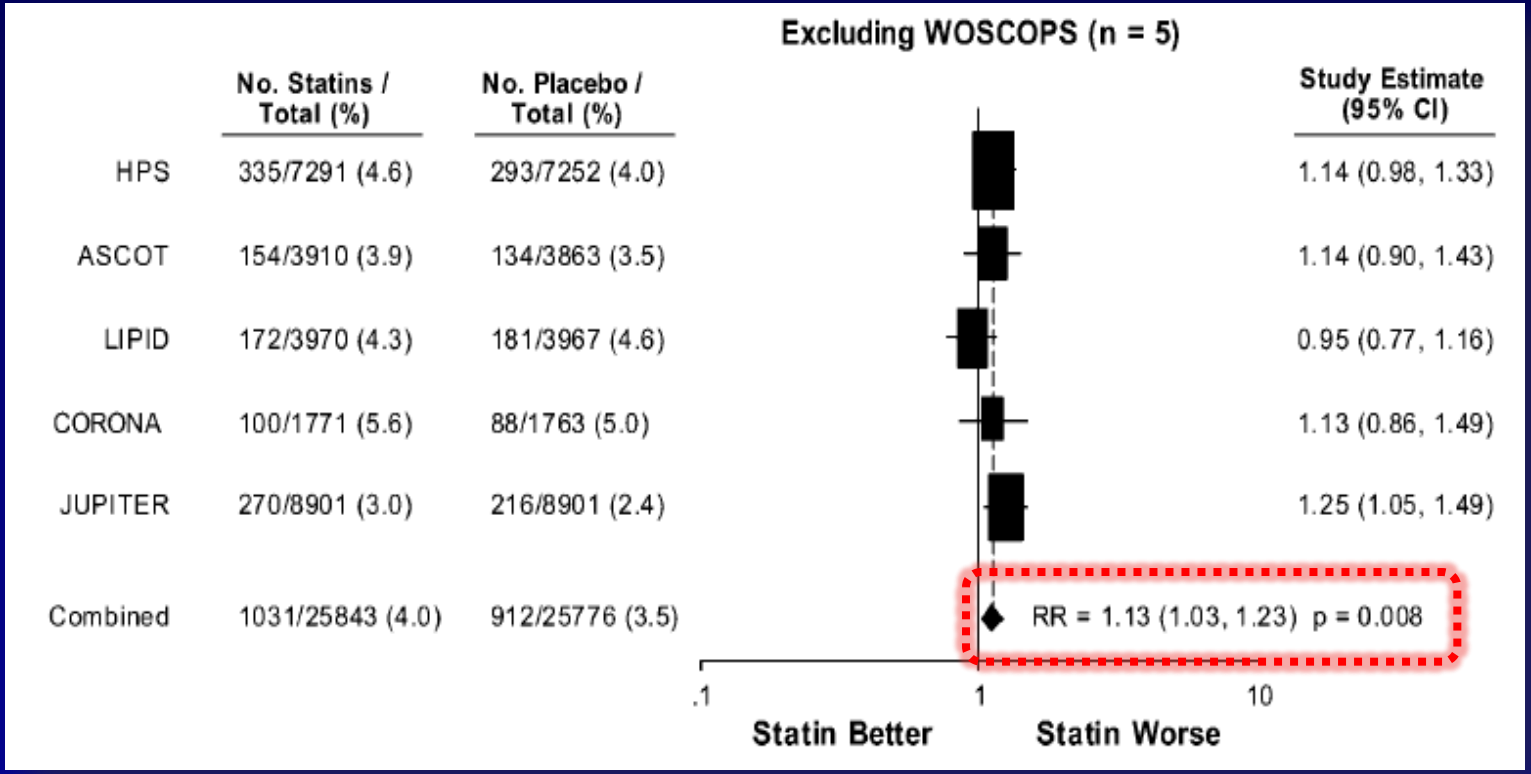
	Statins		F/U (years)	Sample size (Statin/Placebo)	Primary Outcome RR(95%CI)	Result for diabetes	
						Diabetes cases (Staitn/Placebo)	RR (95% CI)
WOSCOPS	Pravastatin	40 mg	4.9	2,999 / 2,975	Nonfatal MI & CV death 0.69 (0.57–0.83)	57 / 82	0.7 (0.50–0.99)
LIPID	Pravastatin	40 mg	5	3,970 /3,967	CV death 0.76 (0.65–0.88)	172 / 181	0.95 (0.77–1.16)
CORONA	Rosuvastatin	10 mg	2.7	1,771 / 1,763	Nonfatal MI & stroke, CV death 0.92 (0.83–1.02)	100/88	1.13 (0.86–1.50)
JUPITER	Rosuvastatin	20 mg	1.9	8,901 / 8,901	Nonfatal MI & stroke, unstable angina, revascularization, CV death 0.56 (0.46–0.69)	270 /216	1.25 (1.05–1.49)
HPS	Simvastatin	40 mg	4.6	7,291 / 7,282	All-cause mortality, 0.87 (0.81–0.94)	335 / 293	1.14 (0.98–1.33)
ASCOT	Atorvastatin	10 mg	3.3	3,910 / 3,863	Nonfatal MI, CV death 0.64 (0.50–0.83)	153 / 134	1.15 (0.91–1.44)

Result: Effect of Statins on Diabetes Risk



Diabetes Care 2009; 32:1924–1929

Result: Effect of Statins on Diabetes Risk



Diabetes Care 2009; 32:1924–1929

Result

WOSCOPS (pravastaitn) reported a statistically significant protective effect of statin use in diabetes incidence. (RR 0.70; p = 0.042)

Whereas JUPITER (rosuvastatin) reported a significant positive association. (RR 1.25; p = 0.01)

Diabetes Care 2009; 32:1924–1929

Summary

- Diabetes is an important risk factor for CVD
- Statins are beneficial in patients with diabetes as well as patients without diabetes
- MEGA study is the first data for Asian and proved effect of pravastatin to diabetes and non-diabetes.
- WOSCOPS study suggests that pravastatin may be protective against the development of diabetes

Thank You

for Your Attention !