Unsettled Issues of Dyslipidemia Management in the Current Guideline

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Daegu, Republic of Korea

Contents

- Evolution of guidelines for dyslipidemia management
- Unsettled issues of dyslipidemia management in the current guideline

  1. Statin therapy in patients with very low LDL-C
  2. Is the best treatment target in the prevention of CVD only LDL-C?
  3. Aggressive lipid therapy for primary prevention
  4. Special patients population: DM, women, elderly, CKD

- Summary

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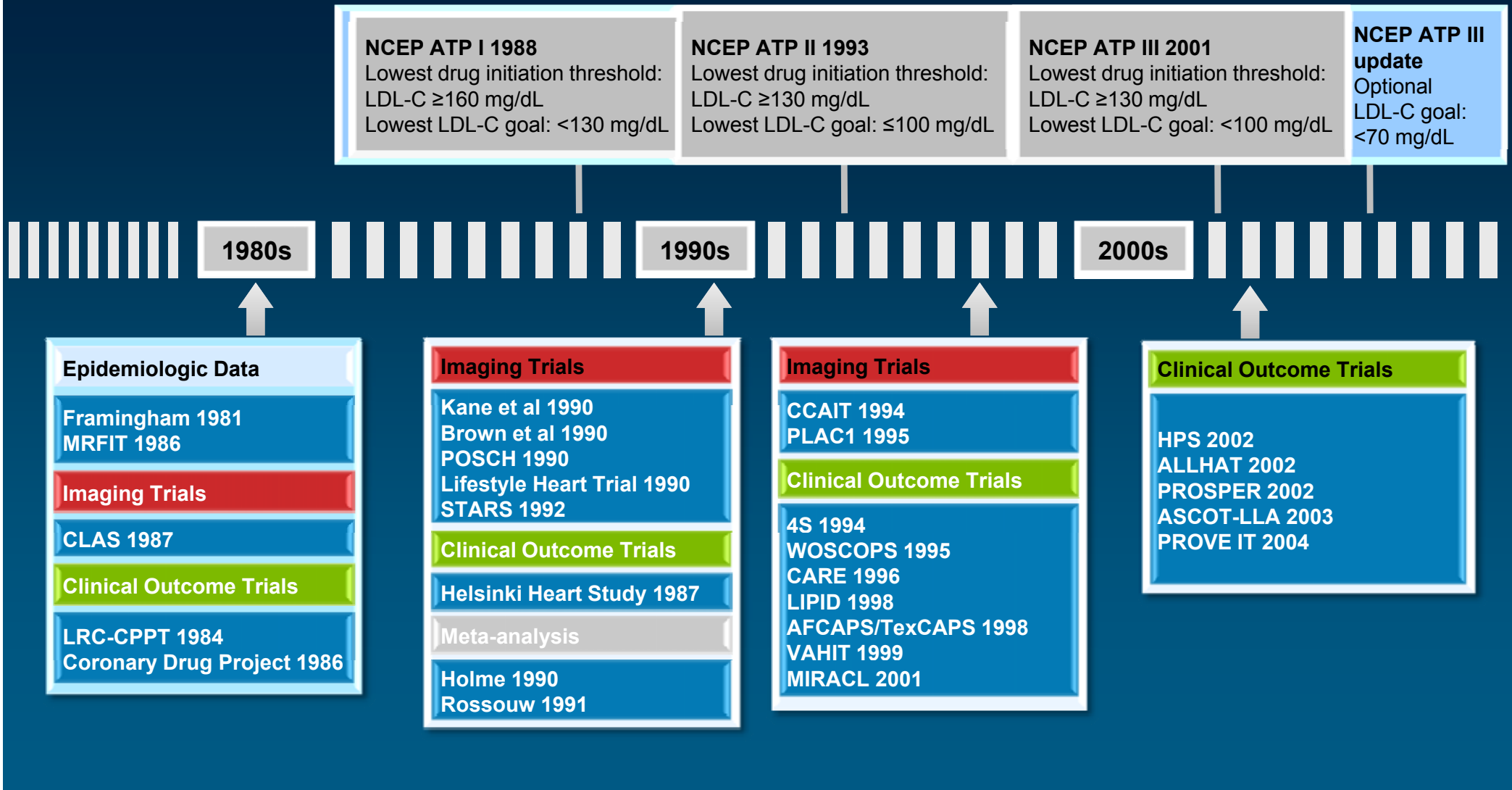
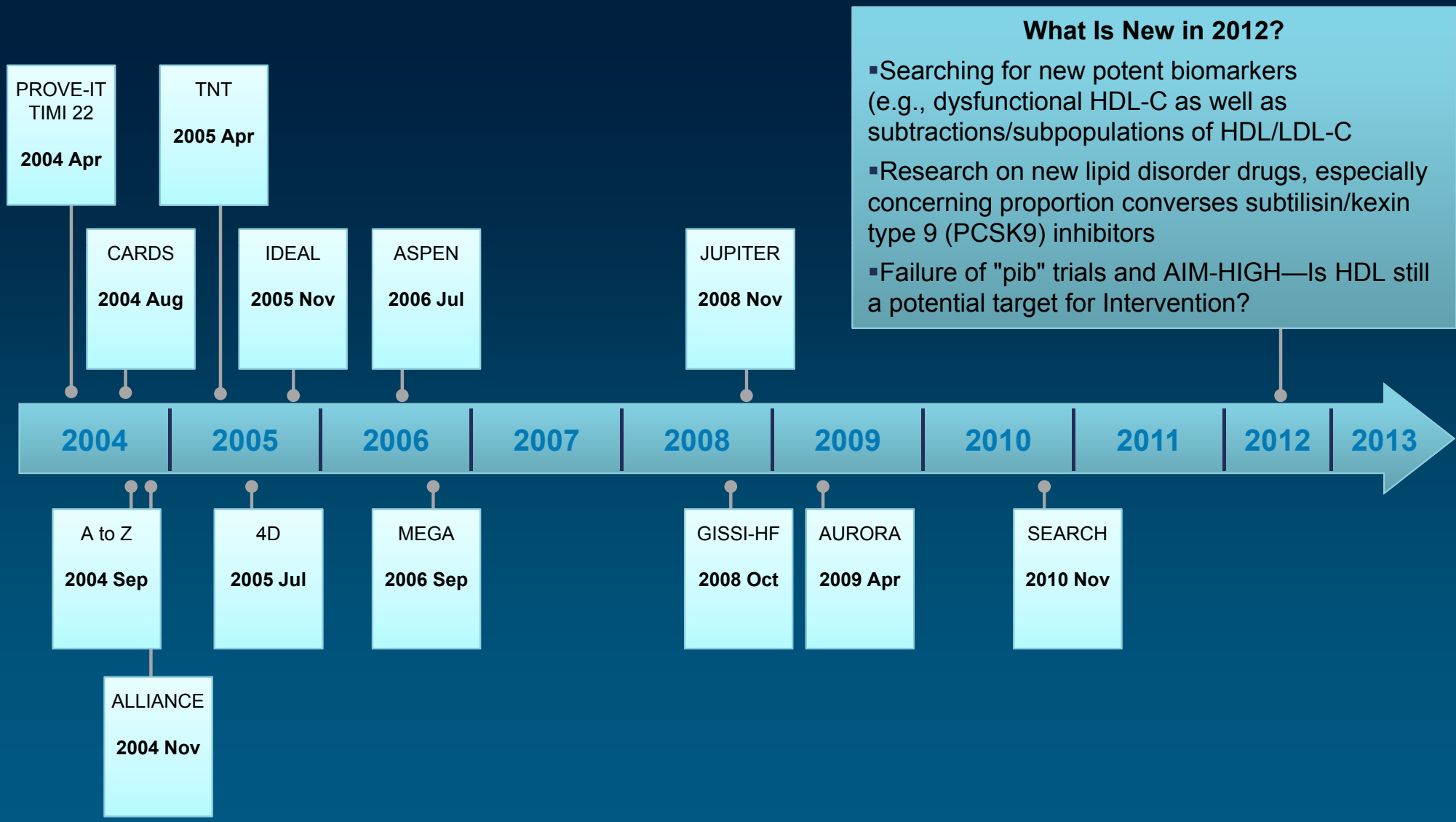
Evolution of NCEP ATP Guidelines: Reducing LDL-C Goals

Information on the combination of apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 mass to risk scores containing total cholesterol and HDL-C led to slight improvement in CVD prediction



Major Clinical Trials on Cholesterol from 2004



What Is New in 2012?

- Searching for new potent biomarkers (e.g., dysfunctional HDL-C as well as subtractions/subpopulations of HDL/LDL-C
- Research on new lipid disorder drugs, especially concerning proportion converses subtilisin/kexin type 9 (PCSK9) inhibitors
- Failure of "pib" trials and AIM-HIGH—Is HDL still a potential target for Intervention?

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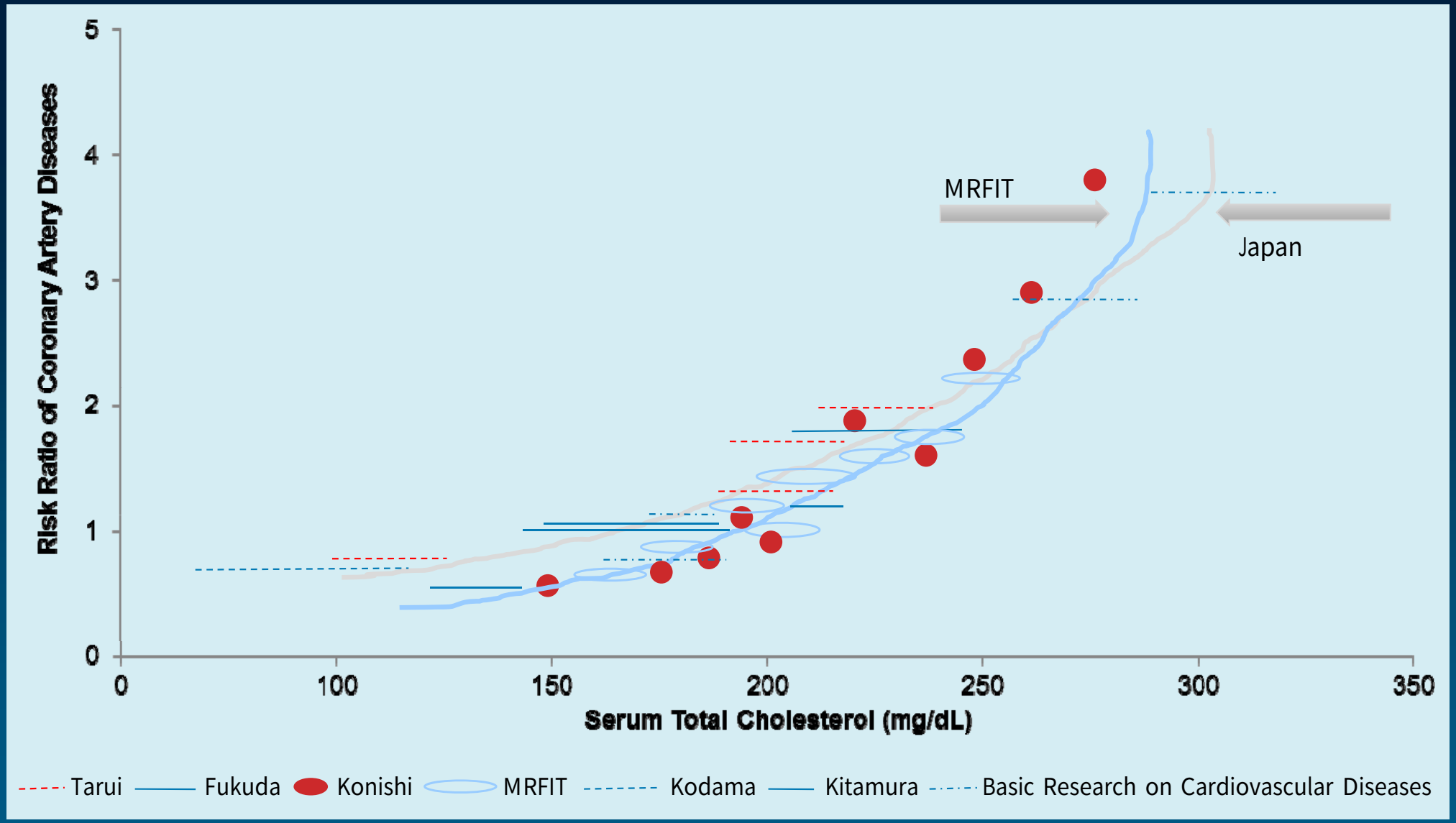
Relationship Between Serum Total Cholesterol and Risk Ratio of Coronary Artery Diseases: US/Japan Comparison



Saito Y. *Eur Heart J.* 2000;2:D49-D50.

Optimal LDL-C Level of <70mg/dl in Guideline

Risk Category

NCEP-ATP III (2004)

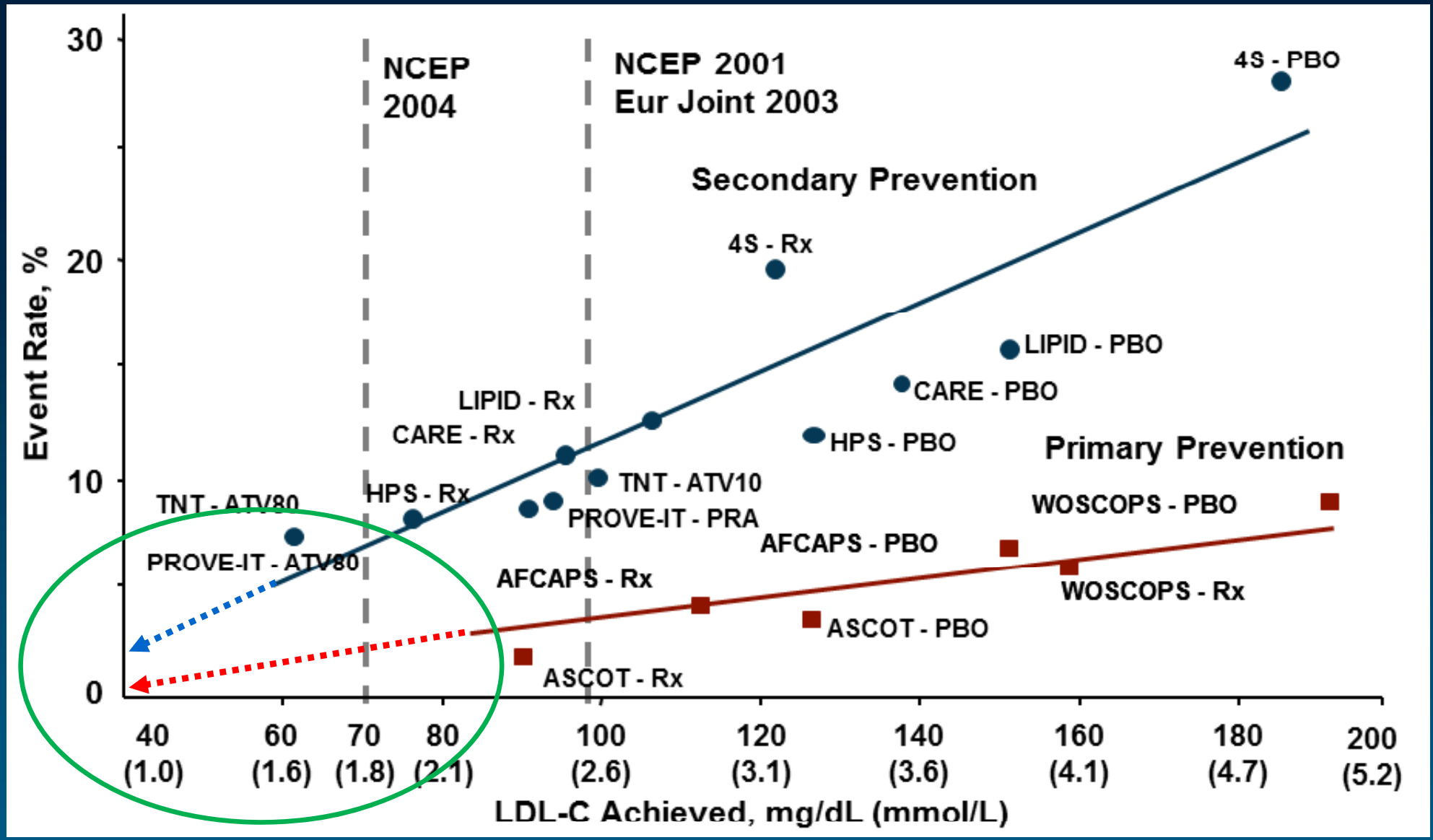
- **LDL-C<70 mg/dL is optional : Very High Risk**

  Established CVD plus
  (1) Multiple risk factors (esp, Diabetes),
  (2) Severe and poorly controlled risk factors (esp, continued cigarette smoking),
  (3) Multiple risk factors of the metabolic syndrome (esp TG ≥ 200 mg/dL + non-HDL-C ≥ 130 mg/dL + HDL-C<40mg/dL**),**
  (4) ACS

ESC/EAS (2011)

Risk Category	LDL Goal
Very High Risk : Estabilished CVD, Previous MI, ACS, Coronary revascularization, Other arterial revascularization, Ischaemic stroke, PAD, Diabetes, CKD(GFR < 60 mL/min/1.73m^2), 10 year risk SCORE ≥ 10 %	< 70 mg/dL and/or ≥ 50 % ↓

LDL-C Lowering and Benefit of Statins



NEJM. 2005; 352: 1425-1435
Exp. Opin Emerg Drugs. 2004; 9 : 269-279

- Is There **Evidence** of **Statin** Therapy in Patients with **Very Low LDL-C Level** ?

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Benefit of Early Statin Therapy in Patients With Acute Myocardial Infarction Who Have Extremely Low Low-Density Lipoprotein Cholesterol

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Gwangju, Busan, Daegu, Daejeon, Busan, Cheongju, Seoul, and Ulsan, South Korea

Objectives We investigated whether statin therapy could be beneficial in patients with acute myocardial infarction (AMI) who have baseline low-density lipoprotein cholesterol (LDL-C) levels below 70 mg/dl.

Background Intensive lipid-lowering therapy with a target LDL-C value <70 mg/dl is recommended in patients with very high cardiovascular risk. However, whether to use statin therapy in patients with baseline LDL-C levels below 70 mg/dl is controversial.

Methods We analyzed 1,054 patients with AMI who had baseline LDL-C levels below 70 mg/dl and survived at discharge from the Korean Acute MI Registry between November 2005 and December 2007. They were divided into 2 groups according to the prescribing of statins at discharge (statin group n = 607; nonstatin group n = 447). The primary endpoint was the composite of 1-year major adverse cardiac events, including death, recurrent MI, target vessel revascularization, and coronary artery bypass grafting.

Results Statin therapy significantly reduced the risk of the composite primary endpoint (adjusted hazard ratio [HR]: 0.56; 95% confidence interval [CI]: 0.34 to 0.89; p = 0.015). Statin therapy reduced the risk of cardiac death (HR: 0.47; 95% CI: 0.23 to 0.93; p = 0.031) and coronary revascularization (HR: 0.45, 95% CI: 0.24 to 0.85; p = 0.013). However, there were no differences in the risk of the composite of all-cause death, recurrent MI, and repeated percutaneous coronary intervention rate.

Conclusions Statin therapy in patients with AMI with LDL-C levels below 70 mg/dl was associated with improved clinical outcome. (J Am Coll Cardiol 2011;58:1664–71) © 2011 by the American College of Cardiology Foundation

Benefit of Early Statin Therapy in AMI Patients with Extremely Low LDL-C

Data from KAMIR (Korean AMI Registry)

- Study Objectives : To investigate whether statin therapy could be beneficial in AMI patients with LDL-C<70 mg/dL

JACC. 2011; 365: 2078-87

Benefit of Early Statin Therapy in AMI Patients with Extremely Low LDL-C

Baseline Clinical Characteristics

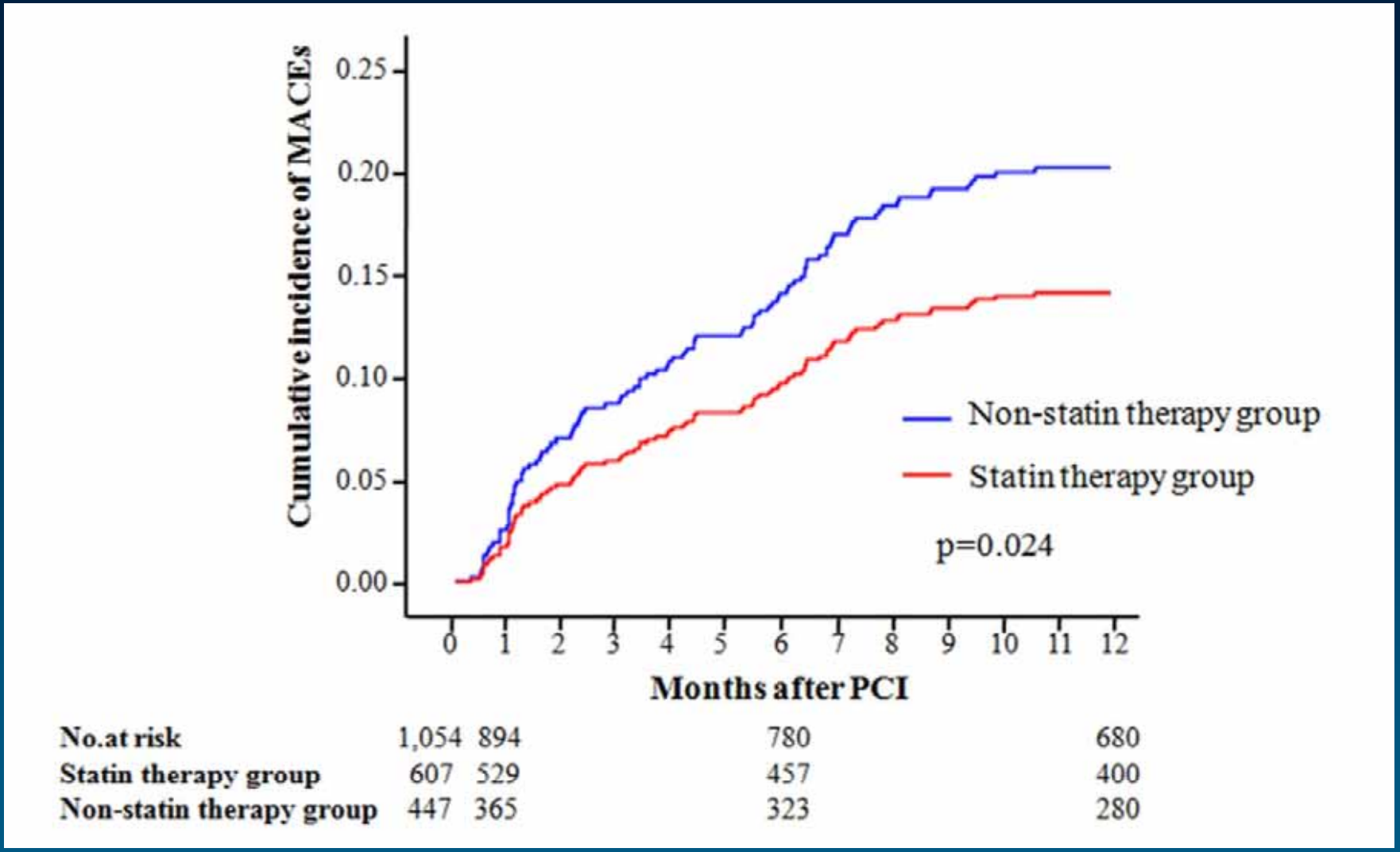
	Statin Group (n = 607)	Nonstatin Group (n = 447)	p Value
Male*	437 (72.0)	314 (70.4)	0.573
Age, yrs†	71.0 (60.0–78.0)	71.0 (62.0–80.0)	0.809
Laboratory findings†			
Total cholesterol, mg/dl	123.0 (108.0–123.0)	122.0 (108.0–136.0)	0.453
HDL-C, mg/dl	40.0 (33.0–48.0)	41.0 (32.0–50.0)	0.929
LDL-C, mg/dl	58.0 (48.0–65.0)	59.0 (48.0–65.0)	0.709
Triglycerides, mg/dl	84.0 (56.0–126.5)	77.0 (54.0–115.0)	0.083
Peak creatine kinase-MB, ng/ml	46.3 (13.2–149.1)	36.5 (11.0–148.4)	0.331
Peak troponin I, ng/ml	13.0 (2.1–42.7)	12.5 (2.5–49.5)	0.834
Serum creatinine, mg/dl	1.0 (0.9–1.3)	1.1 (0.9–1.3)	0.852
hs-CRP, mg/dl	1.4 (0.2–8.5)	1.3 (0.2–7.0)	0.525
NT-proBNP, pg/ml	568.5 (144.0–2,600.0)	659.5 (169.8–2,688.0)	0.386
Indication for PCI*			0.205
ST-segment elevation MI	329 (54.3)	224 (50.3)	
Non–ST-segment elevation MI	277 (45.7)	221 (49.7)	
Medications*			
Aspirin	595 (98.0)	430 (96.2)	0.073
Clopidogrel	581 (95.7)	418 (93.5)	0.112
Beta-blocker	480 (79.1)	311 (69.6)	<0.001
Angiotensin-converting enzyme inhibitor	453 (74.6)	312 (69.8)	0.082
Angiotensin receptor blocker	146 (24.1)	100 (22.4)	0.524
Glycoprotein IIb/IIIa inhibitors	58 (9.6)	40 (8.9)	0.737
Unfractionated heparin	364 (60.0)	240 (53.7)	0.042
Low-molecular-weight heparin	188 (31.0)	159 (35.6)	0.116
Heparin§	459 (75.6)	330 (73.8)	0.507

JACC. 2011; 365: 2078

Benefit of Early Statin Therapy in AMI Patients with Extremely Low LDL-C

Primary Endpoint

: the composite rate of death, recurrent MI, and coronary revascularization



MACE : Major adverse cardiac events, PCI : Percutaneous coronary intervention

JACC. 2011; 365: 2078-87

Benefit of Early Statin Therapy in AMI Patients with Extremely Low LDL-C

Clinical Outcomes at 6 and 12 Months

	Statin Group (n = 607)	Nonstatin Group (n = 447)	p Value
6-month outcomes			
Cardiac death	14 (3.1)	19 (5.9)	0.031
Total death	19 (4.2)	22 (6.8)	0.071
MI	9 (2.0)	2 (0.6)	0.386
Repeated PCI	14 (3.1)	13 (4.0)	0.336
TVR	5 (1.1)	8 (2.5)	0.081
CABG	8 (1.8)	9 (2.8)	0.012
MACE	50 (10.9)	45 (13.9)	0.048
12-month outcomes			
Cardiac death	16 (4.0)	21 (7.5)	0.048
Total death	23 (5.8)	26 (9.3)	0.101
MI	9 (2.3)	5 (1.8)	0.644
Repeated PCI	19 (4.8)	17 (6.1)	0.232
TVR	8 (2.0)	10 (3.6)	0.209
CABG	8 (2.0)	11 (3.9)	0.003
MACE	58 (14.5)	57 (20.4)	0.014

- Statin therapy in patients with AMI with LDL-C levels below 70 mg/dl was associated with improved clinical outcome

JACC. 2011; 365: 2078-87

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Cardiovascular Event Reduction and Adverse Events Among Subjects Attaining Low-Density Lipoprotein Cholesterol <50 mg/dl With Rosuvastatin

The JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)

Judith Hsia, MD,* Jean G. MacFadyen, BA,† John Monyak, PHD,* Paul M. Ridker, MD, MPH†

Wilmington, Delaware; and Boston, Massachusetts

Objectives The purpose of this study was to assess the impact on cardiovascular and adverse events of attaining low-density lipoprotein cholesterol (LDL-C) levels <50 mg/dl with rosuvastatin in apparently healthy adults in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial.

Background The safety and magnitude of cardiovascular risk reduction conferred by treatment to LDL-C levels below current recommended targets remain uncertain.

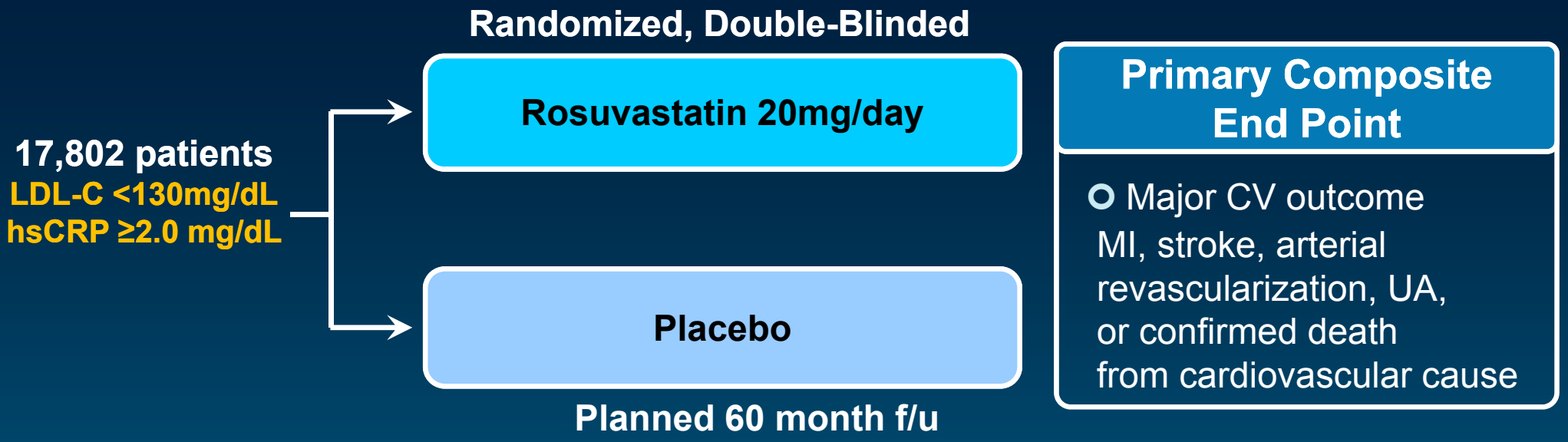
Methods A cohort of 17,802 apparently healthy men and women with high-sensitivity C-reactive protein ≥2 mg/l and LDL-C <130 mg/dl were randomly allocated to rosuvastatin 20 mg daily or placebo, and followed up for all-cause mortality, major cardiovascular events, and adverse events. In a post-hoc analysis, participants allocated to rosuvastatin were categorized as to whether or not they had a follow-up LDL-C level <50 mg/dl.

Results During a median follow-up of 2 years (range up to 5 years), rates of the primary trial endpoint were 1.18, 0.86, and 0.44 per 100 person-years in the placebo group (n = 8,150) and rosuvastatin groups without LDL-C <50 mg/dl (n = 4,000) or with LDL-C <50 mg/dl (n = 4,154), respectively (fully-adjusted hazard ratio: 0.76; 95% confidence interval: 0.57 to 1.00 for subjects with no LDL-C <50 mg/dl vs. placebo and 0.35, 95% confidence interval: 0.25 to 0.49 for subjects attaining LDL-C <50 mg/dl; p for trend <0.0001). For all-cause mortality, corresponding event rates were 0.67, 0.65, and 0.39 (p for trend = 0.004). Rates of myalgia, muscle weakness, neuropsychiatric conditions, cancer, and diabetes mellitus were not significantly different among rosuvastatin-allocated participants with and without LDL-C <50 mg/dl.

Conclusions Among adults with LDL-C <130 mg/dl and high-sensitivity C-reactive protein ≥2 mg/l, rosuvastatin-allocated participants attaining LDL-C <50 mg/dl had a lower risk of cardiovascular events without a systematic increase in reported adverse events. (J Am Coll Cardiol 2011;57:1666–75) © 2011 by the American College of Cardiology Foundation

Safety and Magnitude of CV Risk Reduction among Adults Attaining LDL-C <50 mg/dl

A level below current recommended target: Data from JUPITER

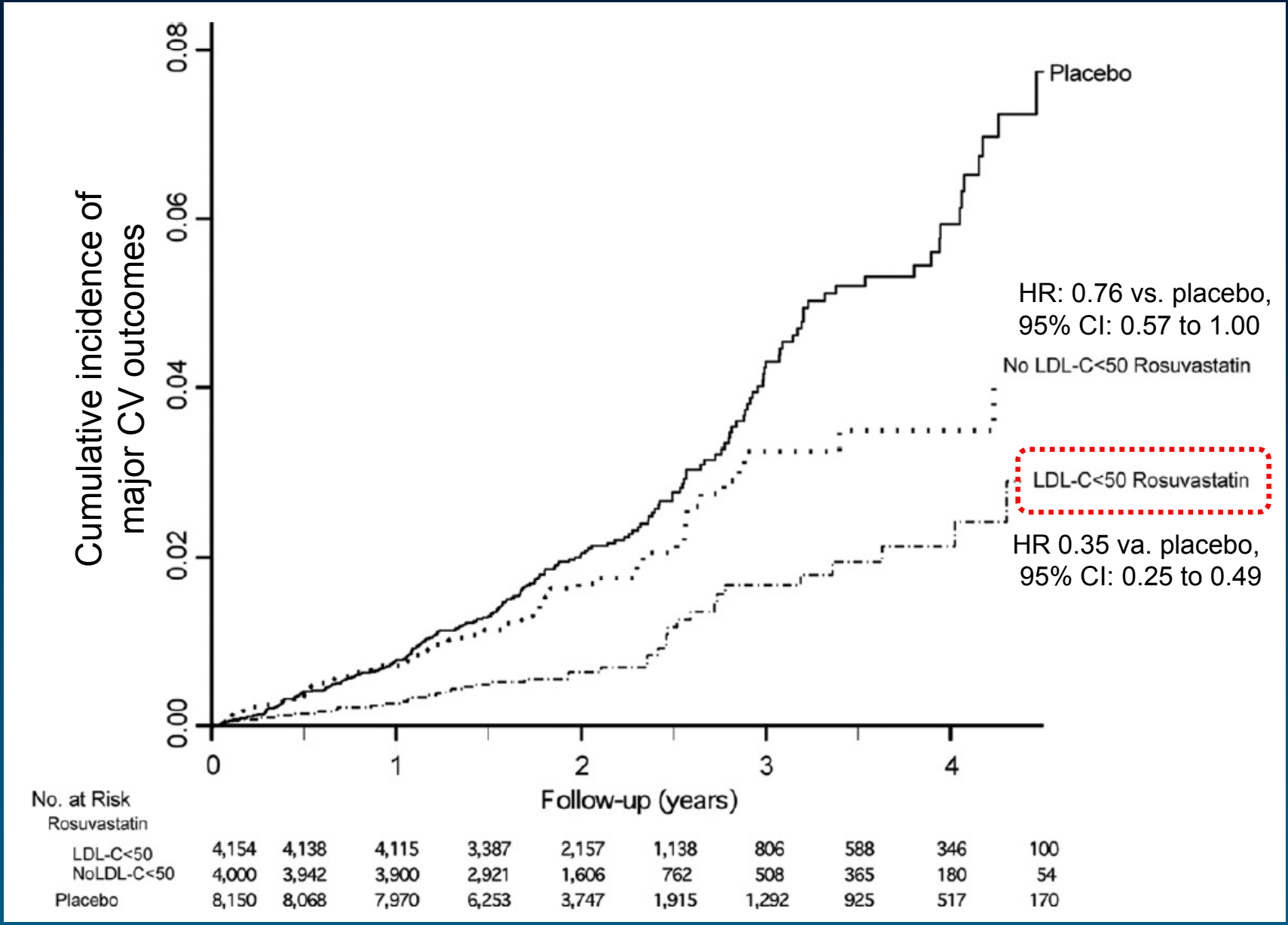


- Independent predictors of attaining LDL-C <50 mg/dl
  - slightly older age,
  - greater medication adherence
  - higher body mass index
  - impaired fasting glucose status
  - lower baseline levels of LDL-C, HDL-C, and hsCRP

Hsia. J et al. JACC. 2011;57:1666

Time to Occurrence of Major CV Outcomes

A level below current recommended target: Data from JUPITER

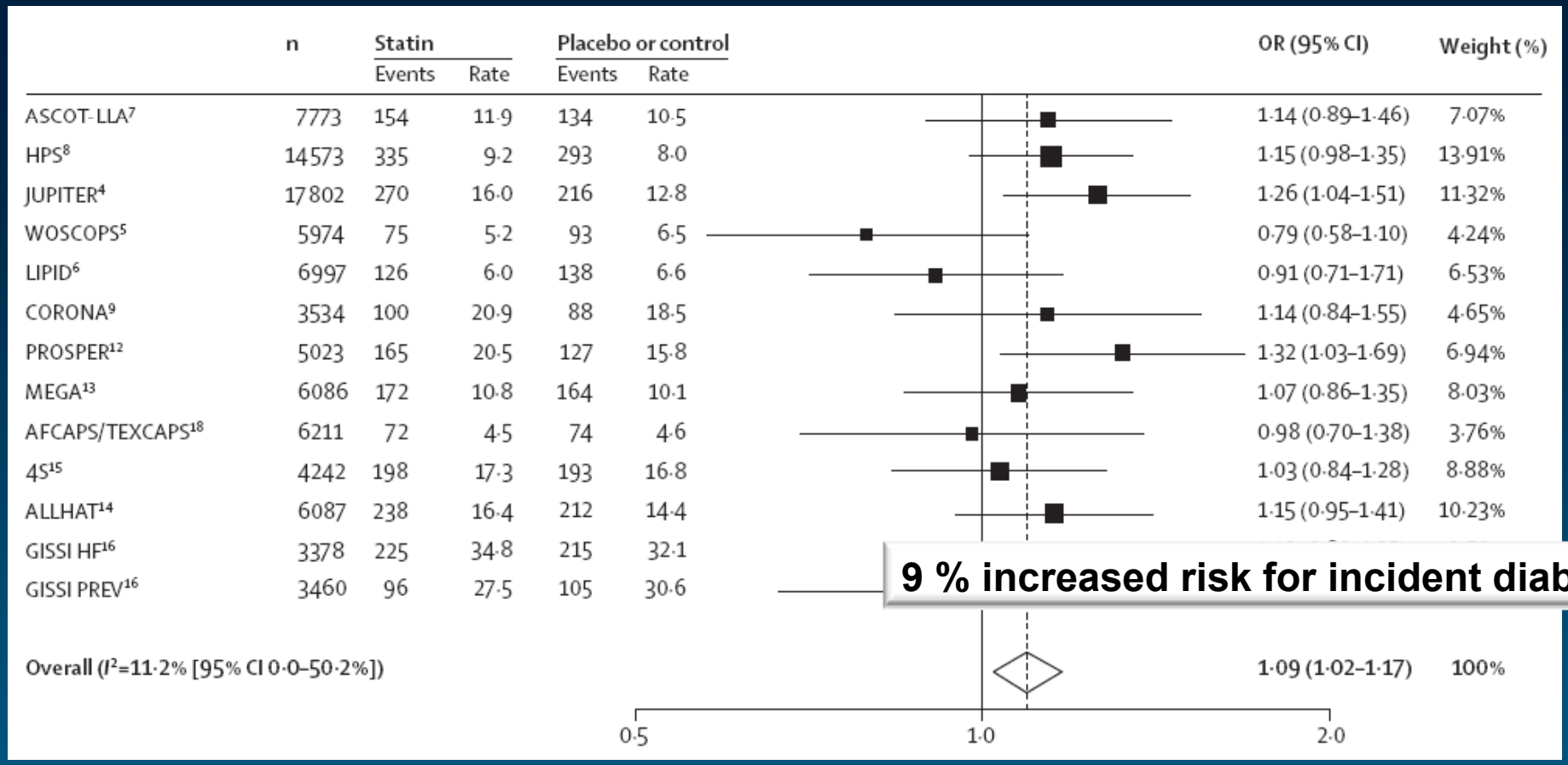


Hsia. J et al. JACC. 2011;57:1666

- Is **Statin** Therapy in Patients with **Very Low LDL-C Level** Always Good?

Statin and New Onset Diabetes

Association between statin therapy and incident diabetes



*Events per 100 patient-years. Weights are from random-effect analysis

- A collaborative meta-analysis of randomized, placebo-controlled statin trials.Searched Medline, Emabase, and the Cochrane Central from 1994 to 2009. Excluded trials of patients with organ transplants. needed hemodialysis or diabetes
- Identified 13 statin trials with 91 140 participants, of whom 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years.

Lancet. 2010; 375:735-42

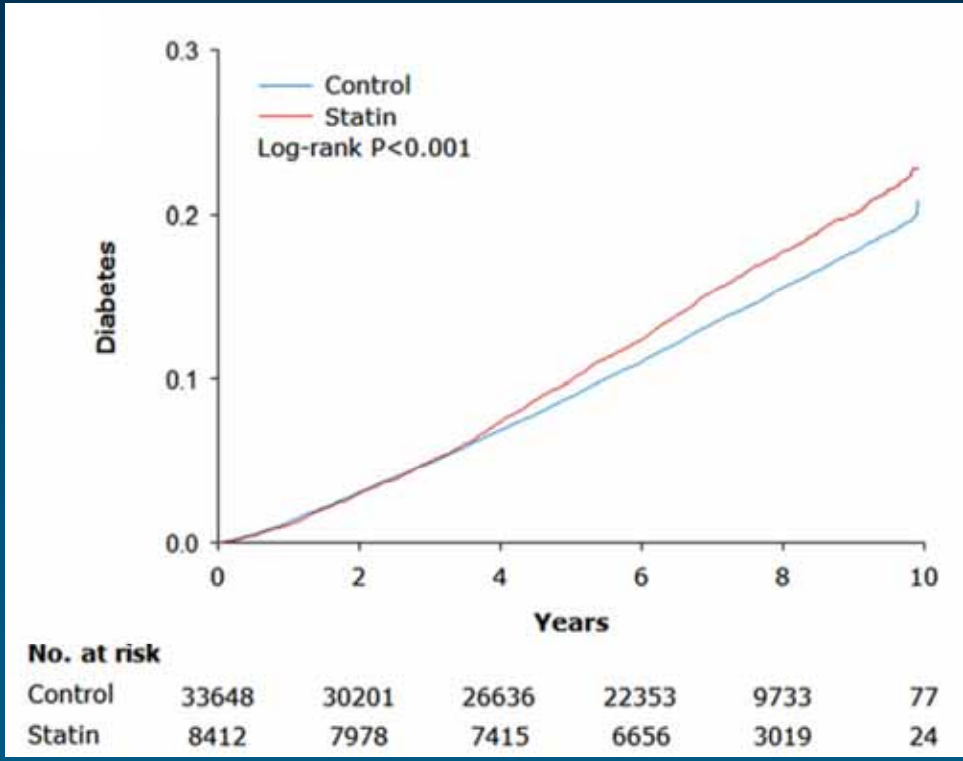
Taiwan National Health Insurance Data

Cardiometabolic Risk

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

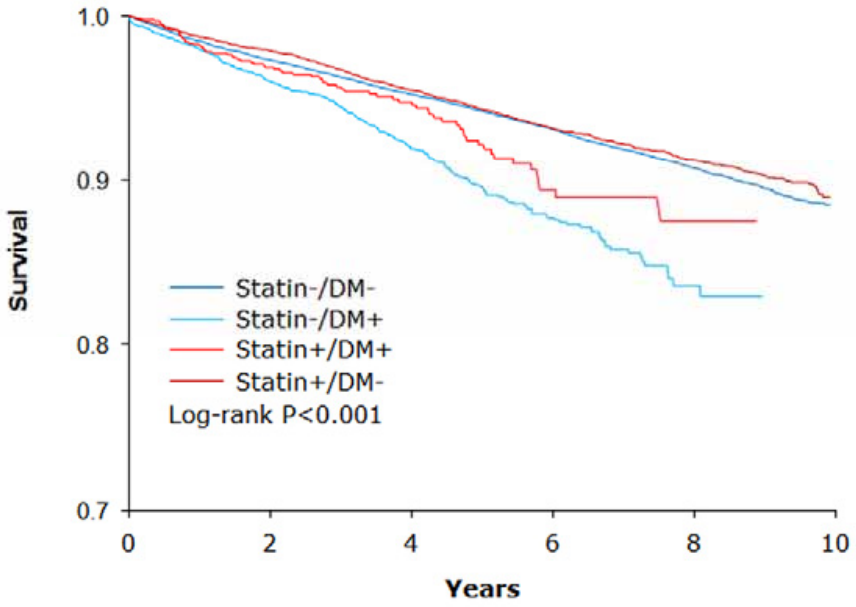
Kang-Ling Wang, MD,*†‡ Chia-Jen Liu, MD,† Tze-Fan Chao, MD,†‡ Chi-Ming Huang, MD,†‡
Cheng-Hsueh Wu, MD,†‡ Su-Jung Chen, MD,†‡ Tzeng-Ji Chen, MD, PHD,§‖
Shing-Jong Lin, MD, PHD,*†‡¶ Chern-En Chiang, MD, PHD*†‡¶#
Taipei, Taiwan

- Median follow-up of 7.2 years (interquartile range: 6.1 to 8.7 years)
- Statin 8,412 vs. Control 33,648
  : 5,754 cases of incident diabetes
- Kaplan-Meier curves suggested statin use increased the hazards of diabetes occurrence (HR: 1.15; 95% CI: 1.08 to 1.22; p < 0.001).



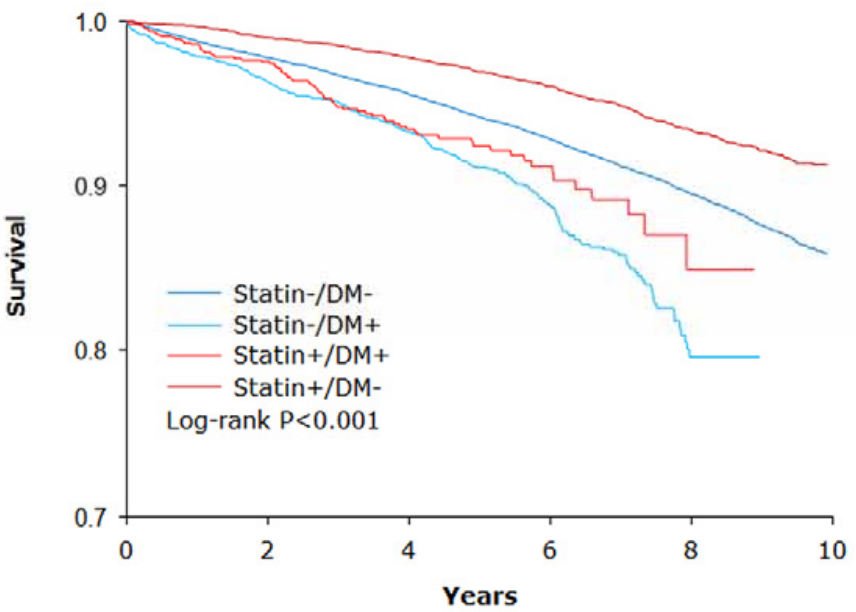
Survival Curves for Subjects Categorized by the Presence of Diabetes and Statin Use

Major CV Event



No. at risk						
Statin-/DM-	29332	26361	23667	20323	8906	75
Statin-/DM+	4316	2887	1729	714	149	
Statin+/DM+	1387	943	531	198	35	
Statin+/DM-	7025	6716	6382	5922	2743	22

In-hospital Death from All Causes



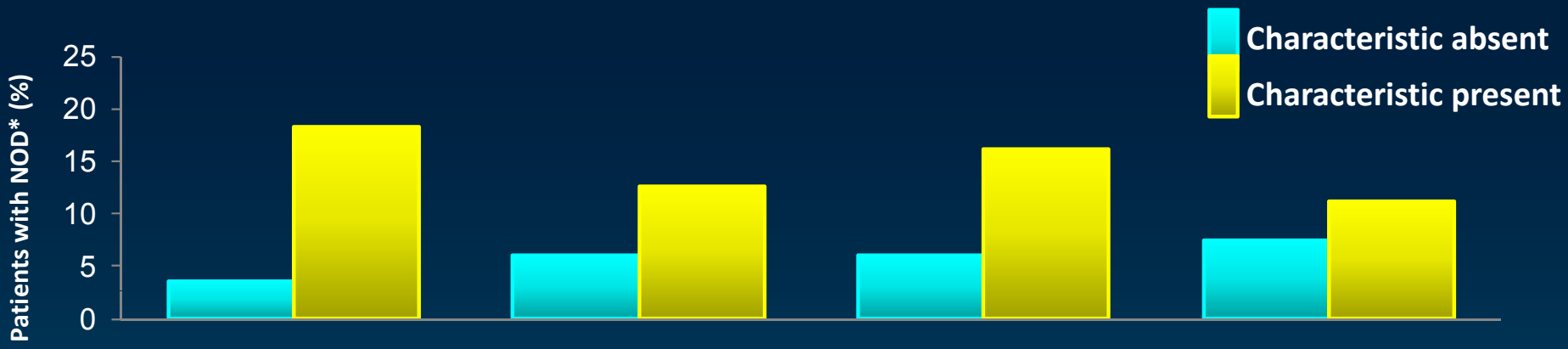
No. at risk						
Statin-/DM-	29332	26876	24456	21275	9459	77
Statin-/DM+	4316	2987	1858	792	162	
Statin+/DM+	1387	971	552	217	37	
Statin+/DM-	7025	6840	6633	6263	2925	24

- This study suggested a similarly small risk of NOD offset by the CV benefits of statin therapy

JACC 2012;60:1231

Risk Factors for NOD after Statin

- **During statin therapy[1]**



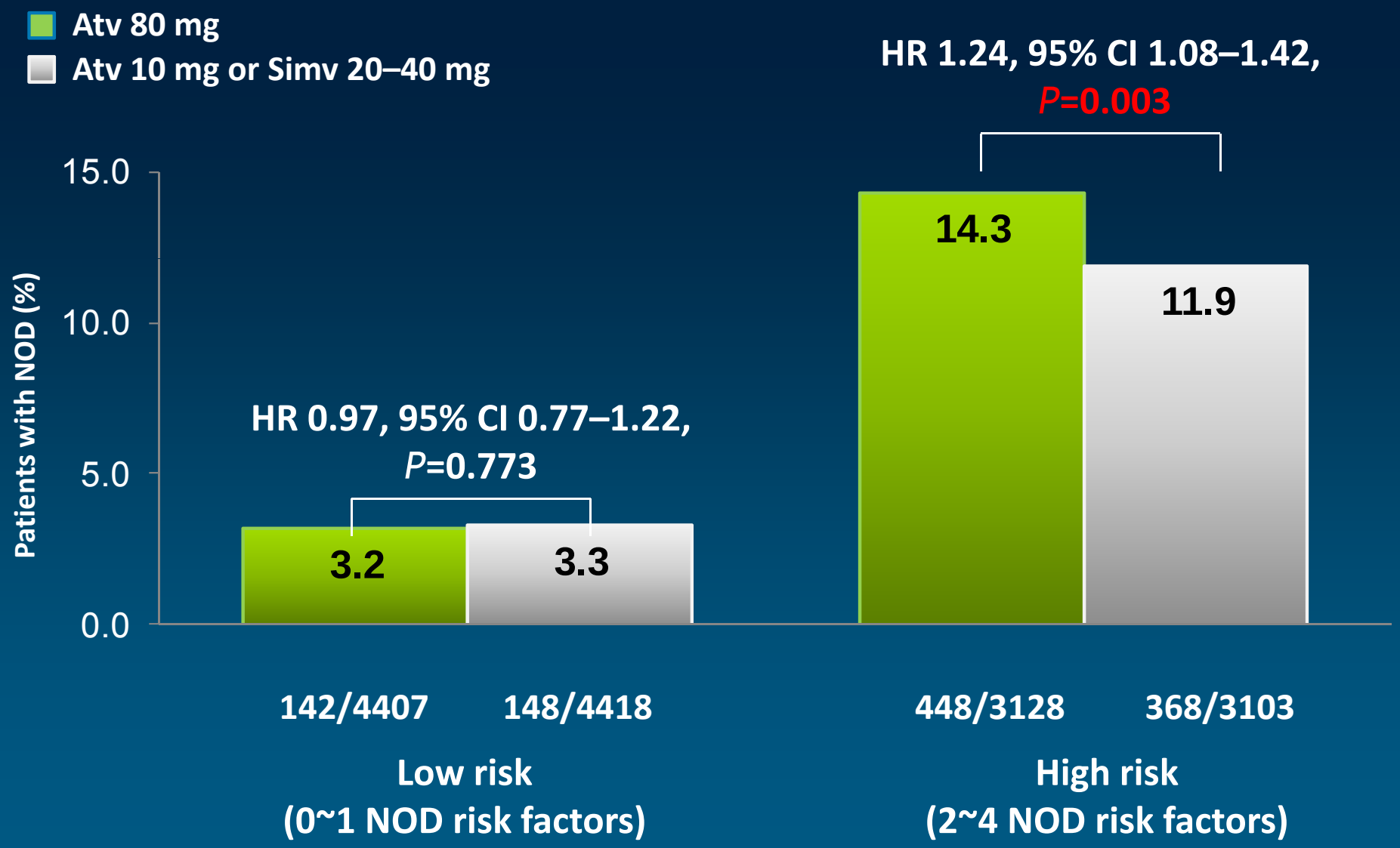
- **Similar to the predictors of incident diabetes not related to statins[2-4]**

*Data shown is from the TNT (Treating to New Targets) trial.[1] The HRs were remarkably consistent across the trials analyzed (TNT, IDEAL, and SPARCL), ranging from 3.49 to 5.78 for FBG, 1.88 to 2.37 for fasting triglycerides, 2.36 to 2.73 for BMI, and 1.60 to 1.91 for history of hypertension (P<0.0001 for all).[1]

1. Waters D, et al, *JACC* 2011;57:1535-45.
2. Wilson P, et al. *Arch Intern Med* 2007;167:1068-74.
3. Rahman M, et al. *Family Practice* 2008;25:191-6.
4. Kanaya A, et al. *Diabetes Care* 2005;28:404-8.

Development of NOD

- total of 15,056 patients : low risk, n=8825 / high risk, n=6231



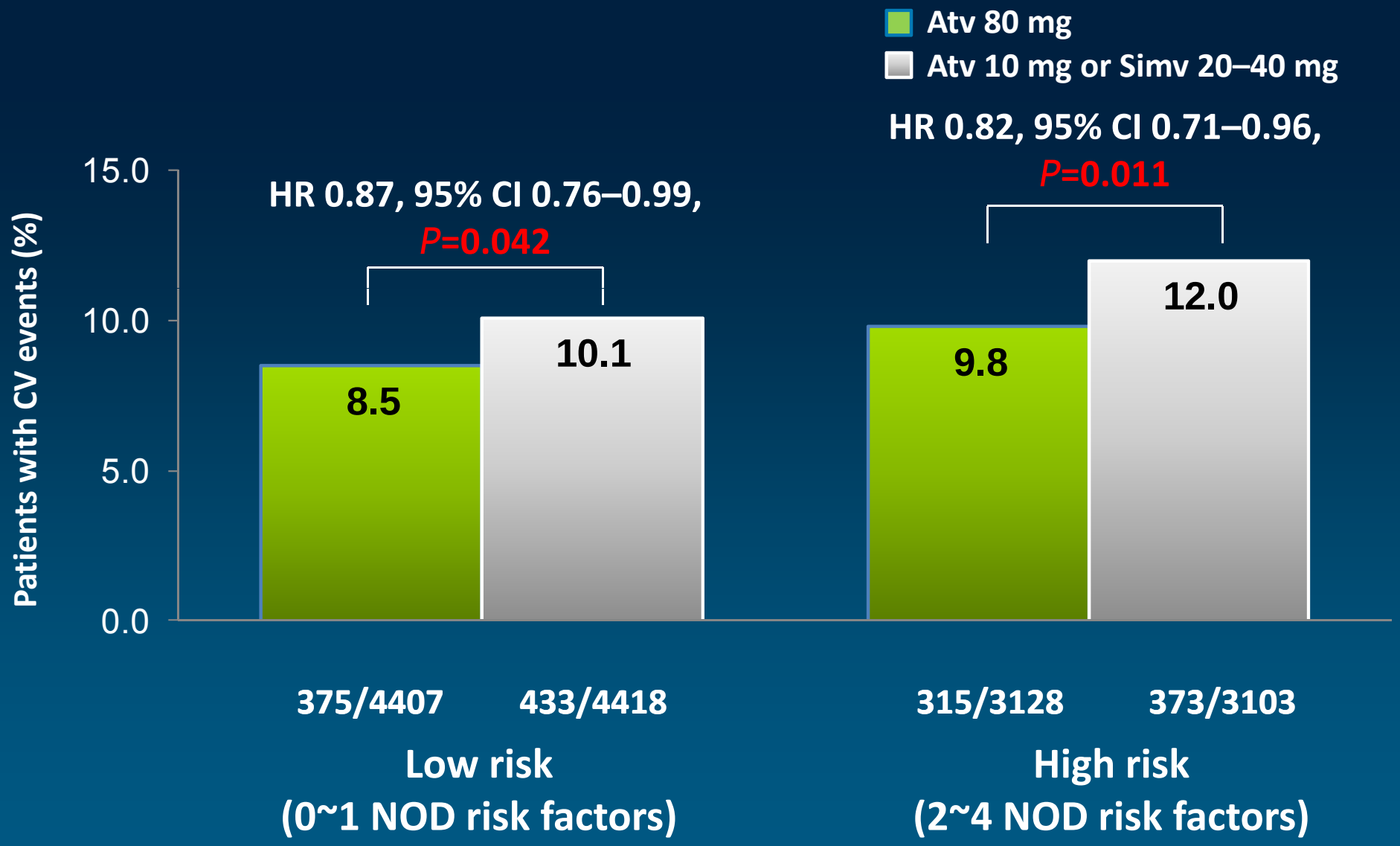
Atv, atorvastatin; Simv, simvastatin

JACC 2013; 61:148-52

Occurrence of CV Events

TNT + IDEAL

- total of 15,056 patients : low risk, n=8825 / high risk, n=6231



CV events included coronary heart disease death, myocardial infarction, stroke, and resuscitated cardiac arrest

Atv, atorvastatin; Simv, simvastatin

JACC 2013; 61(2):148-52

LDL-C Lowering and Cancer Risk

An association between risk of incident cancer and lower achieved LDL levels

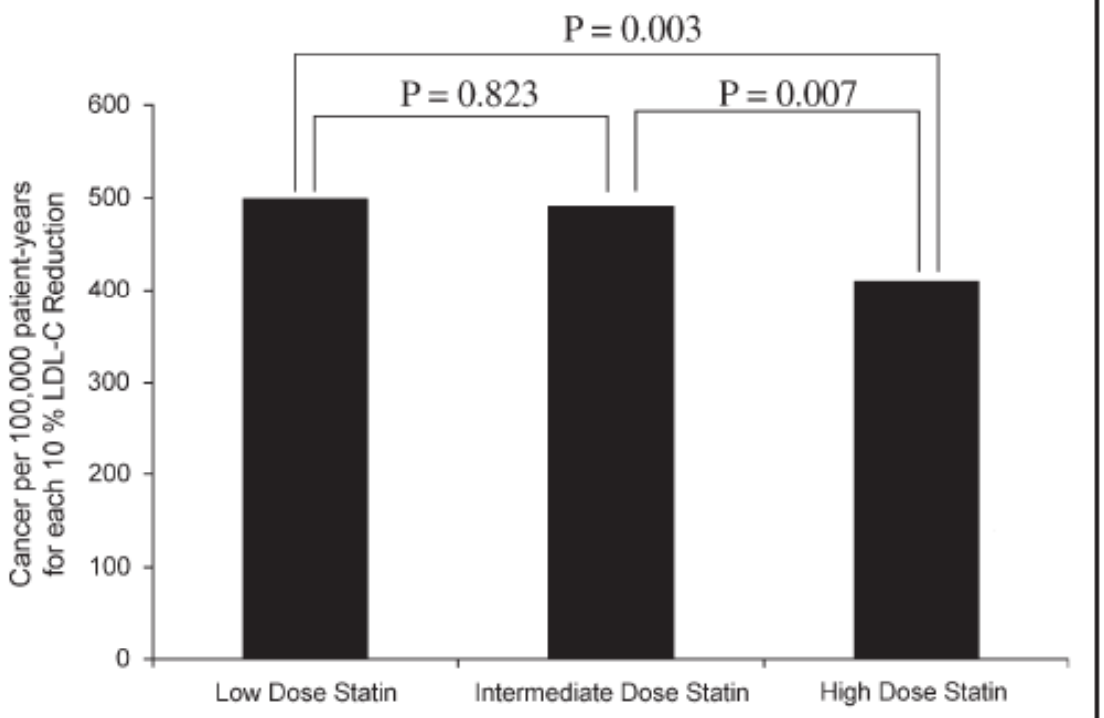


Figure 10 **Rate of Newly Diagnosed Cancer by Statin Dose Category**

Rate of newly diagnosed cancer per 100,000 person-years for each 10% reduction in low-density lipoprotein-cholesterol (LDL-C) for the following statin dose categories: low dose (lovastatin 20 mg), intermediate dose (lovastatin 40 mg, simvastatin 40 mg, and pravastatin 40 mg), and high dose (lovastatin 80 mg, fluvastatin 80 mg).

JACC. 2007; 50:409-418

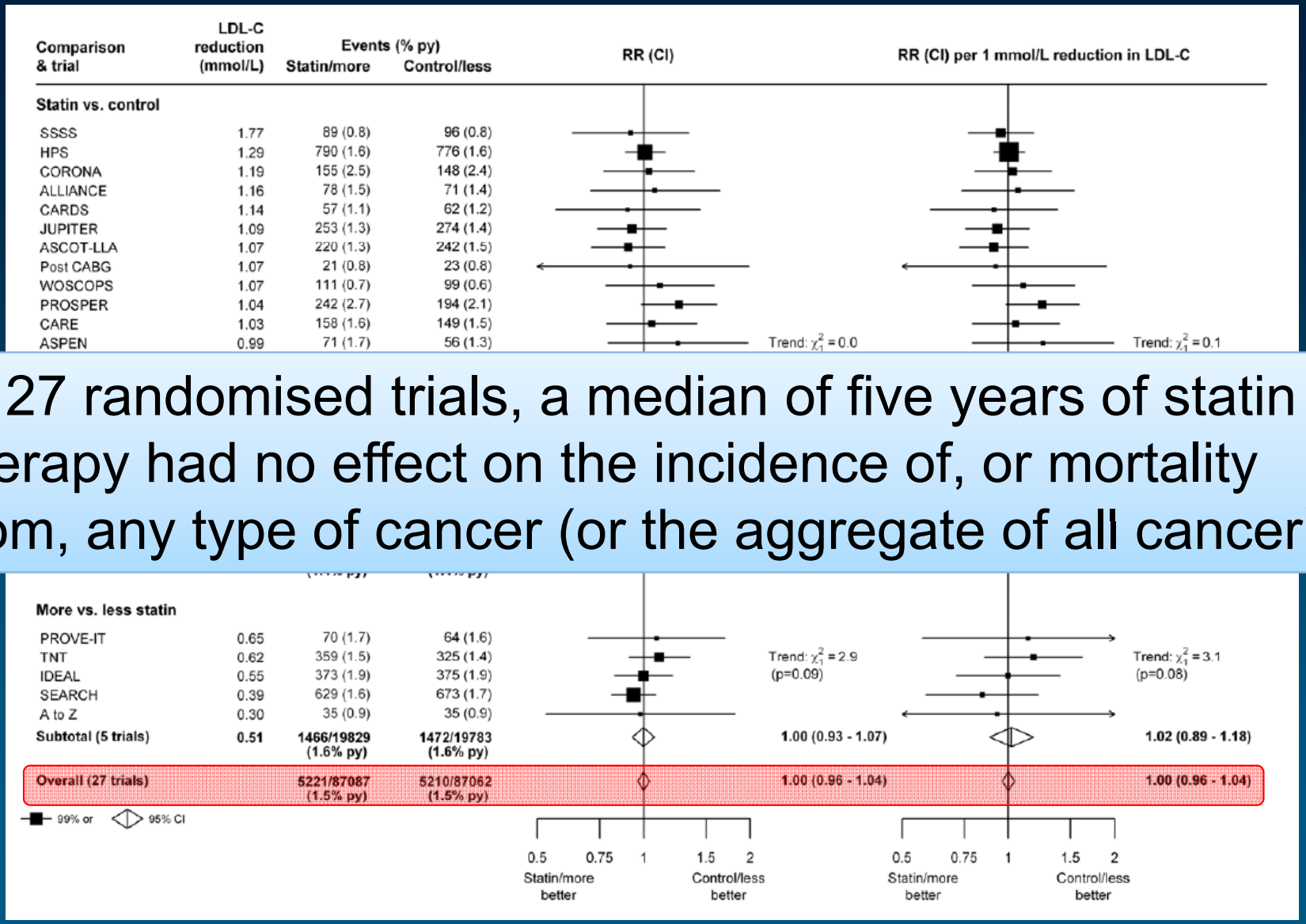
OPEN ACCESS Freely available online

PLoS one

Lack of Effect of Lowering LDL Cholesterol on Cancer: Meta-Analysis of Individual Data from 175,000 People in 27 Randomised Trials of Statin Therapy

Cholesterol Treatment Trialists' (CTT) Collaboration*¶

PLoS One. 2012; 7(1): e29849



In 27 randomised trials, a median of five years of statin therapy had no effect on the incidence of, or mortality from, any type of cancer (or the aggregate of all cancer)

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  4. Special patients population: DM, women, elderly, CKD

- Summary

NCEP-ATPIII : LDL-C Goals in Different Risk Categories

Risk Category	LDL-C Goal
CHD or CHD Risk Equivalents : **Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease)**	**< 100 mg/dL**
Diabetes **10-year risk for CHD>20 %**	
2+ Risk Factors without CHD	< 130 mg/dL
0-1 Risk Factors without CHD	< 160 mg/dL

- **LDL-C<70 mg/dL is optional : Very High Risk**

  Established CVD plus
  (1) Multiple risk factors (esp, Diabetes),
  (2) Severe and poorly controlled risk factors (esp, continued cigarette smoking),
  (3) Multiple risk factors of the metabolic syndrome (esp TG ≥ 200 mg/dL + non-HDL-C ≥ 130 mg/dL + HDL-C<40mg/dL),
  (4) ACS

Secondary Targets : Non-HDL-C

- Non- HDL-C is a secondary target when TG ≥ 200 mg/dL
- Non-HDL-C = Total cholesterol – HDL-C
- Valid even if patients is non-fasting

Risk Category	LDL-C Target	Non-HDL-C
CHD or CHD risk equivalent	<100	<130
2+ Risk Factors without CHD	<130	<160
0-1 Risk Factors without CHD	<160	<190

ESC/EAS Guidelines for the Management of Dyslipidemias (2011)

Recommendations for lipid analyses as treatment target in the prevention of CVD

Recommendations	Class[a]	Level[b]
LDL-C is recommended as target for treatment.	I	A
TC should be considered as treatment target if other analyses are not available.	IIa	A
TG should be analysed during the treatment of dyslipidaemias with high TG levels.	IIa	B
Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	B
Apo B should be considered as a secondary treatment target.	IIa	B
HDL-C is not recommended as a target for treatment.	III	C
The ratios apo B/apo A1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	C

Canadian Guideline 2009

TARGETS OF THERAPY

Risk level	Primary target: LDL-C	Class, level
High	<2 mmol/L	Class I, level A
CAD, PVD, atherosclerosis	or	
Most patients with diabetes	≥50% ↓ LDL-C	
FRS ≥20%	apoB <0.80 g/L	
RRS ≥20%		
Moderate	<2 mmol/L*	Class IIa, level A
FRS 10% to 19%	or	
LDL-C >3.5 mmol/L	≥50% ↓ LDL-C	
TC/HDL-C >5.0	apoB <0.80 g/L	
hs-CRP >2 mg/L in men >50 years and women >60 years of age		
Family history and hs-CRP modulate risk		
Low	≥50% ↓ LDL-C	Class IIa, level A
FRS <10%		

Clinical Limitation of Apo B or Non-HDL-C

- Apo B and non-HDL-C are likely better predictors of risk than LDL-C in patients with cardiometabolic syndrome
- ApoB measurement does require unique, expensive technology

Navigating Another Lipid Parameters

- Target for Lowering TG
  - Statin + Ezetimibe : ENHANCE
  - Statin + Niacin : AIM-HIGH, HPS2-THRIVE
  - Statin + Fenofibrate : ACCORD
- Target for Rasing HDL
  - Statin + CETP inhibitor : ILLUMINATE, dal-OUTCOME

➡ **Negative Results up to Now !**

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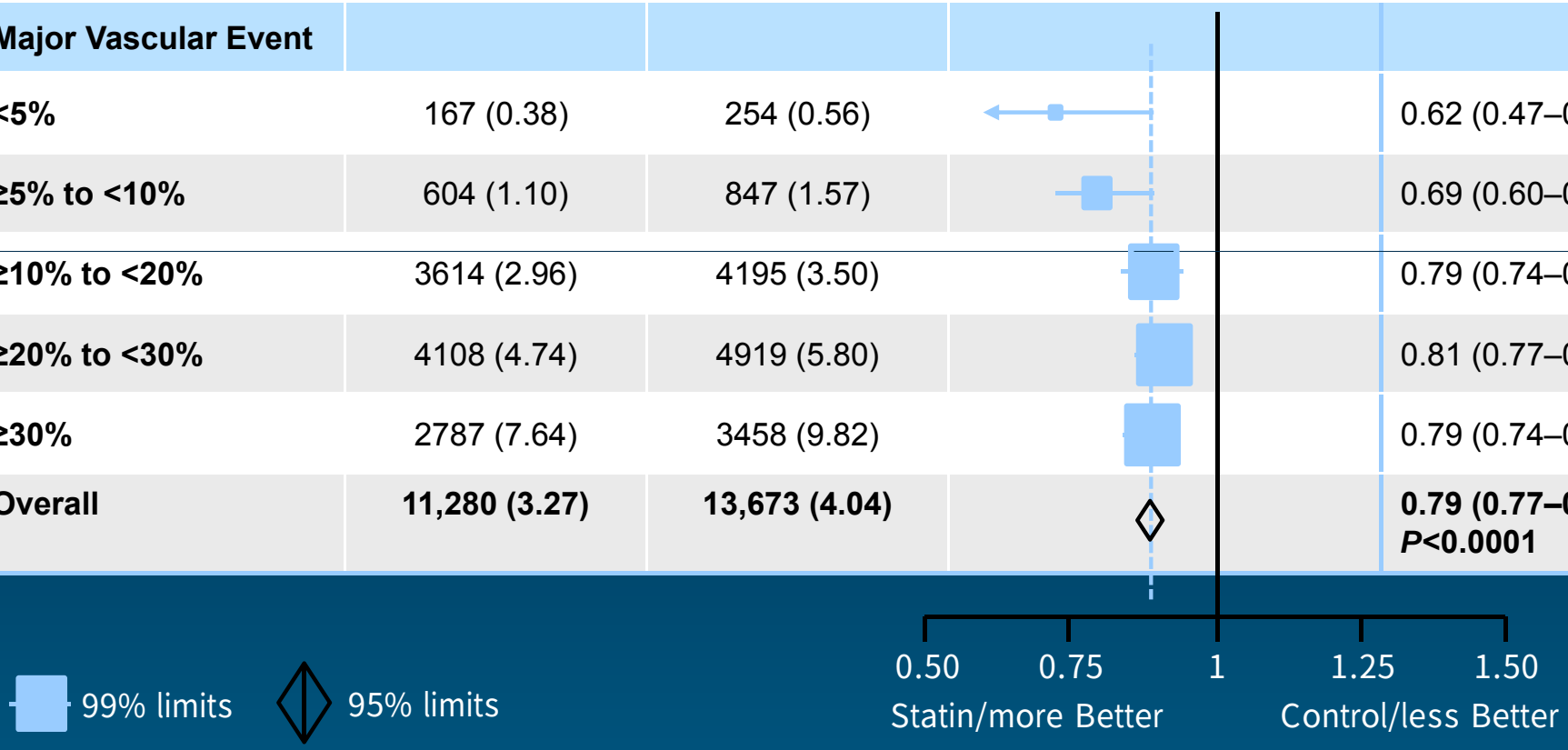
- Summary

Benefits of Treating Low-Risk Patients

5-Year MVE Risk at Baseline	Events (% per annum)		RR (CI) per 1.0 mmol/L Reduction in LDL Cholesterol	Trend Test
	Statin/More	Controls/Less		
Major Vascular Event				
<5%	167 (0.38)	254 (0.56)		0.62 (0.47–0.81)
≥5% to <10%	604 (1.10)	847 (1.57)		0.69 (0.60–0.79)
≥10% to <20%	3614 (2.96)	4195 (3.50)		0.79 (0.74–0.85) X^2_1=4.29
≥20% to <30%	4108 (4.74)	4919 (5.80)		0.81 (0.77–0.86) (*P*=0.04)
≥30%	2787 (7.64)	3458 (9.82)		0.79 (0.74–0.84)
Overall	**11,280 (3.27)**	**13,673 (4.04)**		**0.79 (0.77–0.081) *P*<0.0001**



* MVE(Major Vascular Events) : Major Coronary Events, Strokes, Coronary Revascularizations

* 5-year MVE risk : estimated using separate Cox proportional hazards models for the 67,000 patients allocated the control regimen in the 22 trials of statin versus control and the 20,000 patients allocated the less intensive statin regimen in the 5 trials of more versus less statin.

* CTTC: Cholesterol Treatment Trialists' Collaboration

CTTC. Lancet. 2012;380:581-590.

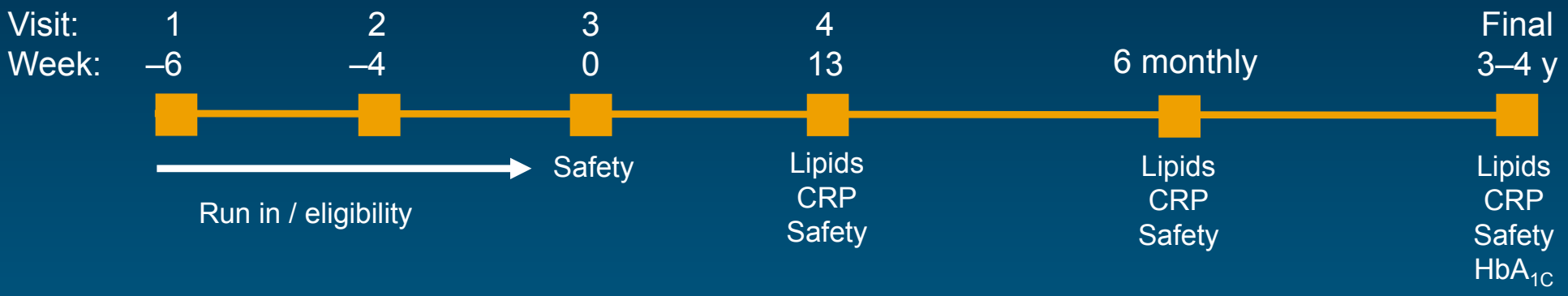
JUPITER Trial

Effect of Rosuvastatin on CV Events in Patients with Elevated hsCRP
Will it be lowered the goal for LDL-C in primary prevention?

Patients (n=17,802)
No history of CVD
LDL-C <3.4 mmol/L (130 mg/dL) and TG <5.6 mmol/L (500 mg/dL)
hsCRP ≥2 mg/L
Men ≥50 years
Women ≥60 years

Rosuvastatin 20 mg (n=8,901)

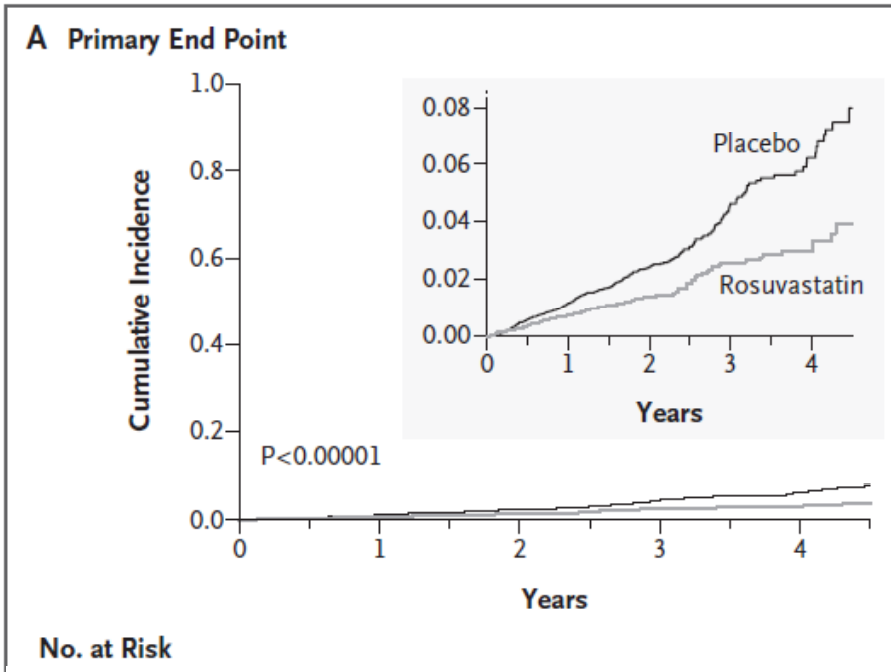
Placebo (n=8,901)

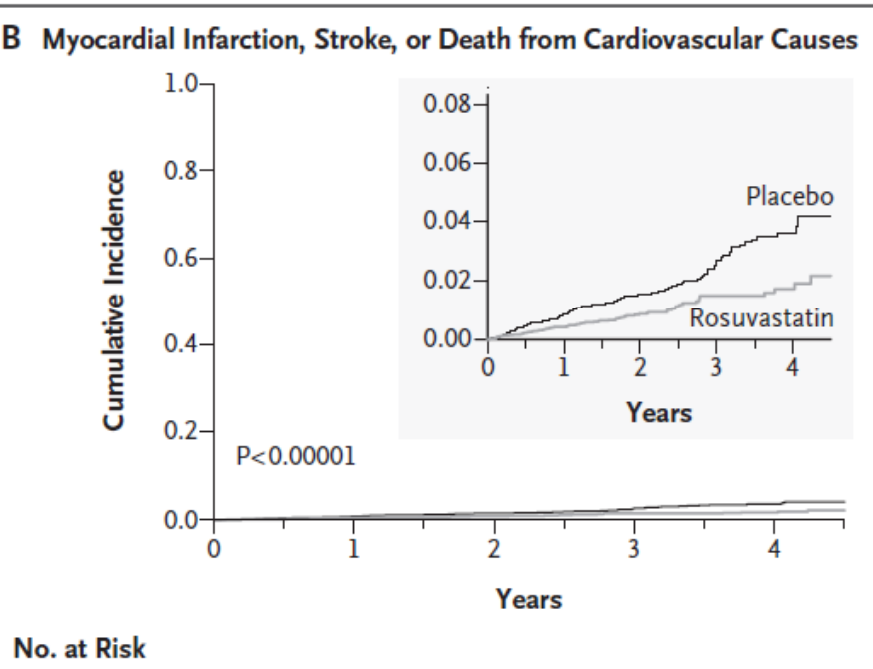


Median follow-up 1.9 years

- primary outcome: the occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes

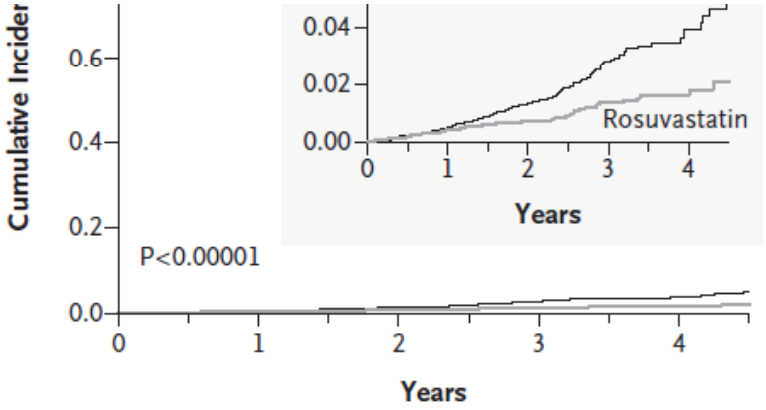
Ridker P et al. N Engl J Med 2008; 359: 2195-2207



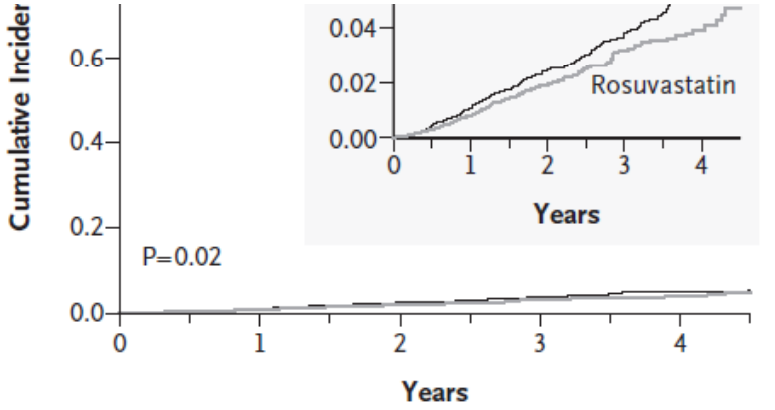


CONCLUSIONS

In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (ClinicalTrials.gov number, NCT00239681.)



No. at Risk										
Rosuvastatin	8901	8640	8426	6550	3905	1966	1359	989	541	158
Placebo	8901	8641	8390	6542	3895	1977	1346	963	535	176



No. at Risk										
Rosuvastatin	8901	8847	8787	6999	4312	2268	1602	1192	676	227
Placebo	8901	8852	8775	6987	4319	2295	1614	1196	681	246

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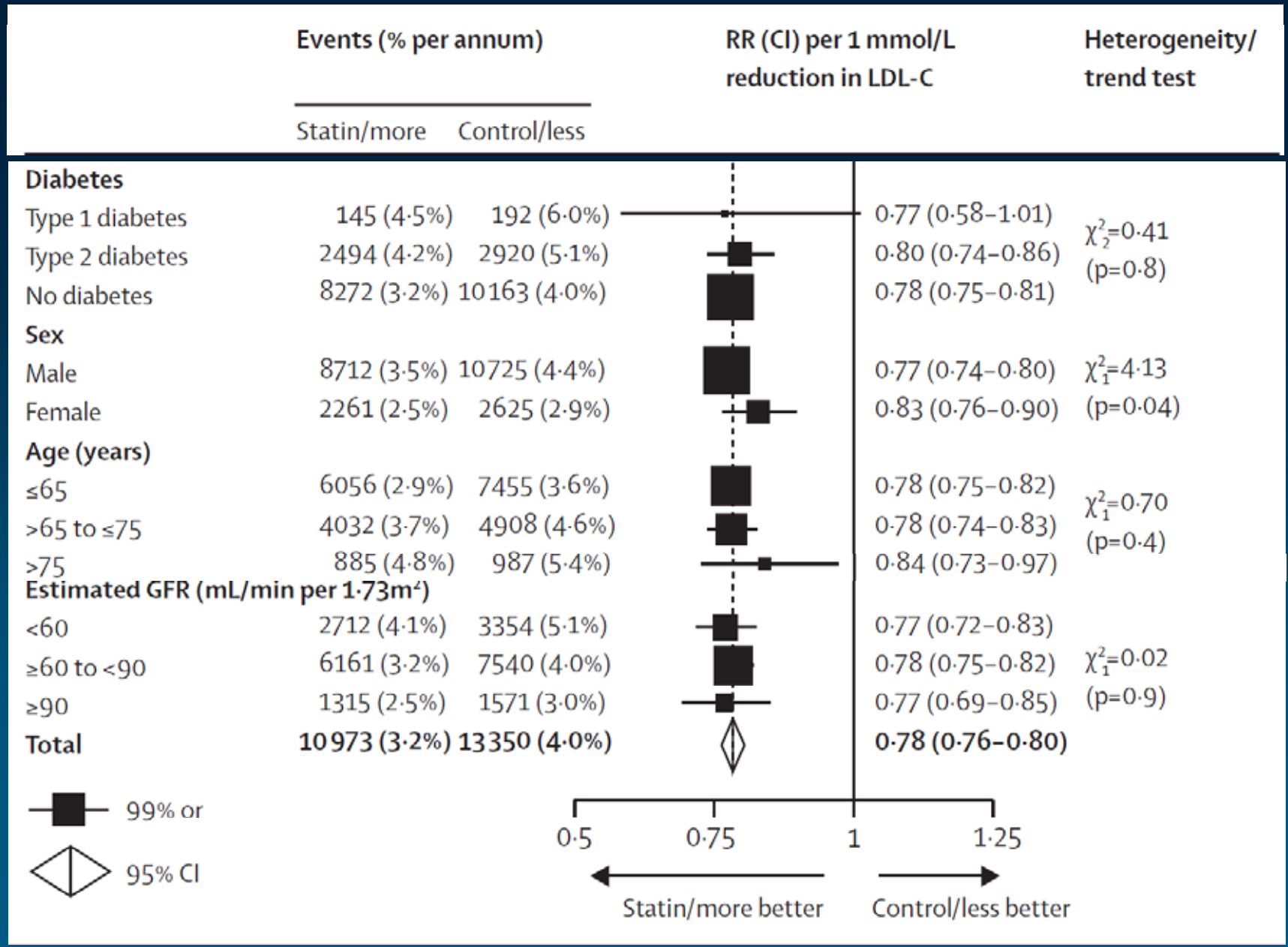
Cholesterol Treatment Trialists' (CTT) Collaboration

Efficacy and safety of more intensive lowering of LDL cholesterol:
a meta-analysis of data from 170 000 participants in 26 randomised trials



DM

All Statin Clinical Outcome Trials: Effects in Diabetes

- Average risk reduction in major vascular events per 1.0 mmol/L (40 mg/dL) reduction in LDL-cholesterol
- Analysis of 26 trials involving 126,138 subjects and 24,323 events

Subgroup	Events (% per Annum)		Relative Risk (95% CI)
	Statin Treatment Arm (N = 84,573)	**Control Arm** (N = 84,565)	
Type 1 Diabetes	145	192	**0.77** (0.58–1.01)
Type 2 Diabetes	2494	2920	**0.80** (0.74–0.86)
No Diabetes	8272	10163	**0.78** (0.75–0.81)

Cholesterol Treatment Trialists' (CTT) Collaboration, et al. Lancet. 2010;**376**:1670-1681

women

JUPITER - Women Subgroup Data Primary Endpoint:

Time to first occurrence of a CV death, non fatal stroke, non-fatal MI, unstable angina or arterial revascularization

	Rosuva	Placebo			
	No. (Rate)*	No. (Rate)*	HR	95% CI	P Value
Women	39 (0.57)	70 (1.04)	0.54	0.37-0.80	P=0.002
Men	103 (0.88)	181 (1.54)	0.58	0.45-0.73	P<0.0001

* Rates are per 100 person-years

Elderly

Japanese Elderly Diabetes Intervention Trial (J-EDIT)

Study Design

Patient population

Type 2 Diabetic patients

Age：65~84

HbA1c ≧7.9%
＝7.4　7.8%※

※：with hypertension, obesity, dyslipidemia

→ 1173 patients

Treat to Target therapy

Management target value
HbA1c≦6.9%、BMI＜25kg/m²、BP＜130/80mmHg、
TC＜200（180*）mg/dL、LDL-C＜120（100*）mg/dL
＊：with history of coronary artery disease
In case of not reaching the management target value, following medication is administered.
HbA1c：Oral hypoglycemic drug or Pioglitazone、Insulin
Serum lipid：Lipitor

Conventional therapy

5.7-year median follow-up

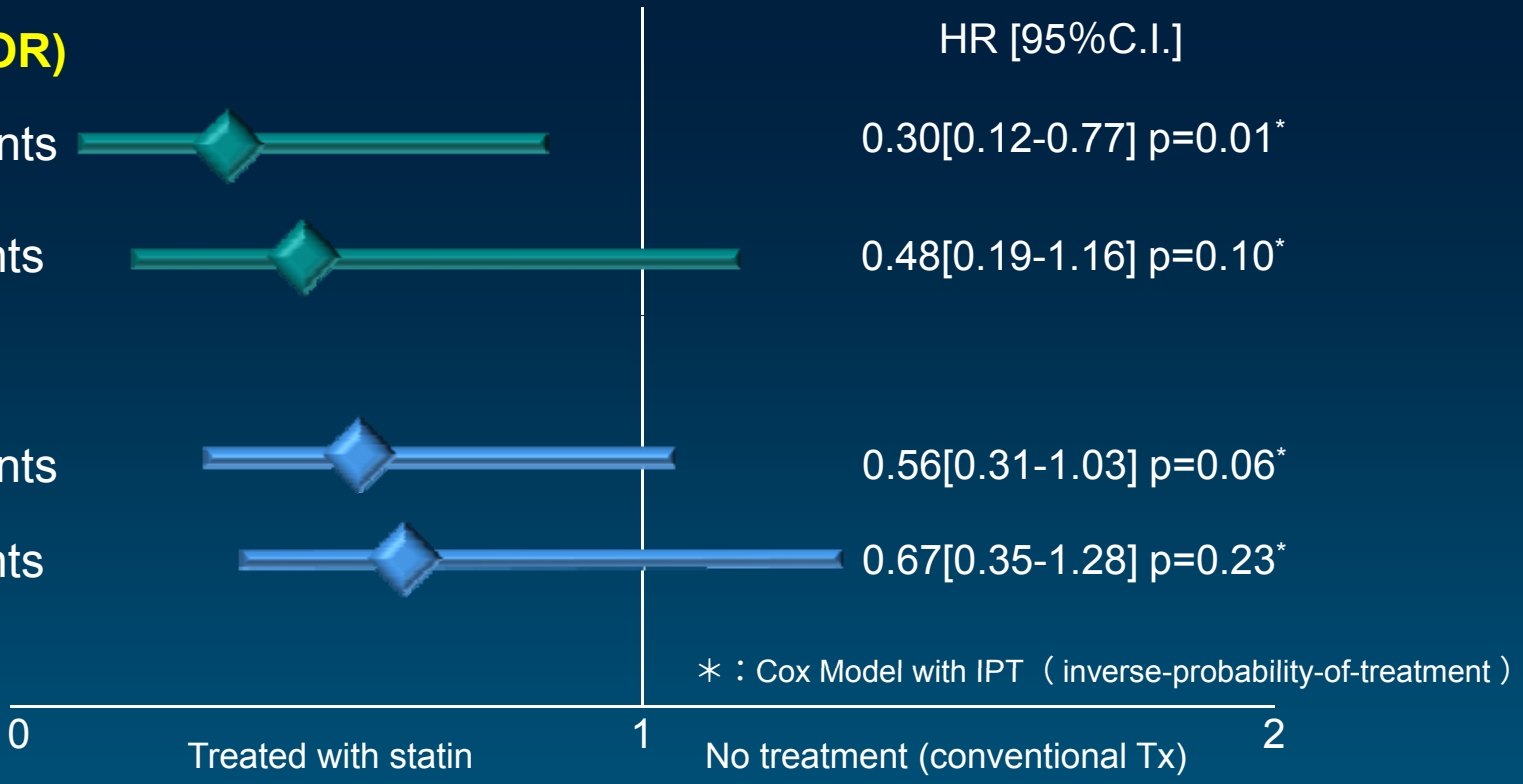
End point:
Fatal Events：Myocardial infarction, sudden death, stroke, death by renal failure, death by hyperglycemia or hypoglycemia
Non-fatal Events：Myocardial infarction, angina pectoris, history of coronary artery bypass graft, hospitalization history from heart failure, stroke, diabetic ulcer or gangrene

Assessed the preventive effect of atorvastatin on cardiovascular disease and diabetic vascular complication in elderly T2DM patients enrolled in J-EDIT

Araki, A. et al.：Geristr Gerontol Int 201212 Suppl 1：7-17.

Elderly

Atorvastatin reduced CVD Risk and Diabetic related Events in Old DM Patients



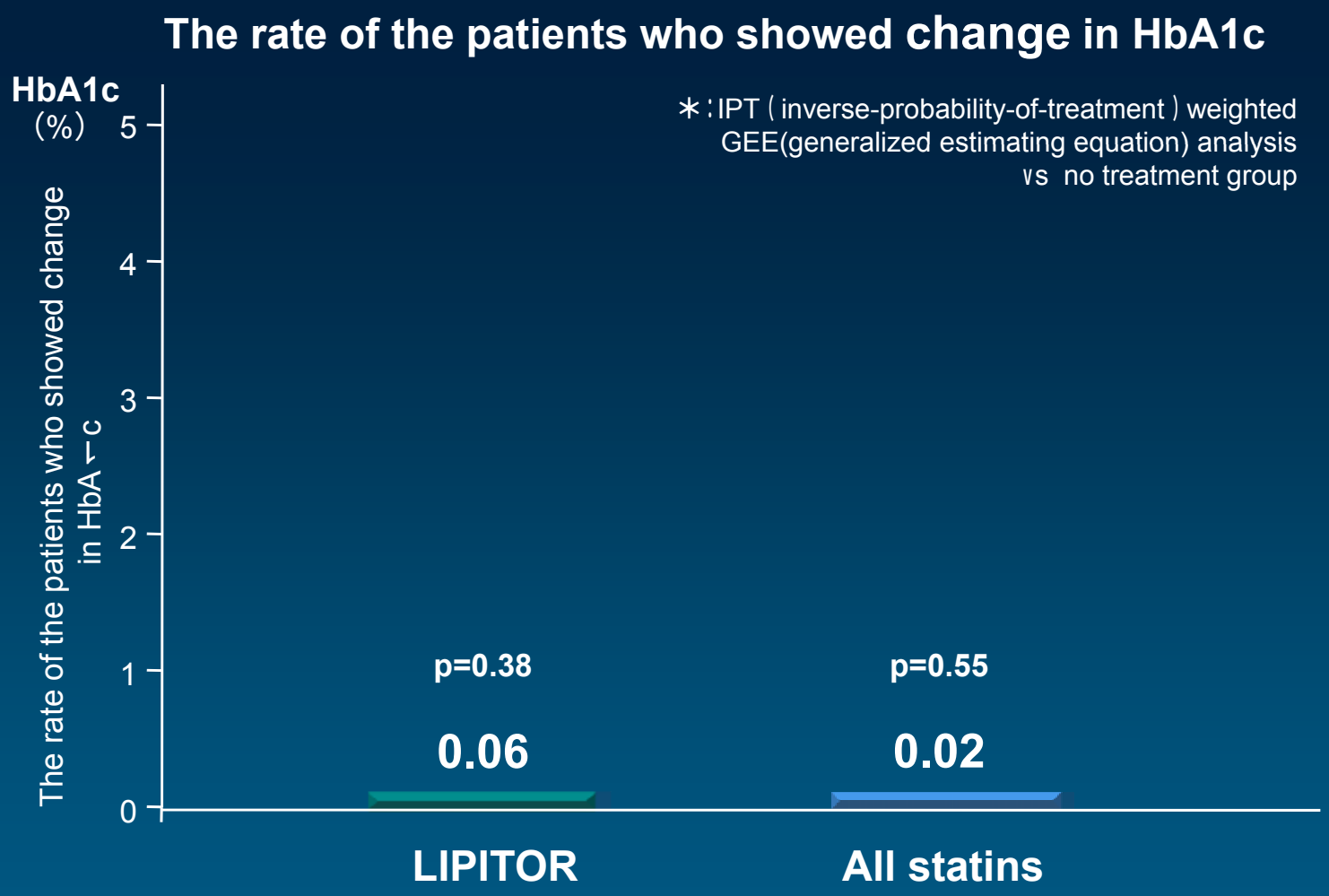
Diabetic related events：sudden death, death due to the following causes（renal failure, hyperglycemia or hypoglycemia, diabetic gangrene, congestive heart failure） and coronary artery disease

Cardiovascular events ：Fatal/nonfatal myocardial infarction, angina pectoris, coronary artery intervention, fatal/nonfatal cerebr al vascular disease

Shinozaki,T. et al.:Geriatr Gerontol Int ;12 Suppl 1:88-102.2012

Elderly

Lipitor did not increase HbA1c in old DM patients



Shinozaki,T. et al.:Geriatr Gerontol Int ;12 Suppl 1:88-102.2012 Made

CKD

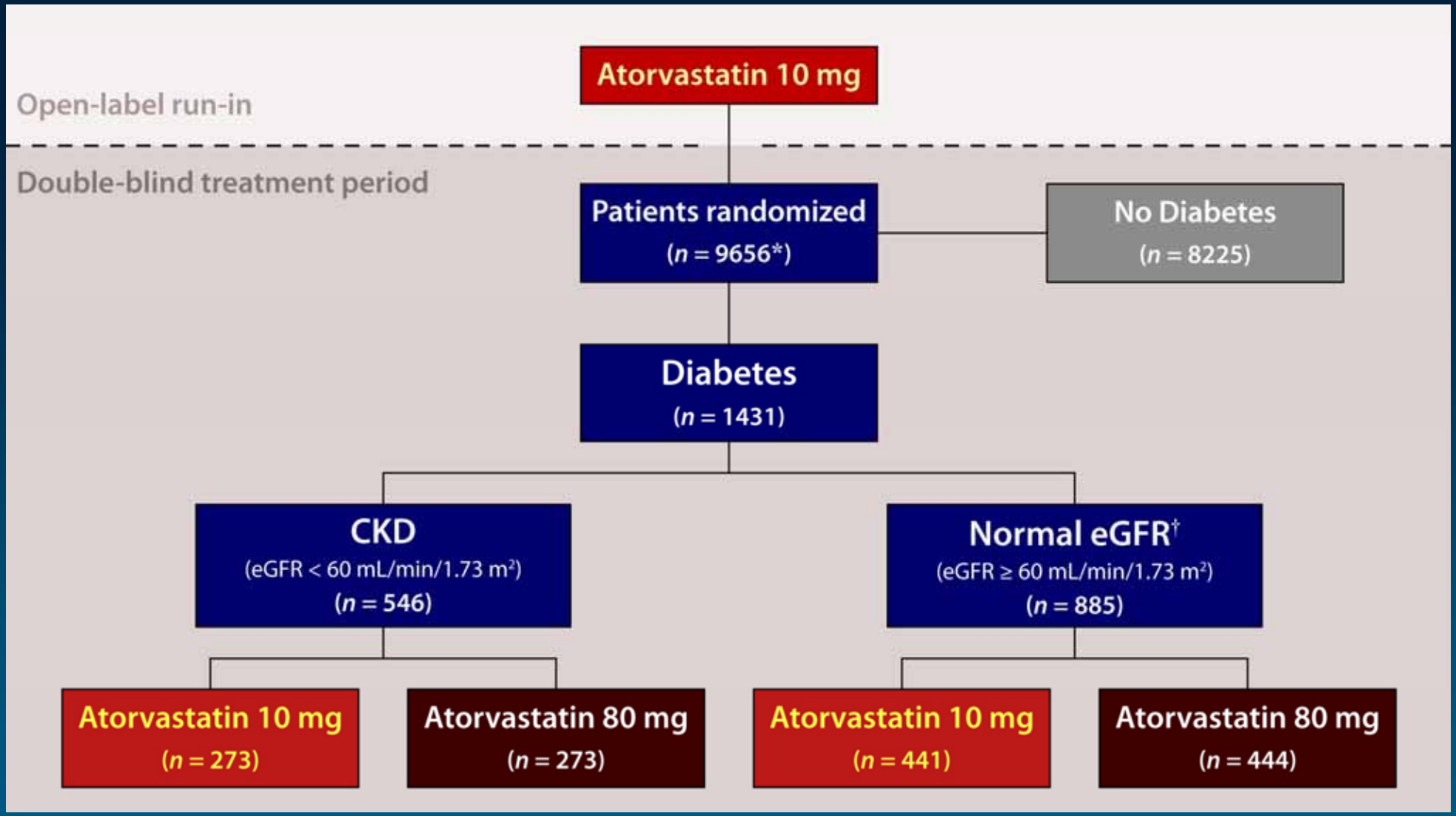
Higher Prevalence of Dyslipidemia in Patients with CKD

Risk Factor	CKD Patients	no CKD Patients	*P* Value
Low HDL *(%)*	45.2	29.4	<0.001
Elevated TG *(%)*	39.9	29.8	<0.001
Elevated LDL *(%)*	60.5	44.7	0.06
Lipid-lowering therapy *(%)*	57.1	42.6	0.09
N=3258			

Parikh NI et al. *Arch Intern Med* 2006;**166**:1884-1891

CKD

TNT Design: Treatment Assignment by Diabetes and CKD Status

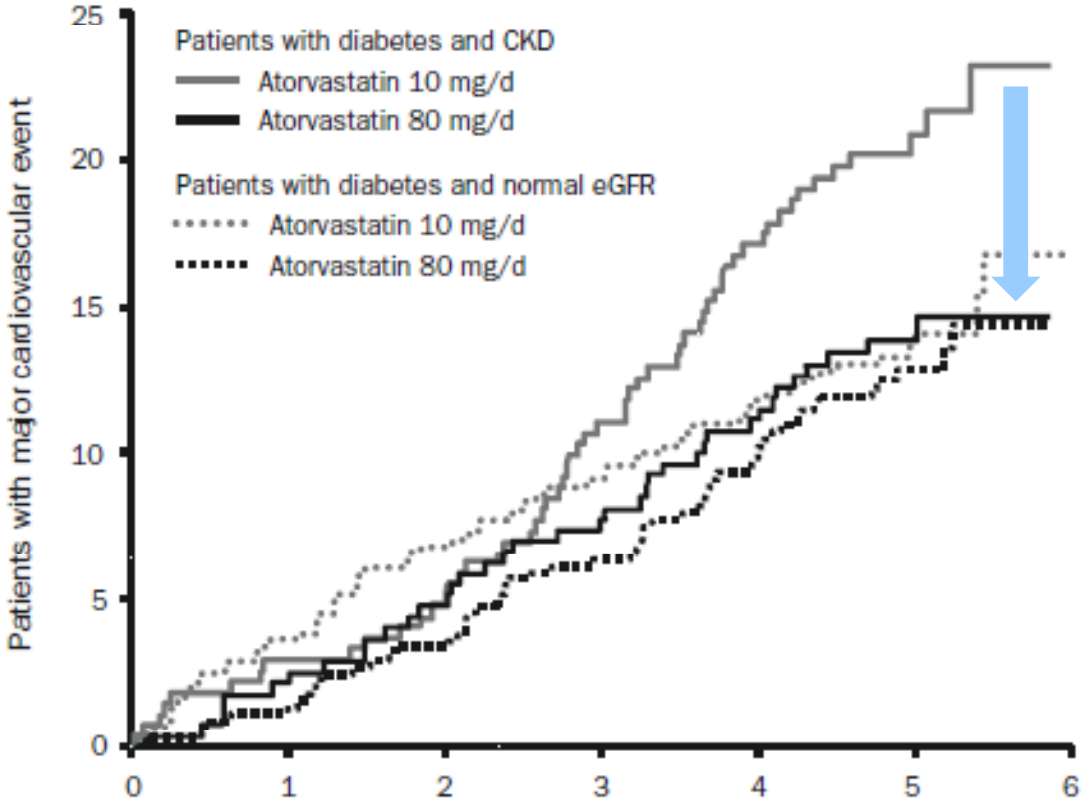


*Included only patients with complete renal data (baseline and follow-up assessments of eGFR).
†Included patients with mild (Stage 2) renal impairment.

Shepherd J, et al. Mayo Clin Proc. 2008;83:870-879

CKD

Time to First Major CV Event By Treatment in Patients w/ Diabetes and CKD



CKD							
Atorvastatin 10 mg	273	264	256	240	218	107	0
Atorvastatin 80 mg	273	265	257	246	234	108	0
Normal eGFR							
Atorvastatin 10 mg	441	424	409	394	380	183	0
Atorvastatin 80 mg	444	437	426	407	388	185	0

Relative Risk Reduction = 35 %
HR 0.65, 95 % CI, 0.43-0.98, p=0.04

Shepherd J, et al. Mayo Clin Proc. 2008;83:870-879

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- Summary

SUMMARY (I)

1. Although optimal LDL target goal is less than 70mg/dl in very high-risk patients in the current guideline, recent studies suggested that statin therapy is still beneficial in patients with a level below current recommended target LDL goal.

2. Statin therapy increases a small risk of new onset diabetes as well as reduces CV events and NOD is most likely to occur in those with risk factors for diabetes. Statin therapy, however, does not affect on the incidence of any type of cancer.

SUMMARY (II)

3. Although a role of statin therapy in primary prevention is a matter of debate, recent analysis demonstrated CV benefits of statin therapy even in low-risk patients.

4. In patients with dyslipidemia, non-HDL, HDL, TG, and Apo B are another treatment target (reflecting residual risk) and showed some positive results in previous studies. However, recent large RCTs did not show the evidence of risk reduction in cardiovascular events.

5. Statin therapy showed consistent CV benefits regardless of patient subsets (DM, women, elderly, and CKD)

Hopefully …

Unsettled Issues of Dyslipidemia Management

Thank you for your attention

NCEP- ATP : Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

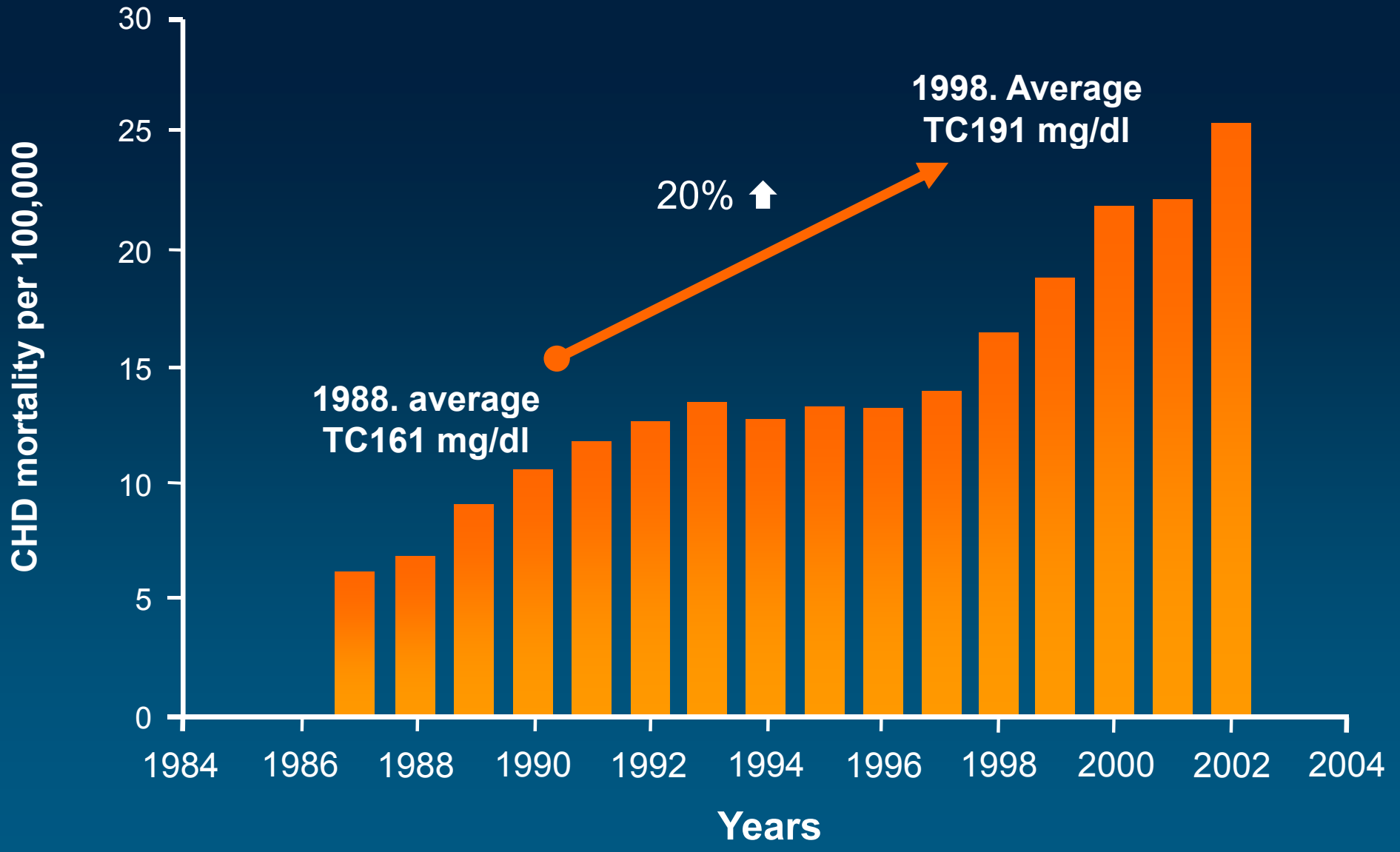
- ATP I : Published 1988
- ATP II : Published 1993
- ATP III : Published 2002, Updated 2004
- **ATP IV : Update of the ATP III Report 2013 ??**

Draft Finished	Federal Review	Expert Review	Advisory Council	Public Comment	HHS Clearance	Release
Completed	**Completed**	**Completed**	In Progress			

• **Draft Completed**: Expert panelists have completed a full draft of the systematic review and recommendations.
• **Federal Review**: Federal agency representatives of the NHLBI's National Program to Reduce Cardiovascular Risk (NPRCR) coordinating committee provide review and comment.
• **Expert Review**: External peer reviewers with expertise in the relevant risk factors provide review and comment.
• **Advisory Council**: The National Heart, Lung, and Blood Advisory Council provides review and comment and recommends approval.
• **Public Comment**: The draft is offered publicly for review and comment.
• **HHS Clearance**: The U.S. Department of Health and Human Services provides editorial review, comment, and approval.

http://www.nhlbi.nih.gov/guidelines/indevelop.htm#status

Correlation with TC and CHD Mortality In KOREA



국민건강영양평가 1998,2001.보건복지부

Lessons of Statins and Diabetes in RCTs

- New onset diabetes is greater with some statins
- Effect is **not** related to degree of LDL lowering
- Effect is related to "potency" of statin
- Most likely to occur in those with risk factors for diabetes, i.e., truncal obesity, family history
- Risk of diabetes was increased after statins, but outcomes were favorable

1. Sattar N, et al. *Lancet*. 375:735-742.
2. Preiss D, et al. *JAMA*. 2011;305:2556-2564.
3. Waters DD, et al. *J Am Coll Cardiol*. 2011;57:1535-1545.
4. Ridker PM, et al. *Lancet*. 2012;380:565-571.
5. Wang KL, et al. *J Am Coll Cardiol*. 2012;60:1231-1238.

DM

Aggressive versus Moderate Statin Therapy: Effects in Diabetes

- Average risk reduction in major vascular events per 1.0 mmol/L (40 mg/dL) reduction in LDL-cholesterol
- Analysis of 5 trials involving 39,612 subjects and 8,253 events

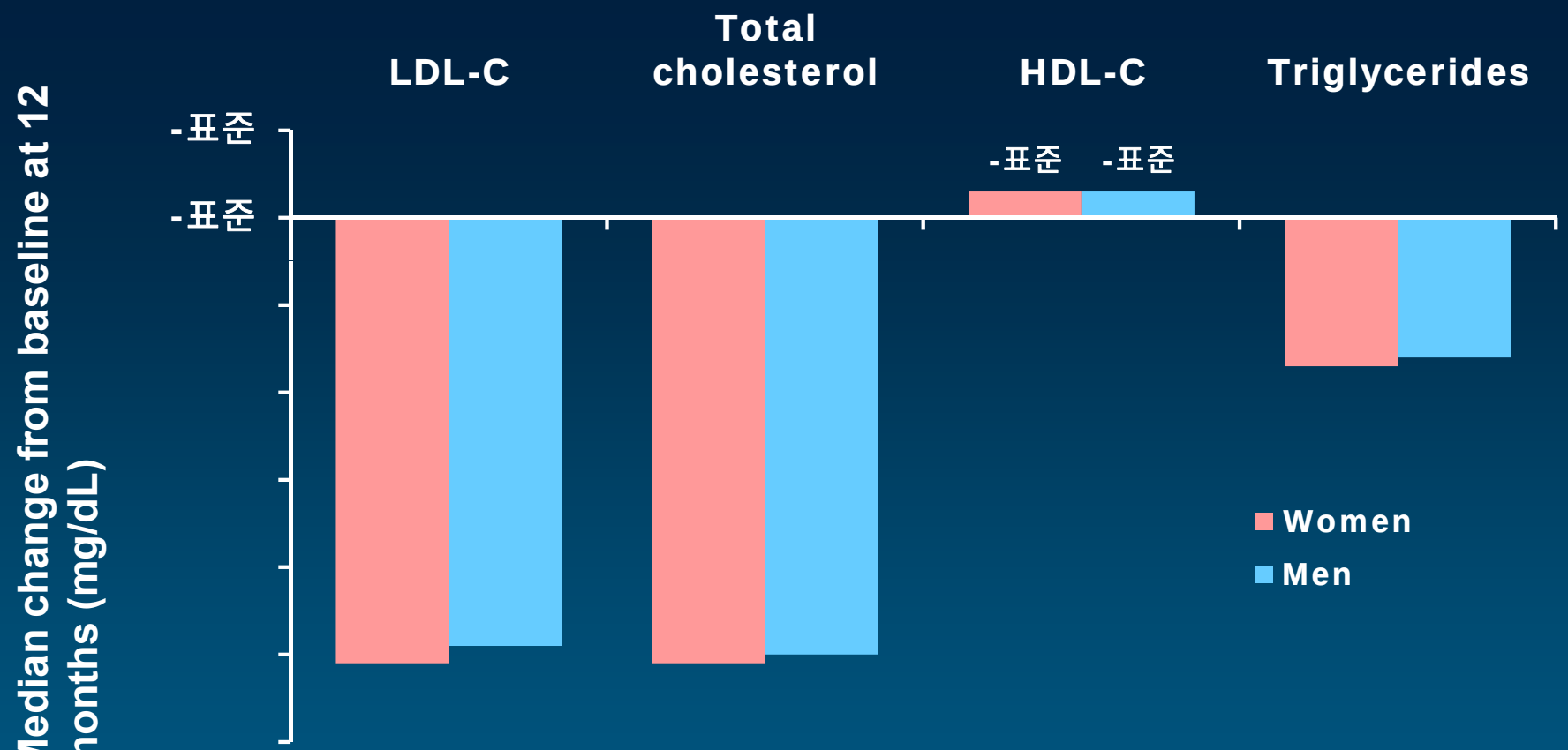
Subgroup	Events (% per Annum)		Relative Risk (95% CI)
	Aggressive (N = 19,829)	**Moderate** (N = 19,783)	
Type 2 Diabetes	703	792	**0.76** (0.59–0.98)
No Diabetes	3126	3616	**0.71** (0.63–0.80)

Cholesterol Treatment Trialists' (CTT) Collaboration, et al. Lancet. 2010;**376**:1670-1681

women

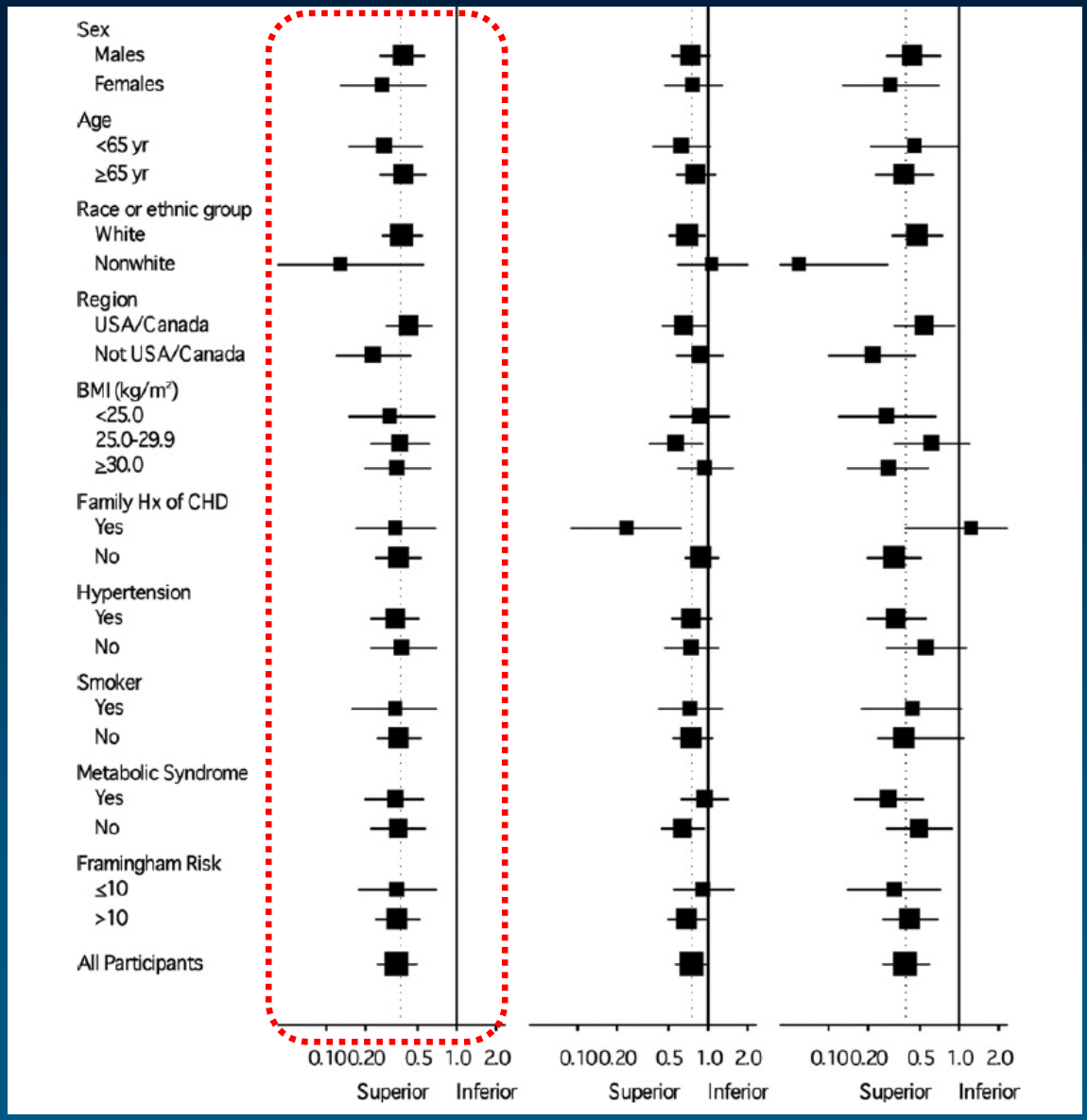
Changes in Lipid Parameters were Similar between Men and Women

Results from JUPITER



Mora M et al. Circulation 2010;121:1069-1077.

Primary Endpoint in Pre-Specified Subgroups Within JUPITER Trial, Stratified by Achieved LDL-C



Meta-Analysis of Impact of Different Types and Doses of Statins on New-Onset Diabetes Mellitus

Eliano Pio Navarese, MD, PhD[a,*], Antonino Buffon, MD[d], Felicita Andreotti, MD, PhD[d], Marek Kozinski, MD, PhD[a], Nicky Welton, PhD[f], Tomasz Fabiszak, MD[a], Salvatore Caputo, MD[e], Grzegorz Grzesk, MD, PhD[a,b], Aldona Kubica, PhD[c], Iwona Swiatkiewicz, MD, PhD[a], Adam Sukiennik, MD, PhD[a], Malte Kelm, MD[g], Stefano De Servi, MD[h], and Jacek Kubica, MD, PhD[a]

Odds ratios and 95% credible intervals of diabetes among different statins adjusted for percentage of LDL cholesterol reduction as covariate

Comparison	OR	95% CI
Atorvastatin 10 mg vs Placebo	1.04	0.74–1.48
Pravastatin 20 mg vs placebo	0.99	0.68–1.41
Rosuvastatin 10 mg vs placebo	1.10	0.78–1.58
Simvastatin 40 mg vs placebo	1.21	0.93–1.57
Atorvastatin 80 mg vs placebo	1.15	0.90–1.51
Lovastatin 40 mg vs placebo	0.97	0.58–1.61
Pravastatin 40 mg vs placebo	1.06	0.85–1.30
Rosuvastatin 20 mg vs placebo	1.25	0.75–2.01

Beta coefficient = 0.0003 (95% CI −0.01 to 0.01); residual deviance = 36.3.

AJC 2013

What Is the Best Lipid Parameter for Assessing the Efficacy of a LLT?

- Estimated LDL-C, non-HDL-C, apoB, and ratios of LDL-C/HDL-C or apoA/apoB have all been suggested as the best predictors of benefit in following patients at risk of CHD

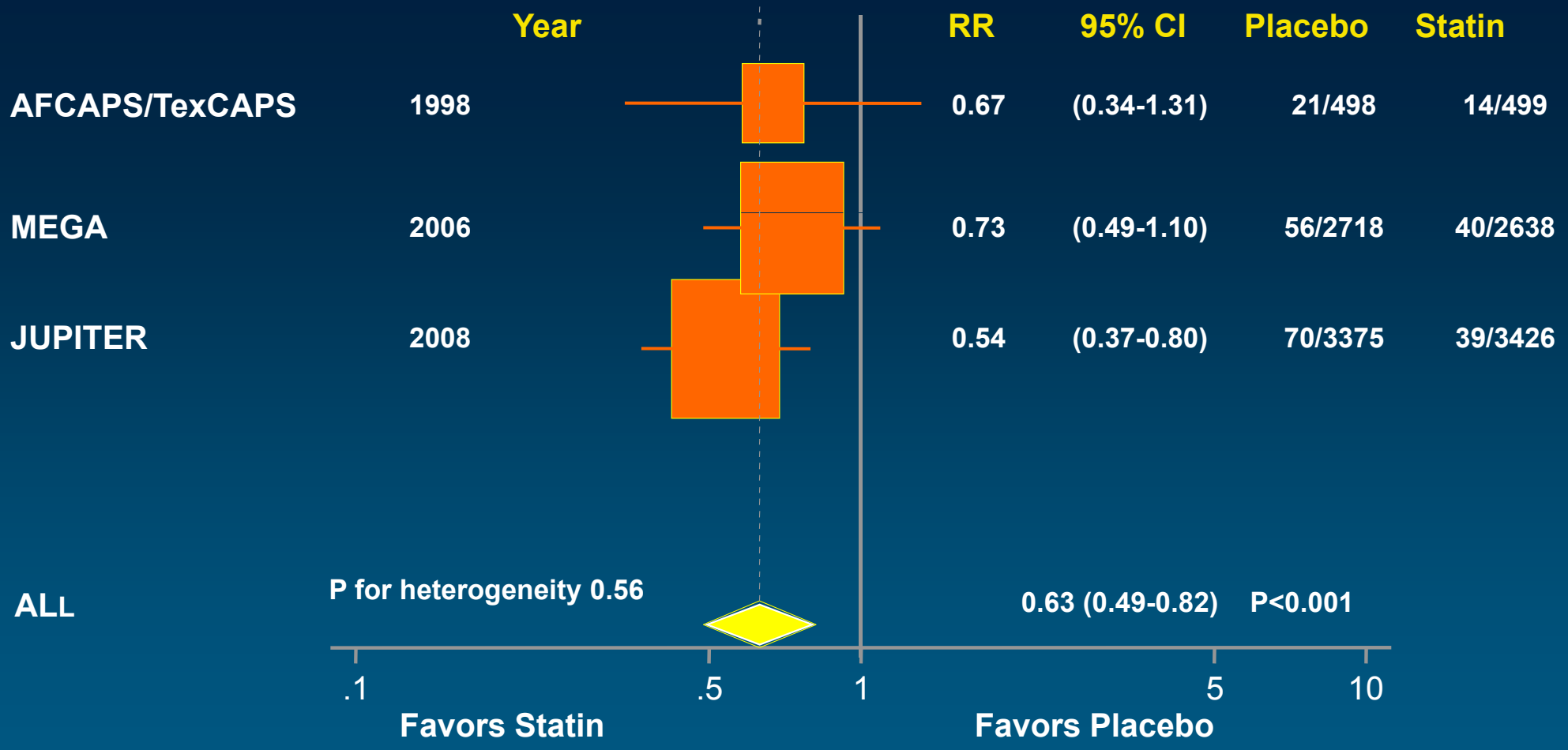
  - Small improvements in CVD prediction seen when information on the combination of apoB and A-I, lipoprotein(a), or lipoprotein-associated PLA2 was added to risk scores containing TC and HDL-C[1]

- What are the advantages and disadvantages of each?
- Potential for non-HDL and apoB to be secondary targets in new guidelines
- Will HDL-C be an important topic, especially given the failure of all the "pibs", with the latest "talk" being that HDL-C might not be telling us anything at all?

1. The Emerging Risk Factors Collaboration. *JAMA*. 2012;307:2499-2506.

Meta-analysis of Exclusively Primary Prevention Statin Trials in Women

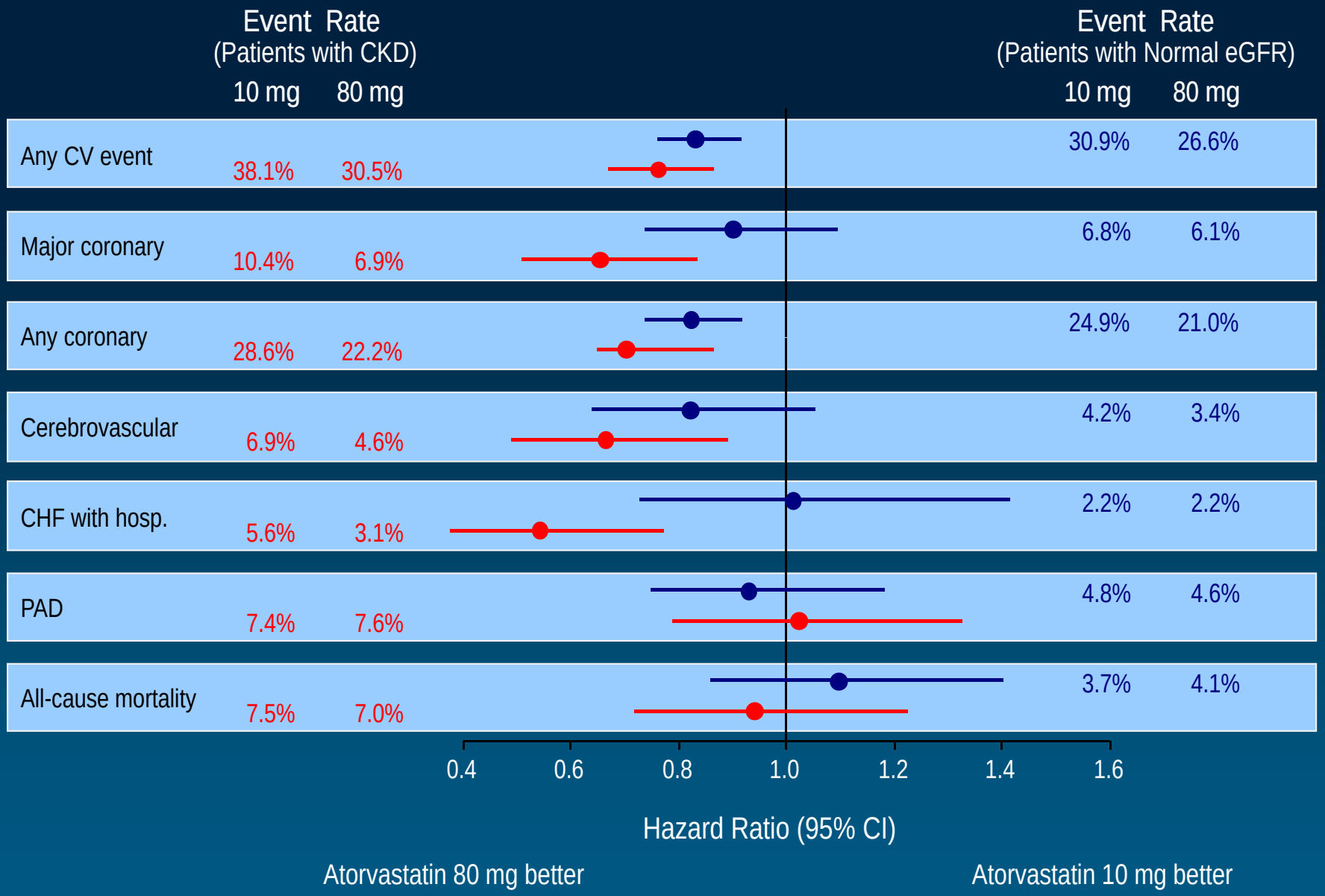
13 154 Women, 240 CVD events



Mora S et al Circulation 2010; 1069

CKD

Intensive Atorva. Therapy in Pts w/ CHD and CKD vs. Normal eGFR



Shepherd J, et al. J Am Coll Cardol. 2008;51:1448-1454