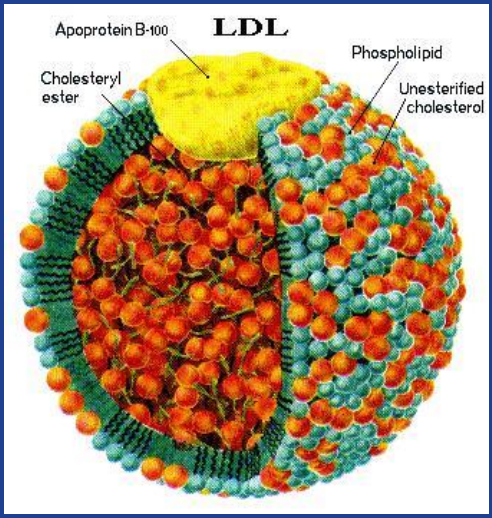
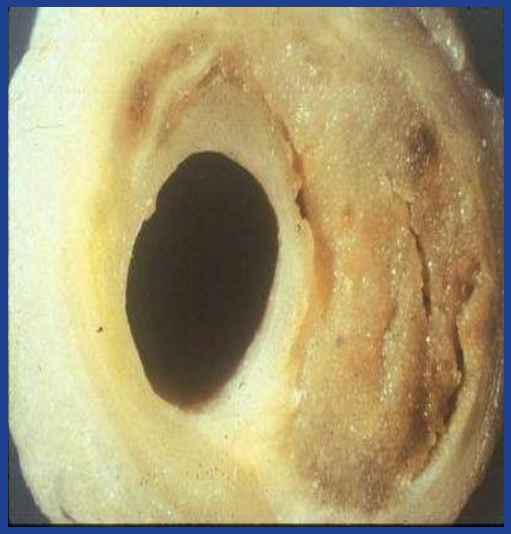
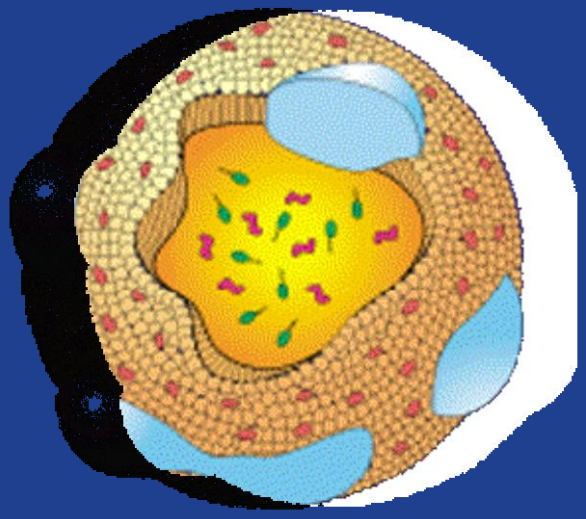
Statins in the Primary Prevention of ASCVD: The New AHA/ACC guideline

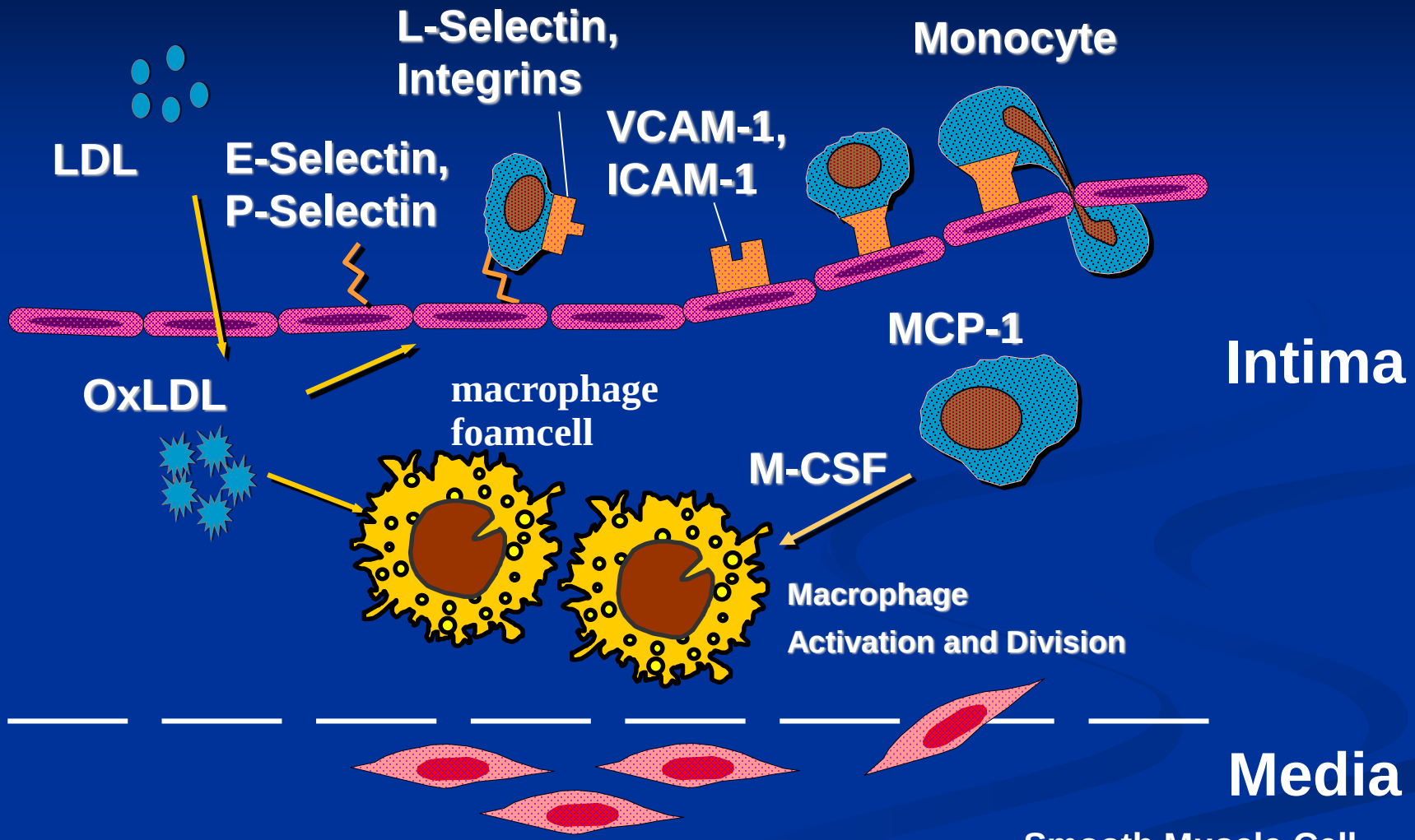






Krittin Bunditanukul Pharm.D, BCPS
Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University

Atherosclerosis: Lesion Initiation



Kinlay et al. *J Cardiovasc Pharmacol*. 1998;32(suppl 3):S62-S66.
Newby et al. *Cardiovasc Res*. 1999;41:345-360.

Friedwald ‘s formula

TC = LDL + VLDL + HDL

= LDL + (TG/5) + HDL

LDL = TC – (TG/5) - HDL

Non HDL = LDL+(TG/5)

- Pateints must be fasting
- TG level < 400 mg/dl
- LDL < 70 mg/dl

Lipid analyses as treatment targets

Recommendations	Class	Level
LDL-C is recommended as the primary target for treatment.	I	A
TC should be considered as a treatment target if other analyses are not available.	IIa	A
Non-HDL-C should be considered as a secondary treatment target.	IIa	B
ApoB should be considered as a secondary treatment target, when available.	IIa	B
HDL-C is not recommended as a target for treatment.	III	A
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B

EAS

www.escardio.org/guidelines

European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281-344-d oi:10.1016/j.atherosclerosis.2016.08.018

EUROPEAN SOCIETY OF CARDIOLOGY®

Focus on ASCVD Risk Reduction: 4 statin benefit groups

Clinical ASCVD

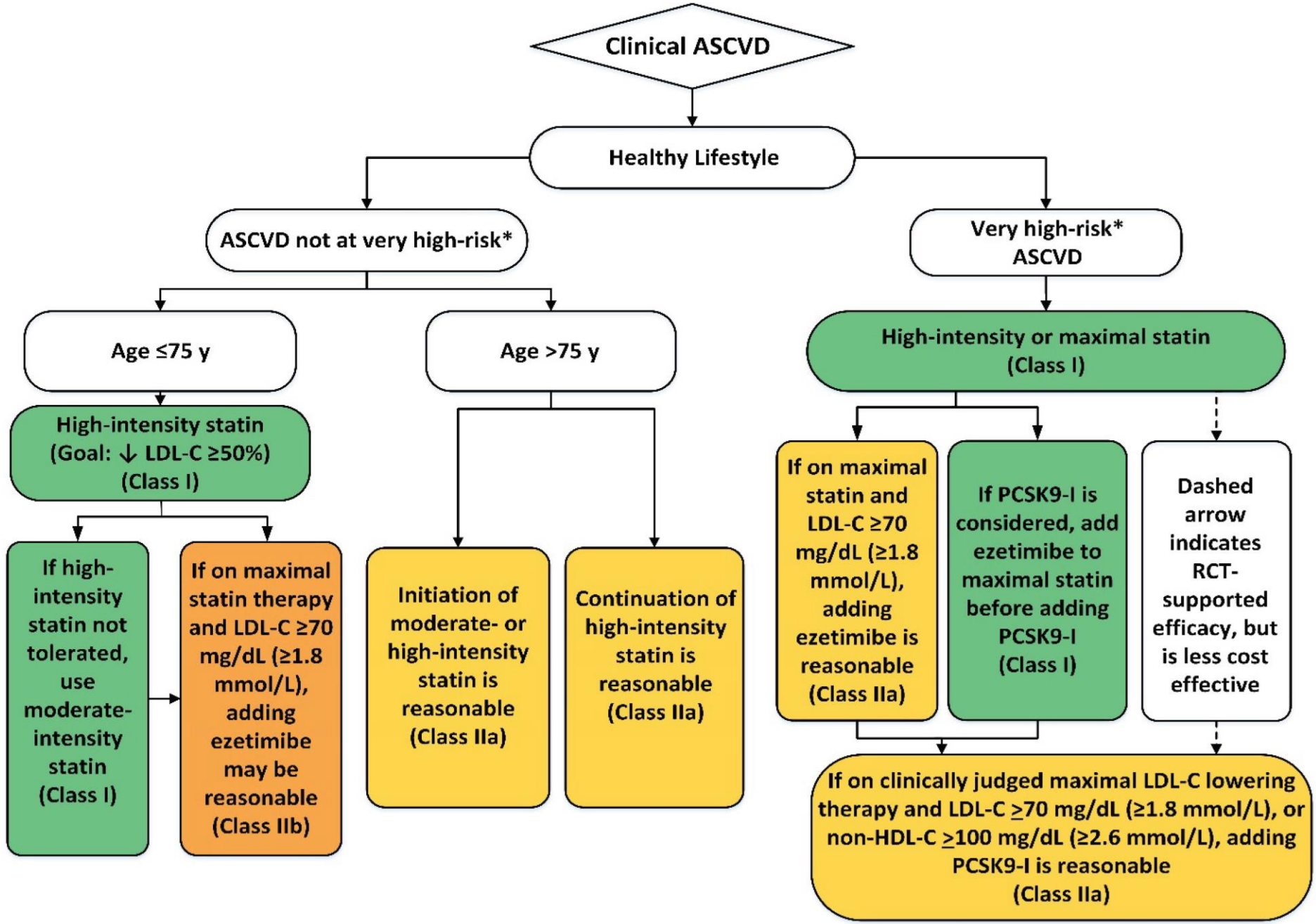
LDL-C level >190mg/dl

Diabetes, aged 40-75 years, with LDL-C 70-189 mg/dl

Estimated 10 –year risk of ASCVD of > 7.5%, 40-75 years of age and with LDL-C 70-189 mg/dl

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013

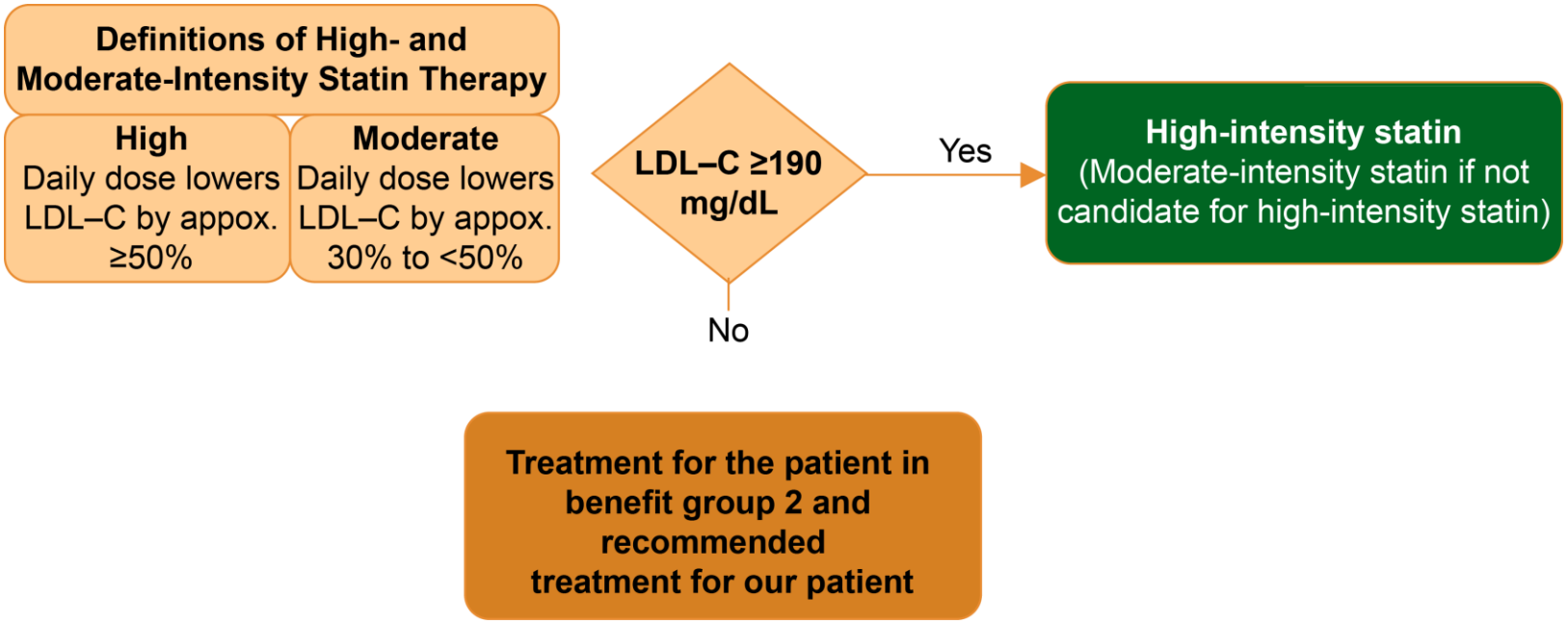
Figure 1. Secondary Prevention in Patients With Clinical ASCVD



High, Moderate and Low-Intensity Statin Therapy

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 mg (*40 mg*	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§	Simvastatin 10 mg
	…	Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

Algorithm for Guideline



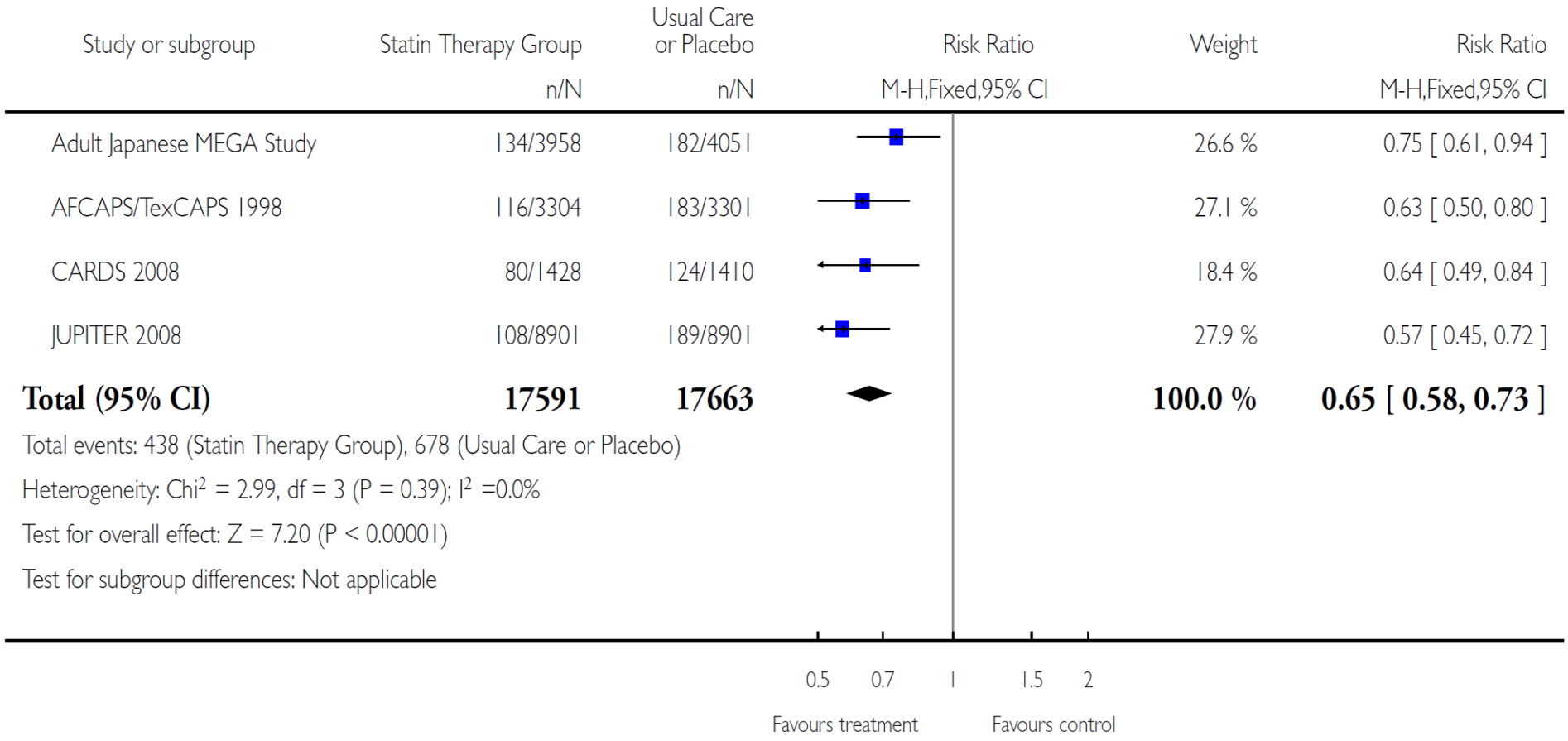
Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013.

Analysis 1.11. Comparison 1 Mortality and Morbidity, Outcome 11 Total Number of Fatal and Non-fatal CHD, CVD and Stroke Events.

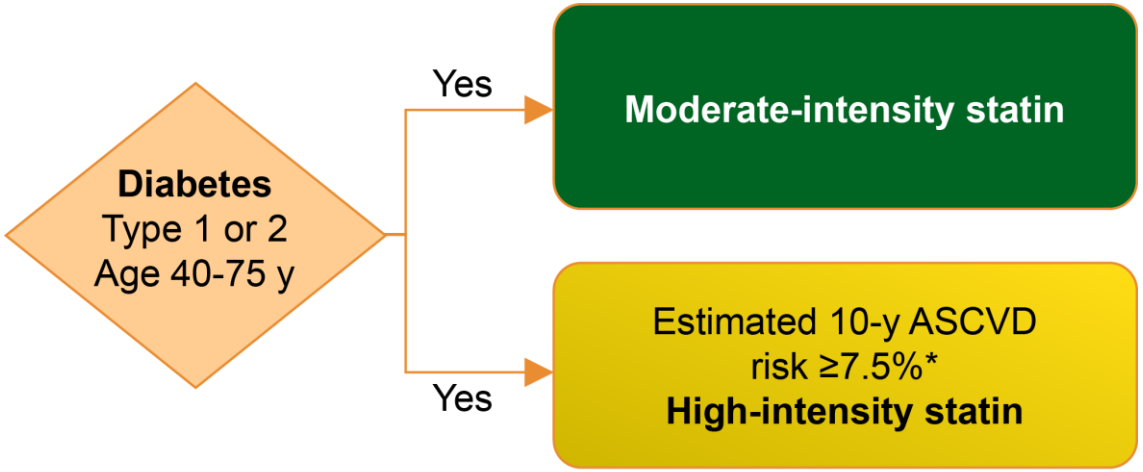
Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 11 Total Number of Fatal and Non-fatal CHD, CVD and Stroke Events



Algorithm for Guideline



Treatment for our diabetic patient is to start on **Moderate intensity statin**

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013.

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

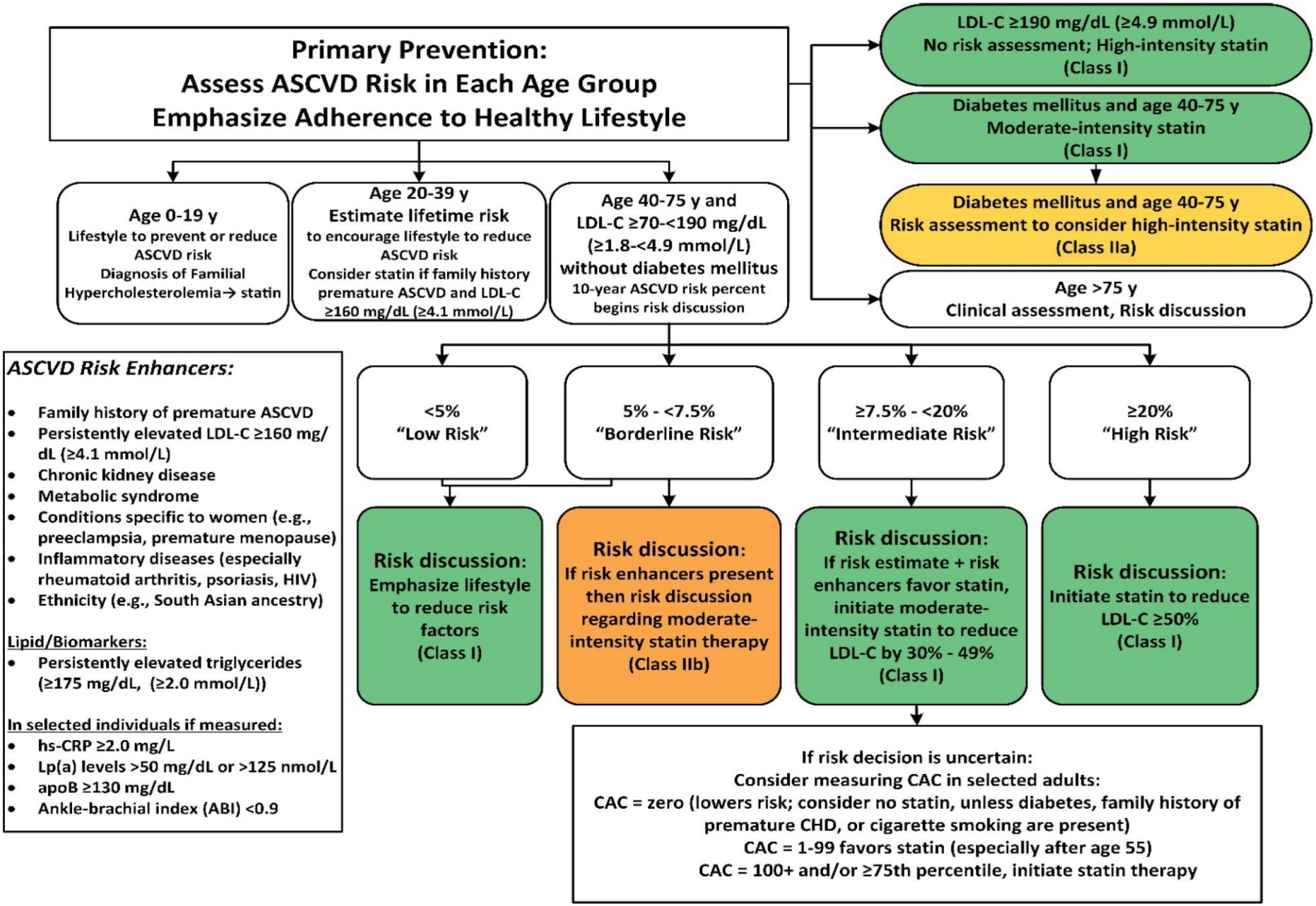
Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

*In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

Trial	AFCAPS/TexCAPS [8]	PROSPER [9]	HPS [10]	CARDS [11]	ASCOT-LLA [7]	ASPEN [6]	MEGA [12]
first author and year	Downs JR 1998	Shepherd J 2002	HPS group 2003	Colhoun H 2004	Sever P 2005	Knopp RH 2006	Tajima N 2008
target population	patients with average or below average cholesterol levels	older patients with cardio-vascular risk factors	patients with non-fasting cholesterol at least 3.5 mmol/l	patients without high LDL-C level, had one or more of the following: hypertension, retinopathy, smoking, micro-albuminuria	patients with hypertension	patients with LDL-C <4.1 mmol/l	patients with hypercholes-terolemia
number of patients (statin/control)	155 (84/71)	623 (303/320)	2912 (1428/1410)	2838 (1428/1410)	2532 (1258/1274)	1905 (959/946)	1746 (853/893)
mean age (years)	58.0	75.0	NA(40–80)	61.5	63.1	60.5	58.3
current smoking (%)	12	27	NA	22	20	13	20
hypertension (%)	22	62	NA	84	100	52	42
mean body mass index (Kg/m^2)	27	27	NA	29	30	29	24
HbA1c (%)	NA	NA	NA	7.8	NA	7.6	6.9
statin type	lovastatin	pravastatin	simvastatin	atorvastatin	atorvastatin	atorvastatin	pravastatin
dosage (mg/day)	20–40	40	40	10	10	10	10–20
baseline TC (mmol/L) (% change)	5.7 (−19.3%)	5.7 (NA)	NA	5.4 (−21.8%)	5.5 (−18.3%)	5.0 (−19.8%)	6.3 (−11.0%)
baseline LDL-C (mmol/L) (% change)	3.9 (−26.5%)	3.8 (NA)	NA	3.0 (−33.9%)	3.4 (−27.6%)	3.0 (−30.5%)	4.0 (−18.0%)
baseline HDL-C (mmol/L) (% change)	1.0 (4.8%)	1.3 (NA)	NA	1.4 (4.0%)	1.3 (1.5%)	1.2 (1.9%)	1.5 (5.0%)
baseline TG (mmol/L) (% change)	1.7 (−12.7%)	1.5 (NA)	NA	2.0 (−15.9%)	1.7 (−12.6%)	1.6 (−4.7%)	1.4 (−7.0%)
outcomes	MACCE	MACCE	MACCE	MACCE; CR; death; stroke;	MACCE; CR; stroke	MACCE; CR; death; stroke;	MACCE; death; MI; stroke; CI
follow-up (years)	5.2	3.2	4.8	3.9	3.3	4.0	5.3

Chen YH, et al. Exp Clin Endocrinol Diabetes. 2012 Feb;120(2):116-20.

Figure 2. Primary Prevention



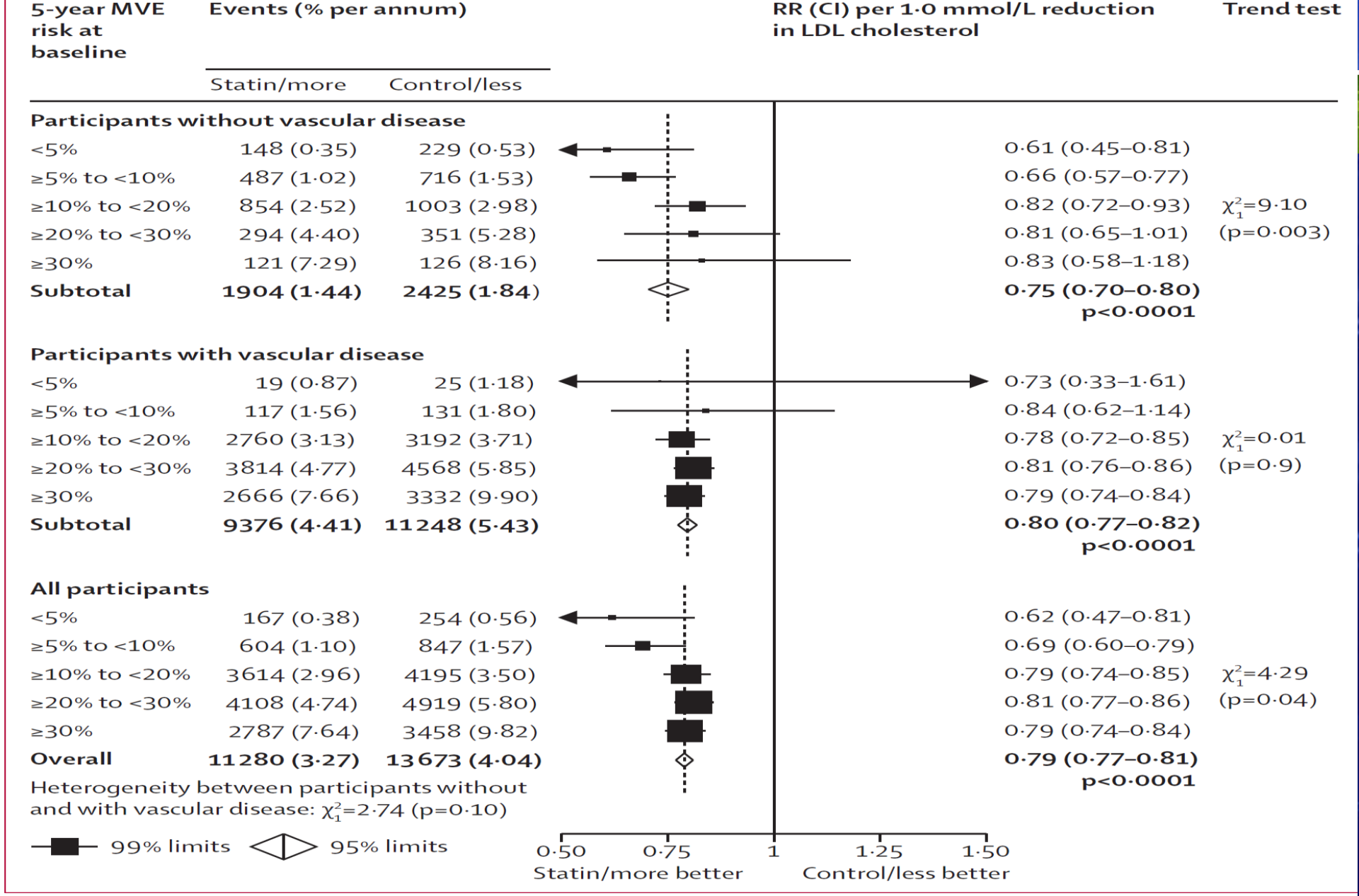


Figure 2: **Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol at different levels of risk, by history of vascular disease**

MVE=major vascular event. RR=rate ratio. CI=confidence interval.

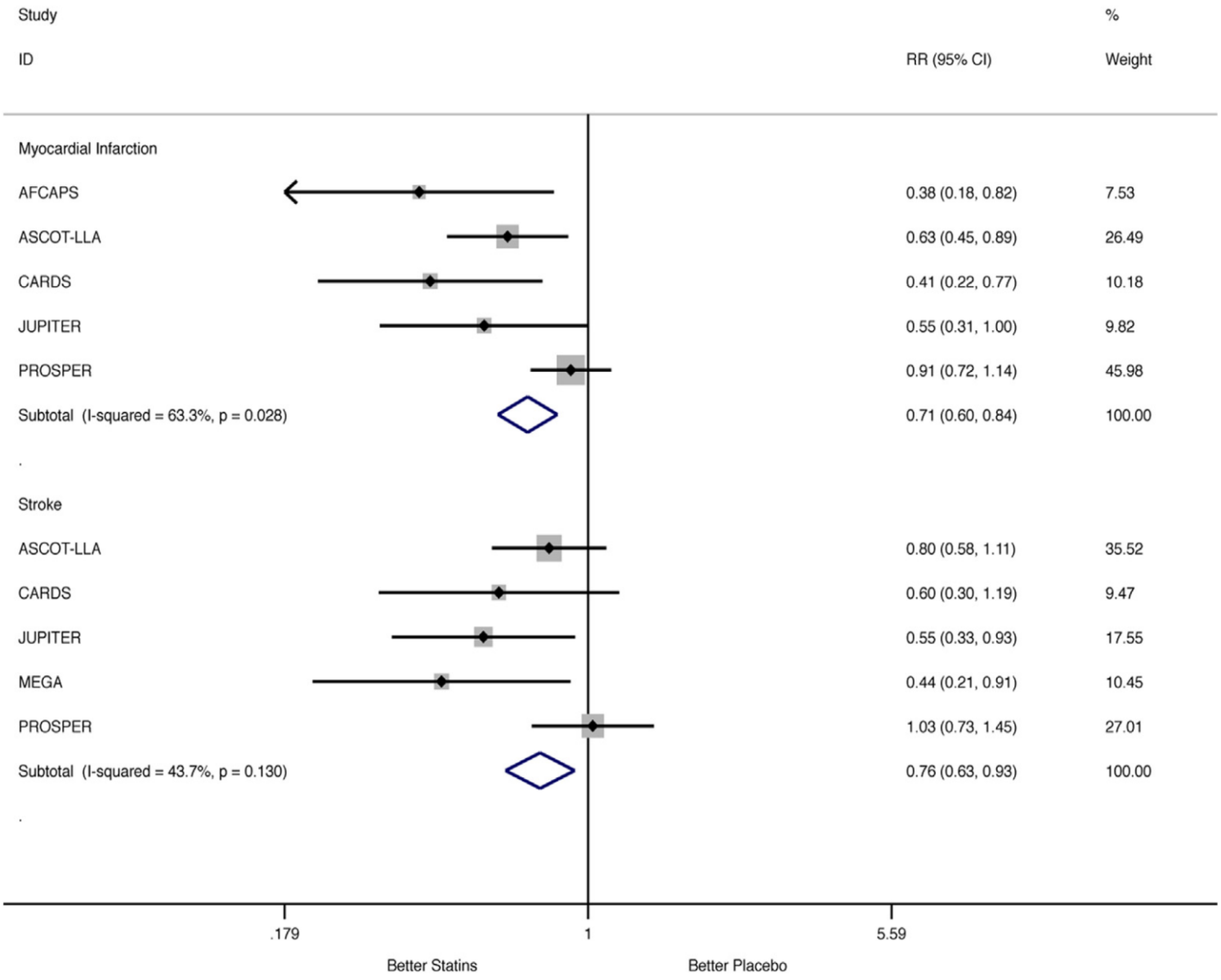


Figure 2 **RRs of Myocardial Infarction and Stroke**

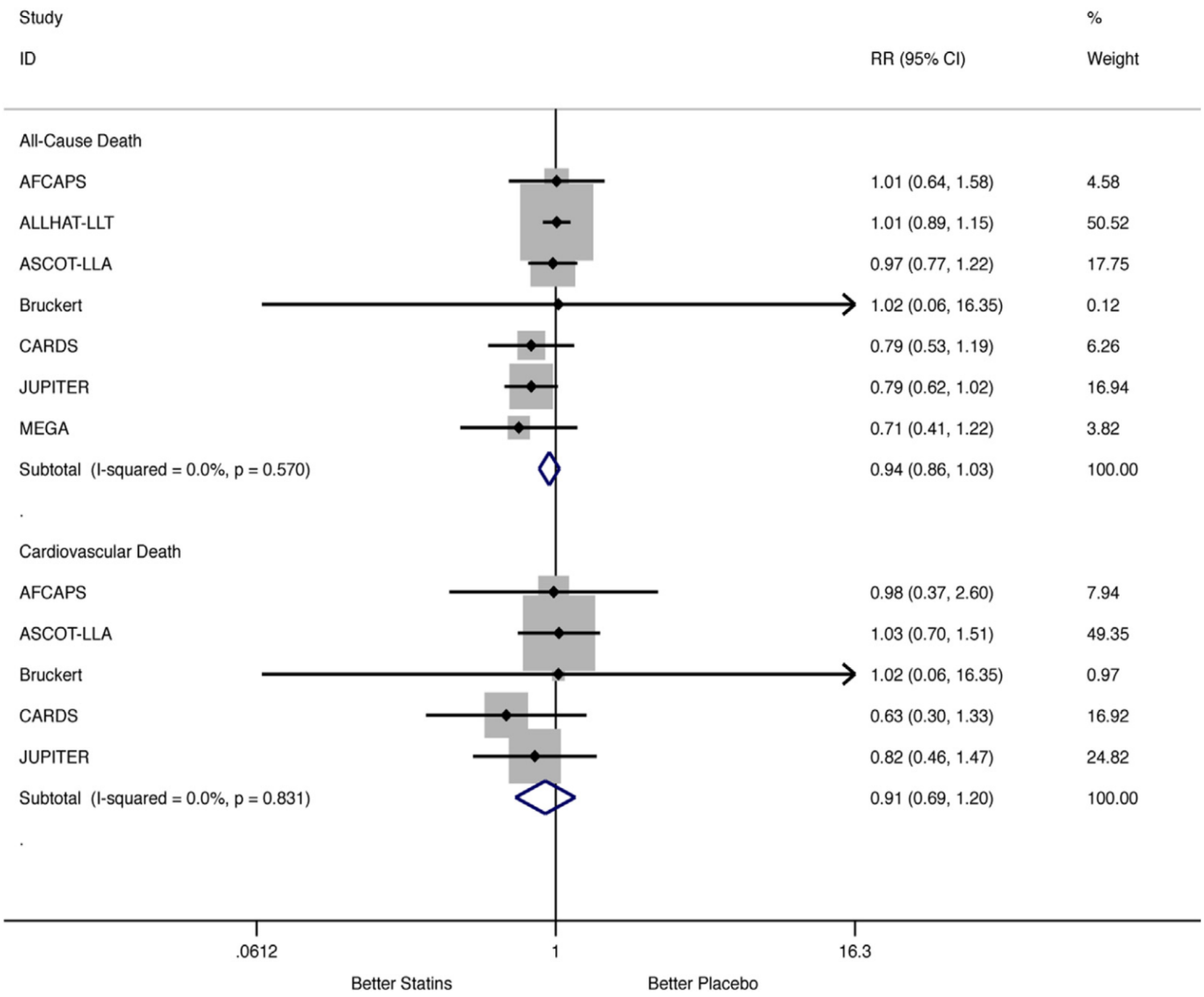


Figure 3 **RRs of All-Cause Death and Cardiovascular Death**

A Randomized Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Apparently Healthy Men and Women With Elevated Levels of C-Reactive Protein (hsCRP): The JUPITER Trial

Paul Ridker*, Eleanor Danielson, Francisco Fonseca*, Jacques Genest*, Antonio Gotto*, John Kastelein*, Wolfgang Koenig*, Peter Libby*, Alberto Lorenzatti*, Jean MacFadyen, Borge Nordestgaard*, James Shepherd*, James Willerson, and Robert Glynn*

on behalf of the JUPITER Trial Study Group

An Investigator Initiated Trial Funded by AstraZeneca, USA

** These authors have received research grant support and/or consultation fees from one or more statin manufacturers, including Astra-Zeneca. Dr Ridker is a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Dade-Behring and AstraZeneca.*

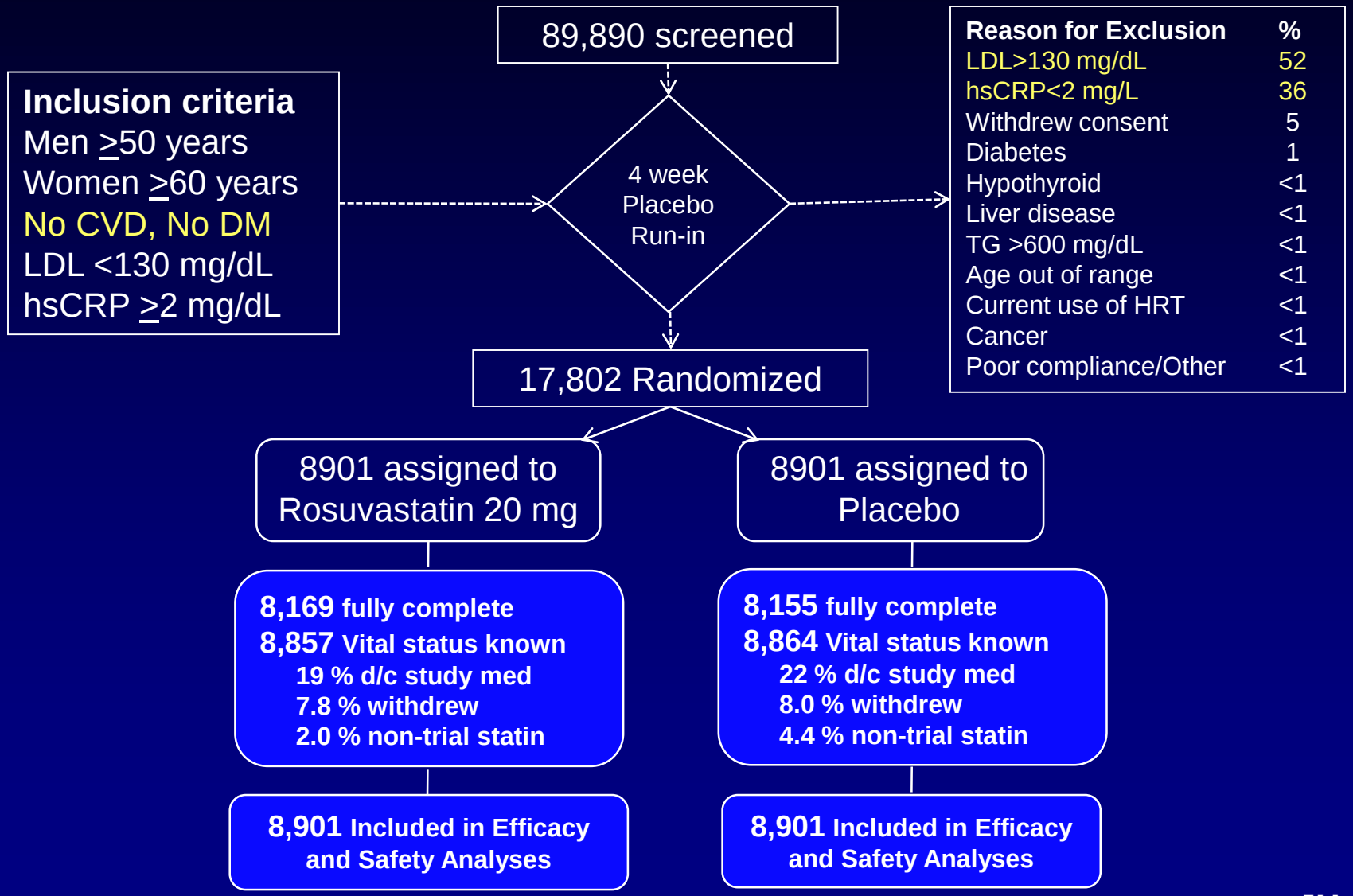
Ridker et al NEJM 2008

Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

To investigate whether rosuvastatin 20 mg compared to placebo would decrease the rate of first major cardiovascular events among apparently healthy men and women with LDL < 130 mg/dL (3.36 mmol/L) who are nonetheless at increased vascular risk on the basis of an enhanced inflammatory response, as determined by hsCRP $\geq$ 2 mg/L.

To enroll large numbers of women and individuals of Black or Hispanic ethnicity, groups for whom little data on primary prevention with statin therapy exists.

JUPITER: Inclusion/Exclusion Criteria, Study Flow



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Baseline Blood Levels (median, interquartile range)

	Rosuvastatin (N = 8901)		Placebo (n = 8901)	
hsCRP, mg/L	4.2	(2.8 - 7.1)	4.3	(2.8 - 7.2)
LDL, mg/dL	108	(94 - 119)	108	(94 - 119)
HDL, mg/dL	49	(40 – 60)	49	(40 – 60)
Triglycerides, mg/L	118	(85 - 169)	118	(86 - 169)
Total Cholesterol, mg/dL	186	(168 - 200)	185	(169 - 199)
Glucose, mg/dL	94	(87 – 102)	94	(88 – 102)
HbA1c, %	5.7	(5.4 – 5.9)	5.7	(5.5 – 5.9)

All values are median (interquartile range). [Mean LDL = 104 mg/dL]

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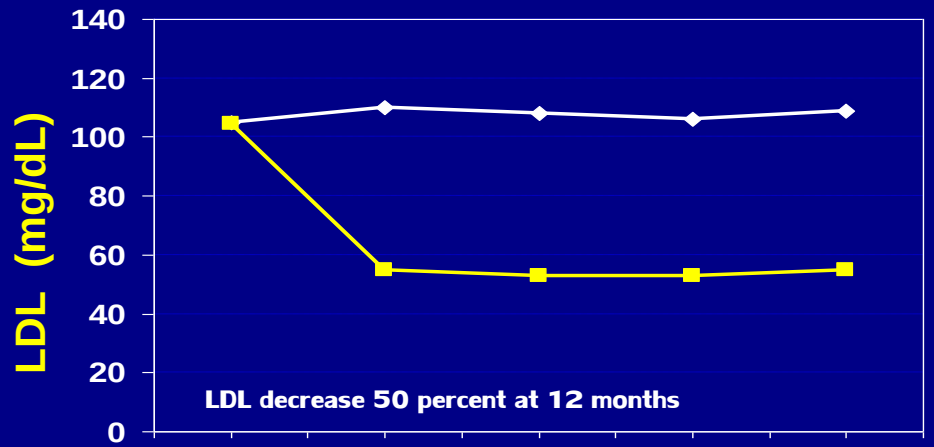
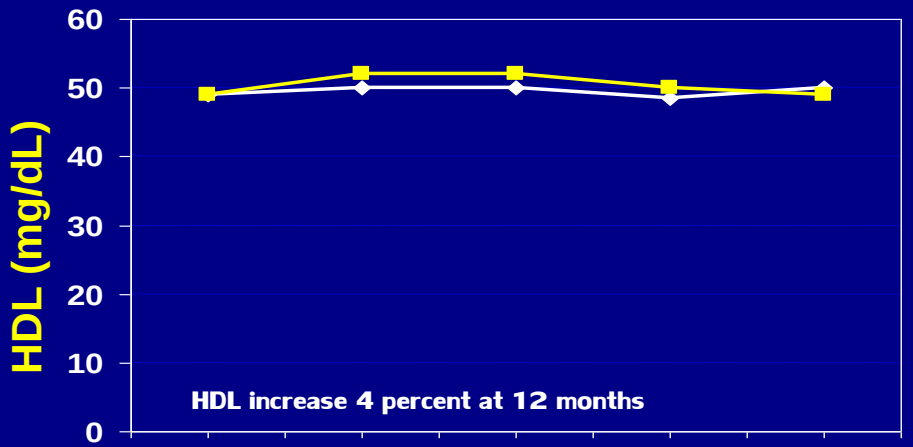
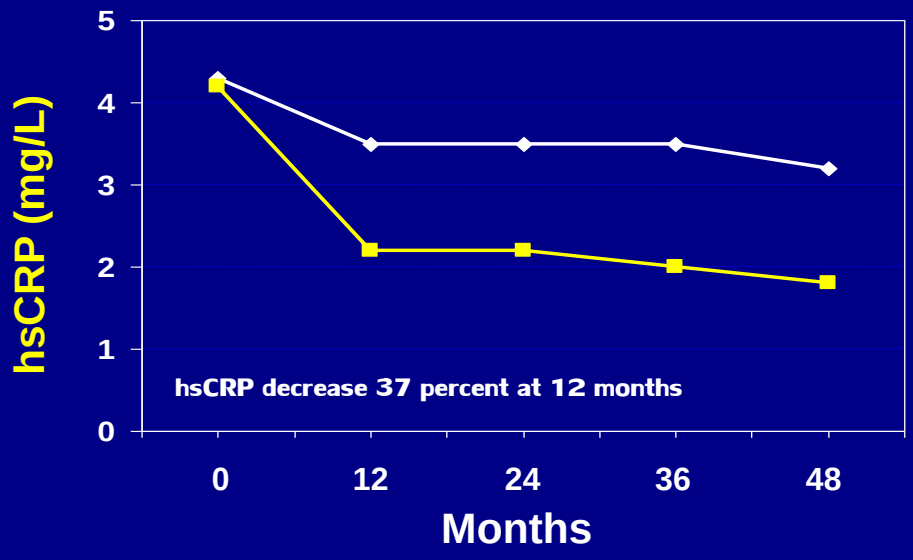
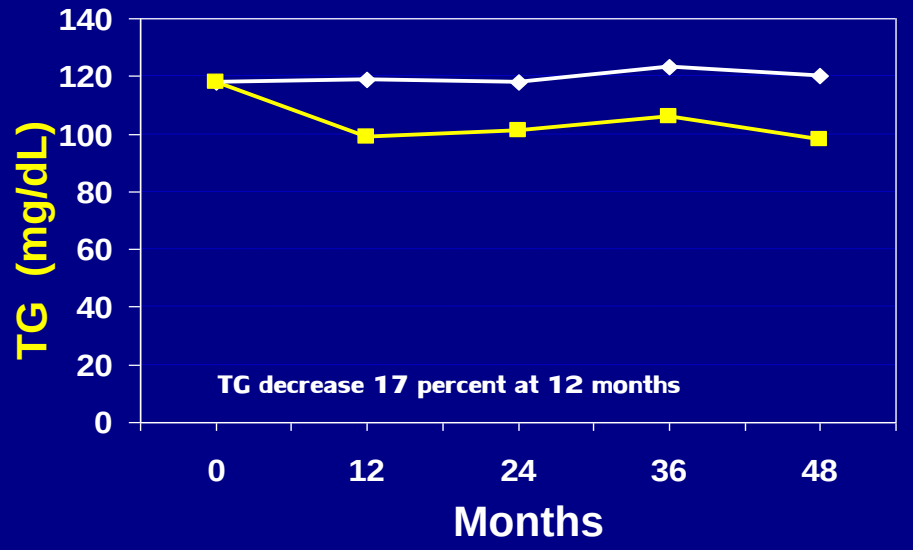
Effects of rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP









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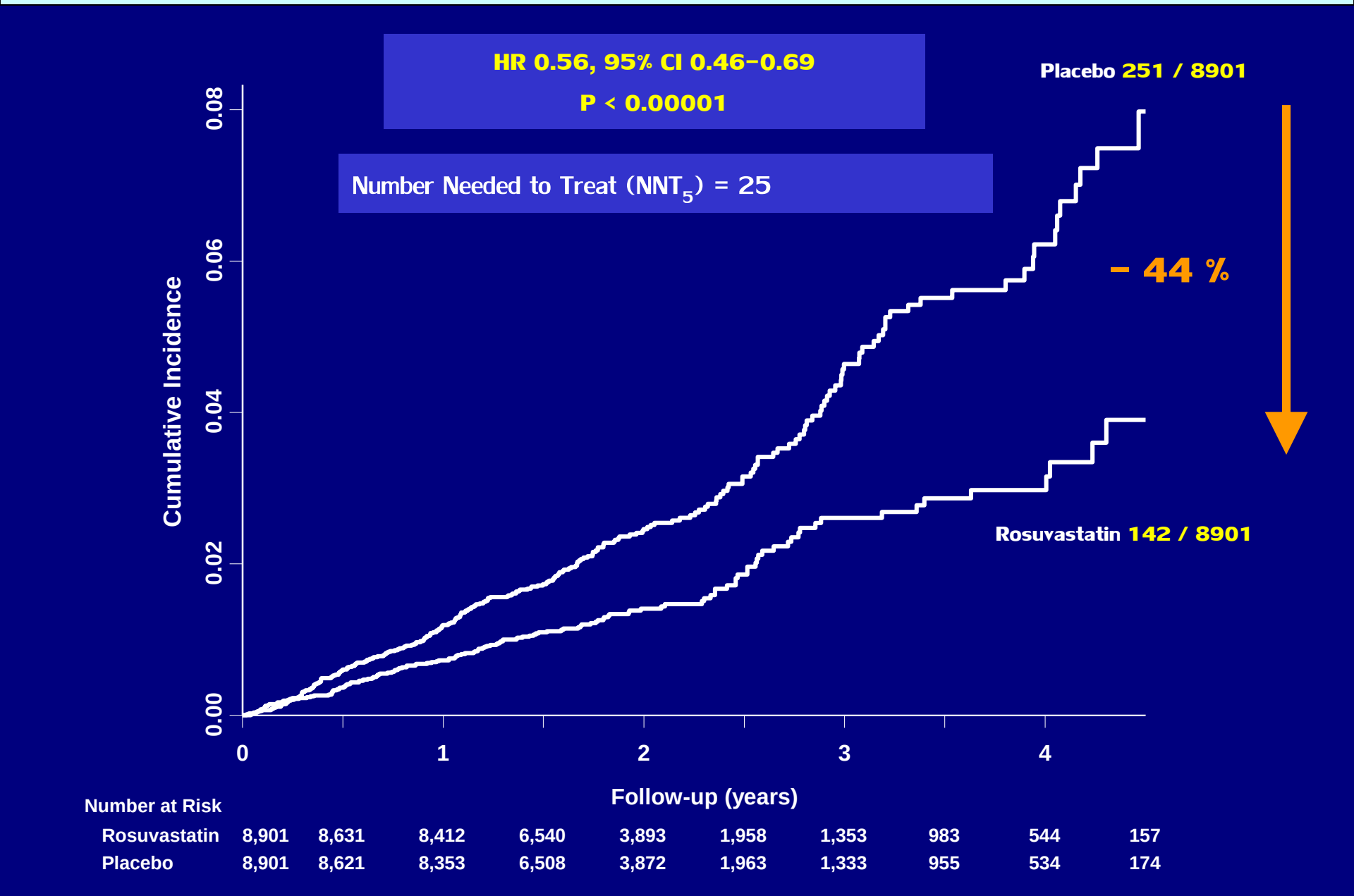
Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death



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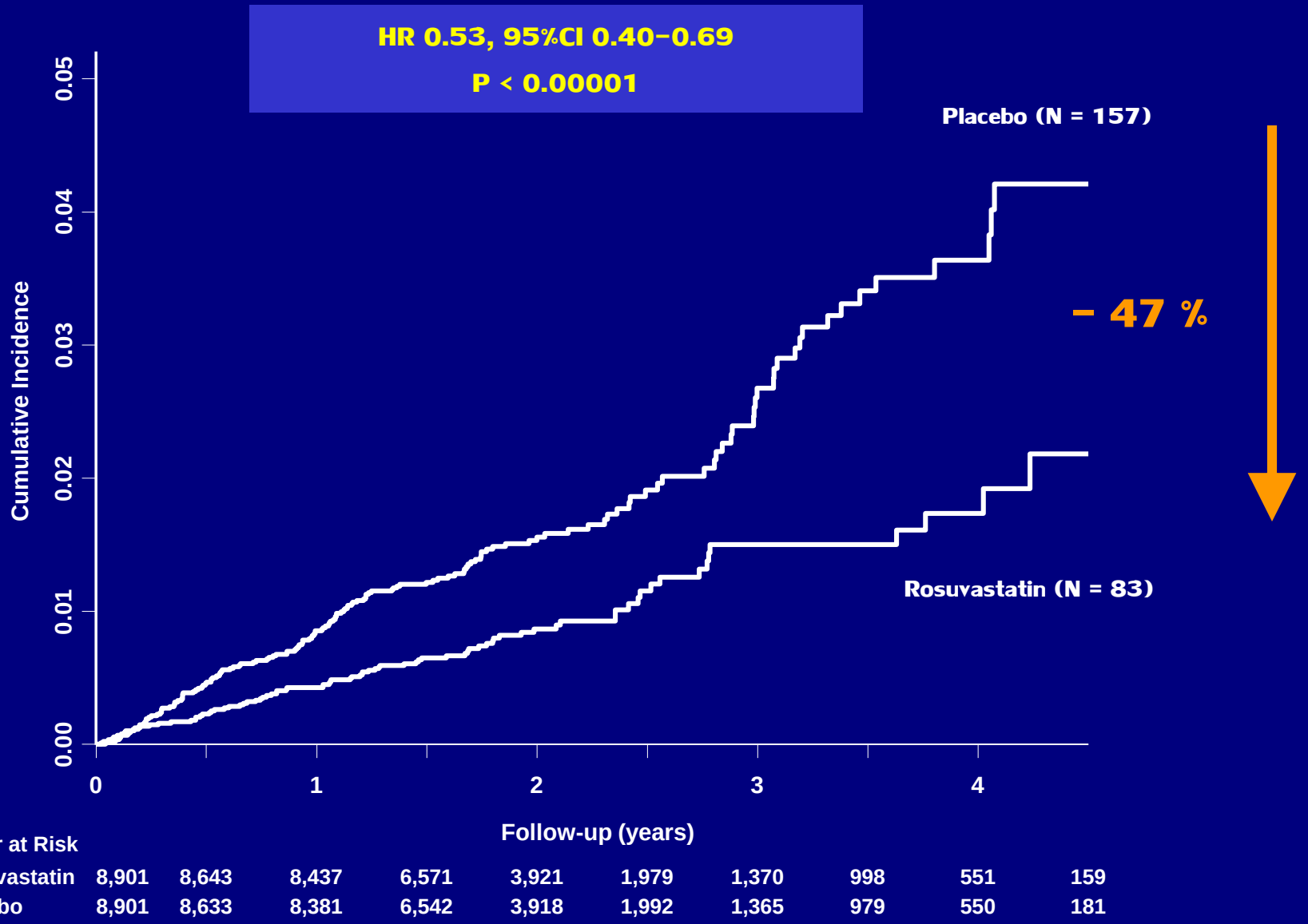
Myocardial Infarction, Stroke, Cardiovascular Death



Number at Risk

Rosuvastatin	8,901	8,643	8,437	6,571	3,921	1,979	1,370	998	551	159
Placebo	8,901	8,633	8,381	6,542	3,918	1,992	1,365	979	550	181

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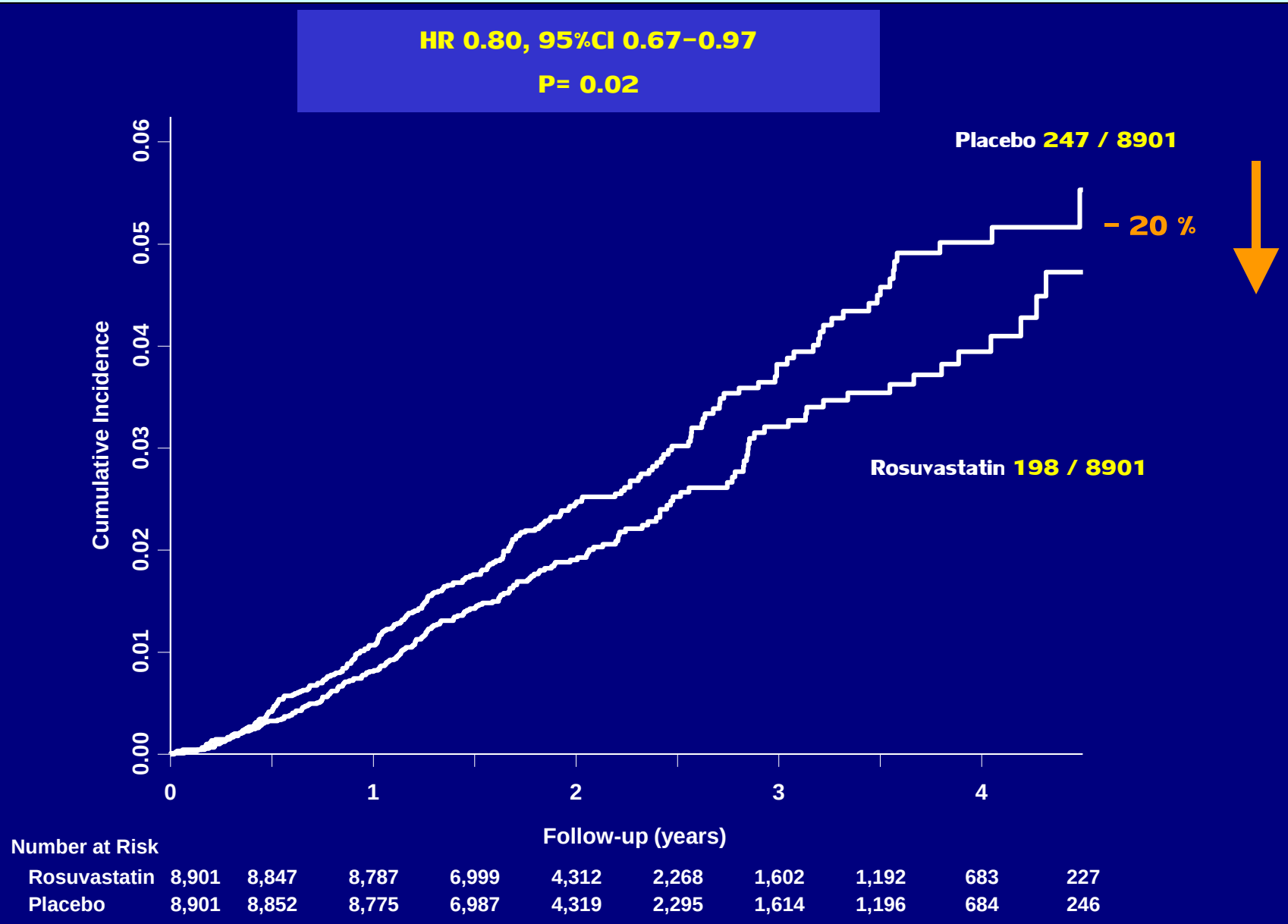
Secondary Endpoint – All Cause Mortality



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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)	314 (3.5)	0.51
Cancer Deaths	35 (0.4)	58 (0.7)	0.02
Hemorrhagic stroke	6 (0.1)	9 (0.1)	0.44
GFR (ml/min/1.73m^2 at 12 mth)	66.8 (59.1-76.5)	66.6 (58.8-76.2)	0.02
ALT > 3xULN	23 (0.3)	17 (0.2)	0.34
Fasting glucose (24 mth)	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

*Occurred after trial completion, trauma induced.

**Physician reported

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

The Heart Outcomes Prevention Evaluation (HOPE) – 3 Trial

Eva Lonn, Jackie Bosch, Salim Yusuf

For the HOPE-3 Investigators

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Canada

Study Objectives

To evaluate in an intermediate risk population without CVD the effects on CV events of:

1. BP lowering with combined Candesartan 16 mg + HCTZ 12.5 mg daily
2. Cholesterol lowering with Rosuvastatin 10 mg daily
3. Combined BP and cholesterol lowering

Intermediate-Risk Population

Inclusion Criteria (Target Risk 1.0%/yr)

Women ≥ 60 yrs, men ≥ 55 yrs with at least one additional Risk Factor

- Increased WHR
- Dysglycemia
- Smoking
- Mild renal dysfunction
- Low HDL
- Family history of CHD

Exclusion Criteria:

CVD or indication(s) or contraindication(s) to study drugs

No strict BP or LDL-C criteria for entry
Uncertainty principle

HOPE-3: 2 by 2 Factorial Design

14,682 Entered Single-blind 4 week Active Run-in
12,705 (87%) Randomized

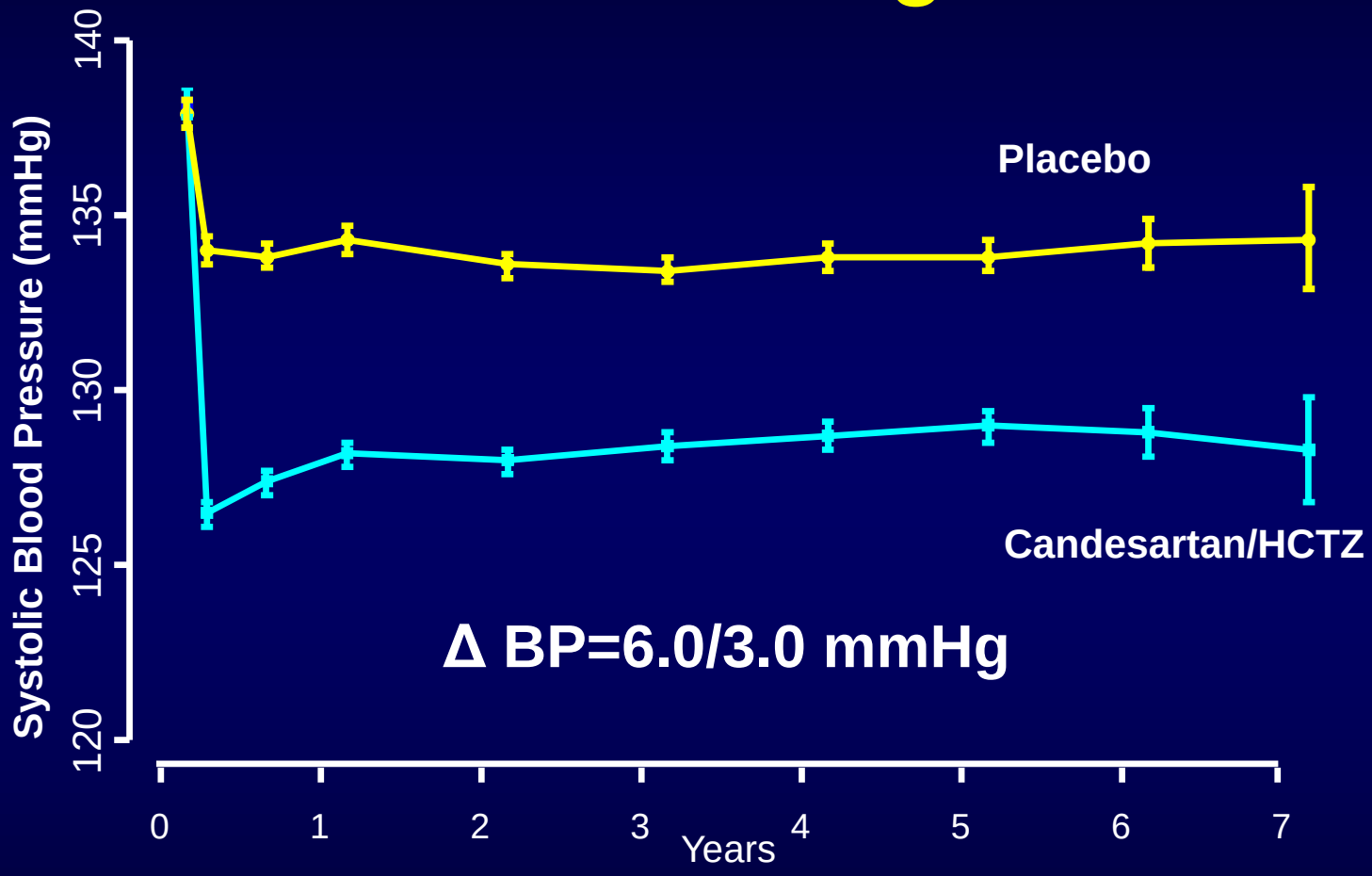
	Candesartan 16 mg + HCTZ 12.5 mg n= 6,356	**Placebo n = 6,349**
Rosuvastatin 10 mg n=6,361	**Rosuvastatin Cand+HCTZ n = 3,180**	**Rosuvastatin n = 3,181**
Placebo n = 6,344	**Cand+HCTZ n = 3,176**	**Double Placebo n = 3,168**

Simple follow-up and few blood tests

Baseline Characteristics

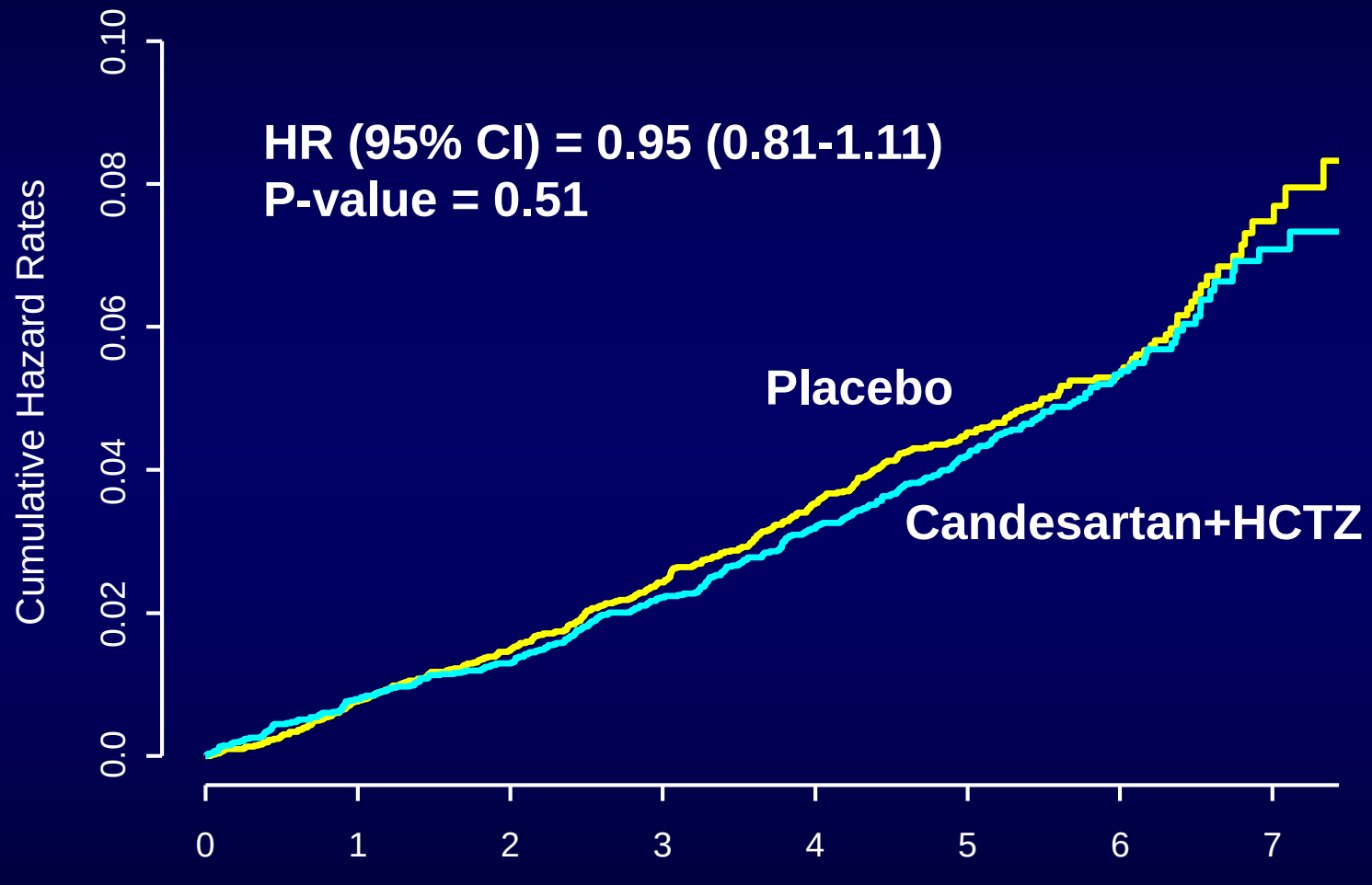
Age (yrs)	66
Female	46%
Blood Pressure (mmHg)	138/82
LDL-Cholesterol (mg/dL)	128
LDL-Cholesterol (mmol/L)	3.4
Elevated waist-to-hip ratio	87%
hsCRP (g/L) median	2.0
Ethnicity	
White Caucasian	20%
Latin American	28%
Chinese	29%
Other Asian	20%
Black African	2%

BP Lowering vs. Placebo: SBP Changes



Cand/HCTZ	6356	5907	5667	5446	5213	3862	1437	350
Placebo	6347	5879	5623	5442	5186	3822	1424	334

CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure

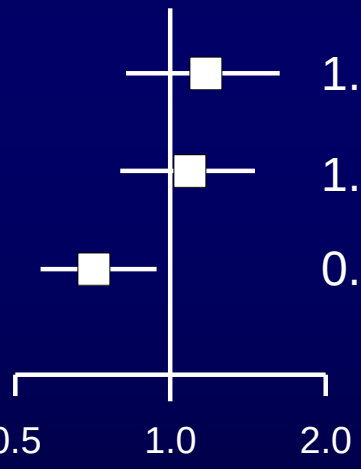


No. at Risk								
Cand + HCTZ	6356	6272	6200	6103	5968	4969	2076	522
Placebo	6349	6270	6198	6096	5967	4970	2075	488

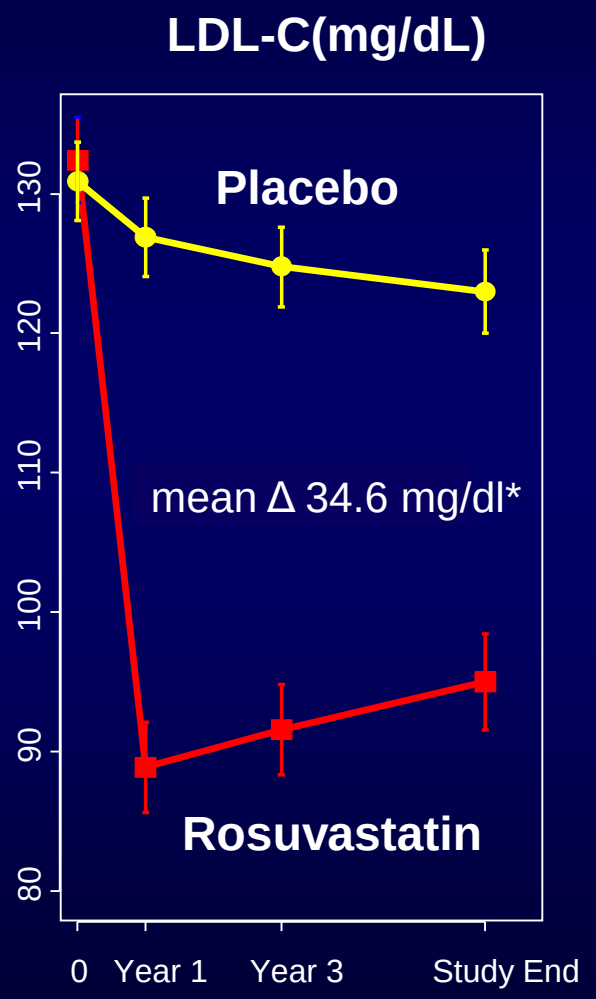
Prespecified Subgroups: By Thirds of SBP

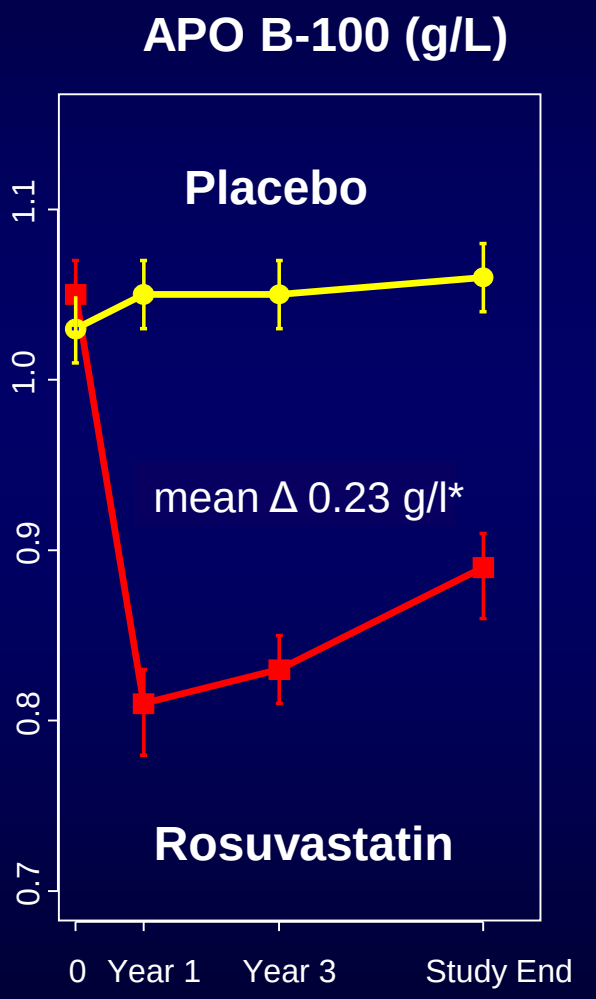
CV Death, MI, Stroke

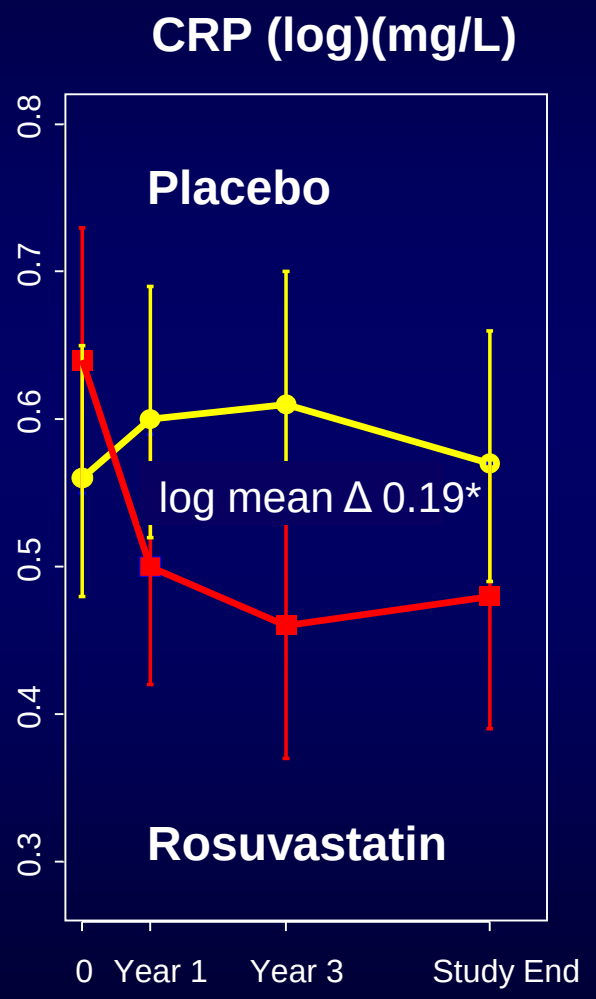
Cutoffs	SBP Mean	Diff	Placebo Event Rate%	HR (95% CI)	P Trend
≤131.5	122	6.1	2.9	1.16 (0.82-1.63)	0.021
131.6-143.5	138	5.6	3.8	1.08 (0.80-1.46)	
>143.5	154	5.8	6.5	0.73 (0.56-0.94)	



Cholesterol Lowering Arm: Change in LDL, Apo-B, and CRP

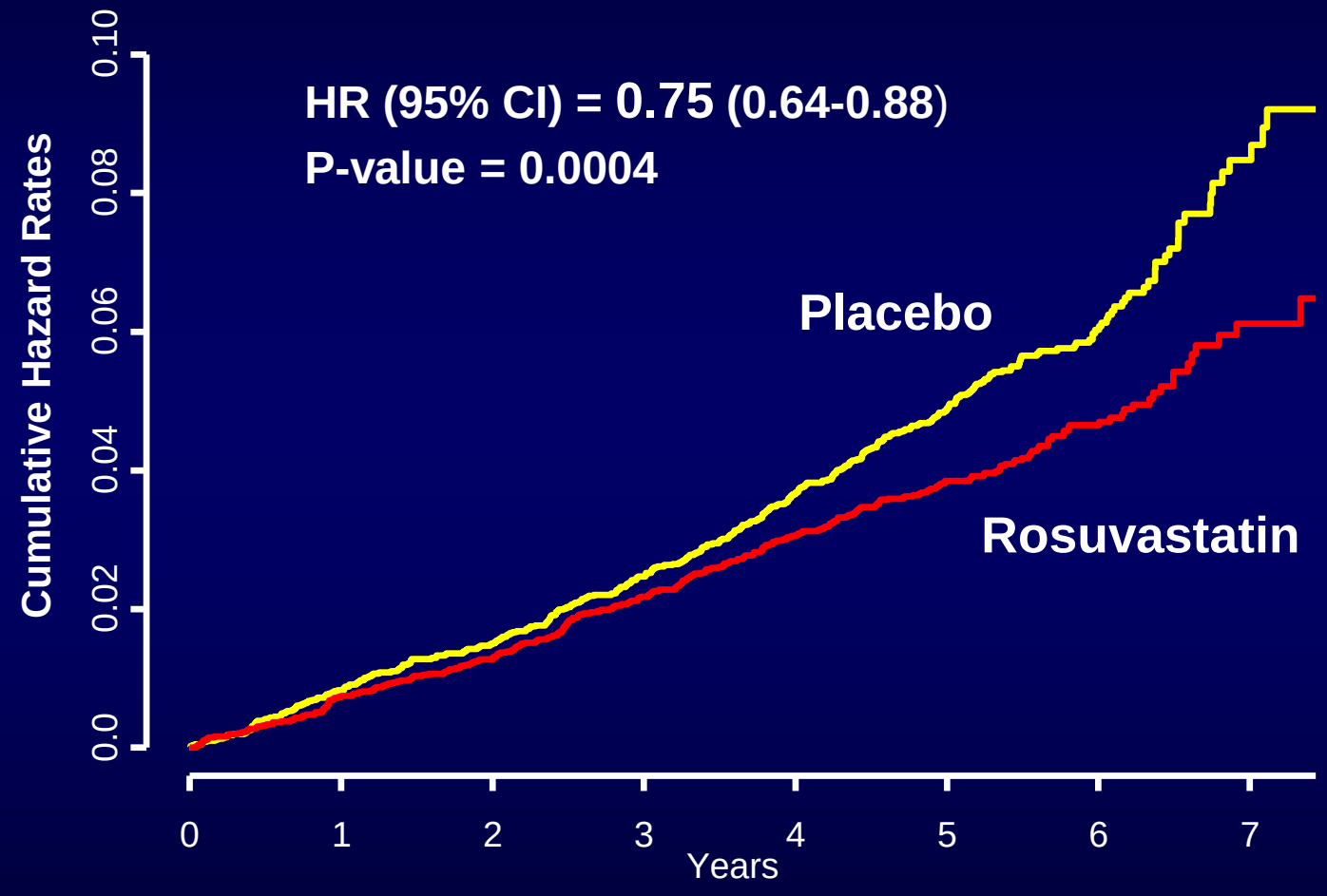






*** P< 0.001**

CV Death, MI, Stroke, Cardiac Arrest, Revasc, Heart Failure

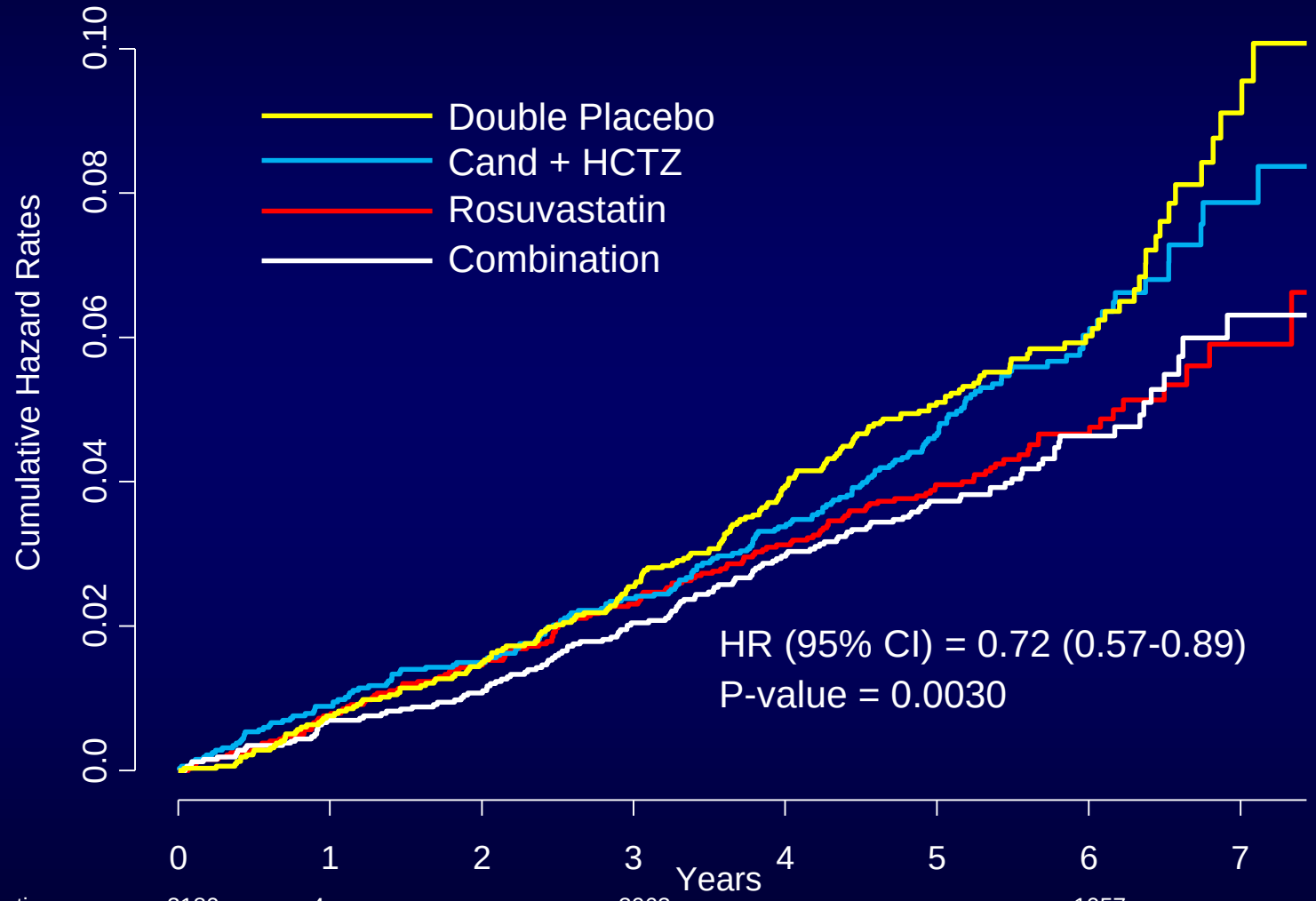


Rosuva	6361	6241	6039	2122
Placebo	6344	6192	5970	2073

Combined BP & Cholesterol Lowering vs Double Placebo

Salim Yusuf

CV Death, MI, Stroke, Cardiac Arrest, Revasc, Heart Failure

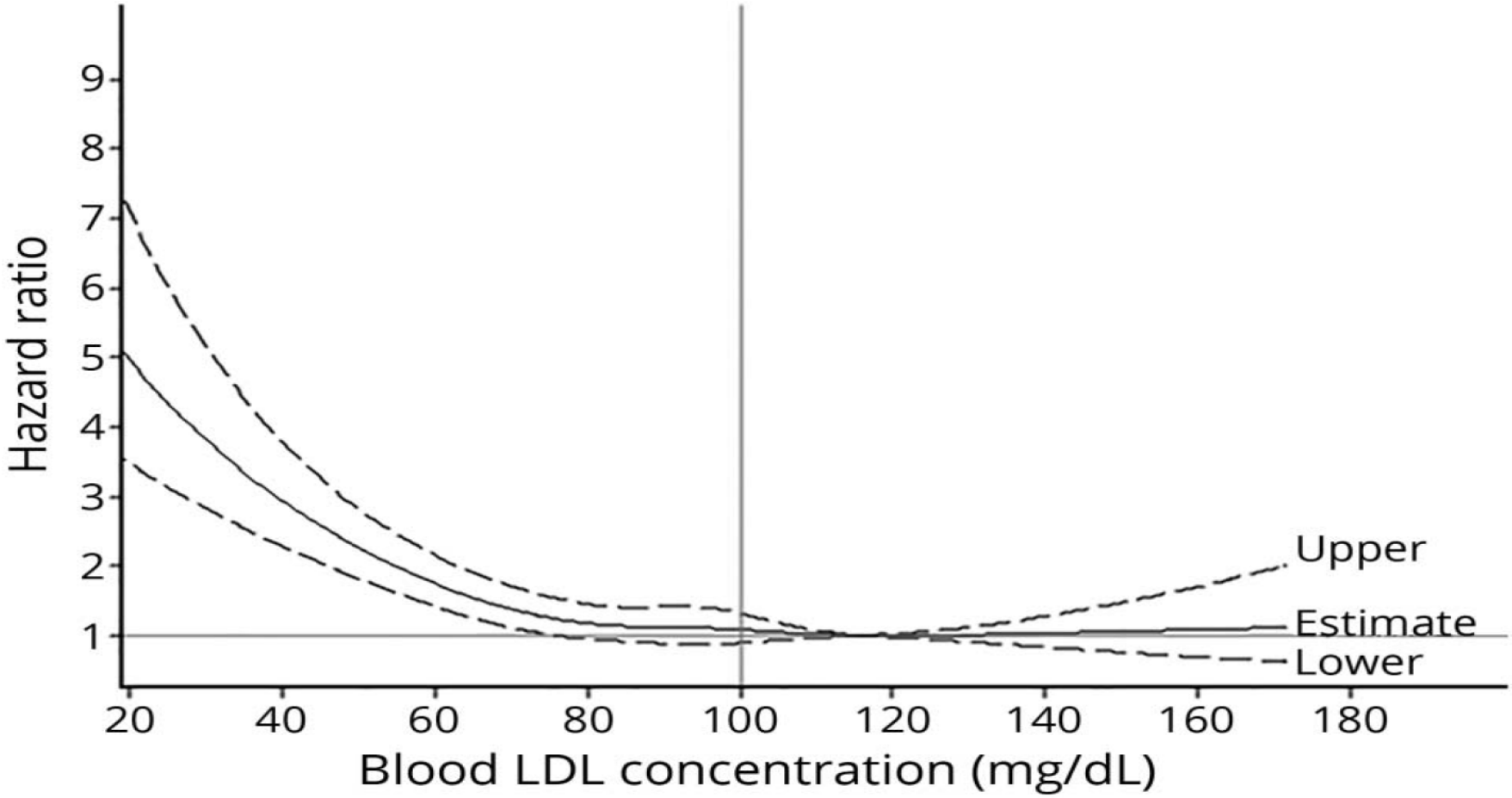


Combination	3180	4			3063			1057
Rosuvastatin	3181				3061			1045
Candesartan/HCTZ	3176				3040			1019
Double Placebo	3168				3035			1030

Combination vs Double Placebo: Safety

	Combination N=3,180 N (%)	Double Placebo N=3,168 N (%)
Permanent Discontinuation of Both	697 (21.9)	757 (23.9)
Rhabdomyolysis/Myopathy of Rosuva	1 (0)	1 (0)
Muscle pain/ weakness	196 (6.2)	131 (4.1)
Lightheadedness (BP Only)	48 (1.5)	40 (1.3)
Renal Dysfunction/Potassium Abn.	6 (0.2)	6 (0.2)
New Diabetes	123 (4.1)	113 (3.8)
Cataract Surgery	84 (2.8)	88 (2.9)

Figure Hazard ratios for intracerebral hemorrhage according to updated cumulative average blood LDL cholesterol from 2006 to 2012 among 96,043 Kailuan participants



ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

Barter PJ, et al. *J Intern Med*. 2006;259:247-258; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387-2397; Grundy SM, et al. *Circulation.* 2004;110:227-239; Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lloyd-Jones DM, et al. *Am J Cardiol*. 2004;94:20-24; McClelland RL, et al. *J Am Coll Cardiol*. 2015;66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, *J Am Coll Cardiol*. 2005;45:1644-1648; Ridker PM, et al. *JAMA*. 2007;297(6):611-619; Sever PS, et al. *Lancet*. 2003;361:1149-1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Smith SC Jr, et al. *Circulation*. 2006;113:2363-2372; Stevens RJ, et al. *Clin Sci*. 2001;101(6):671-679; Stone NJ. *Am J Med*. 1996;101:4A40S-48S; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315.

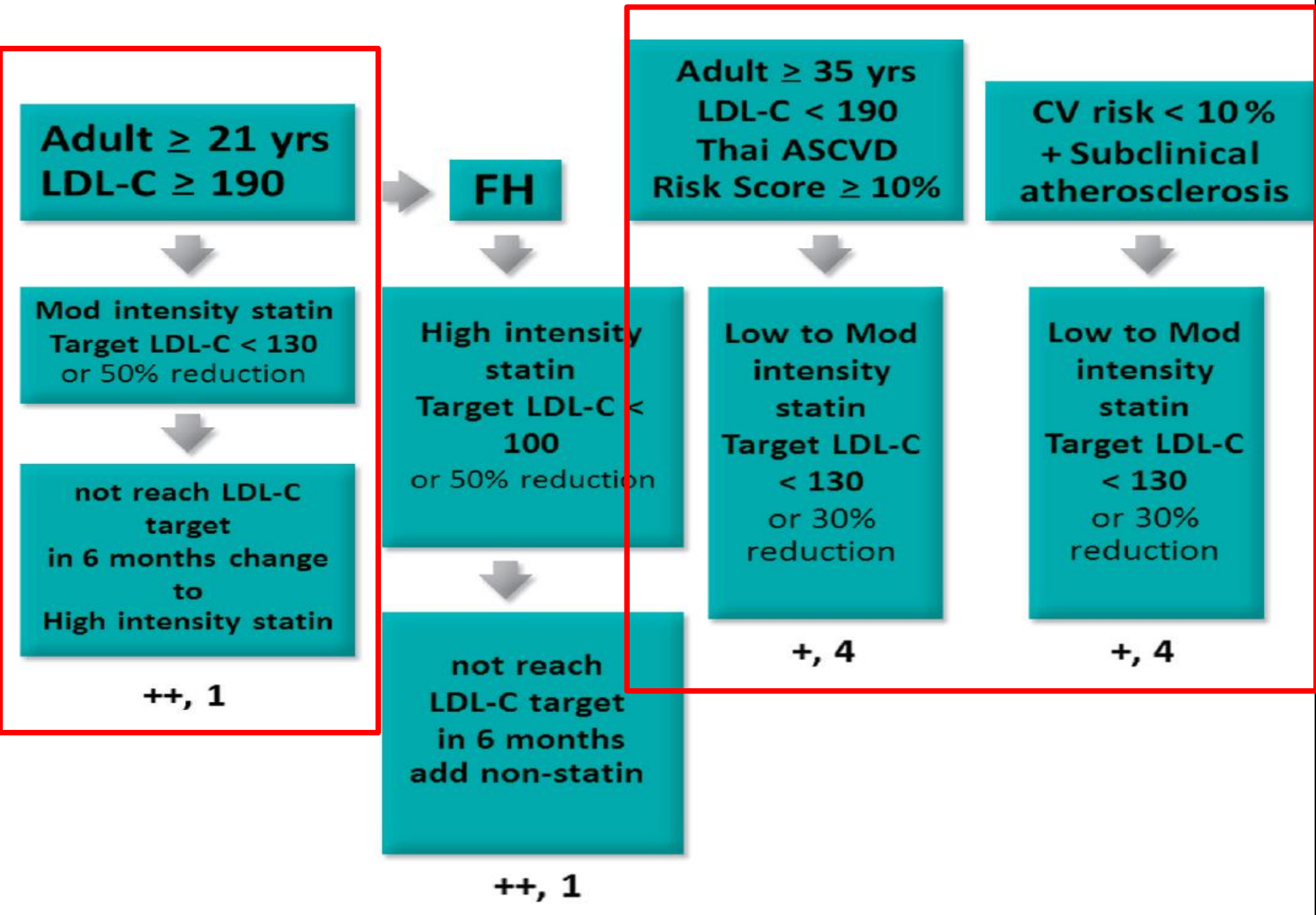
แนวทางเวชปฏิบัติ
การใช้ยารักษาภาวะไขมันผิดปกติ เพื่อป้องกันโรคหัวใจและหลอดเลือด พ.ศ. ๒๕๕๙

2016 RCPT
Clinical Practice Guideline
on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention

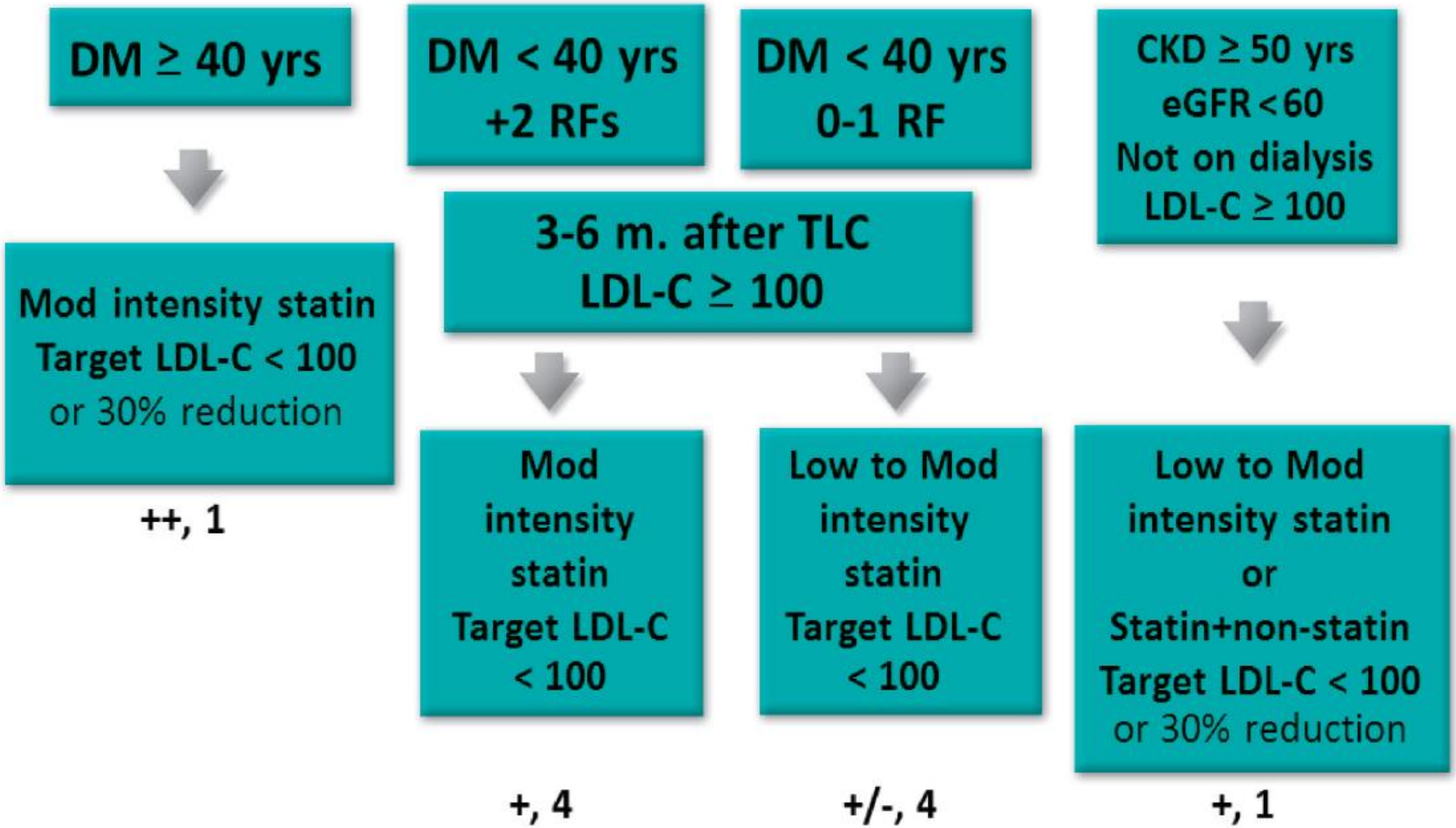




Primary Prevention : No DM / No CKD



Primary Prevention : DM, CKD (3–5)



Testing lipids

How often should lipids be tested?

- Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where concomitant drug treatment is suggested such as ACS and very high-risk patients.

How often should a patient's lipids be tested after starting lipid-lowering treatment?

- 8 (±4) weeks after starting treatment.
- 8 (±4) weeks after adjustment of treatment until within the target range.

How often should lipids be tested once a patient has reached the target or optimal lipid level?

- Annually (unless there is adherence problems or other specific reasons for more frequent reviews).

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

Monitoring liver and muscle enzymes

How often should liver enzymes (ALT) be routinely measured in patients on lipid-lowering drugs?

- Before treatment.
- Once 8–12 weeks after starting a drug treatment or after dose increase.
- Routine control of ALT thereafter is not recommended during lipid-lowering treatment.

What if liver enzymes become elevated in a person taking lipid-lowering drugs?

If ALT <3x ULN:

- Continue therapy.
- Recheck liver enzymes in 4–6 weeks.

If value rises to ≥3x ULN

- Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

How often should CK be measured in patients taking lipid-lowering drugs?

Pre-treatment

- Before starting therapy.
- If baseline CK is 4x ULN, do not start drug therapy; recheck.

Monitoring:

- Routine monitoring of CK is not necessary.
- Check CK if patient develops myalgia.

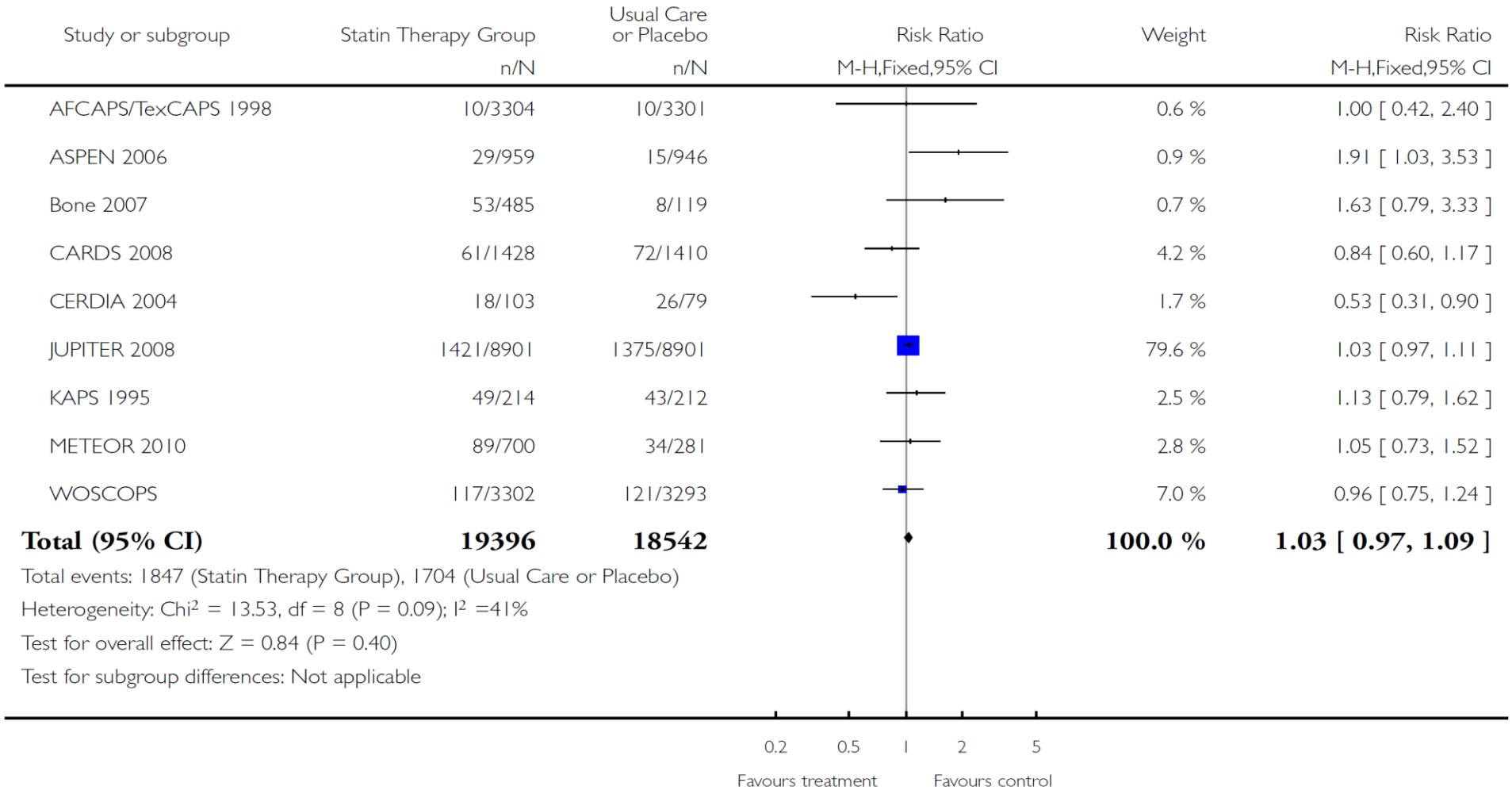
Be alert regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease or sport athletes.

Analysis 3.5. Comparison 3 Adverse Events, Outcome 5 Number of study participants who developed myalgia or muscle pain.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 5 Number of study participants who developed myalgia or muscle pain



What is the nocebo effect?

- ASCOT-LLA trial, 10,000 patients
  - Almost all had never been on a statin before
- Blinded phase events muscle related events similar between groups (2%)
- Unblinded phase AE when patients knew they were on a statin, incidents of myalgias rose 41%

Previous simvastatin label	New simvastatin label
Avoid simvastatin with: • Itraconazole • Ketoconazole • Erythromycin • Clarithromycin • Telithromycin • HIV protease inhibitors • Nefazodone	Contraindicated with simvastatin: • Itraconazole • Ketoconazole • Posaconazole (New) • Erythromycin • Clarithromycin • Telithromycin • HIV protease inhibitors • Nefazodone • Gemfibrozil • Cyclosporine • Danazol
Do not exceed 10 mg simvastatin daily with: • Gemfibrozil • Cyclosporine • Danazol	Do not exceed 10 mg simvastatin daily with: • Verapamil • Diltiazem (Note: These drugs are contraindicated with Simcor as Simcor is only available with 20 mg or 40 mg of simvastatin.)
Do not exceed 20 mg simvastatin daily with: • Amiodarone • Verapamil	Do not exceed 20 mg simvastatin daily with: • Amiodarone • Amlodipine (New) • Ranolazine (New)
Do not exceed 40 mg simvastatin daily with: • Diltiazem	
Avoid large quantities of grapefruit juice (>1 quart daily)	Avoid large quantities of grapefruit juice (>1 quart daily

Table S5. Common Medications That May Potentially Interact With Statins

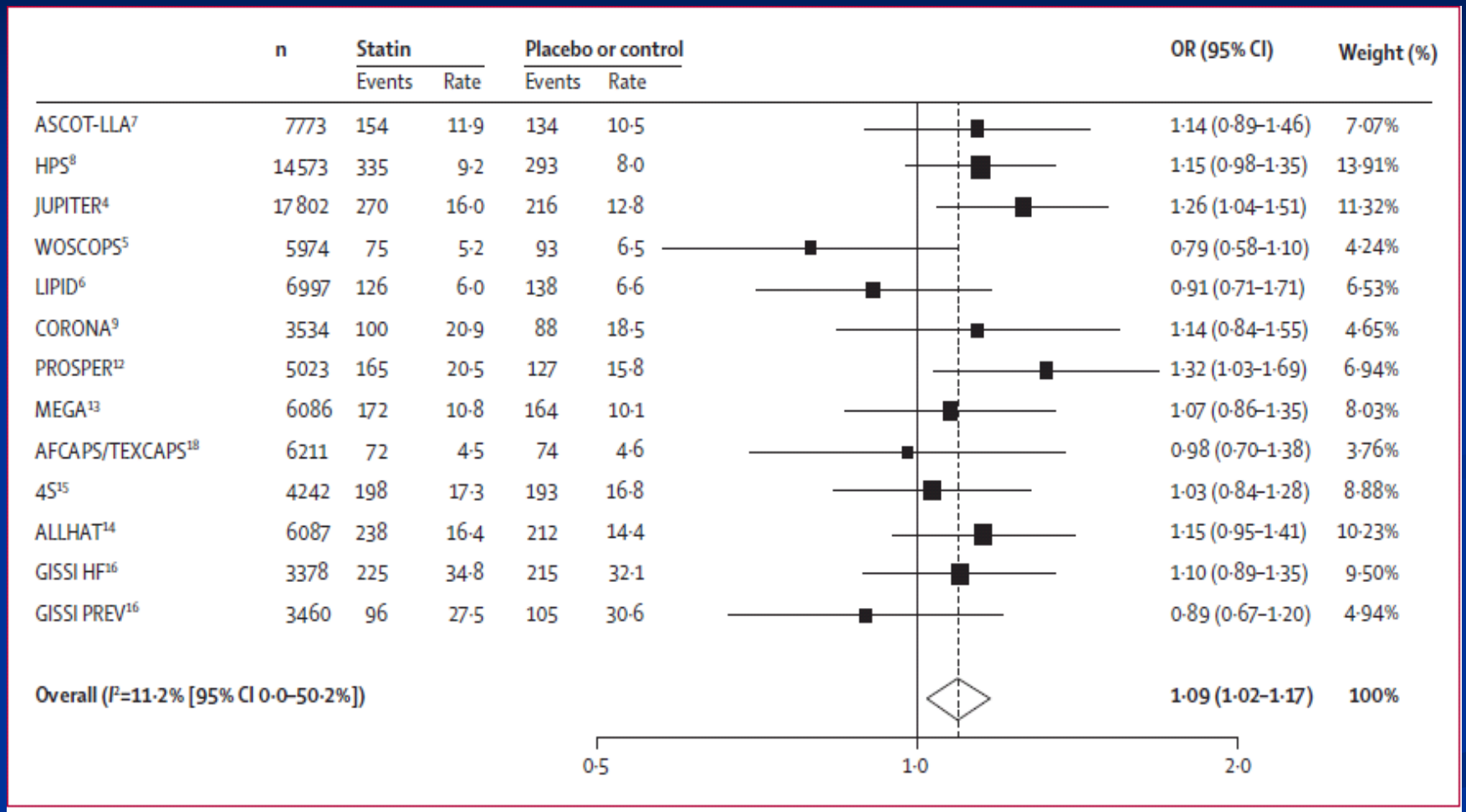
Can Be Used With a Statin Using a Risk-Mitigation Strategy*	Do Not Use With Any Statin
• Amiodarone • Amlodipine • Atazanavir plus ritonavir • Boceprevir • Clarithromycin • Cobicistat-containing products • Colchicine • Cyclosporine • Danazol • Darunavir plus ritonavir • Diltiazem • Dronedarone • Erythromycin • Fenofibrate • Fenofibric acid • Fluconazole • Fosamprenavir (with or without ritonavir) • Itraconazole • Ketoconazole • Lomitapide • Lopinavir plus ritonavir • Nefazodone • Nelfinavir • Niacin (≥1 g/d) • Posaconazole • Ranolazine • Rifampin • Saquinavir plus ritonavir • Telaprevir • Telithromycin • Tipranavir plus ritonavir • Verapamil • Voriconazole • Warfarin	Gemfibrozil

Colchicine – statin interaction

- Both colchicine and statin therapy are associated with myopathy.
- Colchicine is substrate of CYP 3A4 and P-gp
- The concomitant use of colchicine and statin has been associated with the rapid onset of muscle weaknes.

Maria Justiniano,et al. J Clin Rheumatol 2007;13: 266–268

Statins and risk incident diabetes



	n	Statin		Placebo or control		OR (95% CI)	Weight (%)
		Events	Rate	Events	Rate		
ASCOT-LLA[7]	7773	154	11·9	134	10·5	1·14 (0·89–1·46)	7·07%
HPS[8]	14573	335	9·2	293	8·0	1·15 (0·98–1·35)	13·91%
JUPITER[4]	17802	270	16·0	216	12·8	1·26 (1·04–1·51)	11·32%
WOSCOPS[5]	5974	75	5·2	93	6·5	0·79 (0·58–1·10)	4·24%
LIPID[6]	6997	126	6·0	138	6·6	0·91 (0·71–1·71)	6·53%
CORONA[9]	3534	100	20·9	88	18·5	1·14 (0·84–1·55)	4·65%
PROSPER[12]	5023	165	20·5	127	15·8	1·32 (1·03–1·69)	6·94%
MEGA[13]	6086	172	10·8	164	10·1	1·07 (0·86–1·35)	8·03%
AFCAPS/TEXCAPS[18]	6211	72	4·5	74	4·6	0·98 (0·70–1·38)	3·76%
4S[15]	4242	198	17·3	193	16·8	1·03 (0·84–1·28)	8·88%
ALLHAT[14]	6087	238	16·4	212	14·4	1·15 (0·95–1·41)	10·23%
GISSI HF[16]	3378	225	34·8	215	32·1	1·10 (0·89–1·35)	9·50%
GISSI PREV[16]	3460	96	27·5	105	30·6	0·89 (0·67–1·20)	4·94%
Overall (I^2=11·2% [95% CI 0·0–50·2%])						**1·09 (1·02–1·17)**	**100%**

Figure 2: **Association between statin therapy and incident diabetes in 13 major cardiovascular trials†**
*Events per 1000 patient-years. †Weights are from random-effects analysis.

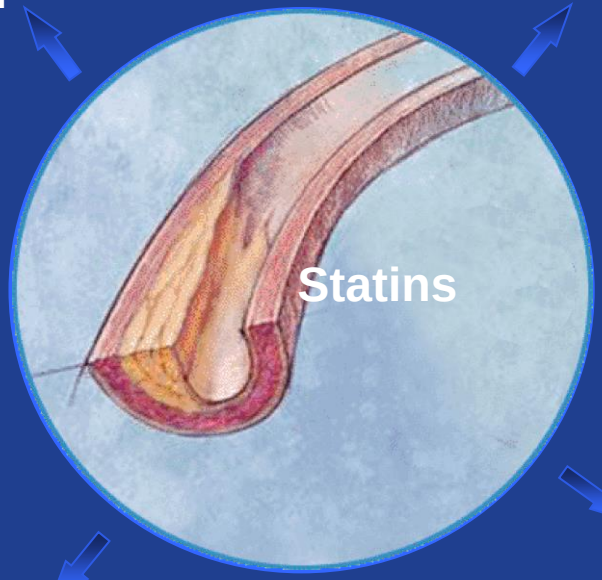
Sattar N, et al. Lancet 2010; 375: 735–42

Statins and risk incident diabetes

- For combined data cohort, the extra 174 cases in the statin group can also be expressed in absolute terms as on additional case of diabetes per 255 patients taking statin therapy for 4 years (95% CI 150-852)
- In contrast, statin therapy was associated with a reduction in major coronary events of 5.4 events per 255 patients treated for 4 years

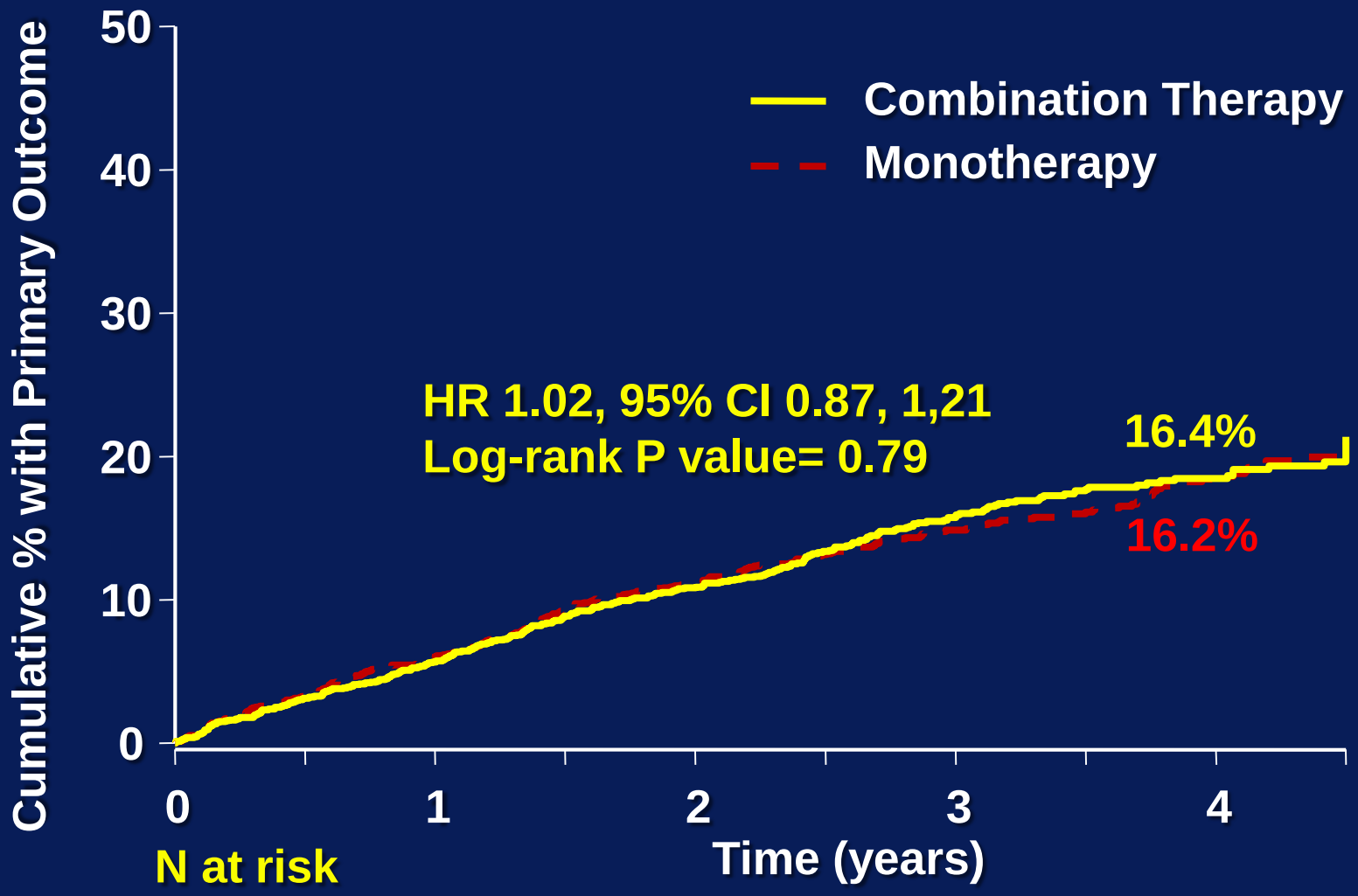
Sattar N, et al. Lancet 2010; 375: 735–42

Pleiotropic effects of statins



Liao JK. *Am J Cardiol*. 2005;96(suppl 1):24F-33F.

AIM-HIGH study



N at risk					
Monotherapy	1696	1581	1381	910	436
Combination Therapy	1718	1606	1366	903	428

AIM-HIGH investigator. N Engl J Med 2011;365:2255-67.

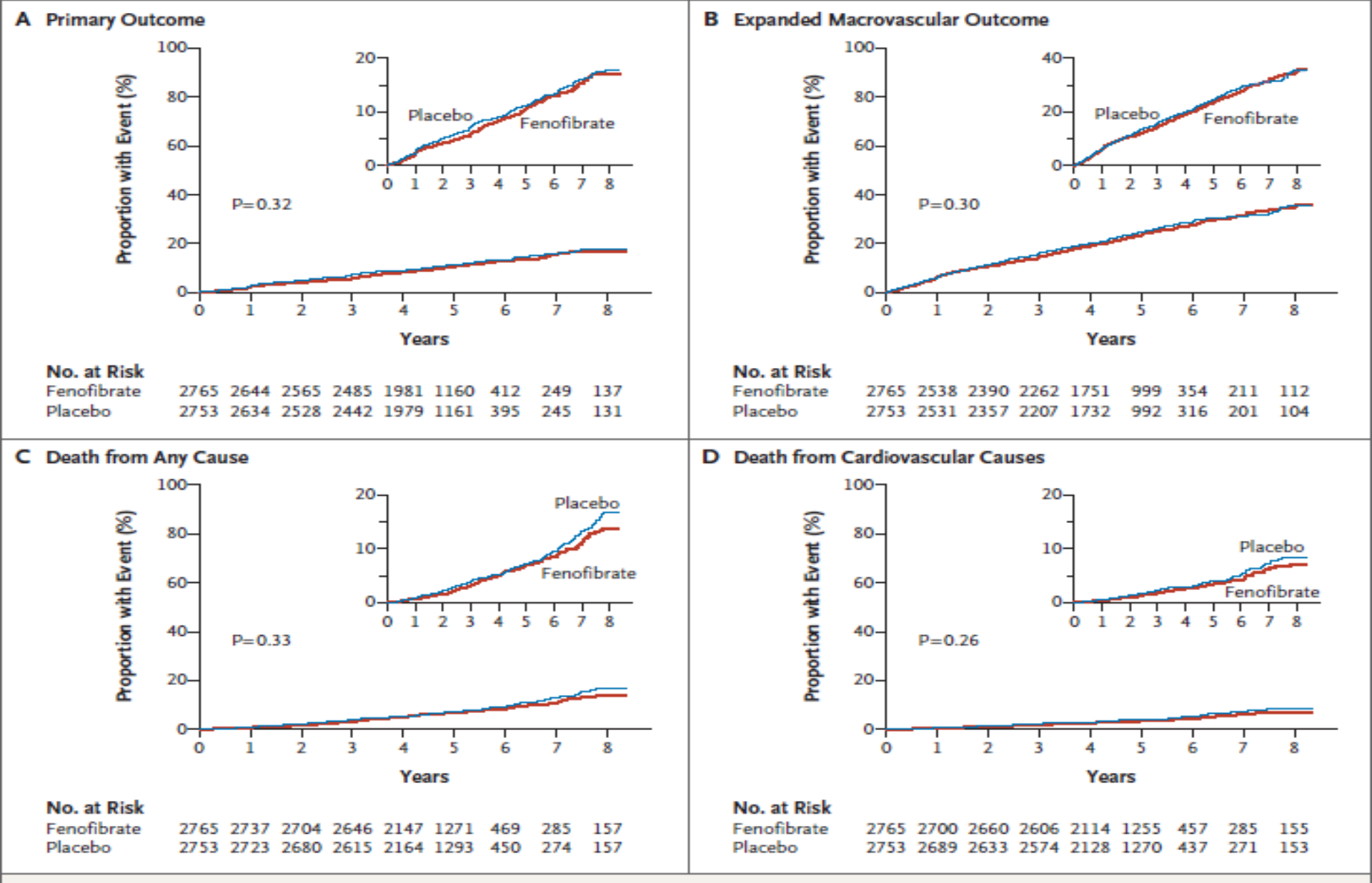


Figure 2. Kaplan–Meier Analyses of the Primary Outcome, Expanded Macrovascular Outcome, and Death.

Shown are the cumulative incidence of the primary outcome (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (Panel A), the expanded macrovascular outcome (a combination of the primary outcome plus revascularization or hospitalization for congestive heart failure) (Panel B), and death from any cause (Panel C) or from cardiovascular causes (Panel D) during follow-up. The insets show close-up versions of the graphs in each panel.

Pharmacological treatment of hypercholesterolaemia

Recommendations	Class	Level
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281-344-d oi:10.1016/j.atherosclerosis.2016.08.018

Thank you