New evidence in benefit of statin in high risk patients:

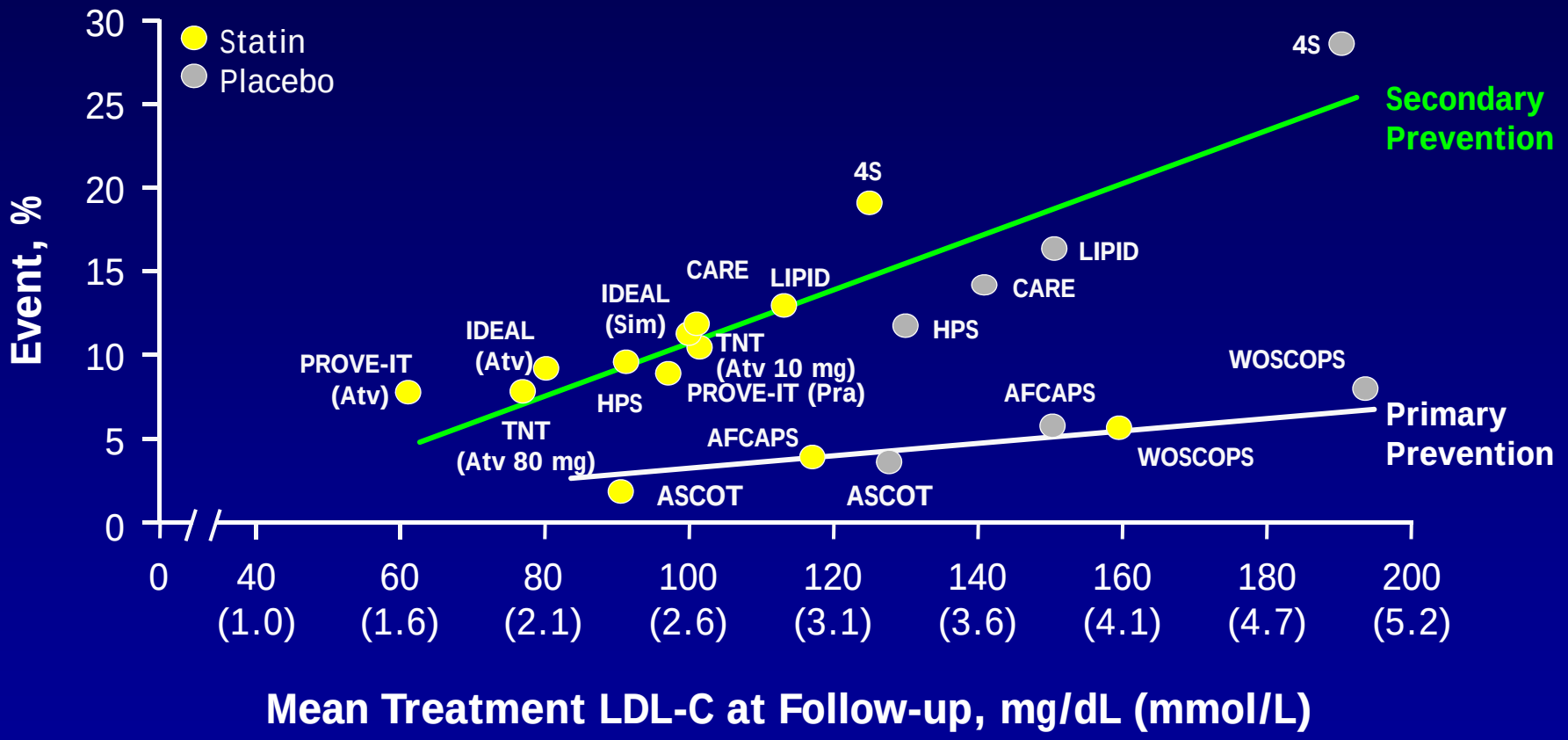
Dyslipidemia Management with Combination Therapy to Reduce Cardiovascular Risk

Contents

- **Guidelines for high risk patients**
- **Limitation of current statin mono therapy**
- **Clinical benefit of combination therapy**
- **Long term clinical benefit of LDL-c Lowering in high risk patients**

Lower is better

Relationship Between LDL-C and CV Incidence



Atv = atorvastatin; Pra = pravastatin; Sim = simvastatin; PROVE-IT = Pravastatin or AtorVastatin Evaluation and Infection Therapy; IDEAL = Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study

Adapted from Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9:269–279; LaRosa JC, et al. *N Engl J Med*. 2005;352:1425–1435; Pedersen TR, et al. *JAMA*. 2005;294:2437–2445.

Consensus statement from ADA and ACC

	Goals		
	LDL cholesterol (mg/dl)	Non-HDL cholesterol (mg/dl)	ApoB (mg/dl)
Highest-risk patients, including those with *1*) known CVD or *2*) diabetes plus one or more additional major CVD risk factor	<70	<100	<80
Highest-risk patients, including those with *1*) known CVD or *2*) diabetes plus one or more additional major CVD risk factor	<100	<130	<90

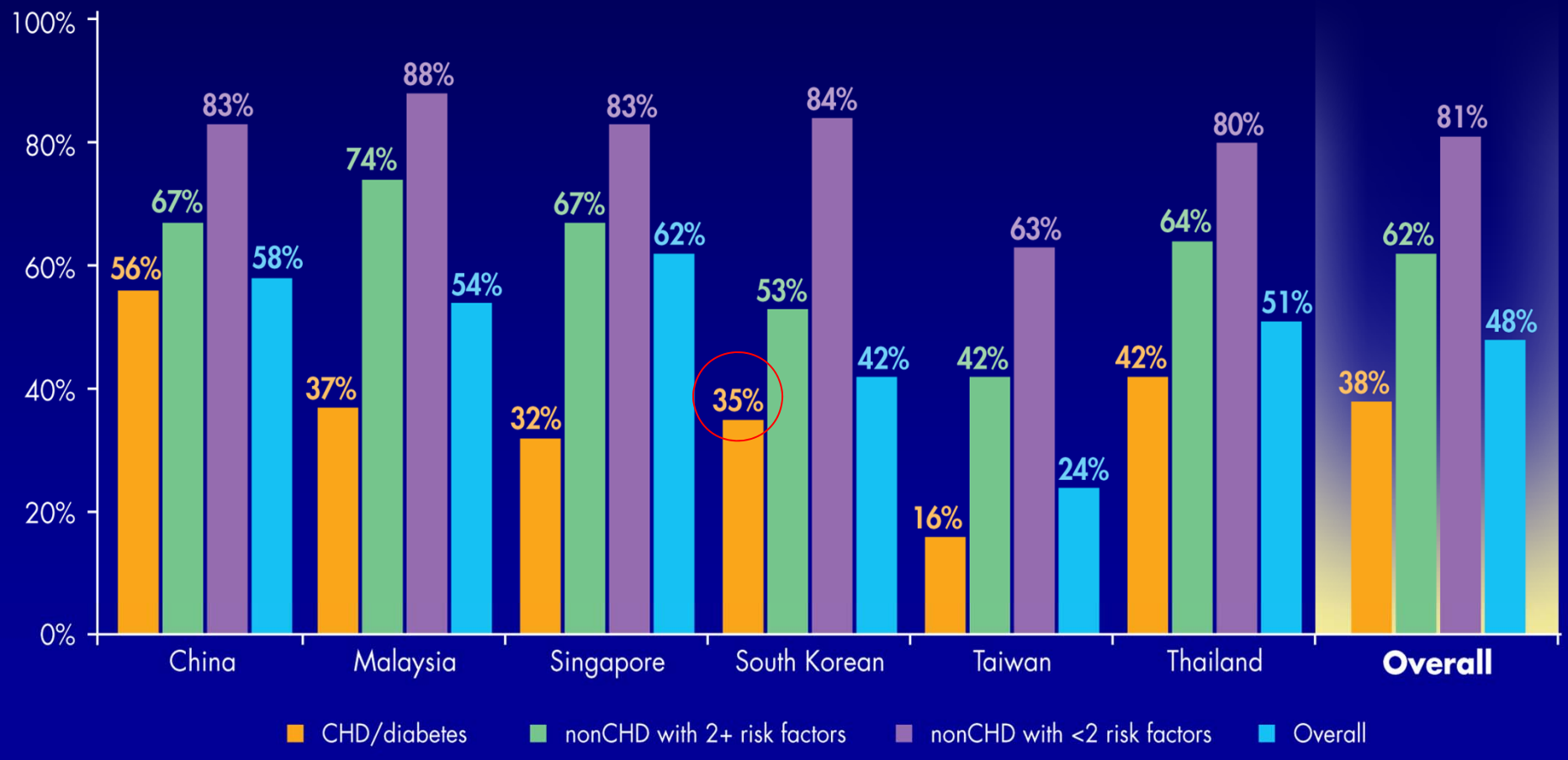
Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD

Table 1—Suggested treatment goals in patients with CMR and lipoprotein abnormalities (DIABETES CARE, VOLUME 31, NUMBER 4, APRIL 2008)

Limitation of current statin monotherapy:
Can statin monotherapy get these patients <70mg/dl?
How effectively?

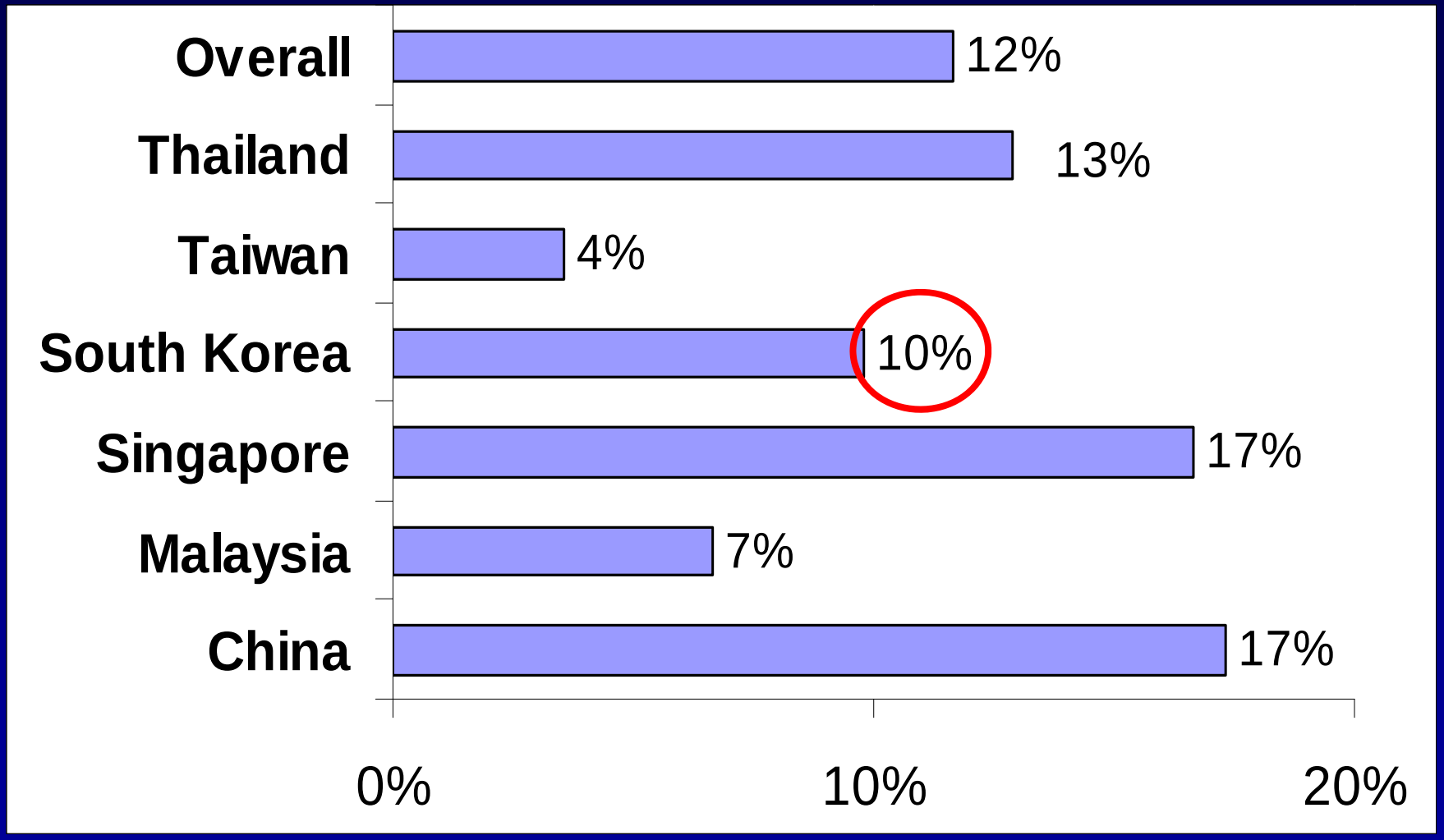
Cholesterol Goal Attainment in the Real World: The REALITY Asia Study

LDL-C Goal Attainment by Risk and Country



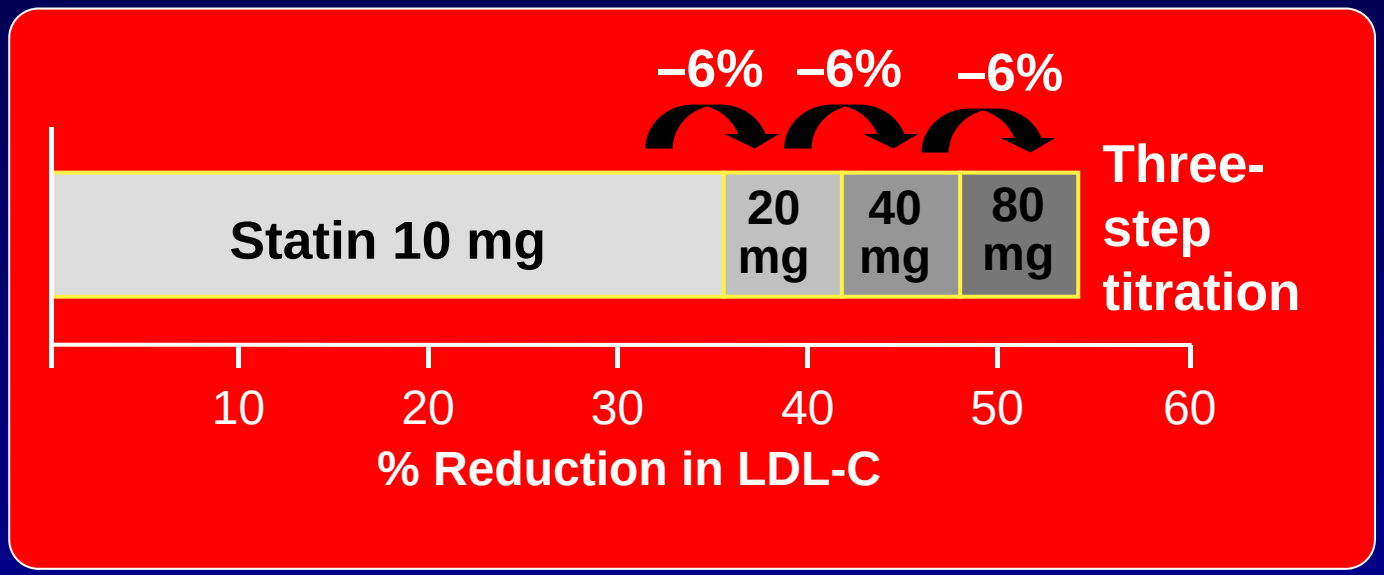
Kim H-S, Wu Y, Lin S-J et al. Current status of cholesterol goal attainment after statin therapy among patients with hypercholesterolemia in Asian countries and region: the Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY-Asia) study. *Curr Med Res Opin* vol. 24, No.7, 2008:1951-1963.

LDL-C Goal (< 70 mg/dl) Attainment Among Diabetic CHD Patients by Country



Why Are Patients Not Reaching Goals?

Effect of statin therapy on LDL-C levels: "The Rule of 6"



Other possible reasons

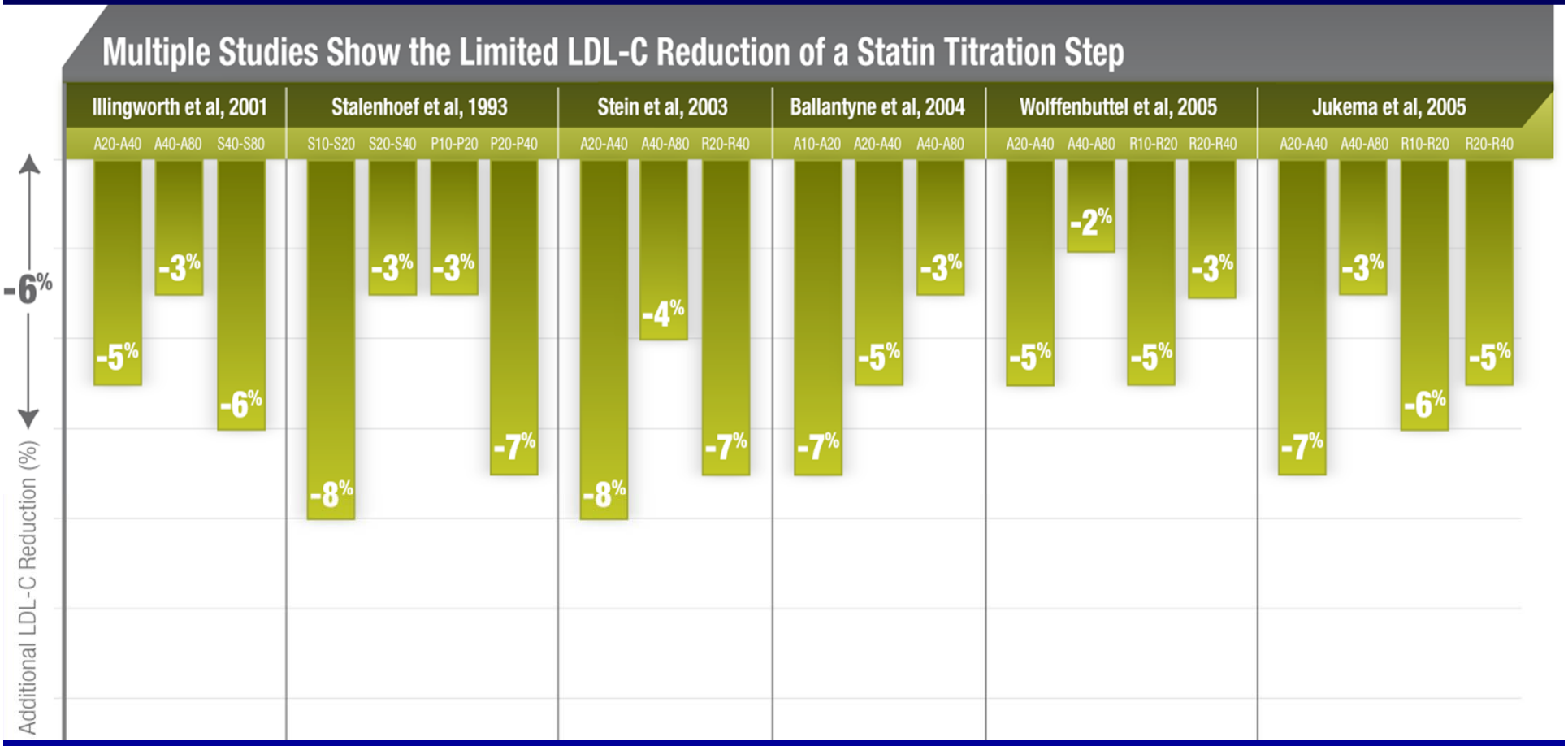
- Lack of treatment due to underdiagnosis of dyslipidemia
- Poor patient adherence to prescribed therapy
- Inadequate dose titration
- Fears of side effects with high-dose statins
- Under use of newer therapies that help get patients to target cholesterol levels

Stein E. Eur Heart J 2001; 3(Suppl E):E11-E16.

Multiple Studies Show the Limited LDL-C Reduction of Statin Titration Step

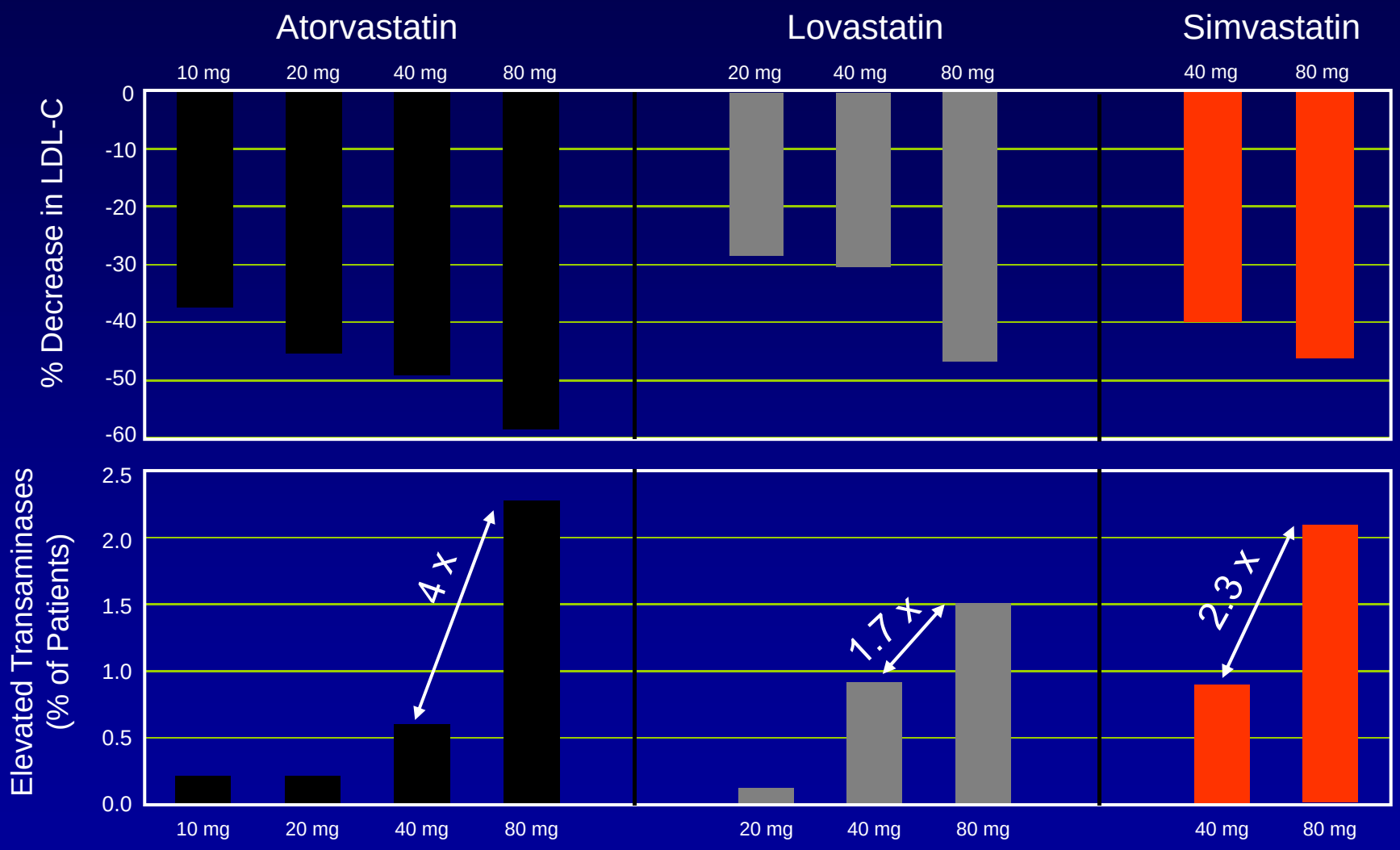
"…With each doubling of the dose of statin, LDL-C levels fall by about 6 percent."

NCEP ATP III Final Report



A10, 20, 40, 80 = atorvastatin 10, 20, 40, 80 mg, respectively; S10, 20, 40, 80 = simvastatin 10, 20, 40, 80 mg, respectively; P10, 20, 40 = pravastatin 10, 20, 40 mg, respectively; R20, 40 = rosuvastatin 20, 40 mg, respectively.

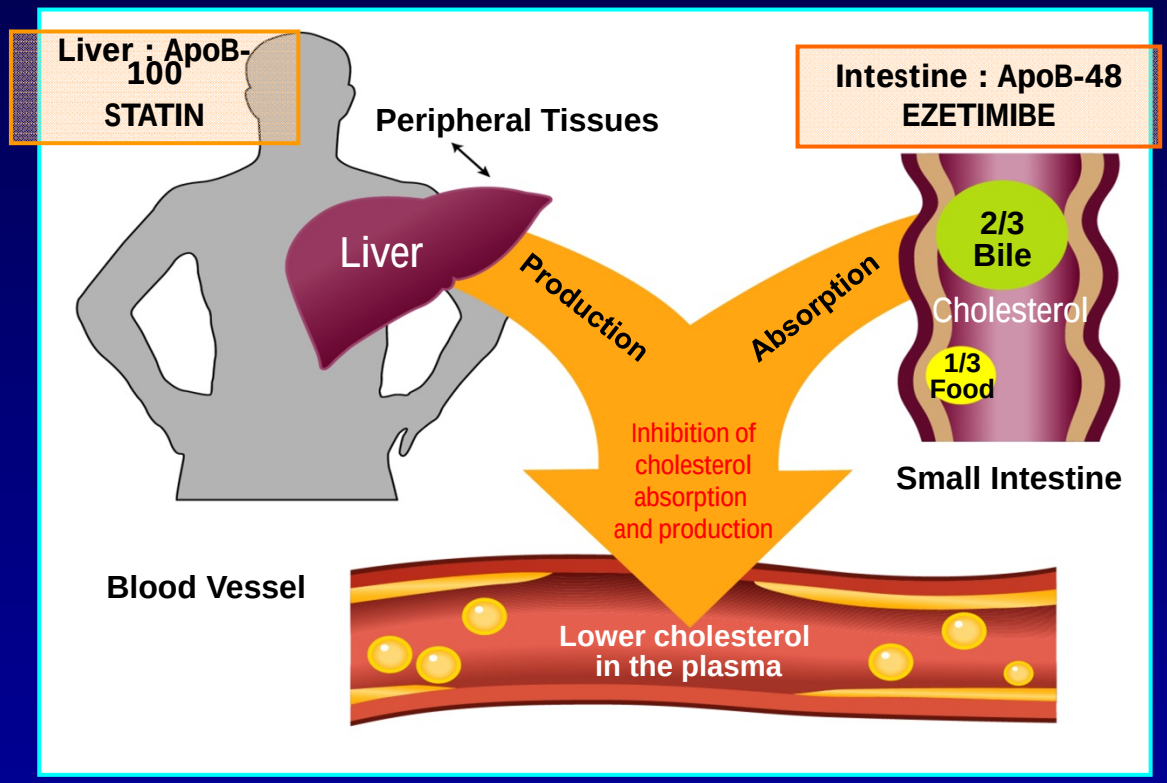
Risk: Benefit Ratio of Statin Titration



Data from prescribing information for atorvastatin, lovastatin, simvastatin.
This does not represent data from a comparative study.

What can we do to Improve It?
Clinical benefit of combination therapy

Dual Inhibition of Cholesterol Absorption and Production



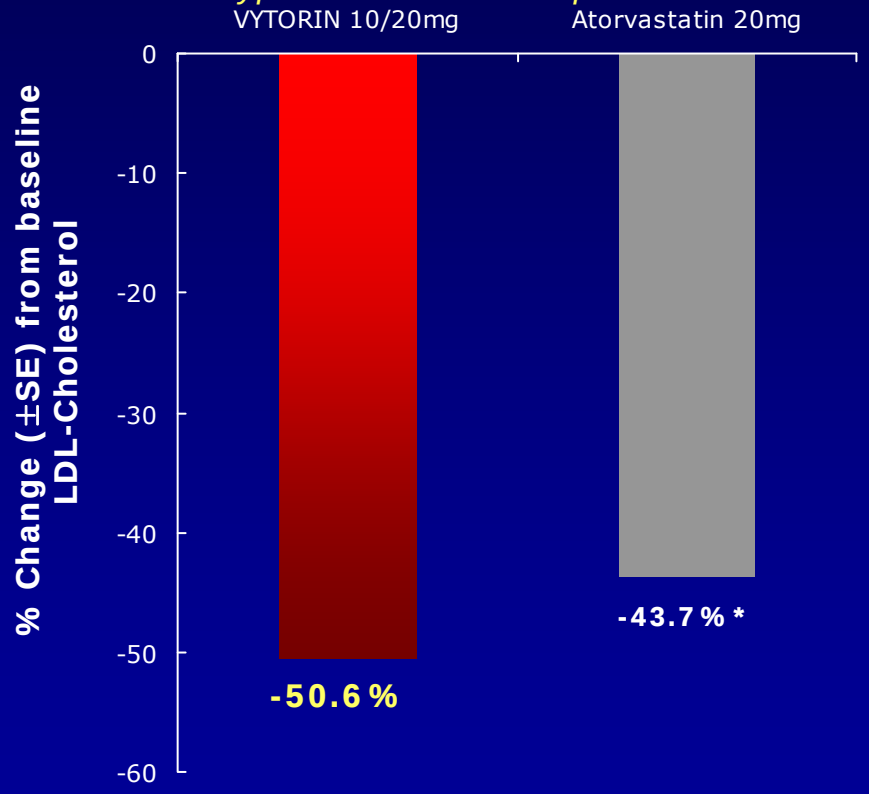
Adapted from van Heek M, et al. *Br J Pharmacol.* 2000;129:1748–1754; Shepherd J. *Eur Heart J Suppl.* 2001;3(suppl E):E2–E5; Bays H. *Expert Opin Investig Drugs* 2002;11:1587–160

VYTORIN cuts more than 50% of LDL-C at initial dose in hypercholsterolemia

Superior LDL-C reduction vs. Atova & Rosouva

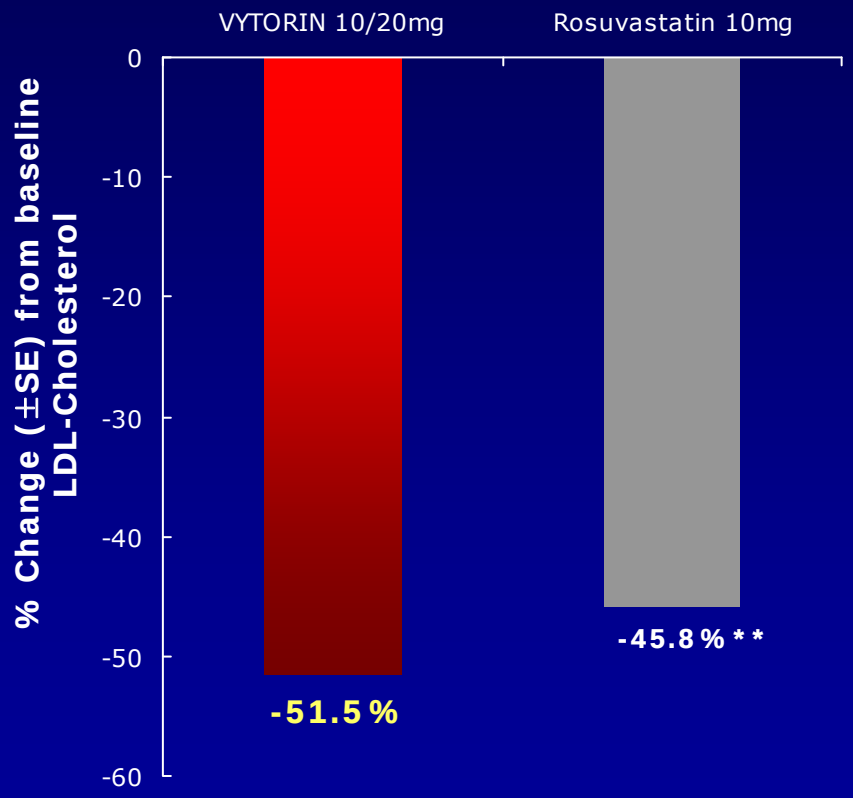
The VYVA Study

in hypercholesterolemia patients



The VYRO Study

in hypercholesterolemia patients

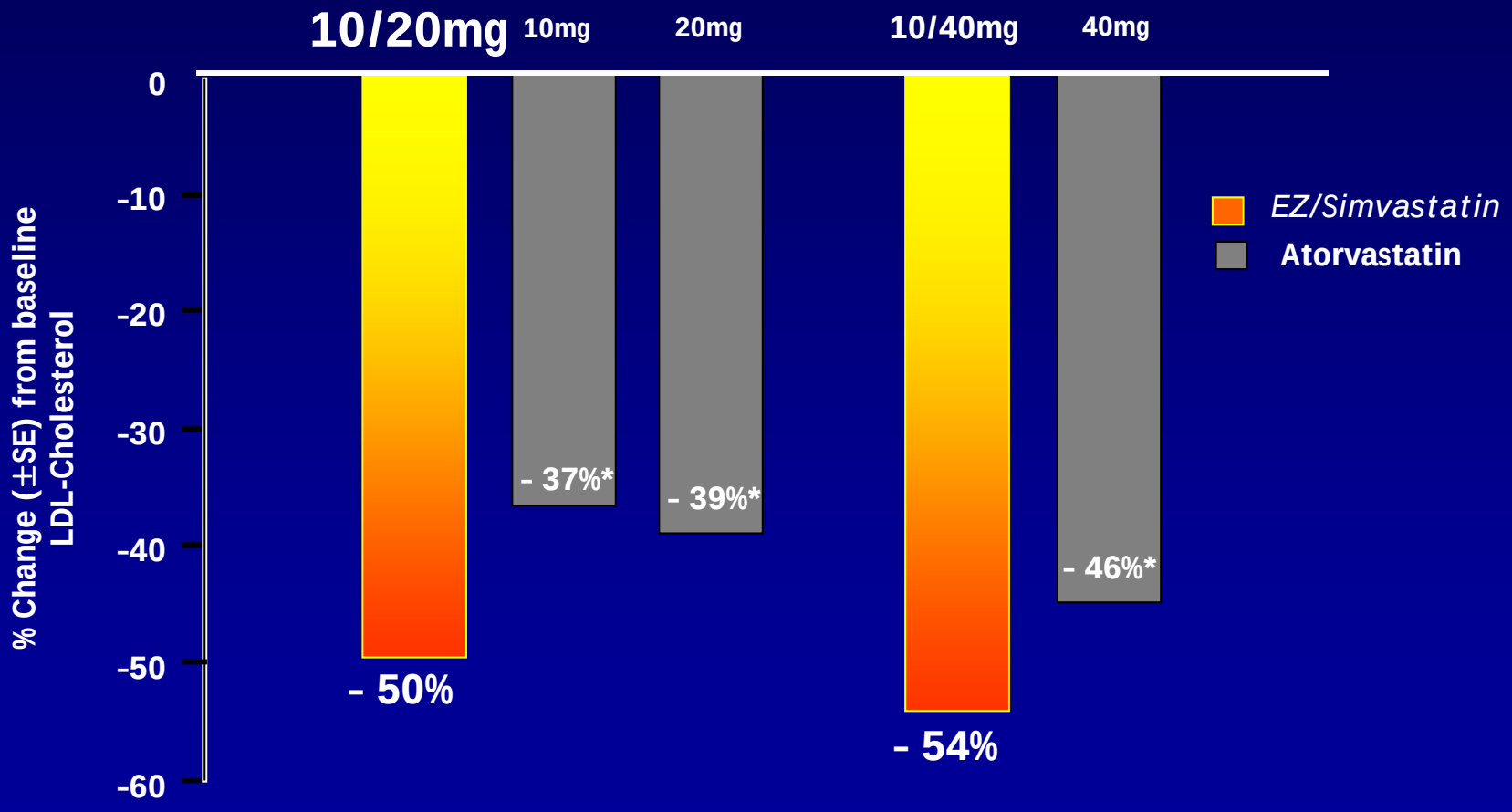


* p<0.001 vs. atorvastatin / Adapted from Ballantyne CM *et al* American Heart Journal. 2005;149(3):464-473.
**P<0.001 vs. rosuvastatin / Adapted from Catapano AL *et al* Curr Med Res Opin. 2006;22:2041–2053.

Superior efficacy at initial dose in metabolic syndrome patients

LDL-C Reduction (%) Superior to Atorvastatin

The VYMET Study with Metabolic Syndrome patients

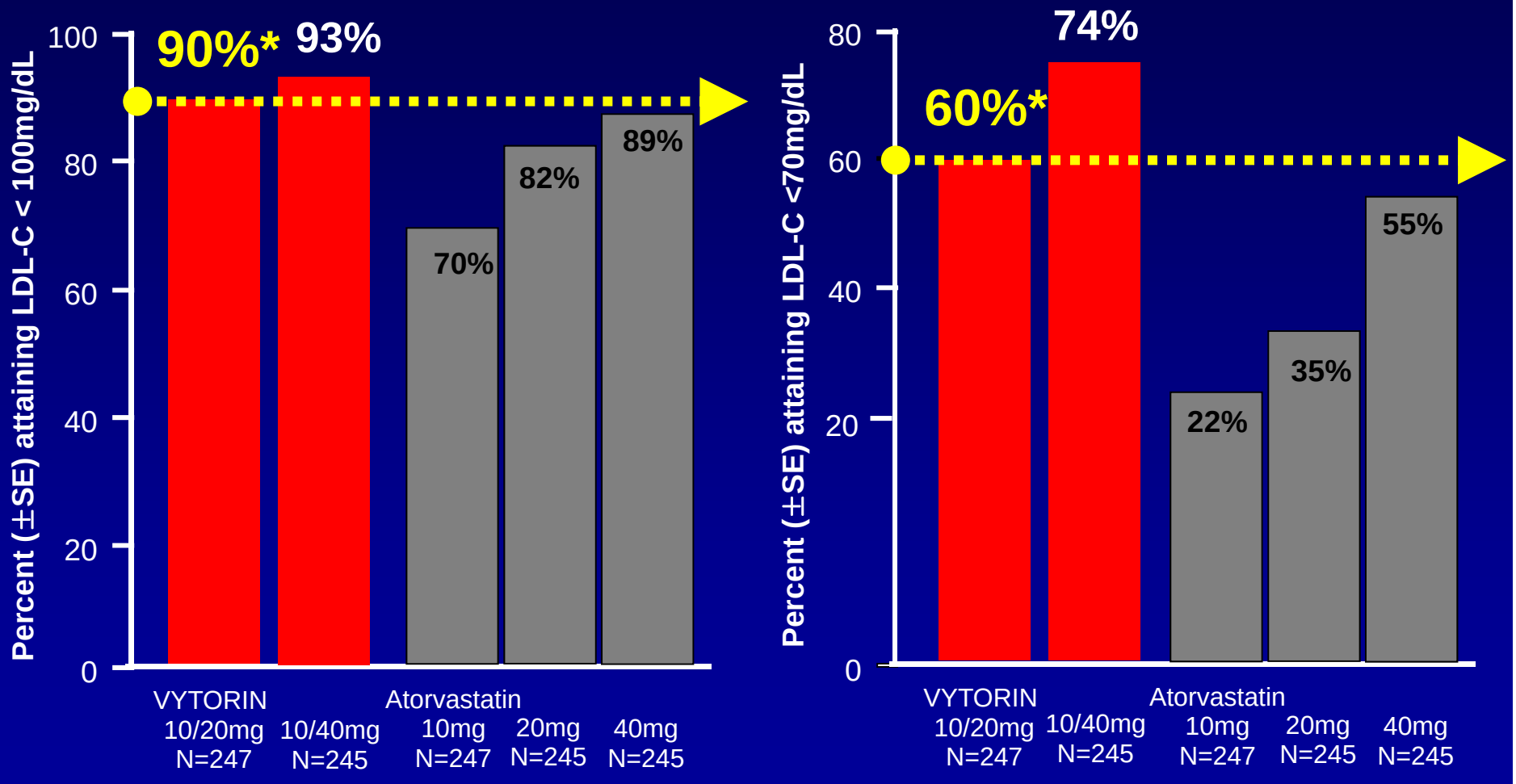


* p<0.001 vs. atorvastatin

Am J Cardiol 2009;103:1694-1702

VYTORIN has superior target goal attainment

The VYTAL Study: *NCEP ATP III LDL-C Goal Attainment*



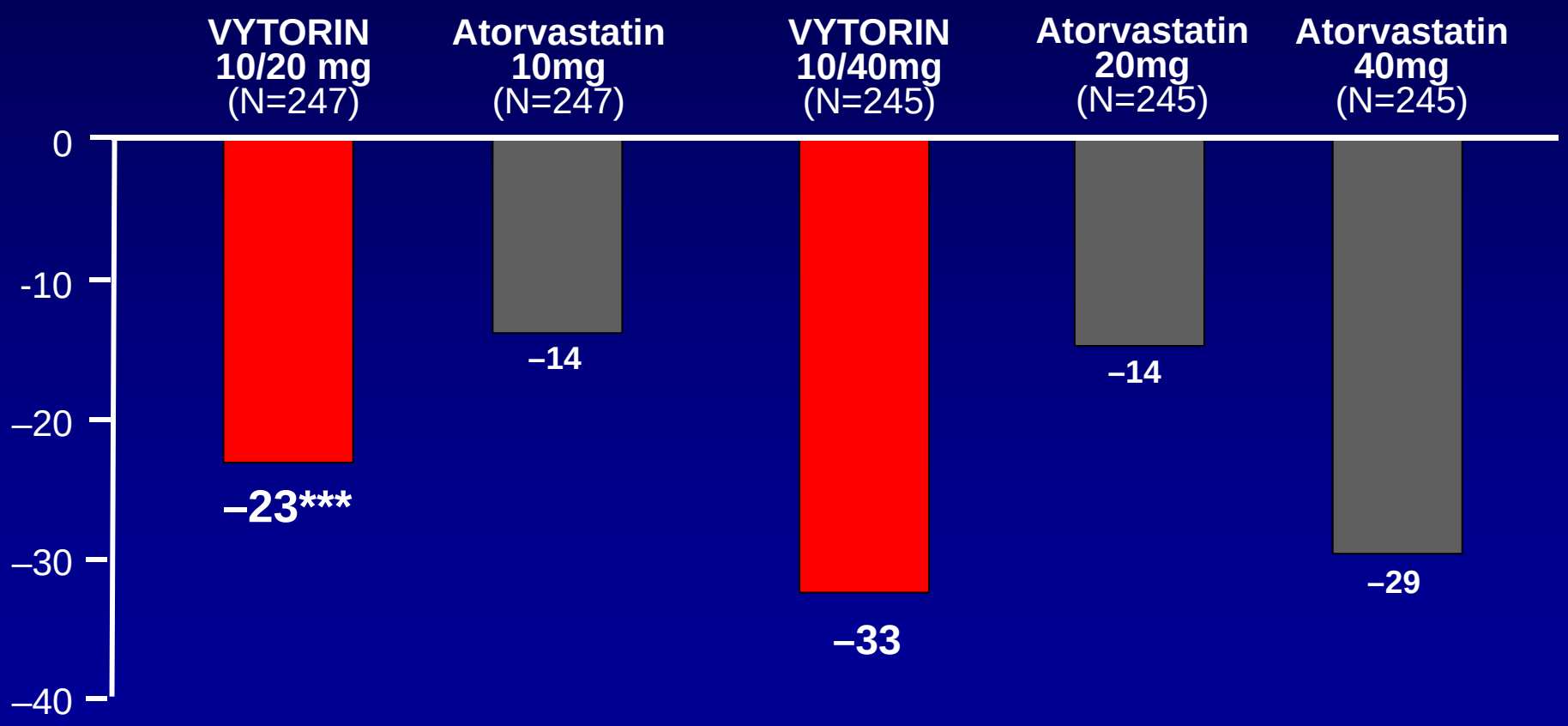
* p<0.001 vs. atorvastatin

Adapted from Goldberg RB et al *Mayo Clin Proc.* 2006;81(12):1579-1588.

VYTORIN™

Atorvastatin

hs-CRP Reductions: VYTORIN Superior to Atorvastatin at Usual Starting Dose



**p=0.02

Adapted from Goldberg RB et al *Mayo Clin Proc.* 2006;81(12):1579-1588.

Clinical benefit of combination therapy: Beyond LDL-C reduction

New Guideline for Apo B

2008 ADA & ACC Statement (Consensus statement from the ADA and the ACC foundation)

Table 1—*Suggested treatment goals in patients with CMR and lipoprotein abnormalities*

	Goals		
	LDL cholesterol (mg/dl)	Non-HDL cholesterol (mg/dl)	ApoB (mg/dl)
Highest-risk patients, including those with *1*) known CVD or 2) diabetes plus one or more additional major CVD risk factor	<70	<100	<80
High-risk patients, including those with *1*) no diabetes or known clinical CVD but two or more additional major CVD risk factors or 2) diabetes but no other major CVD risk factors	<100	<130	<90

Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.

DM

+

1개 이상 risk factor

혹은

CVD

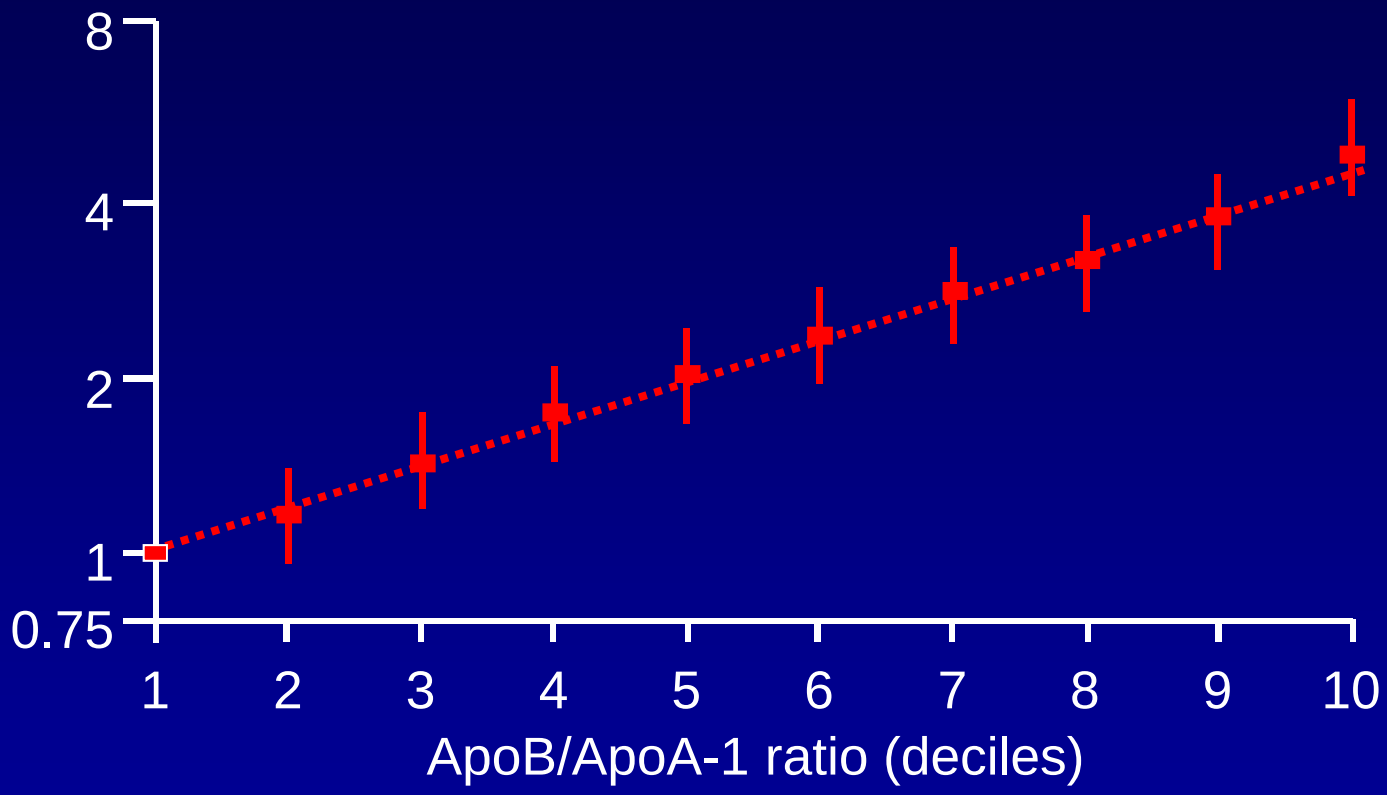
ApoB < 80 mg/dL

Brunzell et al. Diabetes Care 2008;31:811-822

Apolipoprotein B

- One apo B molecule/non-HDL particle
- Assesses potentially atherogenic particle number
- Helps to distinguish risk of CHD in patients with hypertriglyceridemia
- Highly correlated with non-HDL cholesterol
  - 0.95 when TG < 300 mg/dl
  - 0.80 when TG higher

INTERHEART: ApoB/ApoA-1 ratio—Graded relation to MI risk



Number of controls	1210	1206	1208	1207	1210	1209	1207	1208	1208	1209
Number of cases	435	496	610	720	790	893	1063	1196	1366	1757
Median	0.43	0.53	0.60	0.66	0.72	0.78	0.85	0.93	1.04	1.28

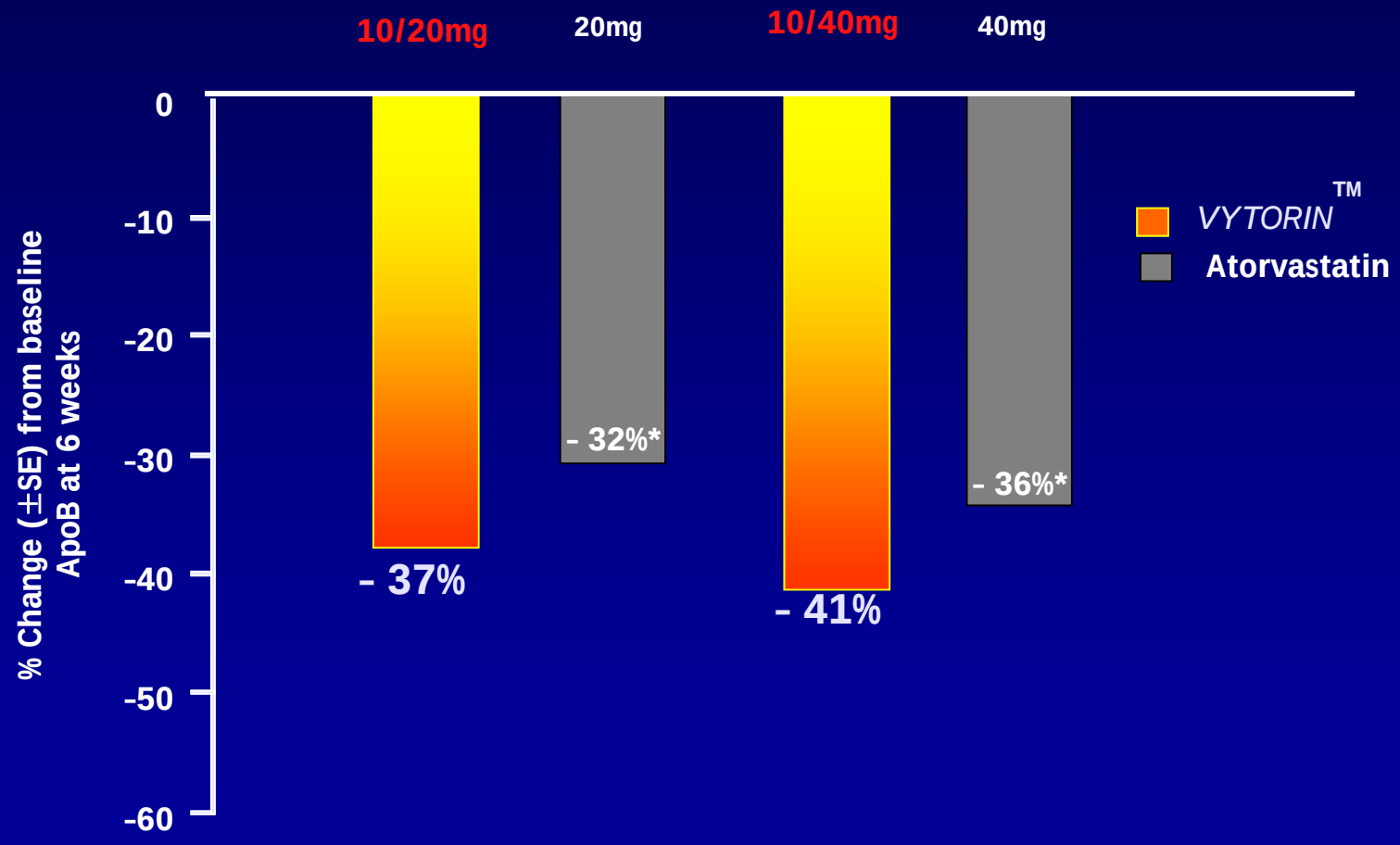
Note: odds ratio plotted on a doubling scale

Yusuf S et al. *Lancet*. 2004;364:937-52.

Powerful ApoB reduction at initial dose

VYTORIN : ApoB Reduction (%) Superior to Atorvastatin

The VYMET Study with Metabolic Syndrome patients



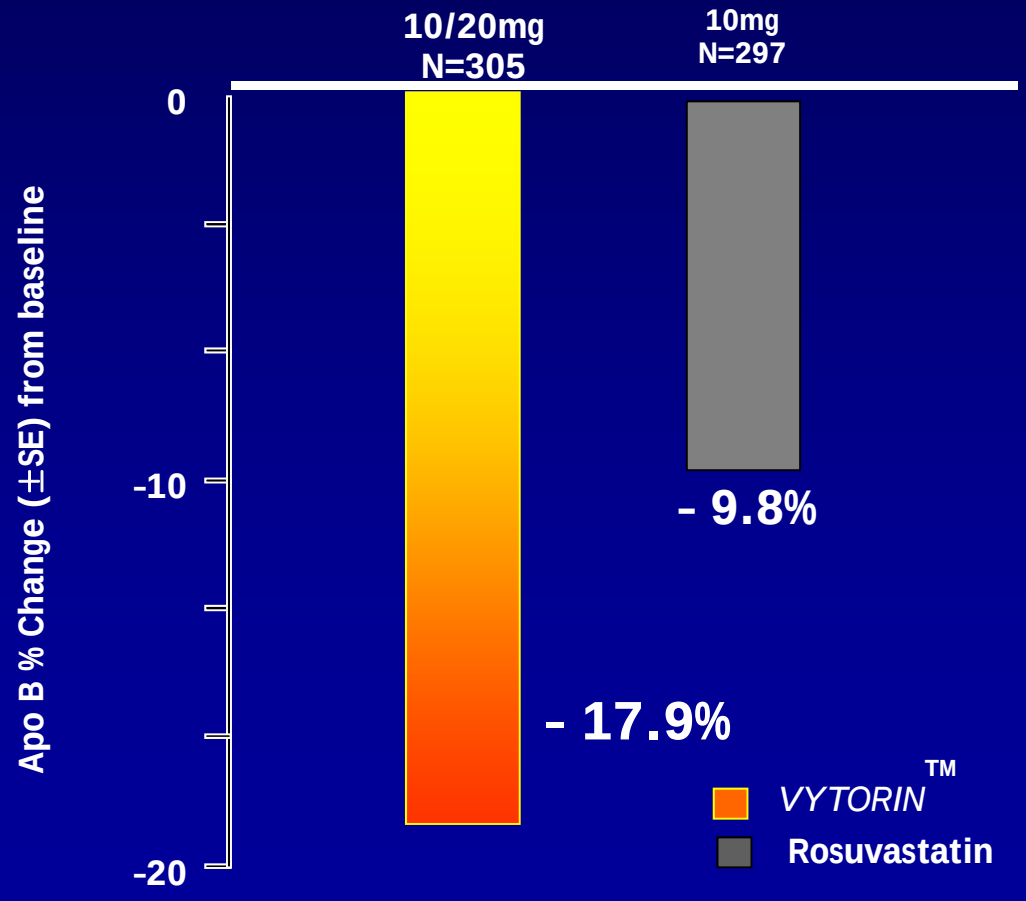
* p<0.001 vs. atorvastatin

Adapted from Robinson JG. *at al* Am J Cardiol 2009;103:1694-1702

Superior ApoB reduction at initial dose in DM

VYTORIN: strong efficacy in ApoB (100+48) reduction vs. rosuvastatin

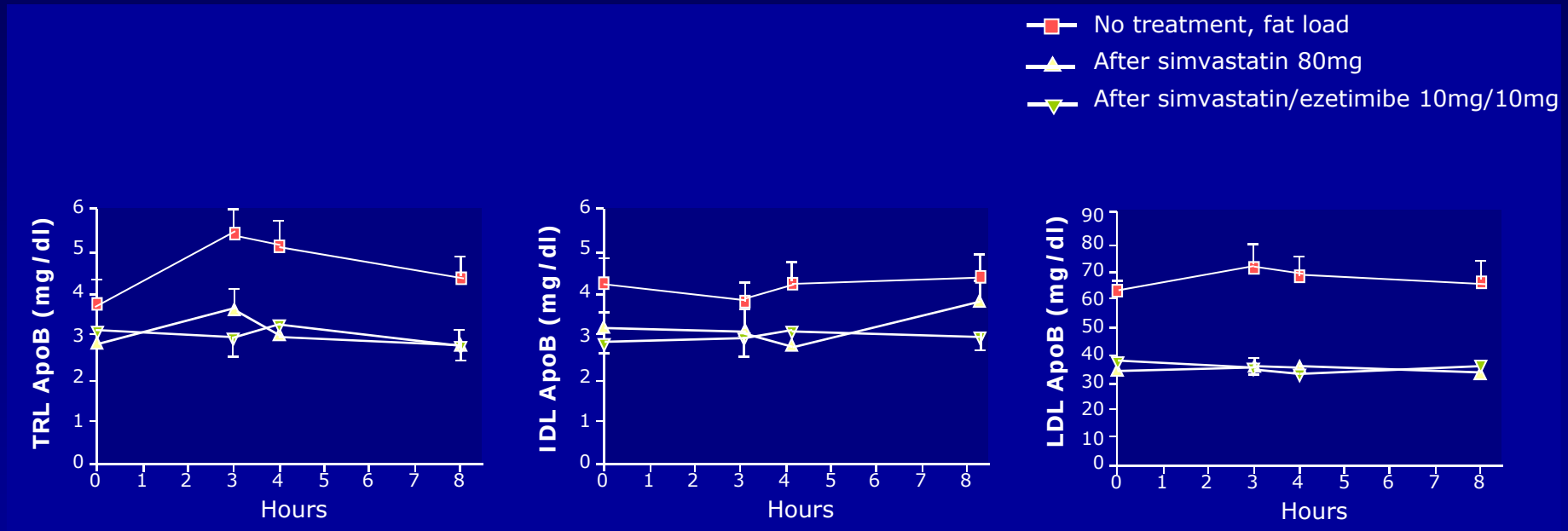
The INCROSS Study: *Apo B (100+48) reduction (%) from baseline (high risk patients including T2DM patients)*



* p<0.001 vs. rosuvastatin

Adapted from M. Farnier et al.

Effect of VYTORIN and/or simvastatin on postprandial lipoprotein composition in obese metabolic syndrome patients



Postprandial ApoB content in lipoprotein fractions.

Hajer. *Atherosclerosis*. 2008, doi:10.1016/j.atherosclerosis.2008.04.035

Newest Data

Study of Heart and Renal Protection (SHARP)

Colin Baigent, Martin Landray
the SHARP Investigators

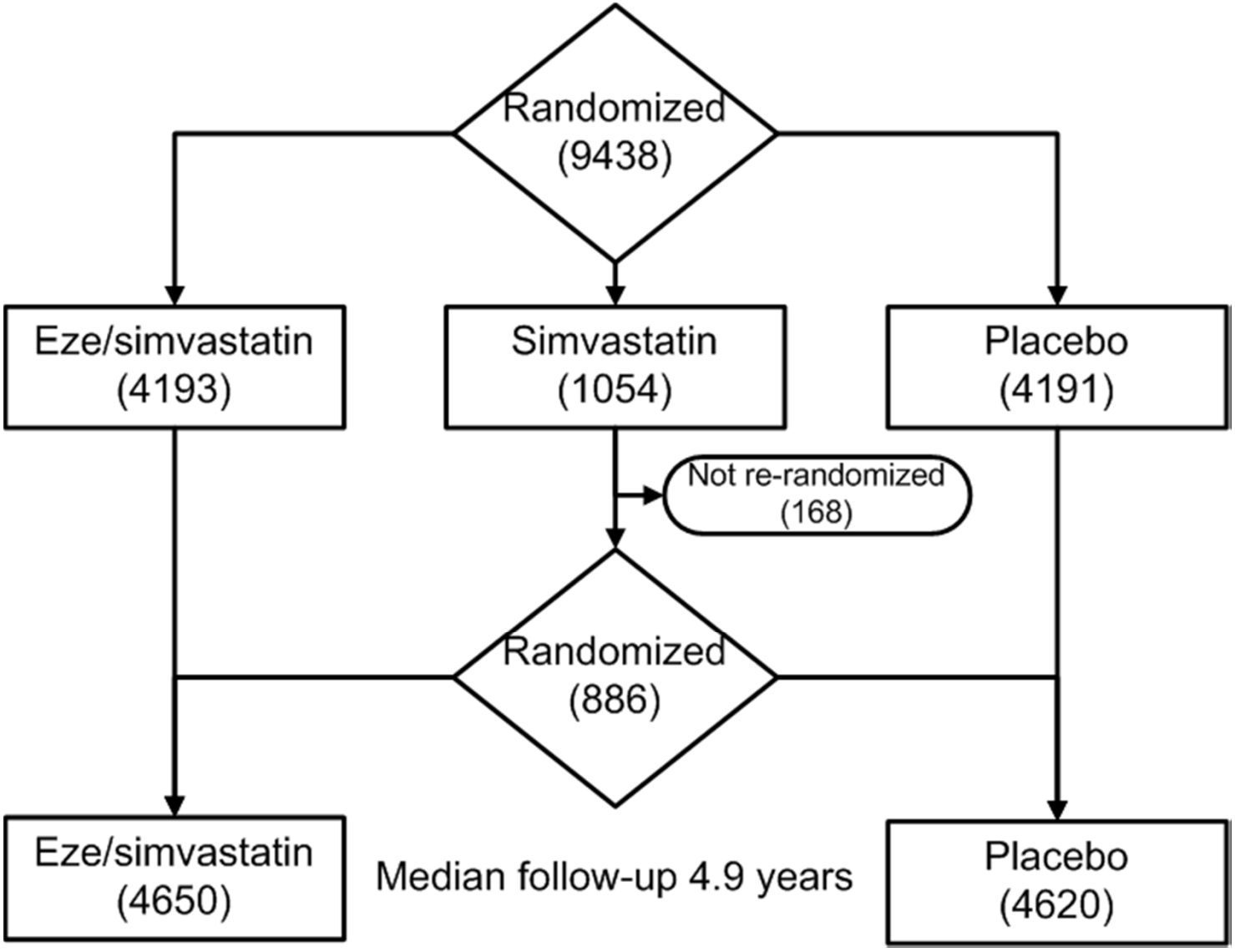
SHARP: Rationale

- Risk of vascular events is high among patients with chronic kidney disease
- Lack of clear association between cholesterol level and vascular disease risk
- Pattern of vascular disease is atypical, with a large proportion being non-atherosclerotic
- Previous trials of LDL-lowering therapy in chronic kidney disease are inconclusive

SHARP: Eligibility

- History of chronic kidney disease
  - not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 µmol/L)
    - Women: ≥1.5 mg/dL (130 µmol/L)
  - on dialysis: haemodialysis or peritoneal dialysis
- Age ≥40 years
- No history of myocardial infarction or coronary revascularization
- Uncertainty: LDL-lowering treatment not definitely indicated or contraindicated

SHARP: Assessment of LDL-lowering



SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Baseline characteristics

Characteristic	**Mean (SD) or %**
Age	62 (12)
Men	63%
Systolic BP (mm Hg)	139 (22)
Diastolic BP (mm Hg)	79 (13)
Body mass index	27 (6)
Current smoker	13%
Vascular disease	15%
Diabetes mellitus	23%
Non-dialysis patients only	**(n=6247)**
eGFR (ml/min/1.73m^2)	27 (13)
Albuminuria	80%

SHARP: Compliance and LDL-C reduction at study midpoint

	Eze /simv	Placebo
Compliant	66%	64%
Non-study statin	5%	8%
Any lipid-lowering	71%	8%

~2/3 compliance

LDL-C reduction of 32 mg/dL with 2/3 compliance, equivalent to 50 mg/dL with full compliance

SHARP: Baseline paper and Data Analysis Plan

Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease

SHARP Collaborative Group

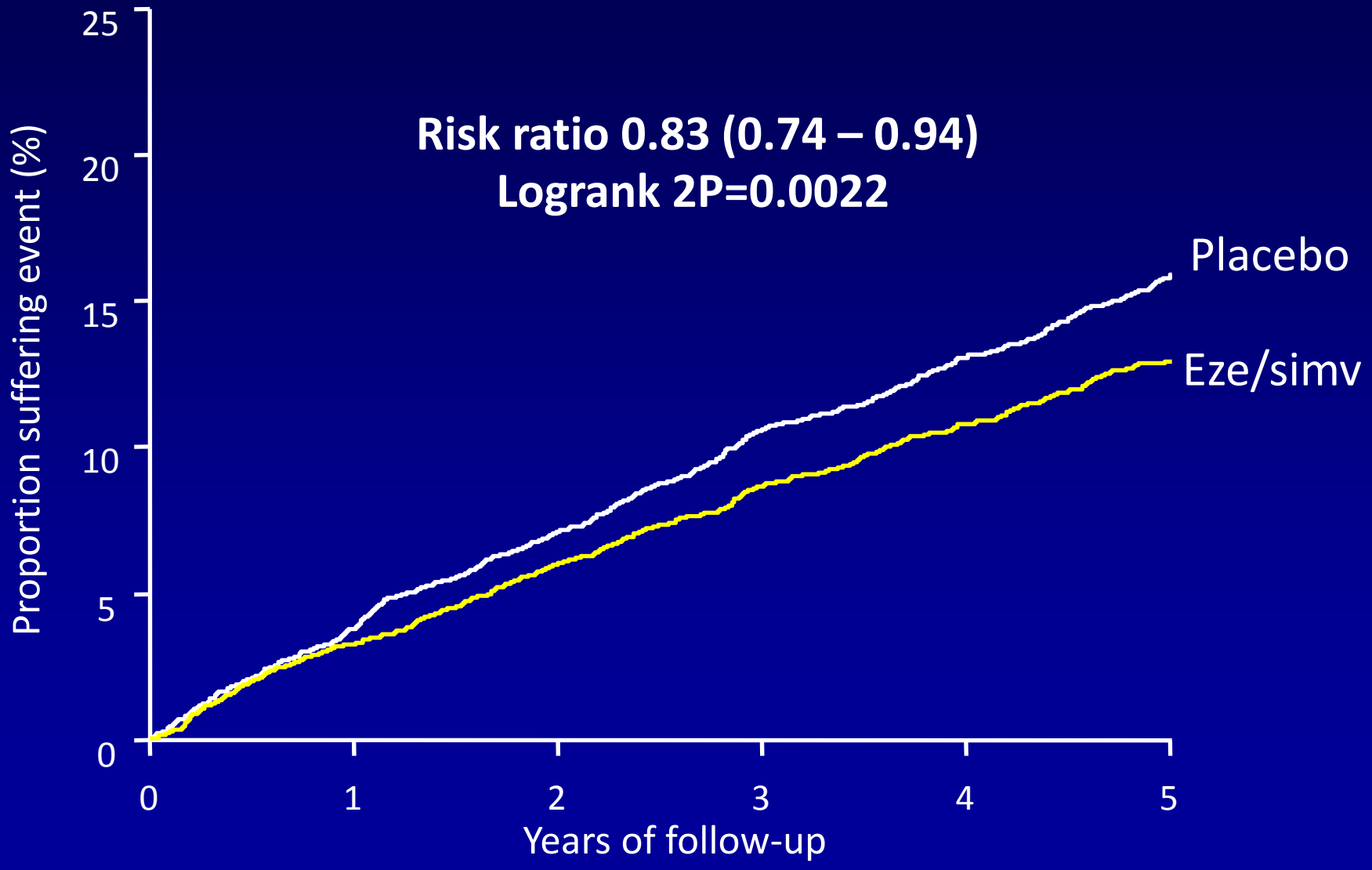
Am Heart J 2010;0:1-10.e10

- 1-year LDL-C reduction of 30 mg/dL with simvastatin 20 mg alone and of 43 mg/dL with eze/simv 10/20mg
- Confirmation of safety of ezetimibe when added to simvastatin (1-year results)
- Revised data analysis plan published as an appendix before unblinding of main results

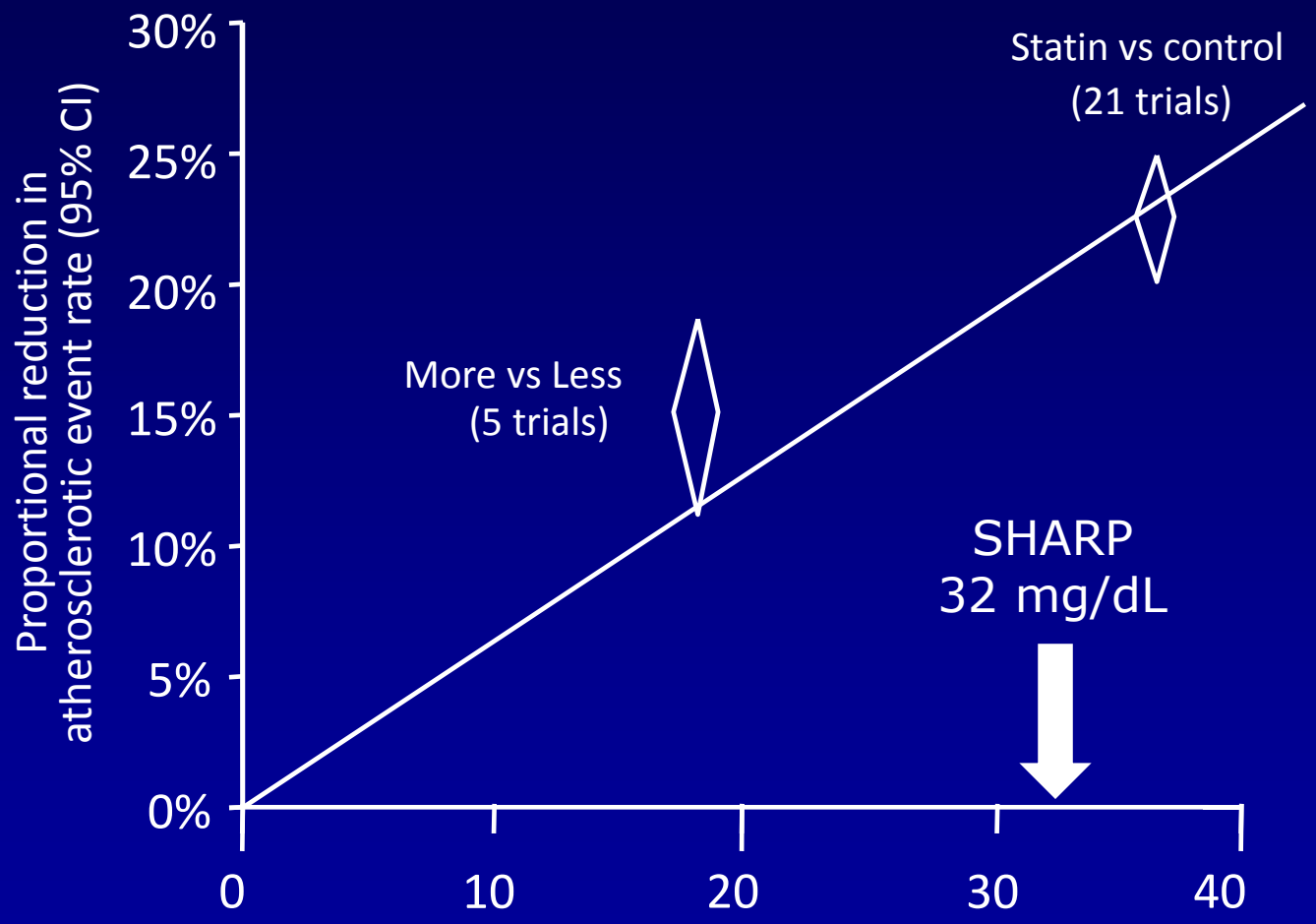
SHARP: Main outcomes

- **Key outcome**
  - Major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke, or any revascularization)
- **Subsidiary outcomes**
  - Major vascular events (cardiac death, MI, any stroke, or any revascularization)
  - Components of major atherosclerotic events
- **Main renal outcome**
  - End stage renal disease (dialysis or transplant)

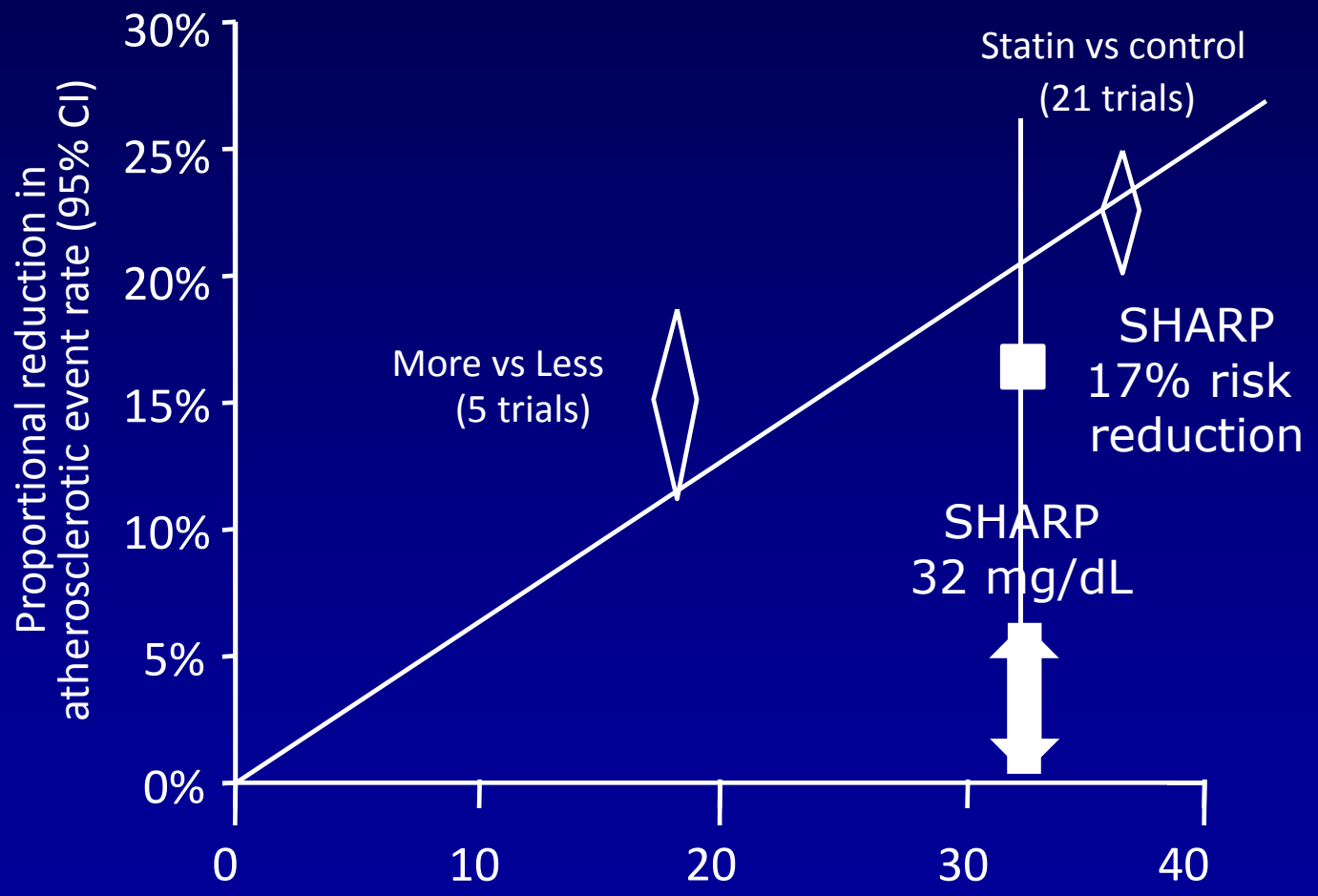
SHARP: Major Atherosclerotic Events



CTT: Effects on Major Atherosclerotic Events

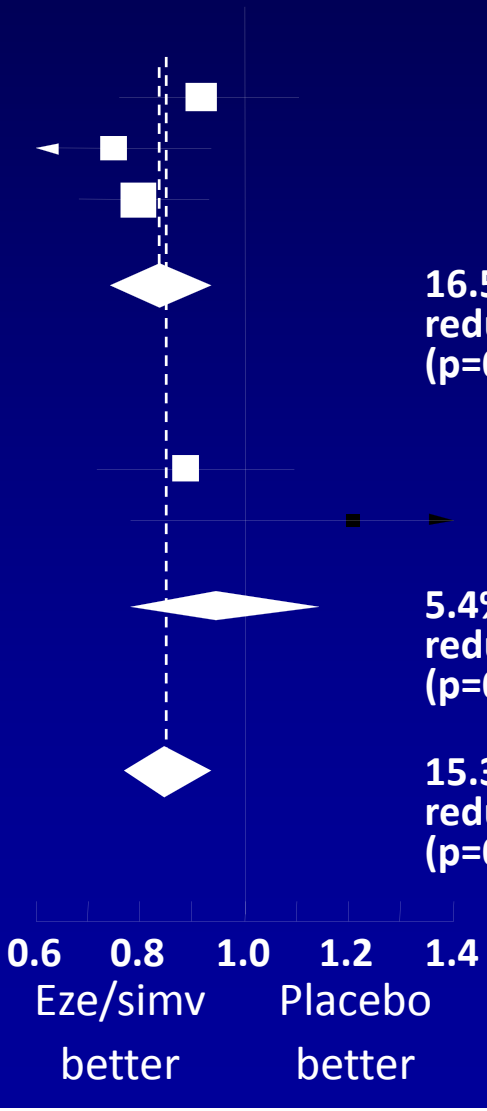


CTT: Effects on Major Atherosclerotic Events



SHARP: Major Vascular Events

Event	Eze/simv (n=4650)		Placebo (n=4620)		Risk ratio & 95% CI
Major coronary event	213	(4.6%)	230	(5.0%)	
Non-haemorrhagic stroke	131	(2.8%)	174	(3.8%)	
Any revascularization	284	(6.1%)	352	(7.6%)	
Major atherosclerotic event	**526**	**(11.3%)**	**619**	**(13.4%)**	**16.5% SE 5.4 reduction (p=0.0022)**
Other cardiac death	162	(3.5%)	182	(3.9%)	
Haemorrhaghic stroke	45	(1.0%)	37	(0.8%)	
Other major vascular events	**207**	**(4.5%)**	**218**	**(4.7%)**	**5.4% SE 9.4 reduction (p=0.57)**
Major vascular event	**701**	**(15.1%)**	**814**	**(17.6%)**	**15.3% SE 4.7 reduction (p=0.0012)**



SHARP: Effects in subgroups

Among 8384 patients originally randomized to eze/simv vs placebo, major vascular events risk ratio = 0.84 (95% CI 0.75 – 0.93; p=0.0010)

Similar reductions in major atherosclerotic events in all subgroups studied (including non-dialysis and dialysis patients)

SHARP: Safety

	Eze/simv (n=4650)	Placebo (n=4620)
Myopathy		
CK >10 x but ≤40 x ULN	17 (0.4%)	16 (0.3%)
CK >40 x ULN	4 (0.1%)	5 (0.1%)
Hepatitis	21 (0.5%)	18 (0.4%)
Persistently elevated ALT/AST >3x ULN	30 (0.6%)	26 (0.6%)
Complications of gallstones	85 (1.8%)	76 (1.6%)
Other hospitalization for gallstones	21 (0.5%)	30 (0.6%)
Pancreatitis without gallstones	12 (0.3%)	17 (0.4%)

SHARP: Conclusions

No increase in risk of myopathy, liver and biliary disorders, cancer, or nonvascular mortality

No substantial effect on kidney disease progression

Two-thirds compliance with eze/simv reduced the risk of major atherosclerotic events by 17% (consistent with meta-analysis of previous statin trials)

Similar proportional reductions in all subgroups (including among dialysis and non-dialysis patients)

Full compliance would reduce the risk of major atherosclerotic events by one quarter, avoiding 30–40 events per 1000 treated for 5 years

CONCLUSION

- More aggressive treatment guideline for high risk patients
- High statin dose use is limited due to safety concerns
- VYTORIN is superior in lowering LDL-C (Vs. Atova & Cresto) at initial dose
- VYTORIN is superior in reducing both atherogenic cholesterols: apoB100 and especially apoB48 (Vs. Atova & Cresto) at initial dose
- VYTORIN LDL-C efficacy proved CV outcomes with long-term safety in high risk patients

Thank You!

Back Up

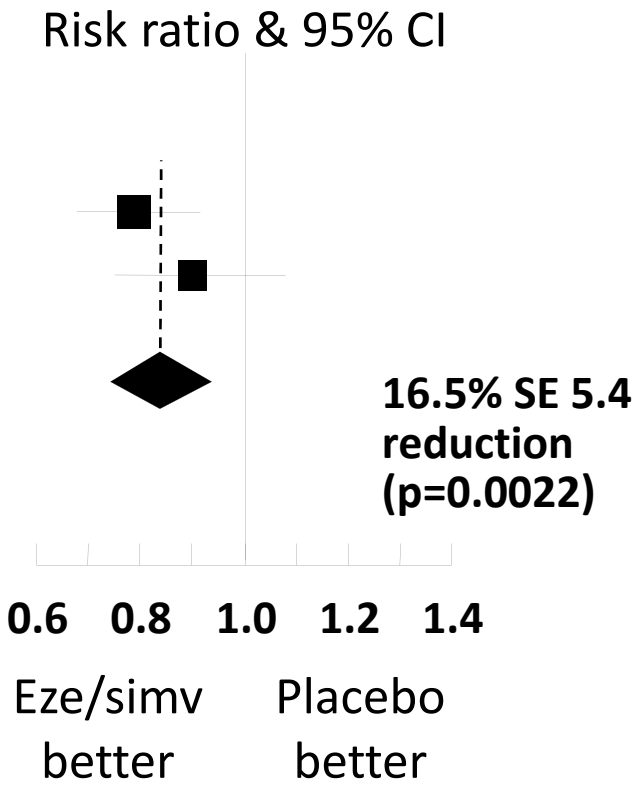
SHARP: Effects in subgroups

- Among 8384 patients originally randomized to eze/simv vs placebo, major vascular events risk ratio = 0.84 (95% CI 0.75 – 0.93; p=0.0010)
- Similar reductions in major atherosclerotic events in all subgroups studied (including non-dialysis and dialysis patients)

SHARP: Major Atherosclerotic Events by renal status at randomization

	Eze/simv (n=4650)	Placebo (n=4620)
Non-dialysis (n=6247)	296 (9.5%)	373 (11.9%)
Dialysis (n=3023)	230 (15.0%)	246 (16.5%)
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**

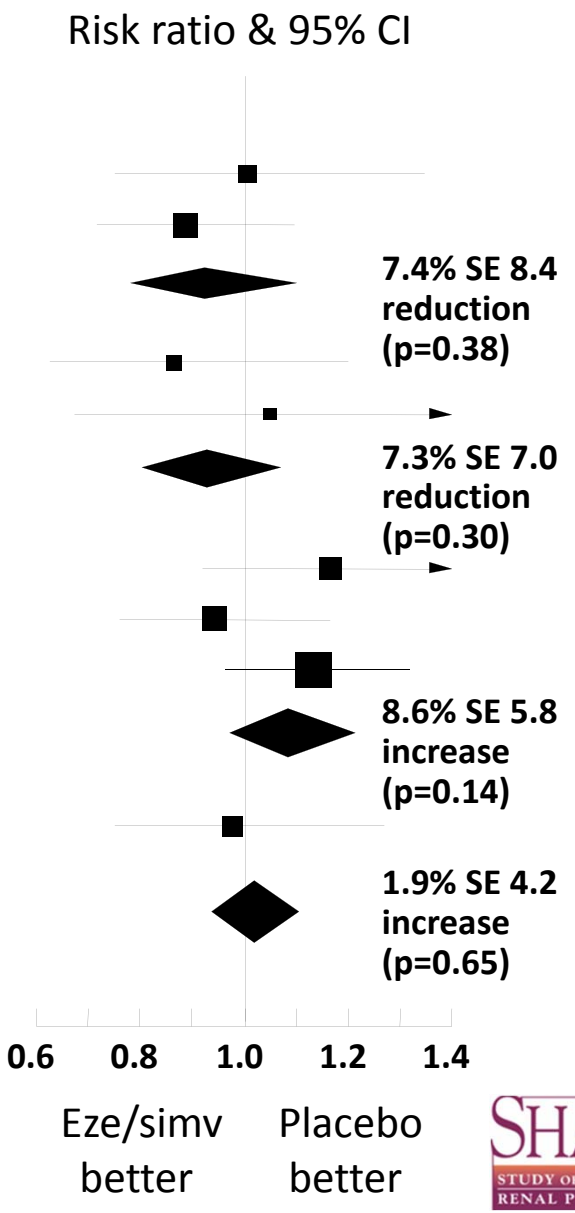
No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)



SHARP STUDY OF HEART AND RENAL PROTECTION

SHARP: Cause-specific mortality

Event	Eze/simv (n=4650)		Placebo (n=4620)	
Coronary	91	(2.0%)	90	(1.9%)
Other cardiac	162	(3.5%)	182	(3.9%)
Subtotal: Any cardiac	**253**	**(5.4%)**	**272**	**(5.9%)**
Stroke	68	(1.5%)	78	(1.7%)
Other vascular	40	(0.9%)	38	(0.8%)
Subtotal: Any vascular	**361**	**(7.8%)**	**388**	**(8.4%)**
Cancer	150	(3.2%)	128	(2.8%)
Renal	164	(3.5%)	173	(3.7%)
Other non-vascular	354	(7.6%)	311	(6.7%)
Subtotal: Any non-vascular	**668**	**(14.4%)**	**612**	**(13.2%)**
Unknown cause	113	(2.4%)	115	(2.5%)
Total: Any death	**1142**	**(24.6%)**	**1115**	**(24.1%)**



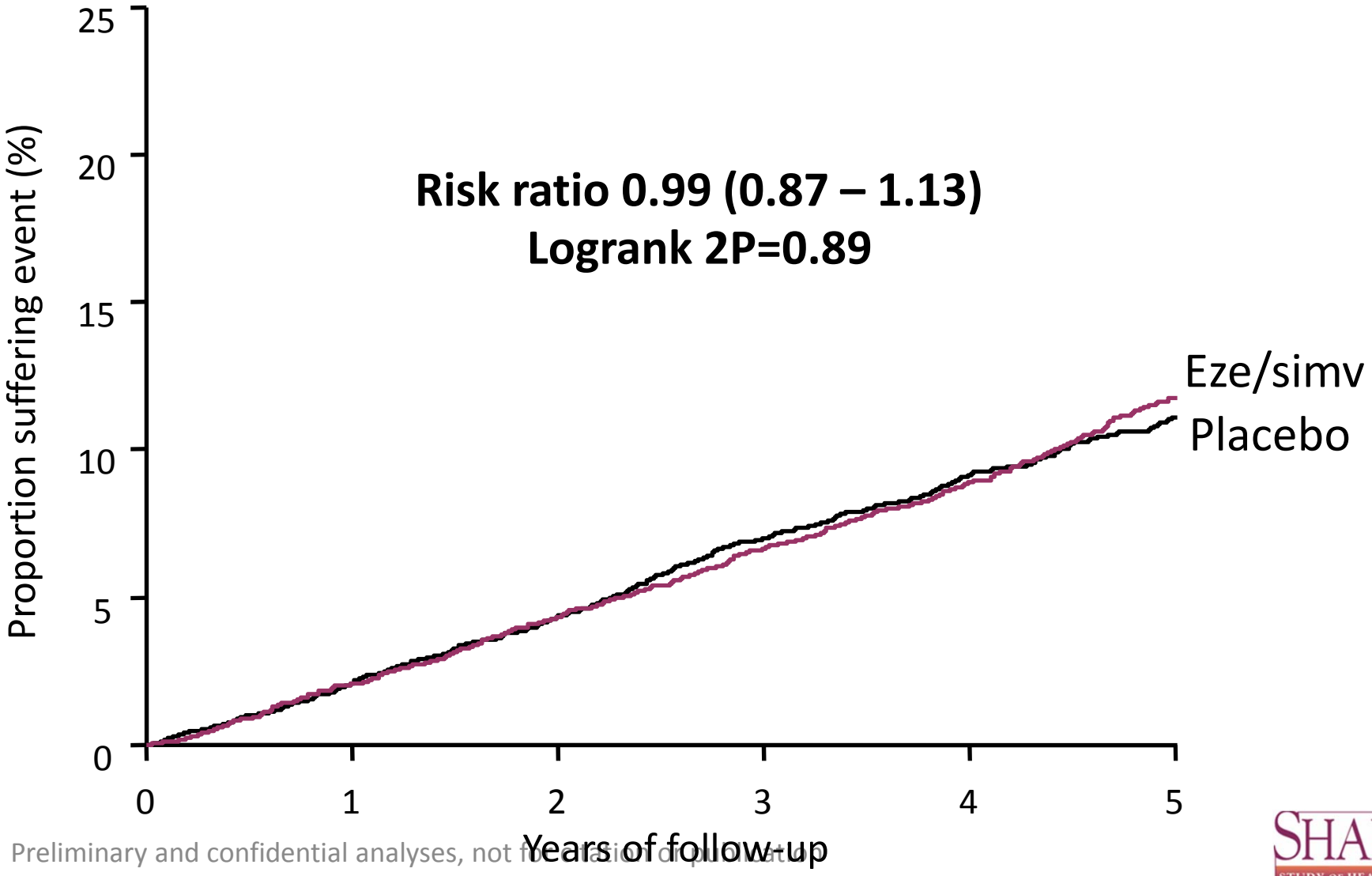
SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Renal outcomes

Event	Eze/simv (n=3117)	Placebo (n=3130)	Risk ratio & 95% CI
Main renal outcome			
End-stage renal disease (ESRD)	1057 (33.9%)	1084 (34.6%)	0.97 (0.89-1.05)
Tertiary renal outcomes			
ESRD or death	1477 (47.4%)	1513 (48.3%)	0.97 (0.90-1.04)
ESRD or 2 x creatinine	1190 (38.2%)	1257 (40.2%)	0.94 (0.86-1.01)

SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Cancer incidence



SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Cancer incidence by site

	Eze/simv (n=4650)	Placebo (n=4620)
Oropharynx/oesophagus	14	16
Stomach	11	14
Bowel	53	35
Pancreas	9	10
Hepatobiliary	8	4
Lung	42	35
Other respiratory	3	4
Skin cancer	136	153
Breast	29	21
Prostate	39	52
Kidney	31	23
Bladder & urinary tract	26	32
Genital	12	14
Haematological	26	27
Other known site	9	12
Unspecified site	13	7
Any incident cancer	**438 (9.4%)**	**439 (9.5%)**

No significant differences

SHARP
STUDY OF HEART AND RENAL PROTECTION