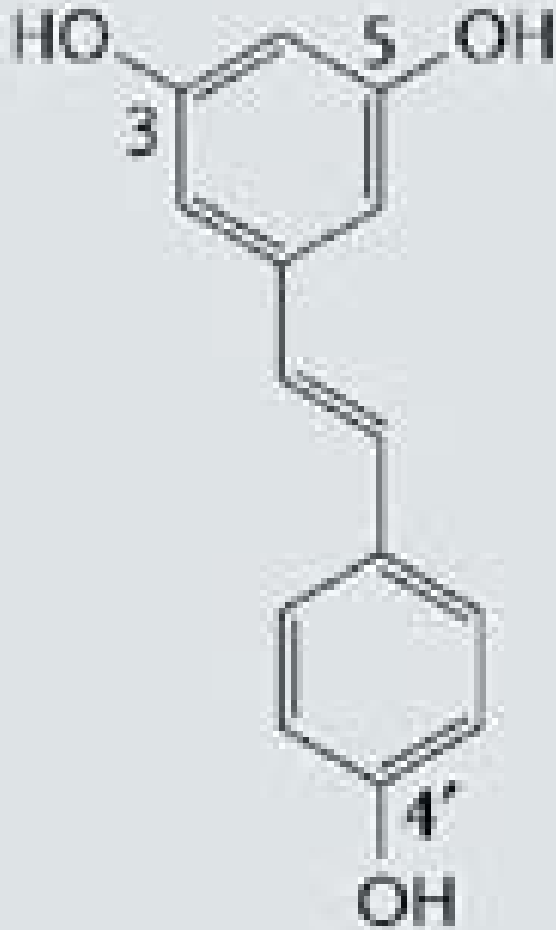


**trans-Resveratrol**



**trans-Resveratrol**

## RESVERATROL

(Wine and grape extracts)

- lowers platelet aggregation
- promotes vasorelaxation
- suppress atherosclerosis
- reduce lipid peroxidation
- improve TG and LDL/HDL
- mice get fat but live longer

Google Search

## Pfizer Stops All Torcetrapib Clinical Trials



New York ([eCanadaNow](#)) - Pfizer Inc said that in the interests of patient safety it is stopping all torcetrapib clinical trials and that it has informed the Food and Drug

Administration. The Company is in the process of notifying all clinical investigators in the program as well as other regulatory authorities.

# Case report 1

71 yr old male, retired

+smoker; +family history; +hypertension (unRx'd)

MI 1989; stable angina

Multiple drug intolerance: AV, SV, PV, lipidil, eze

OE: BP 134/76

LP: TC 6.5; LDL-C 3.9; HDL-C 1.5; TG 2.5; CK 203

Rx: Lescol XL 80 mg; cardiazem; ASA; hydralazine

LP: TC 4.3; LDL-C 2.5; HDL-C 1.2; TG 1.3; CK 210

# Case report 2

77 yr old male, retired

MI 1989; CAD; PTCA > RCA; stable angina

Multiple drug intolerances: AV, RV, niacin, lipidil, eze

OE: BP 144/76

LP: TC 7.9; LDL-C 5.4; HDL-C 1.5; TG 1.0; CK 152

Rx: Lescol XL 80 mg; ASA; plavix; norvasc; atenolol

LP: TC 5.5; LDL-C 3.6; HDL-C 1.4; TG 1.4; CK 132

# Case report 3

53 yr old male, sales

+FH; +carotid doppler shows early atherosclerosis

Multiple drug intolerances: AV, RV, SV, lipidil

OE: BP 139/84

LP: TC 6.5; LDL-C 4.2; HDL-C 1.3; TG 2.4; CK 334

Rx: Lescol XL 80 mg; ASA; ezetimibe 10 mg

LP: TC 3.1; LDL-C 1.4; HDL-C 1.2; TG 1.3; CK 260

# The 2006 Lipid Guidelines

## Canadian Cardiovascular Society position statement – Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease

R McPherson, J Frohlich, G Fodor, J Genest. Canadian Cardiovascular Society position statement – Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol* 2006;22(11):913-927.

**ACKNOWLEDGEMENTS:** Primary review panel members: Steven Grover, Rafik Habib, Stewart Harris, Heather Arthur. Secondary review panel members: Peter Bogaty, Dominic Ng, André Carpentier, Robert A Hegele, Ehud Ur, John Mancini, Glen J Pearson, Milan Gupta.

# The 2006 Lipid Guidelines

## HIGHLIGHTS OF THE 2006 LIPID GUIDELINES

### Process

- Collaboration with the Canadian Cardiovascular Society;
- Primary and secondary review panels;
- Adherence to the Appraisal of Guidelines Research and Evaluation principles of guideline formation; and
- Grading of evidence for each recommendation.

### Content

- LDL-C treatment target of lower than 2.0 mmol/L for high-risk patients;
- Intervention point for initiation of lipid-lowering therapy in most low-risk individuals changed to an LDL-C of 5.0 mmol/L or a total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C) ratio of 6.0; and
- Recommendations regarding potential additional investigations for the further evaluation of CAD risk in subjects in the moderate-risk category.

# The 2006 Lipid Guidelines

## Screening (Class 2a, level C)

- Men > 40 y; Post-menopausal women (>50 y)
- Diabetes, Hypertension, MetS (visc obese)
- Family of premature CAD
- Dyspnea, erectile dysfunction, renal disease, SLE or atherosclerosis.

# The 2006 Lipid Guidelines

**TABLE 4**  
**Risk categories and treatment recommendations**

<b>Risk level</b>	<b>10-year CAD risk</b>	<b>Recommendations</b>	<b>Grade, level of evidence</b>
High*	≥20%	<i>Treatment targets</i> <sup>†</sup> : Primary: LDL-C <2.0 mmol/L Secondary: TC/HDL-C <4.0	Class I, level A Class IIa, level A
Moderate <sup>‡§</sup>	10% – 19%	<i>Treat when</i> : LDL-C ≥3.5 mmol/L or TC/HDL-C ≥5.0	Class I, level A Class I, level A
Low <sup>‡§</sup>	<10%	<i>Treat when</i> : LDL-C ≥5.0 mmol/L or TC/HDL-C ≥6.0	Class IIa, level A Class IIa, level A

# The 2006 Lipid Guidelines

## ADDITIONAL INVESTIGATIONS OF POTENTIAL USE IN RISK ASSESSMENT

For patients with a low FRS (10-year risk less than 10%), no indicators of possible subclinical atherosclerosis and no family history of early CAD, additional investigations are not usually indicated. Individuals in the intermediate-risk category (FRS between 10% and 20%) may be moved to a higher or lower risk category based on additional investigations. Investigations of possible clinical use include:

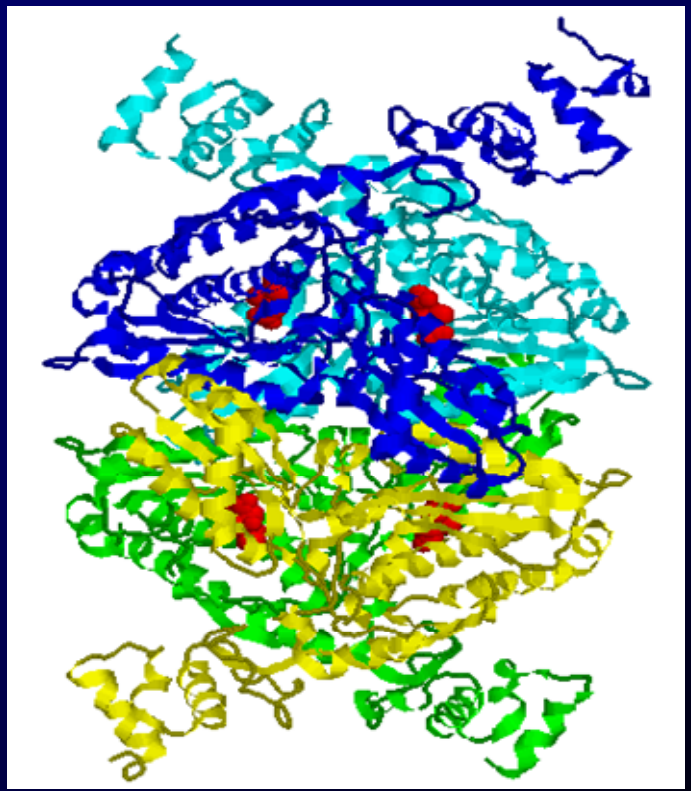
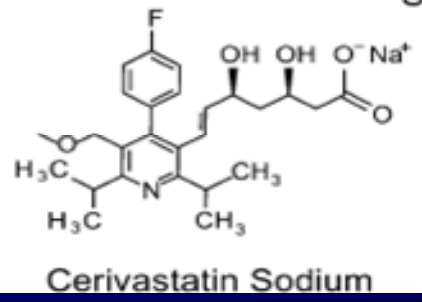
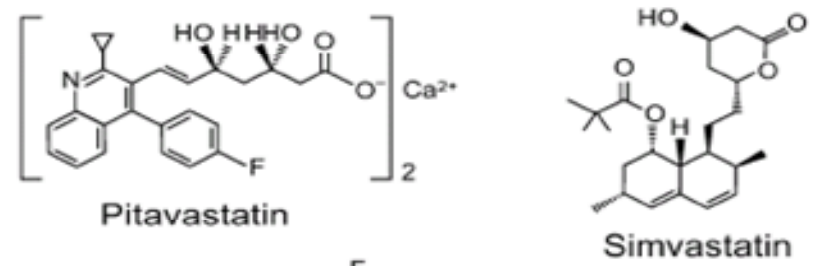
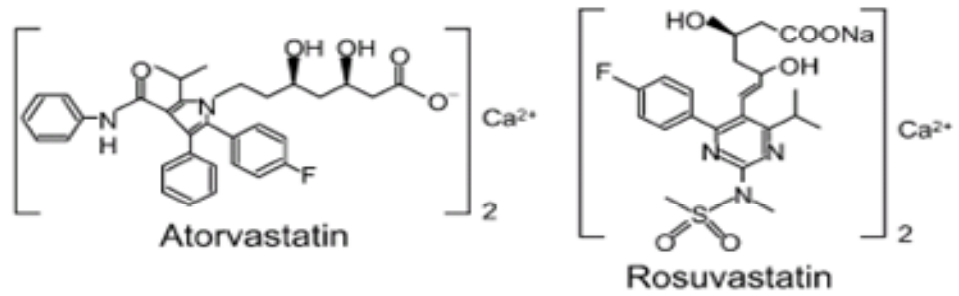
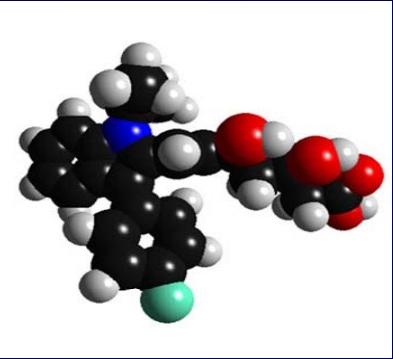
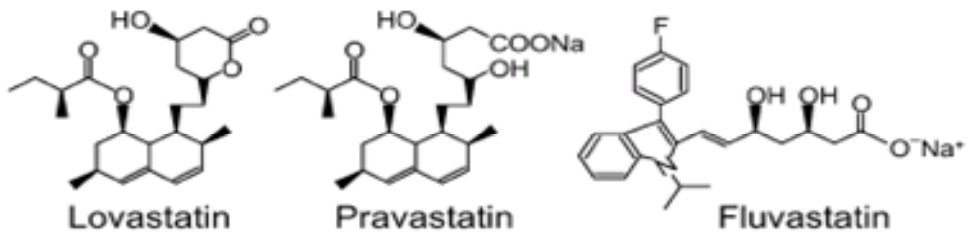
- laboratory measurements such as apo B, hsCRP, Lp(a) and, for individuals with elevated plasma glucose, glycated hemoglobin (HbA1c);
- assessment of exercise capacity (metabolic equivalent [MET] level achieved) by graded exercise stress testing (61-64); and
- noninvasive assessment of atherosclerosis such as determination of ankle-brachial index (ABI) (65) and carotid imaging (66,67).

# The 2006 Lipid Guidelines

Generic name	Trade name	Recommended dose range
<b>Statins</b>		
Atorvastatin	Lipitor (Pfizer Canada Inc)	10 mg – 80 mg
Fluvastatin	Lescol (Novartis Pharmaceuticals Canada Inc)	20 mg – 80 mg
Lovastatin	Mevacor (Merck Frosst Canada)	20 mg – 80 mg
Pravastatin	Pravachol (Bristol-Myers Squibb, Canada)	10 mg – 40 mg
Rosuvastatin	Crestor (AstraZeneca Canada)	5 mg – 40 mg
Simvastatin	Zocor (Merck Frosst Canada)	10 mg – 80 mg
<b>Bile acid and/or cholesterol absorption inhibitors</b>		
Cholestyramine	Generic	2 g – 24 g
Colestipol	Colestid (Pfizer Canada Inc)	5 g – 30 g
Ezetimibe	Ezetrol (Merck Frosst/Schering Pharmaceuticals Canada)	10 mg
<b>Fibrates*</b>		
Bezafibrate	Bezalip (Hoffman-La Roche Limited, Canada)	400 mg
Fenofibrate	Lipidil Micro/Lipidil Supra/Lipidil EZ (Fournier Pharma Inc, Canada)	100 mg, 145 mg, 160 mg, 200 mg
Gemfibrozil	Lopid (Pfizer Canada Inc)	600 mg – 1200 mg
<b>Niacins</b>		
Nicotinic acid	Generic crystalline niacin	1 g – 3 g
	Niaspan (Oryx Pharmaceuticals Inc, Canada)	0.5 g – 2 g

*\*Fibrates should be generally be reserved if triglyceride levels are greater than 10 mmol/L despite lifestyle changes; follow creatinine levels*

# Statin structures

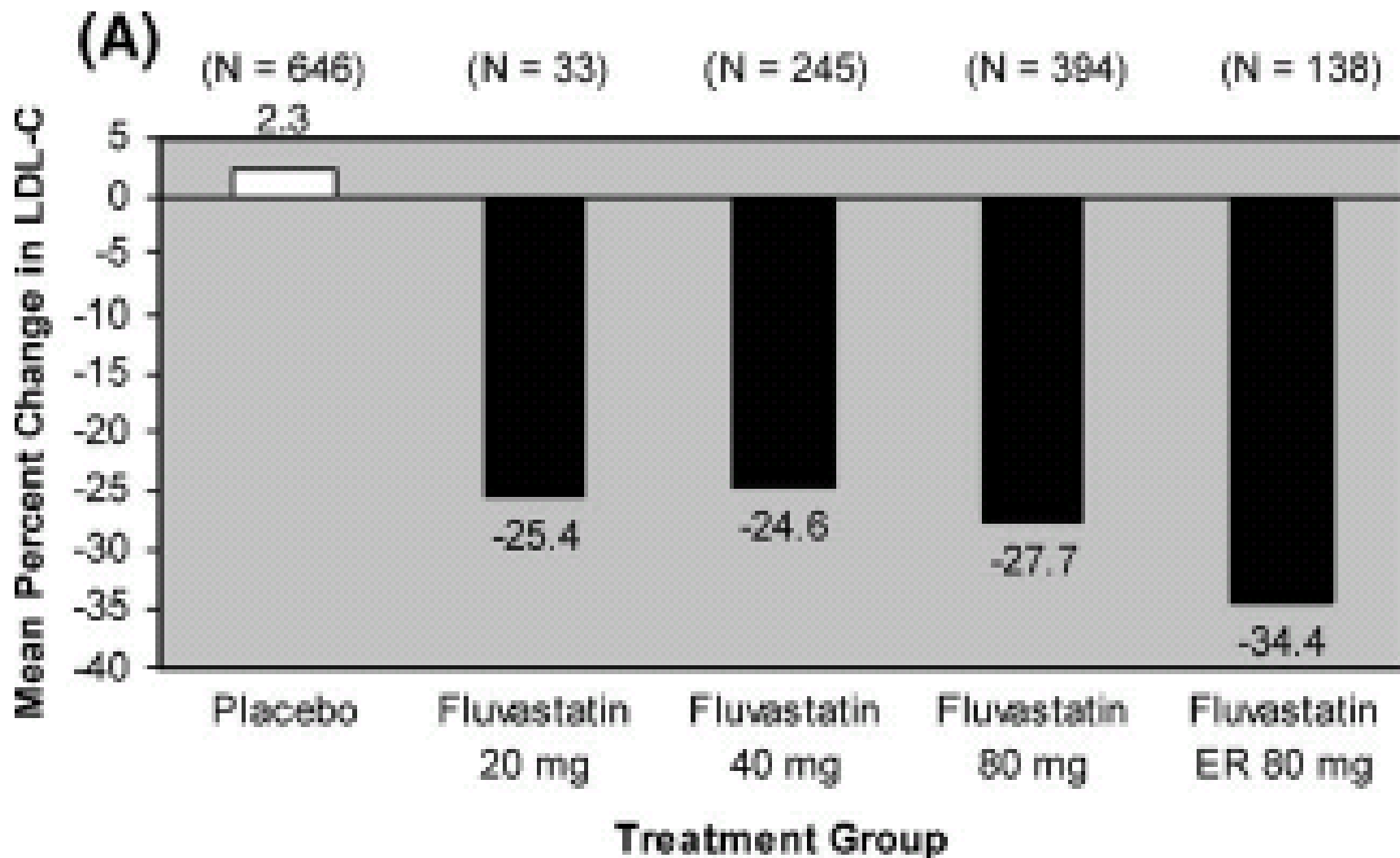


# Statin properties

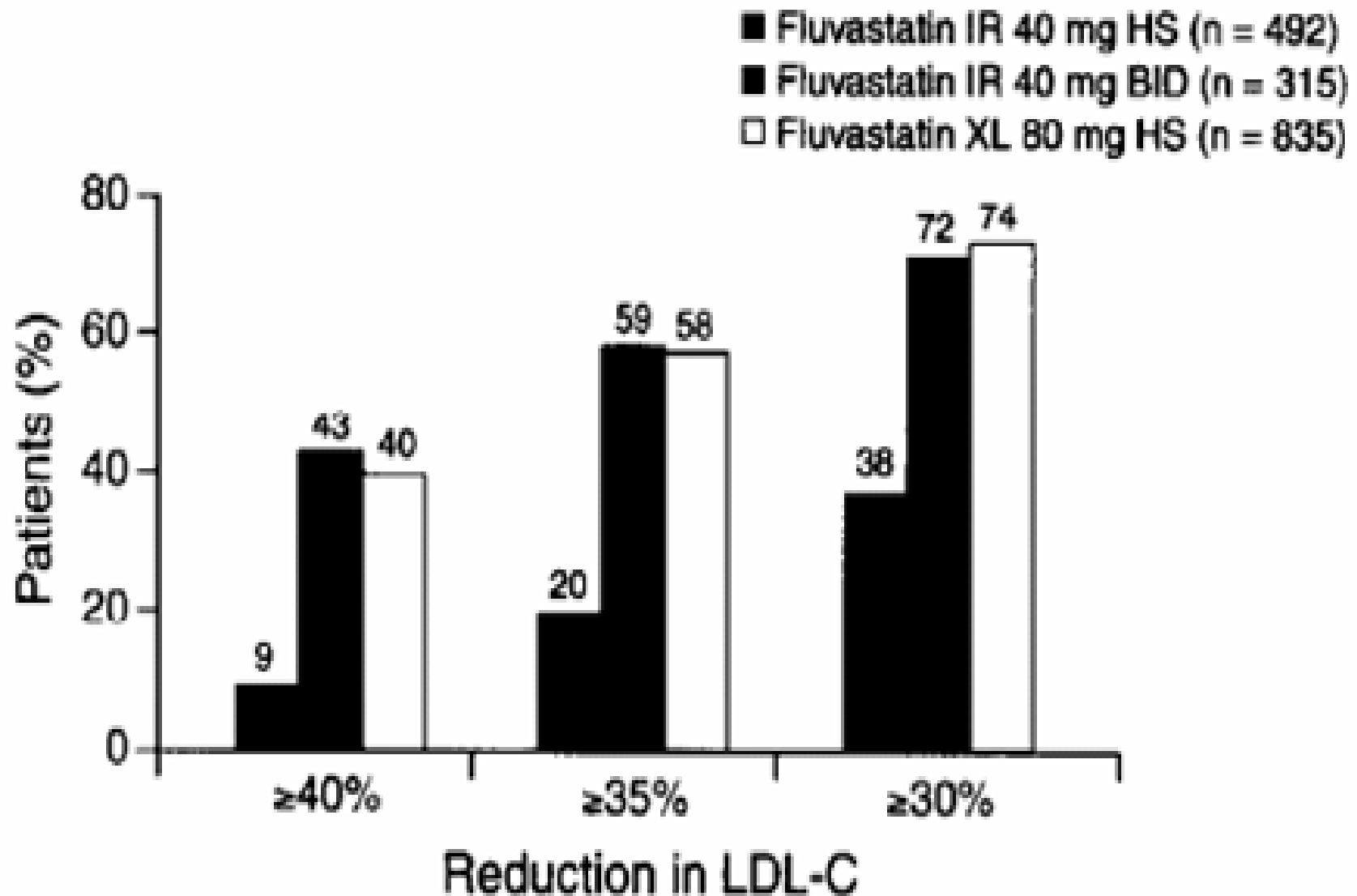
**Table 1** Biochemical and pharmacological characteristics of the statins

<i>Drug</i>	<i>Generation</i>	<i>Origin</i>	<i>Administered form</i>	<i>Solubility</i>	<i>Principally metabolised by CYP3A4</i>	<i>Cytochrome(s) involved in metabolism</i>	<i>Glucuronidation involved in metabolism</i>	<i>Half-life (h)</i>
Atorvastatin	3rd	Synthetic	Active	Lipophilic	Yes	3A4	Yes (acid form)	15–30
Cerivastatin	3rd	Synthetic	Active	Lipophilic	Yes	3A4, 2C8	Yes (acid form)	2–3
Fluvastatin	3rd	Synthetic	Active	Lipophilic	No	2C9	Unknown	0.5–2.3
Lovastatin	1st	Fungal	Pro-drug	Lipophilic	Yes	3A4	Yes (acid form)	2–3
Pitavastatin	3rd	Synthetic	Active	Lipophilic	No	2C9 (minor)	Yes	11–18
Pravastatin	2nd	Fungal	Active	Hydrophilic	No	None	Yes	1.3–2.8
Rosuvastatin	3rd	Synthetic	Active	Hydrophilic	No	2C9/2C19 (minor)	Yes (acid form)	20
Simvastatin	1st	Semisynthetic	Pro-drug	Lipophilic	Yes	3A4	Yes (acid form)	2–3

# Fluvastatin LDL lowering



# Fluvastatin LDL lowering



# Statin end point studies

## 2° prevention

## statin

4S	simva
CARE	prava
LIPID	prava
MIRACL	atorva
AVERT	atorva
LCAS	fluva
LIPS	fluva
HPS	simva
PROVEIT	atorva
TNT	atorva

## 1° prevention

## statin

WOSCOPS	prava
AFCAPS	lova
CARDS	atorva
ASCOT	atorva

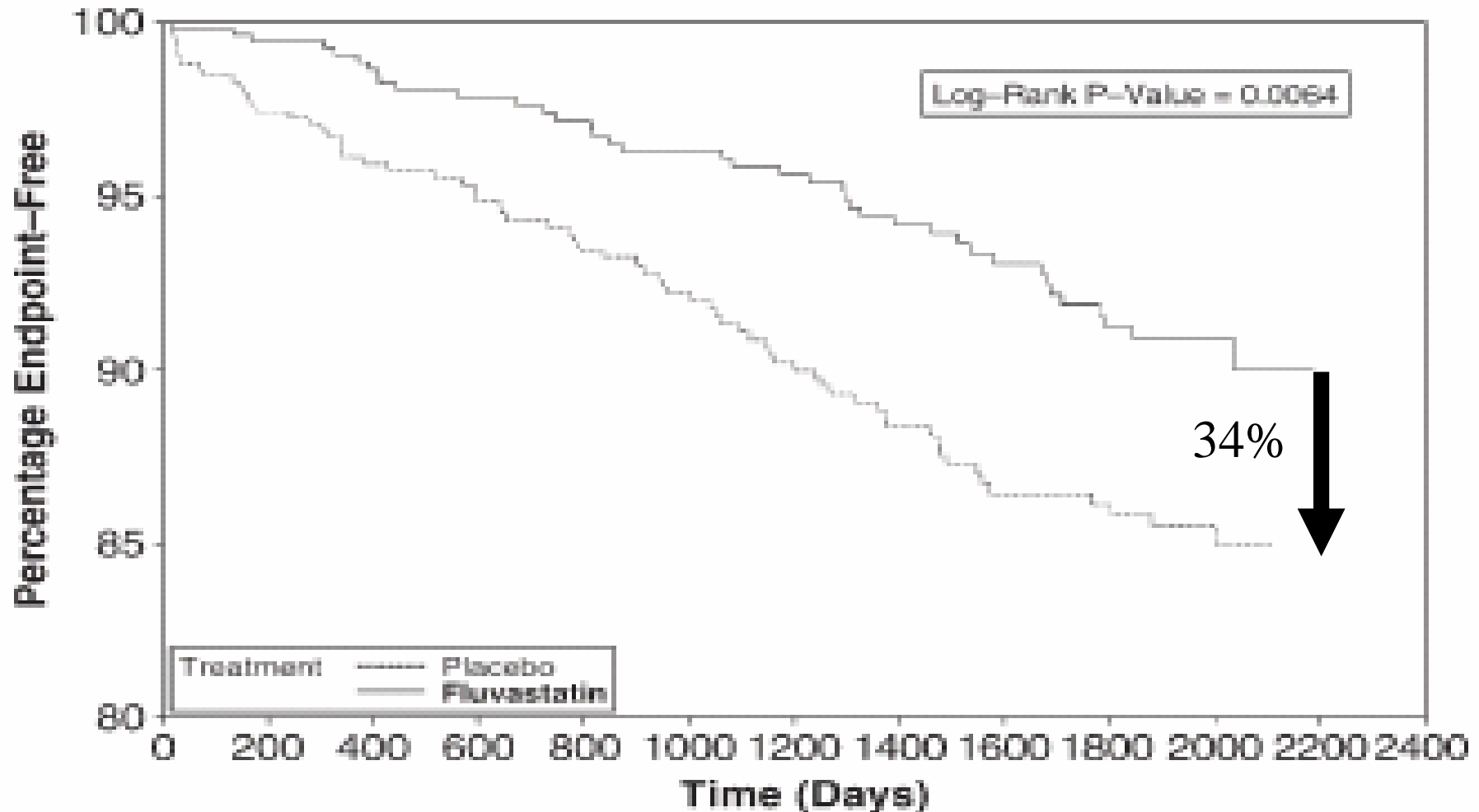
# Fluvastatin clinical trials

Table 3. Major clinical trials with fluvastatin

Study	Patient population (n)	Results
FLARE <sup>137,138</sup>	Primary CHD amenable to PTCA (1054)	No difference in the process of restenosis; fewer cardiovascular events ( $p = 0.025$ )
LCAS <sup>139,140</sup>	Primary CHD (429)	Slower CHD progression ( $p < 0.01$ ) Fewer cardiovascular events ( $p = \text{NS}$ ) The greatest angiographic and clinical benefit was observed in patients with low HDL-C levels compared to patients with higher HDL-C levels ( $p = 0.01$ )
LiSA <sup>141</sup>	Symptomatic CHD (365)	Cardiovascular benefit even during the first year of treatment ( $p < 0.05$ )
LIPS <sup>142,144,145,147</sup>	After first percutaneous coronary intervention (1677)	Decrease by 22% in cardiovascular events ( $p = 0.01$ ). This decrease was more pronounced in high risk groups
FLORIDA <sup>149</sup>	Patients following acute myocardial infraction (540)	No significant difference between fluvastatin and placebo overall; trend towards reduction in major cardiovascular events in patients with profound ischaemia at baseline
BCAPS <sup>150</sup>	Asymptomatic carotid atherosclerotic plaque (793)	Fluvastatin reduced the rate of common carotid intima-media thickness progression by 69% compared with placebo
ALERT <sup>153,154,159</sup>	Renal transplant recipients (2102)	No significant reduction in major cardiovascular events; significant reduction of combined cardiac death and nonfatal myocardial infarction by 35% ( $p = 0.005$ )
HYRIM <sup>167</sup>	Treated hypertension (568)	Fluvastatin significantly retarded the progression of carotid intima-media thickness and the development of left ventricular hypertrophy compared with placebo

# Fluvastatin meta-analysis

The pooled database included data from 7463 patients randomly assigned to fluvastatin treatment and 4352 patients randomly assigned to placebo treatment.



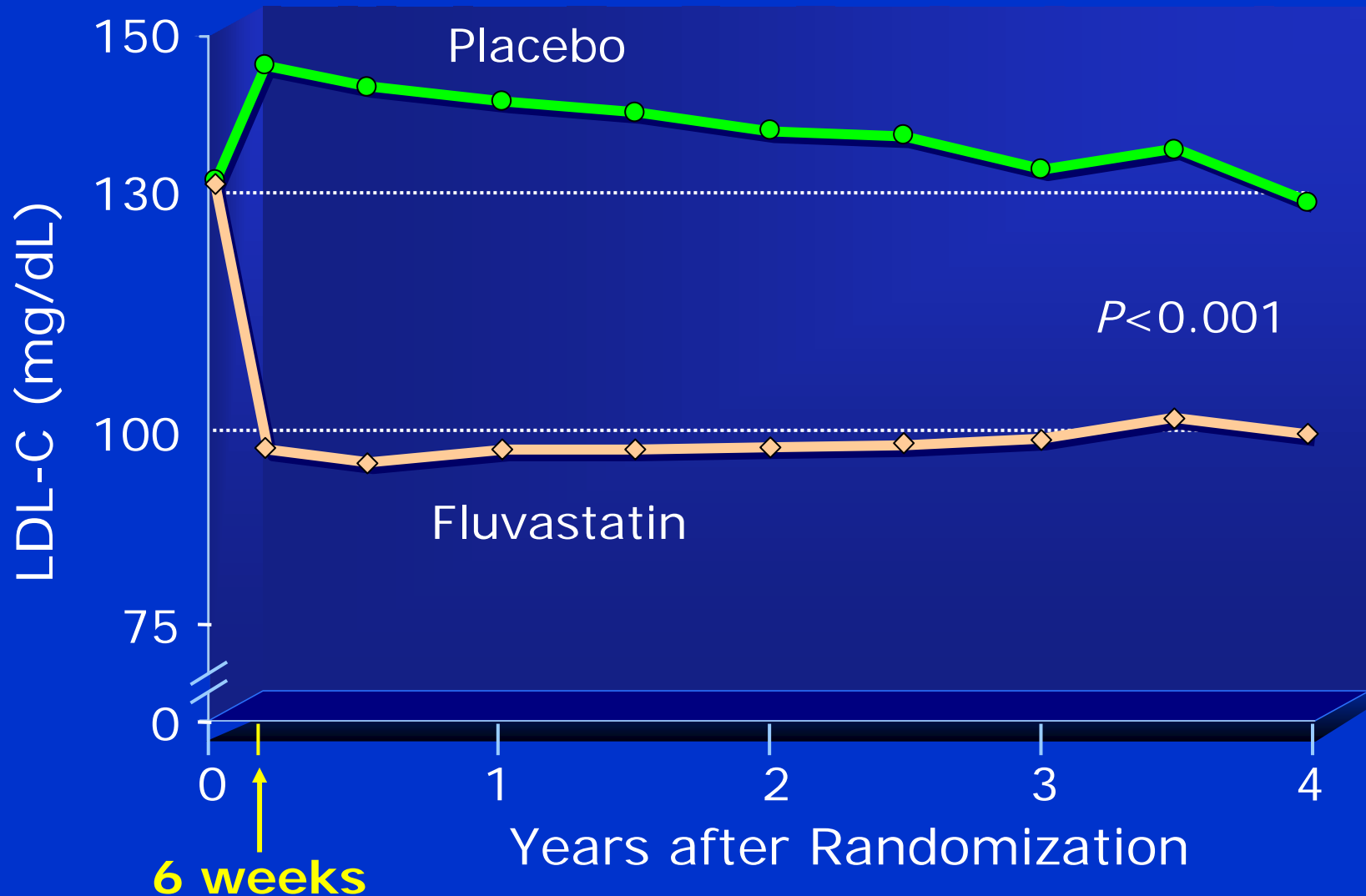
# Lescol Intervention Prevention Study (LIPS): *Design*

- 1677 men and women (aged 18–80 years)  $\leq 6$  months post PCI, with total cholesterol 135–270 mg/dl and triglycerides  $< 400$  mg/dl
- Randomized to receive fluvastatin 80 mg/d or placebo
- Primary endpoint: survival time free of major adverse cardiac events (cardiac death, nonfatal MI, CABG, repeat PCI)

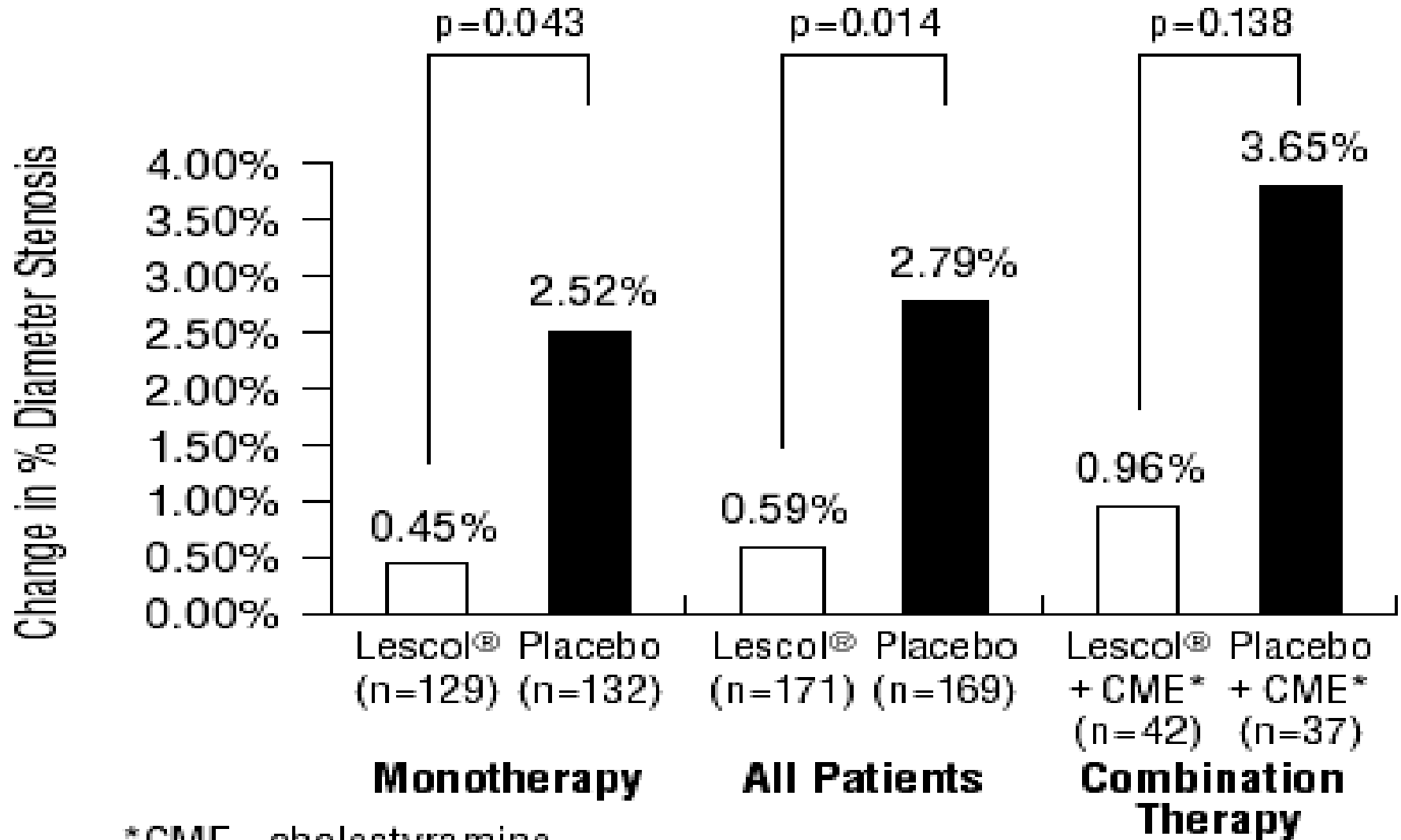
Serruys PWJC et al. / *JAMA* 2002; 287: 3215–3222

- Patients followed up 3–4 years

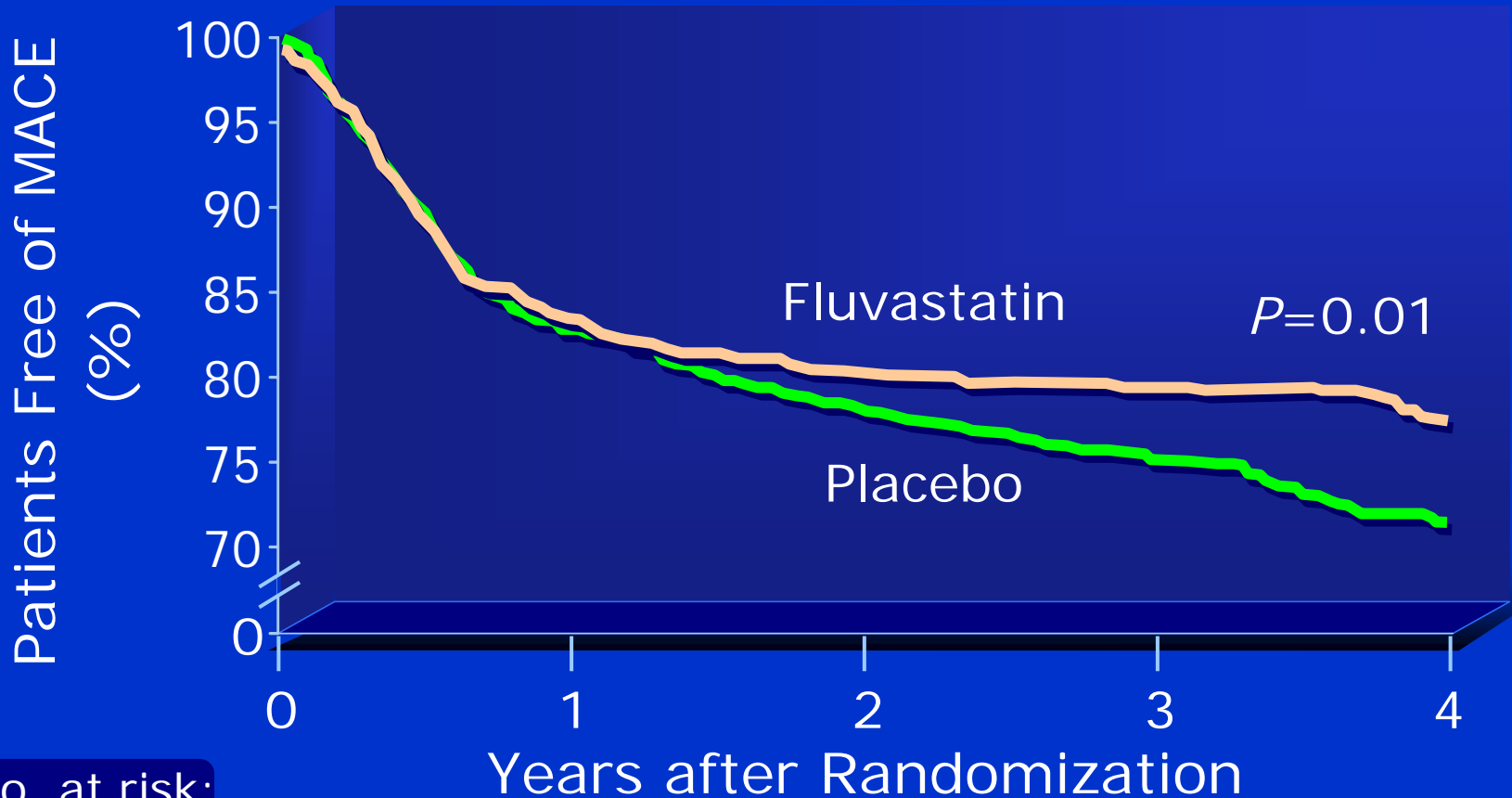
# LIPS: Change in LDL-C Levels



# LIPS: Change in % stenosis



# LIPS Primary Endpoint: MACE-Free Survival Time



No. at risk:

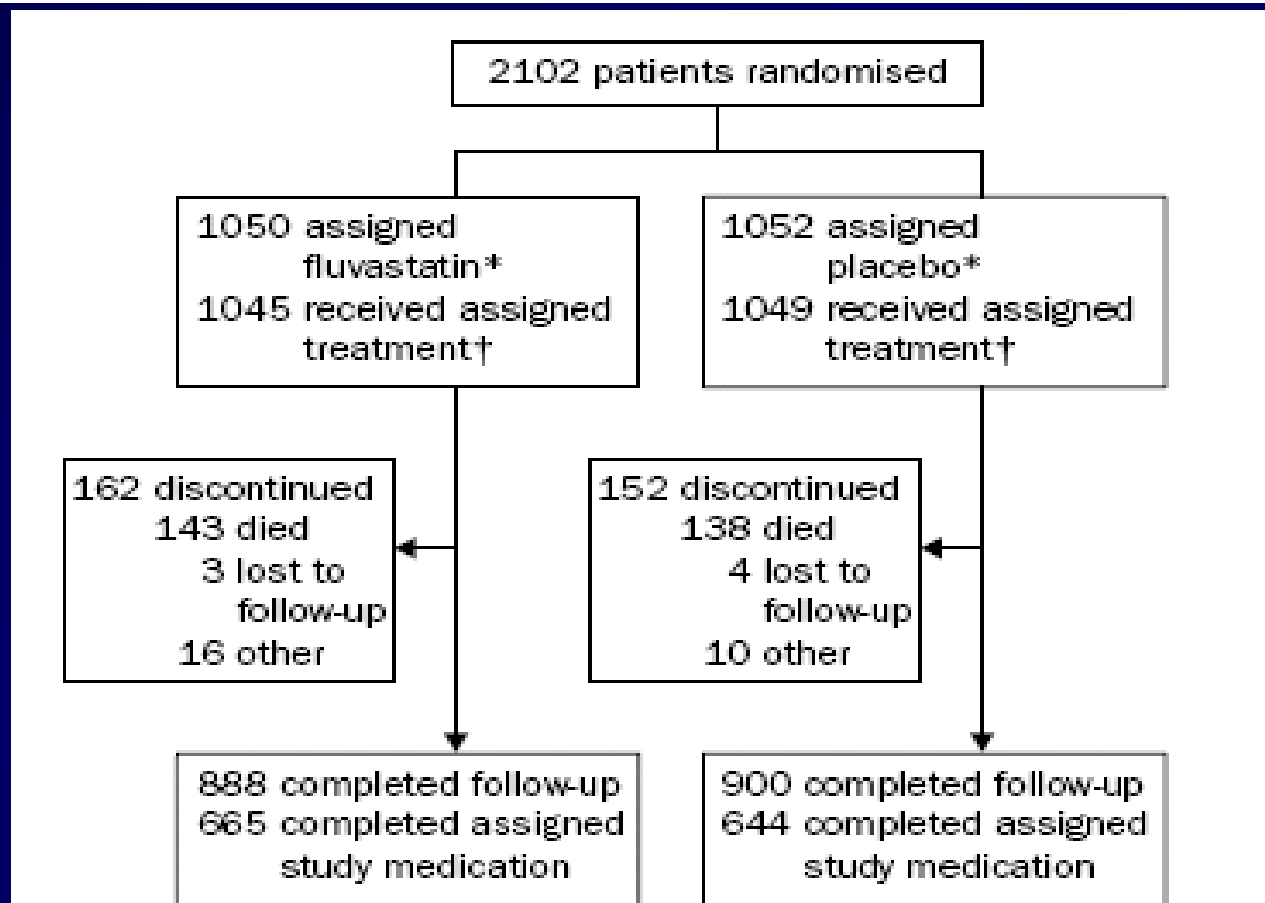
Fluvastatin	844	703	666	647	250
Placebo	833	686	642	610	228

Serruys PWJC et al. *JAMA* 2002;287:3215-3222.  
 Copyright ©2002, American Medical Association.

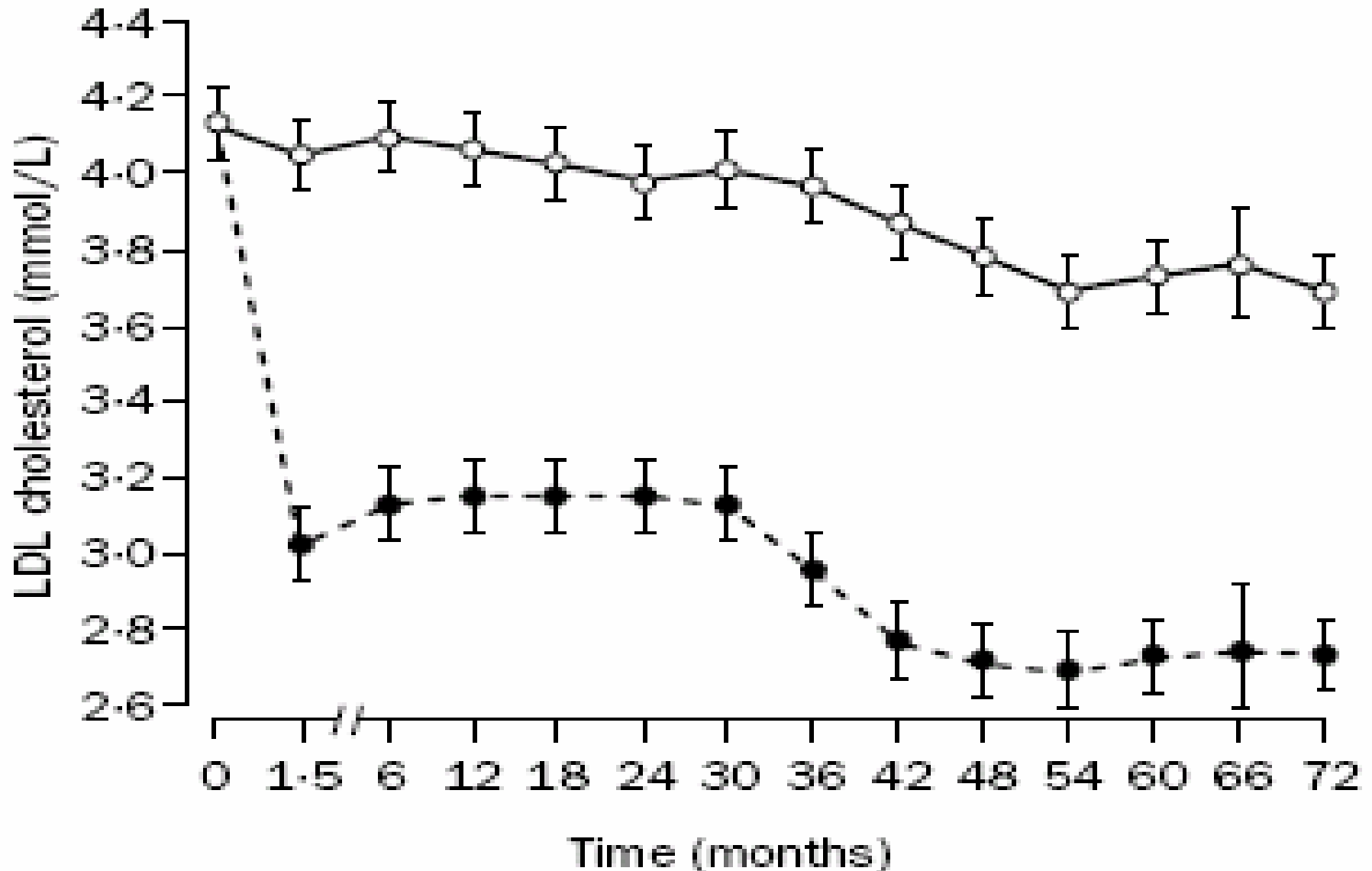
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[www.lipidsonline.org](http://www.lipidsonline.org)

# ALERT: renal patients

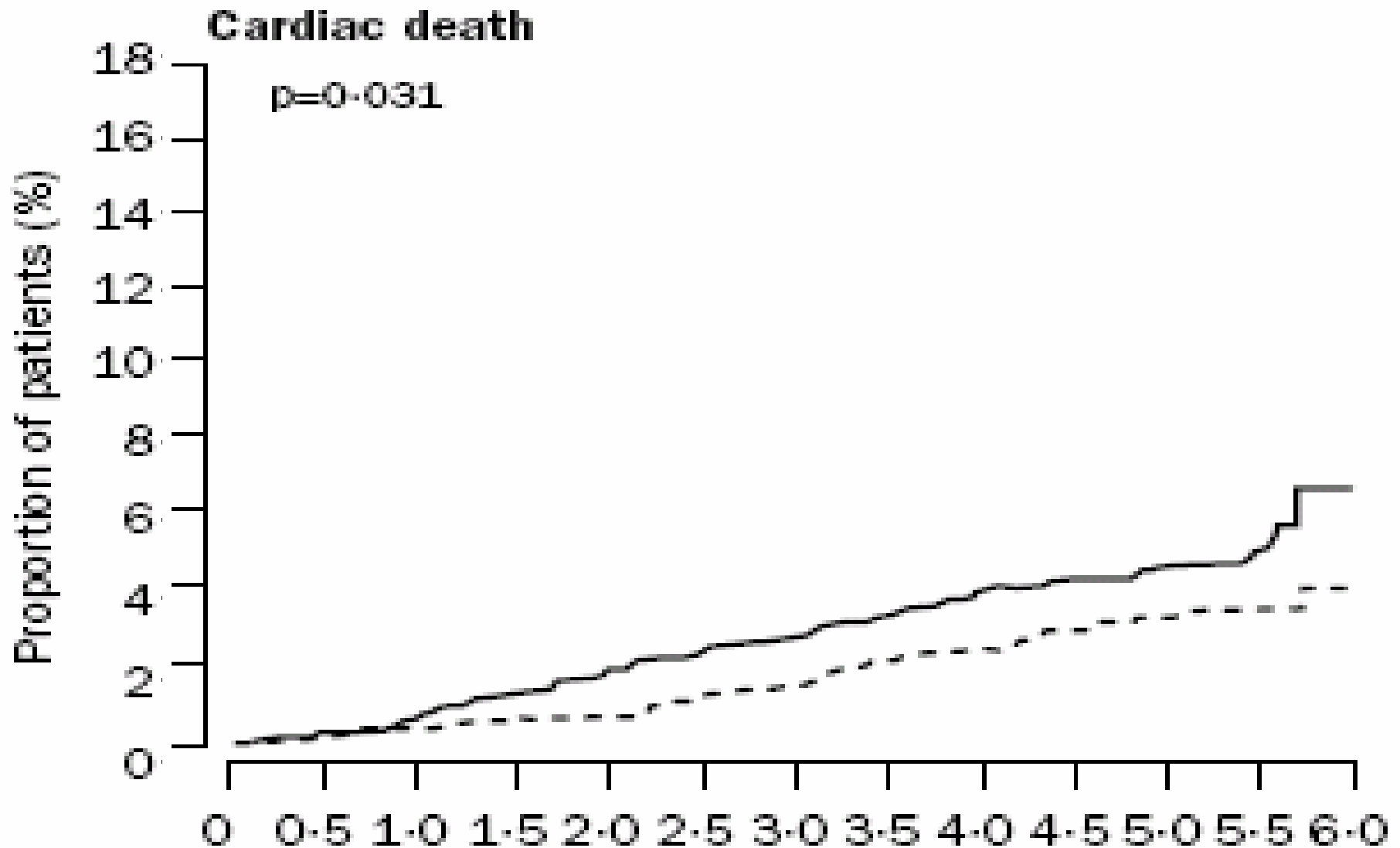
## Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial



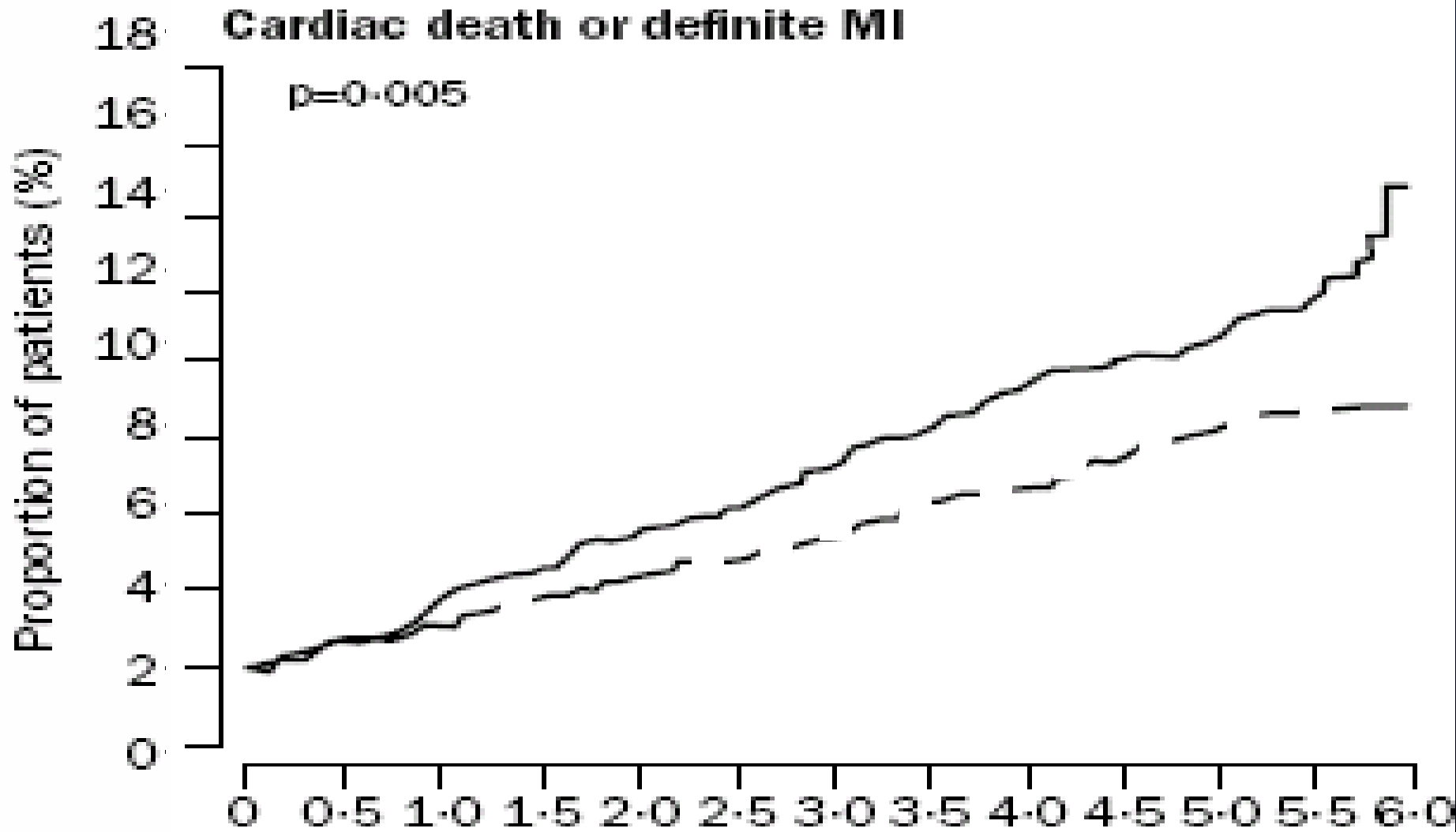
# ALERT: change in LDL cholesterol



# ALERT: CARDIAC DEATH



# ALERT: DEATH OR MI



# ALERT: adverse events

	Fluvastatin (n=1045; n [%])	Placebo (n=1049; n [%])
Total adverse events	1029 (98.5)	1034 (98.6)
Infections	678 (64.9)	671 (64.0)
Gastrointestinal	562 (53.8)	541 (51.6)
Malignancies	296 (28.3)	316 (30.1)
Skin papilloma	138 (13.2)	115 (11.0)
Non-melanoma skin cancer	116 (11.1)	137 (13.1)
Melanoma	2 (0.2)	5 (0.5)
Haematological	11 (1.1)	18 (1.7)
Solid-organ	57 (5.5)	52 (5.0)
Other	38 (3.6)	52 (5.0)
Musculoskeletal	526 (50.3)	531 (50.6)
Hepatobiliary	38 (3.6)	57 (5.4)
Alanine transaminase		
>3× upper limit of normal*		
Once	11 (1.1)	12 (1.1)
Twice, non-consecutive	1 (0.1)	3 (0.3)
Twice, consecutive	0	2 (0.2)
Creatine kinase		
≥5 to <10× upper limit of normal†	3 (0.3)	4 (0.4)
≥10× upper limit of normal†	3 (0.3)	1 (0.1)

# Fluvastatin: adverse events

Table 1. Rates of rhabdomyolysis with statins and in combination therapy with gemfibrozil (from Psaty BM et al. 2004)<sup>21</sup>

Statin	Atorvastatin 1997-2001	Cerivastatin 1998-2001	Fluvastatin 1994-2001	Lovastatin 1988-2001	Pravastatin 1992-2001	Simvastatin 1992-2001
Monotherapy						
Prescriptions ( $\times 10^6$ )	147.6	11.0	38.8	97.3	82.0	119.0
Cases of rhabdomyolysis	45	200	1	120	17	99
Rate of rhabdomyolysis/ $10^5$ scripts	0.03	1.81	0.00	0.12	0.02	0.08
Combination therapy with gemfibrozil						
Prescriptions ( $\times 10^6$ )	1.2	0.2	0.3	2.1	1.4	0.96
Cases of rhabdomyolysis	6	279	0	60	2	37
Rate of rhabdomyolysis/ $10^5$ scripts	0.50	1248.66	0	2.84	0.14	3.85

# Fluvastatin: adverse events

Variable	Patients $\geq 65$ Yrs of Age	
	Placebo (n = 1,481) n (%)	All-Fluvastatin (n = 2,236) n (%)
Alanine transaminase		
$>3 \times$ ULN	9 (0.6%)	46 (2.1%)
$>3 \times$ ULN on 2 consecutive occasions	0 (0.0%)	3 (0.1%)
Aspartate transaminase		
$>3 \times$ ULN	3 (0.2%)	33 (1.5%)
$>3 \times$ ULN on 2 consecutive occasions	2 (0.1%)	4 (0.2%)
Creatine kinase		
$>5 \times$ ULN to $\leq 10 \times$ ULN	2 (0.1%)	1 (0.0%)
$>10 \times$ ULN	0 (0.0%)	0 (0.0%)
$>10 \times$ ULN on 2 consecutive occasions	0 (0.0%)	0 (0.0%)

ULN = upper limit of normal.

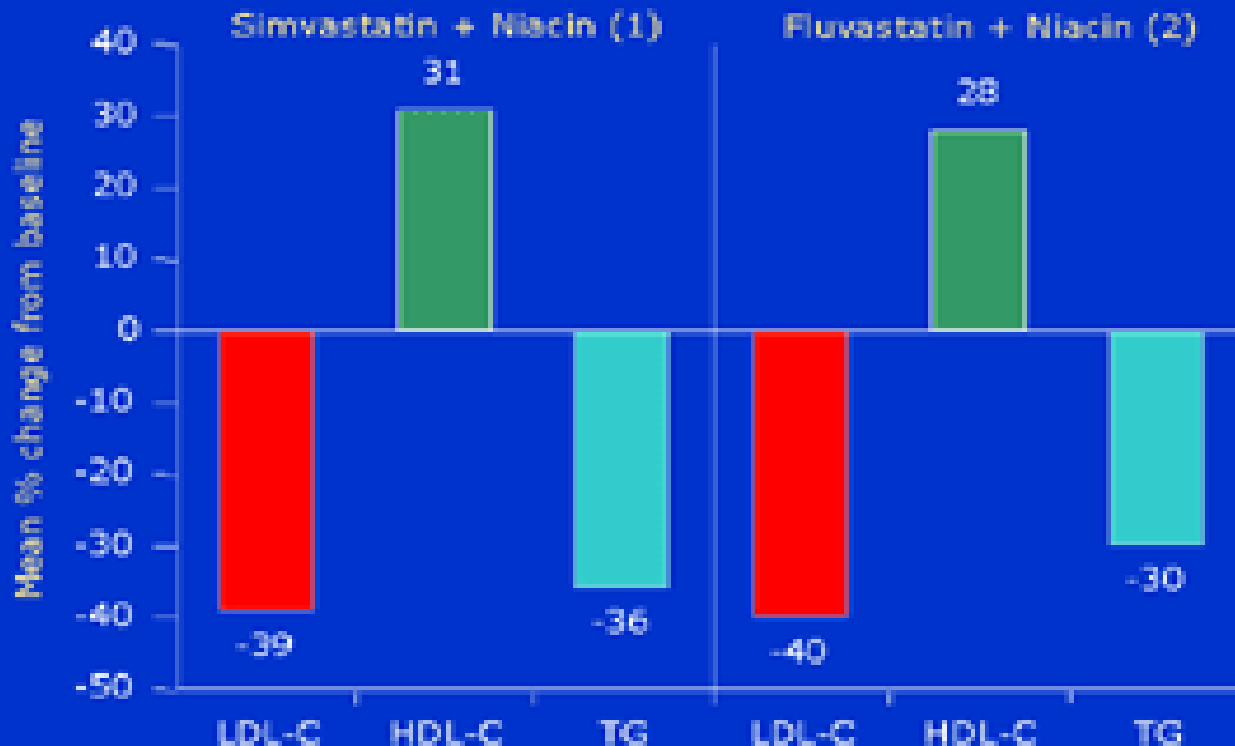
# Fluvastatin-eze: combination

Parameter	EZE 10	FLX 80	FLX + EZE
Muscle-related SE	24.2%	17.4%	14.1%
Discontinuation due to MRSE	7.6%	4.3%	3.1%
Mean LDLC change	-15.6%	-32.8% <sup>**</sup>	-46.1% <sup>**</sup>
Mean triglyceride change	6.2%	-12.4% <sup>**</sup>	-16.9% <sup>**</sup>
Median change in hs-CRP	0%	-7.9%	-18.6% <sup>*</sup>
LDLC <2.0 mmol/L	1.5%	33.3%	67.2% <sup>*</sup>

Stein EA, Ballantyne CM, Gimplewicz C, et al AHA 2006 Chicago

# Fluvastatin: combination

## Combination Therapy Statin Plus Niacin



1. Guyton JR, Capuzzi DM. *Am J Cardiol* 1998;82:82U-84U

2. Jacobson TA et al. *Am J Cardiol* 1994;74:149-154

