

Dyslipidaemia/statins



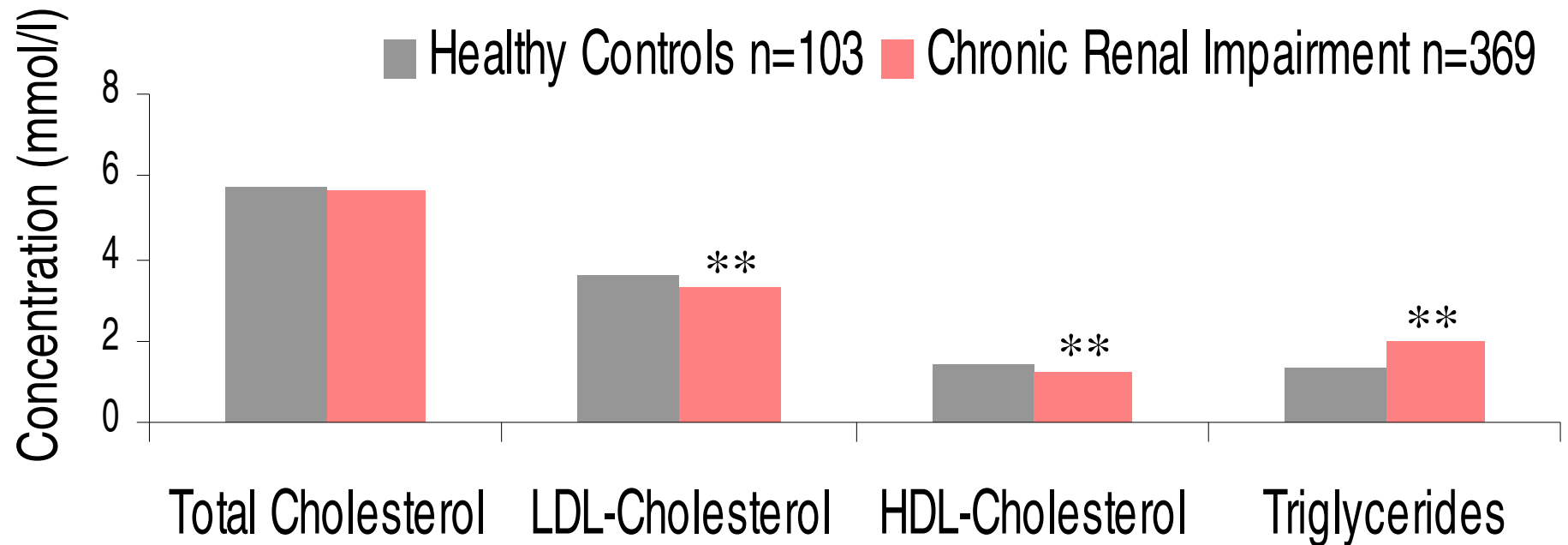
David Wheeler
Royal Free Campus
UCL Medical School
London



What is he going to talk about?

- Patterns of dyslipidaemia in CKD
- Is cholesterol a reasonable target?
- Evidence from RCTs of statins in CKD

Plasma lipids in stage 3-5 CKD The Chronic Renal Impairment in Birmingham (CRIB) study



** p < 0.01 vs. controls

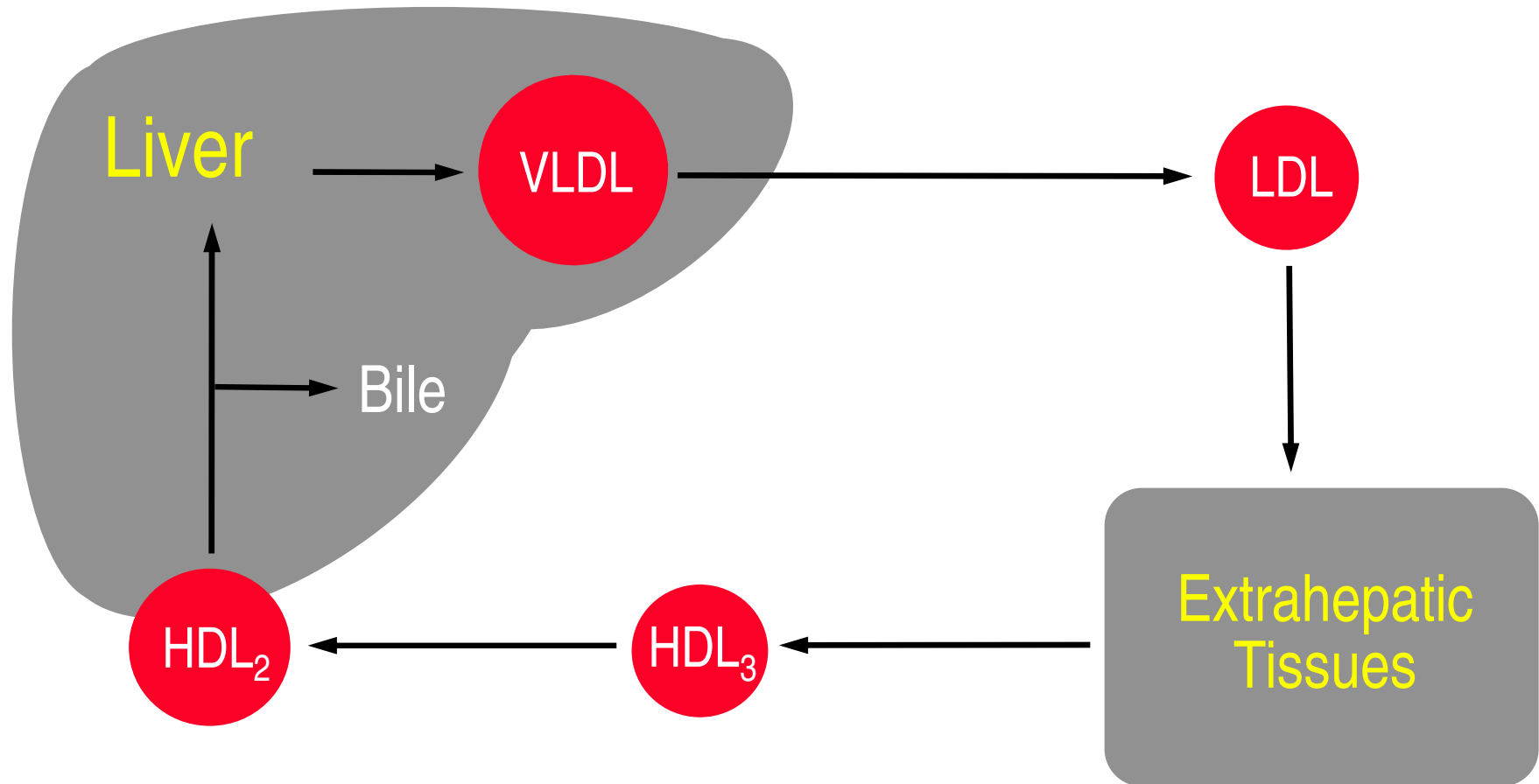
Landray et al, AJKD 2001:38:537-46

Dyslipidemia in stage 3-5 CKD

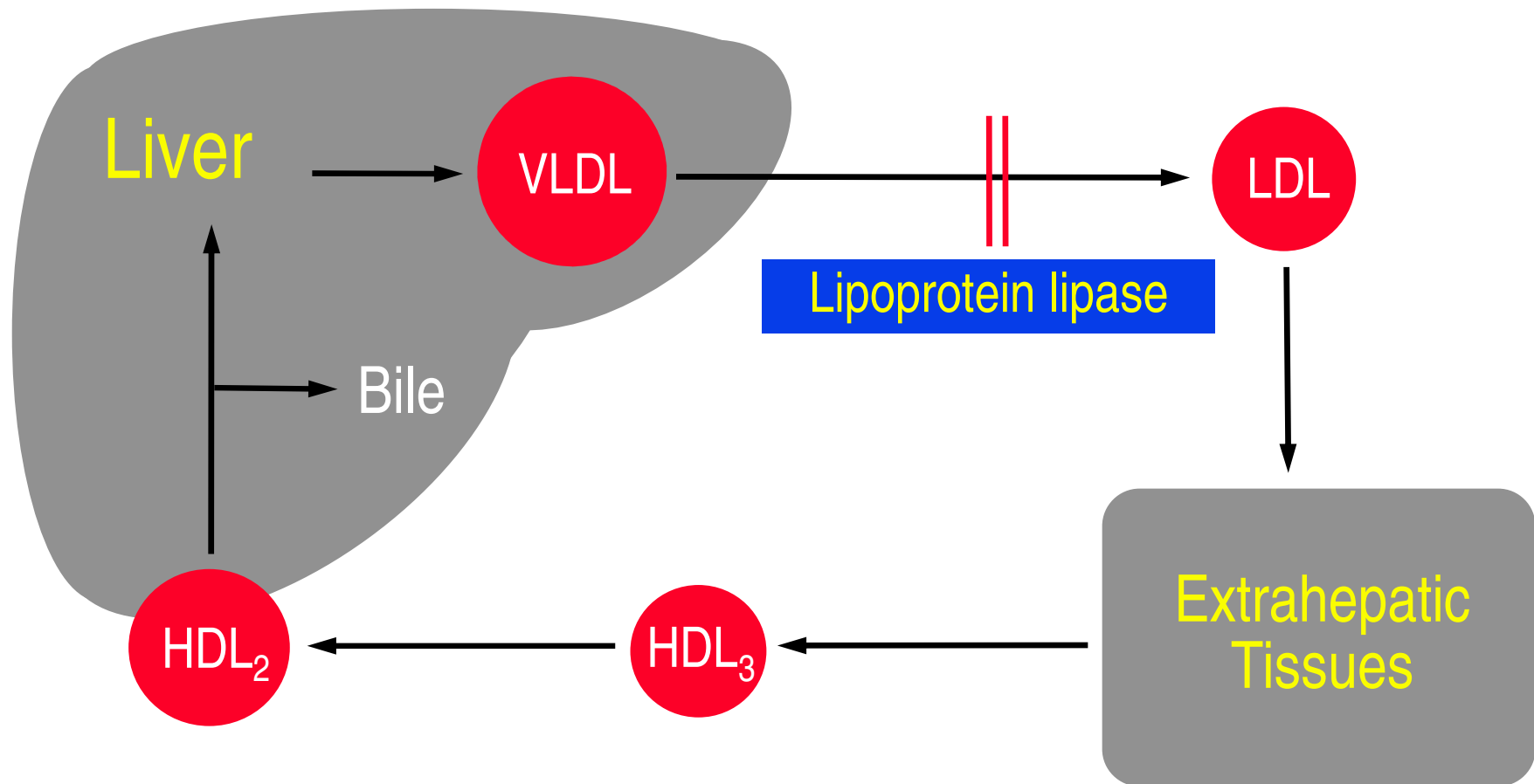
↑↑ Triglyceride

↑ VLDL remnants
Normal or low LDL
Small dense LDL
↑ Lipoprotein (a)
↓ HDL

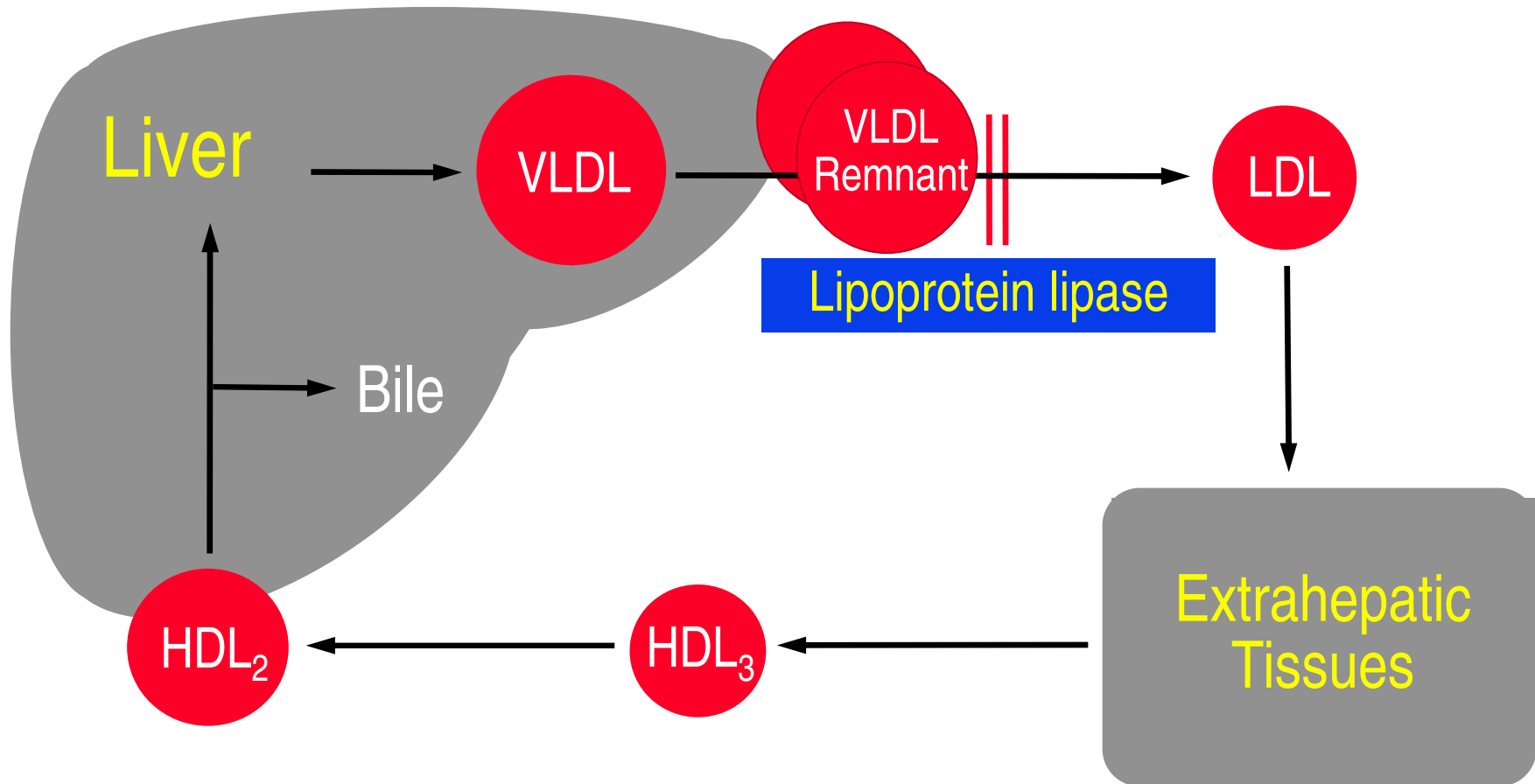
Mechanisms of dyslipidemia (stage 3-5 CKD)



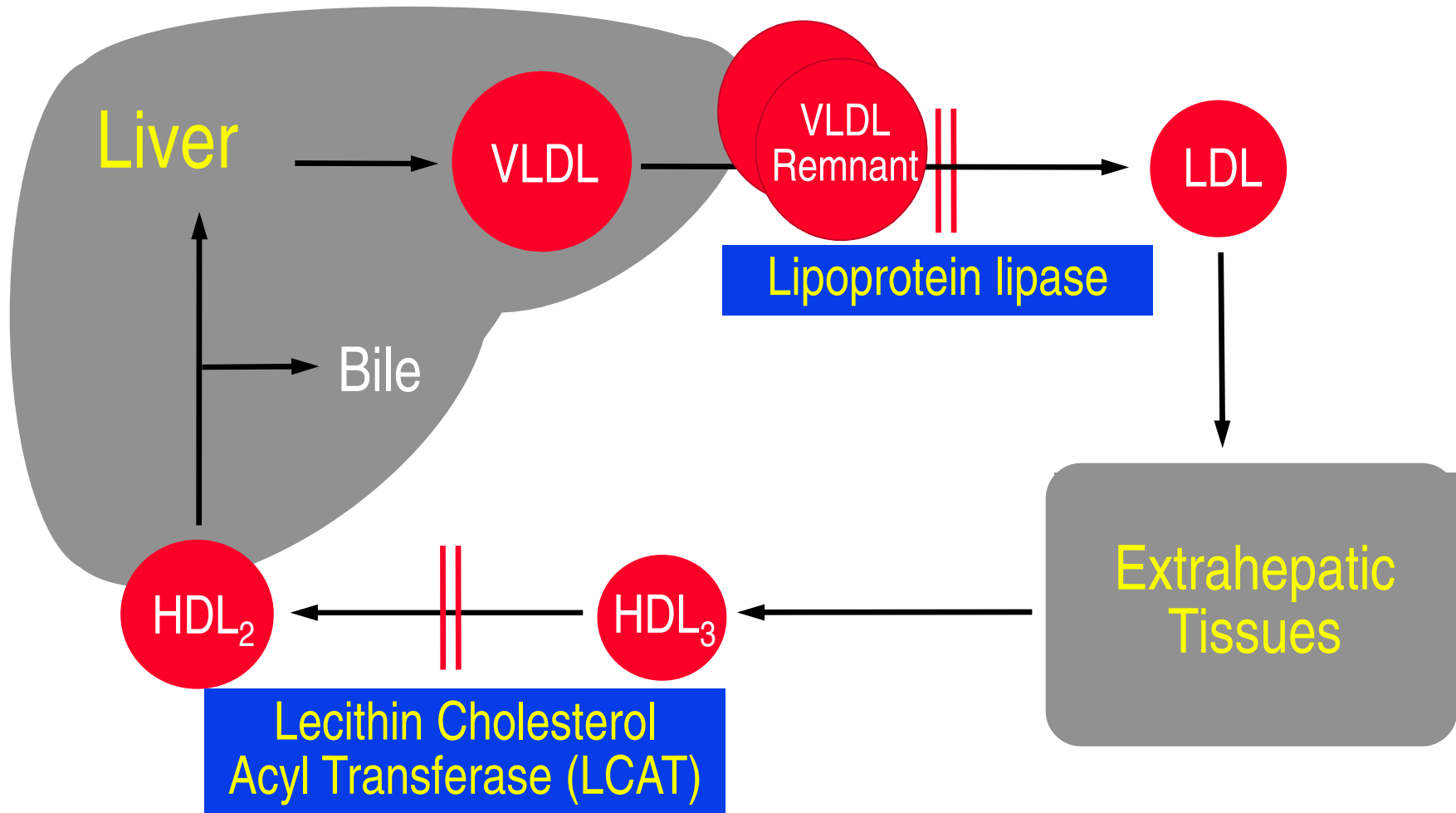
Mechanisms of dyslipidemia (stage 3-5 CKD)



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Mechanisms of dyslipidemia (stage 3-5 CKD)



Lipid abnormalities in CKD patients

Group	Cholesterol	Triglyceride	HDL
Stage 3-5 CKD	—	↑	↓
Haemodialysis	—	↑	↓
CAPD	↑	↑	↓
Transplant recipients	↑	↑	—
Nephrotic syndrome	↑↑	↑	—

Prevalence of Dyslipidemia: Haemodialysis vs Peritoneal Dialysis

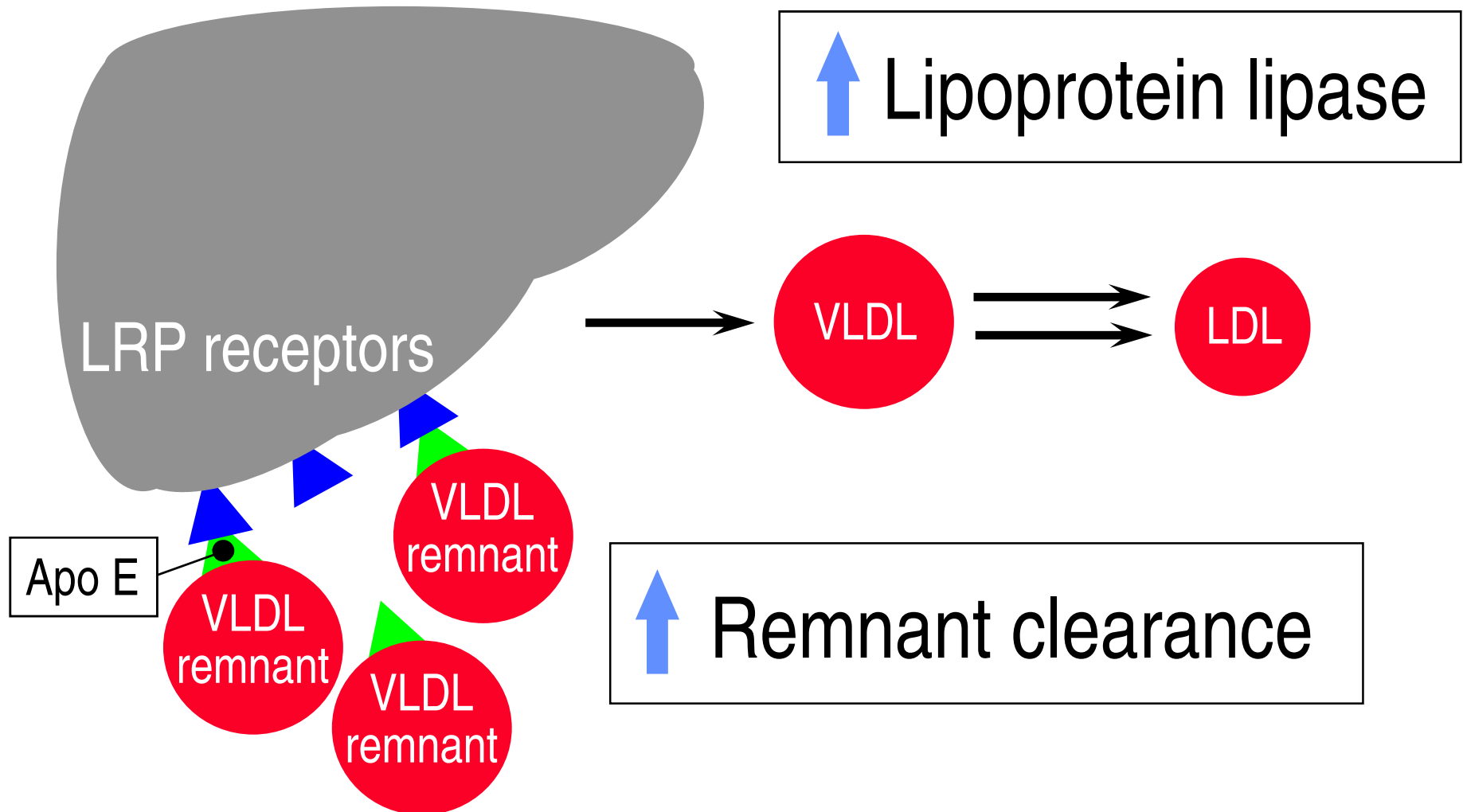
Lipid measurement	HD n=16507	PD n=1708
Cholesterol \geq 6.2 mmol/l	9.5%	25.7%*
Triglyceride \geq 2.2 mmol/l	28.9%	41.2%*
HDL Chol \leq 0.9 mmol/l	44.3%	38.3%

Dialysis Morbidity and Mortality Study.

*p<0.0001 vs. HD

Fox CS, Clin Nephrol 2004;61:229-307

Mechanisms of action of fibrates

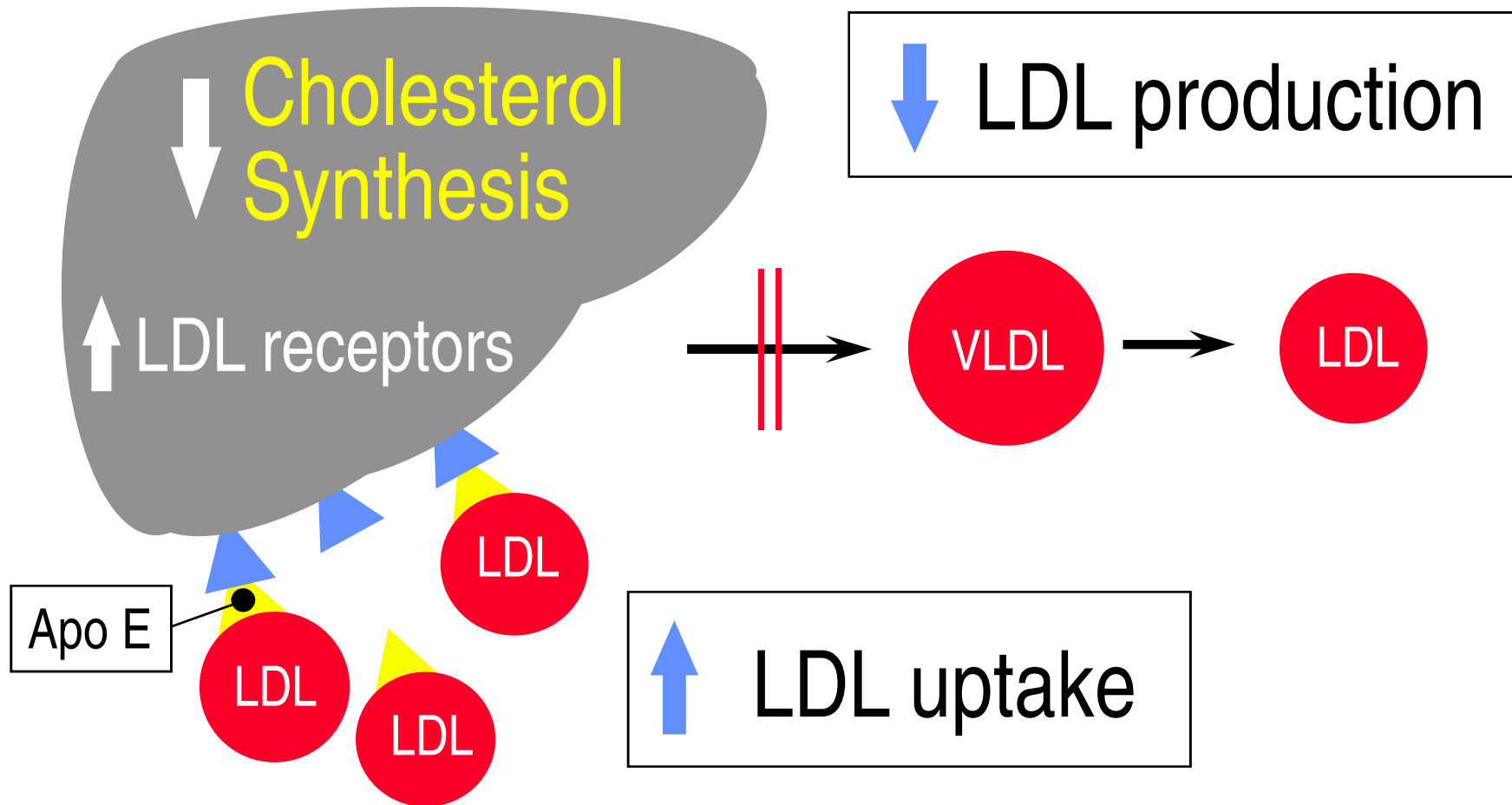


Lipid-Lowering agents in CKD: Safety issues

Agent	GFR 60-90	GFR 15-59	GFR <15	Notes
Statin	OK	OK	↓ 50%	Start at low doses
Fibrate	↓ 50%	↓ 75%	Avoid	Except Gemfibrozil
Bile acid sequestrant	OK	OK	OK	
Nicotinic acid	OK	OK	↓ 50%	35% renal excretion

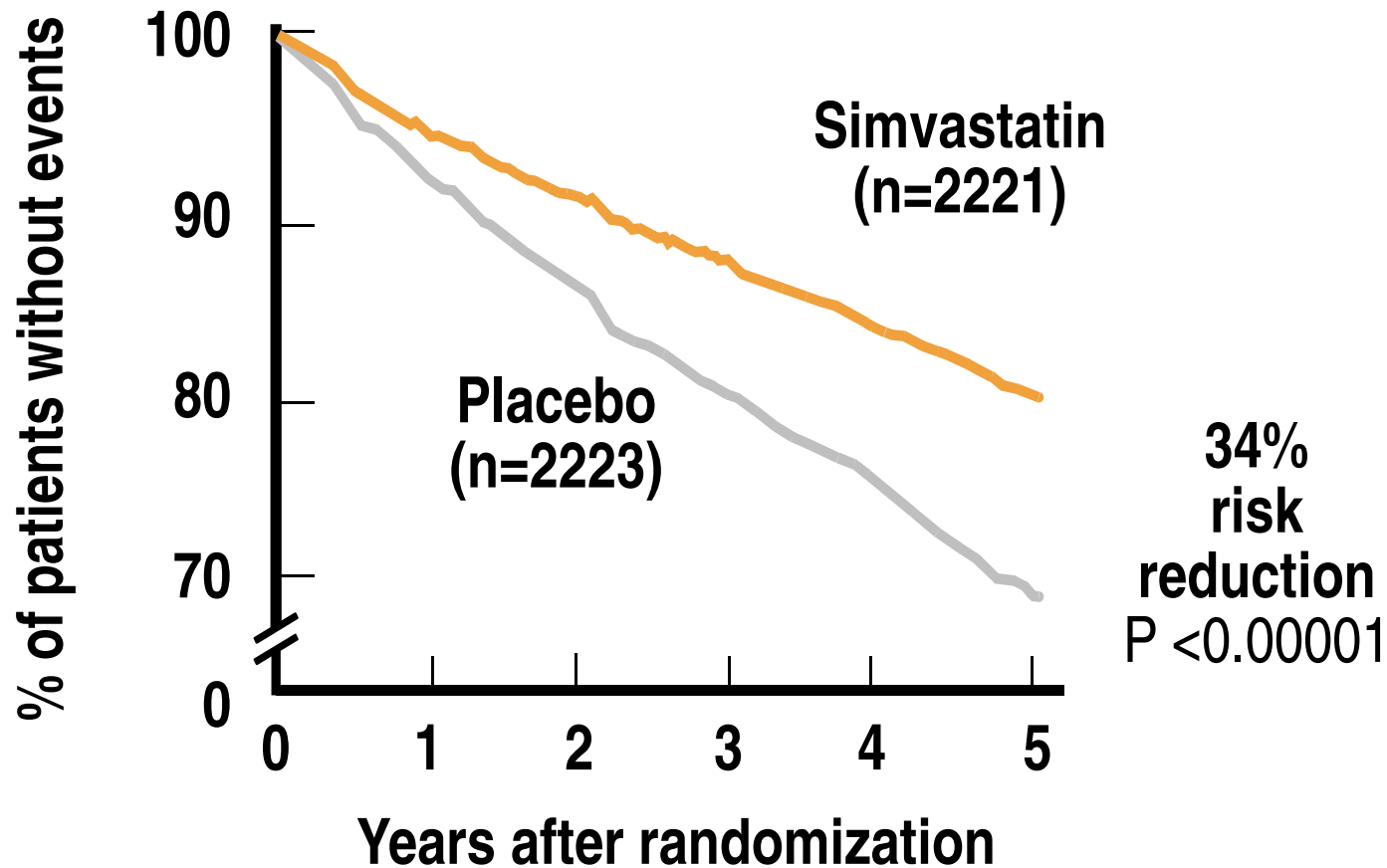
K/DOQI dyslipidemia guidelines AJKD 2003;41 (suppl 3):S1-S92

Mechanisms of action of statins



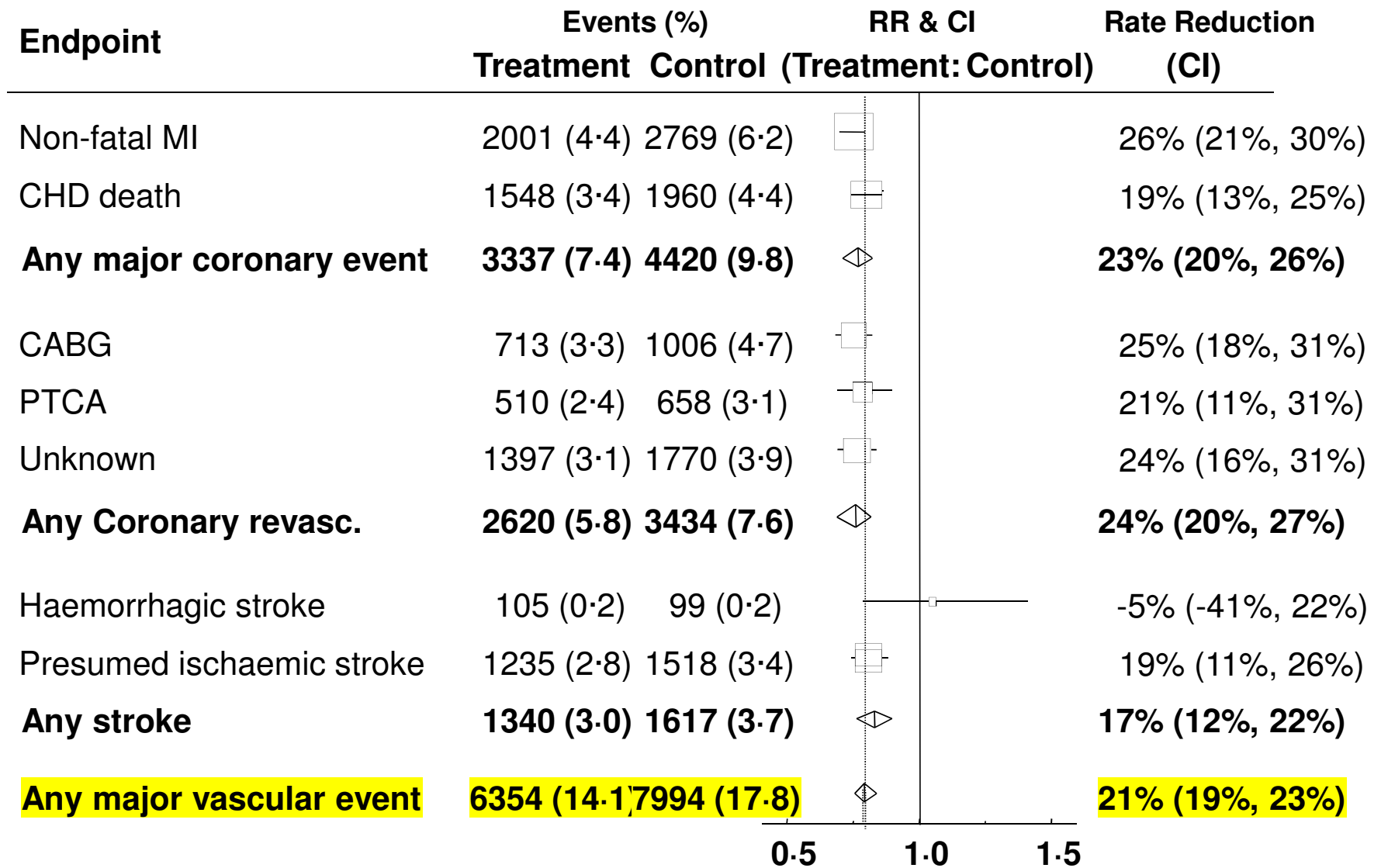
4S Study: The first major statin trial

Coronary Death or Nonfatal MI



4S Study Group *Lancet* 1994;344:1383-1389.

Proportional effects on major vascular events per mmol/L LDL cholesterol reduction



Baigent et al (Cholesterol Trialists Collaboration), Lancet 2005;366:1276-78 90,056 participants in 14 randomised trials

Statins for all?



CORONA: Statins meet their match

Inclusion criteria:

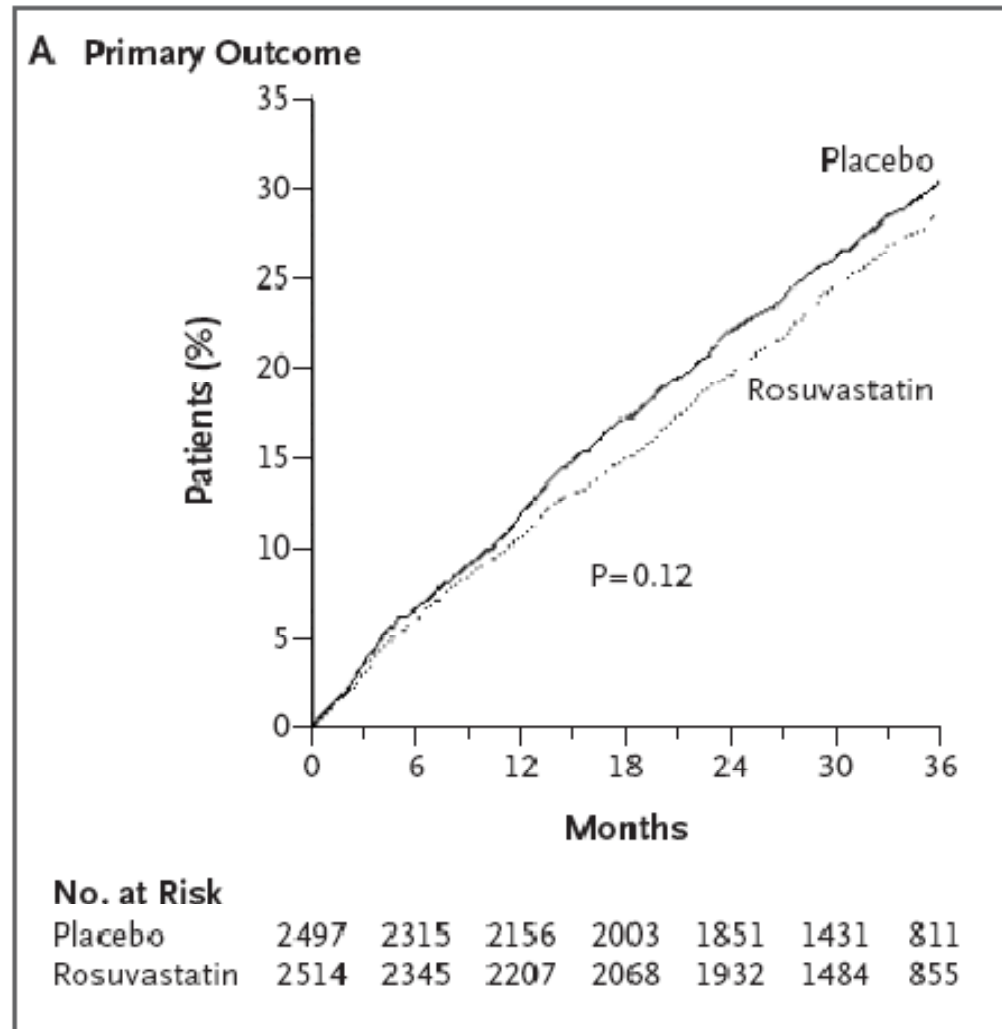
Age >60 years
Systolic heart failure
NYHA stage II, III, or IV
Ischaemic aetiology

Intervention:

Rosuvastatin 10 mg
vs. Placebo

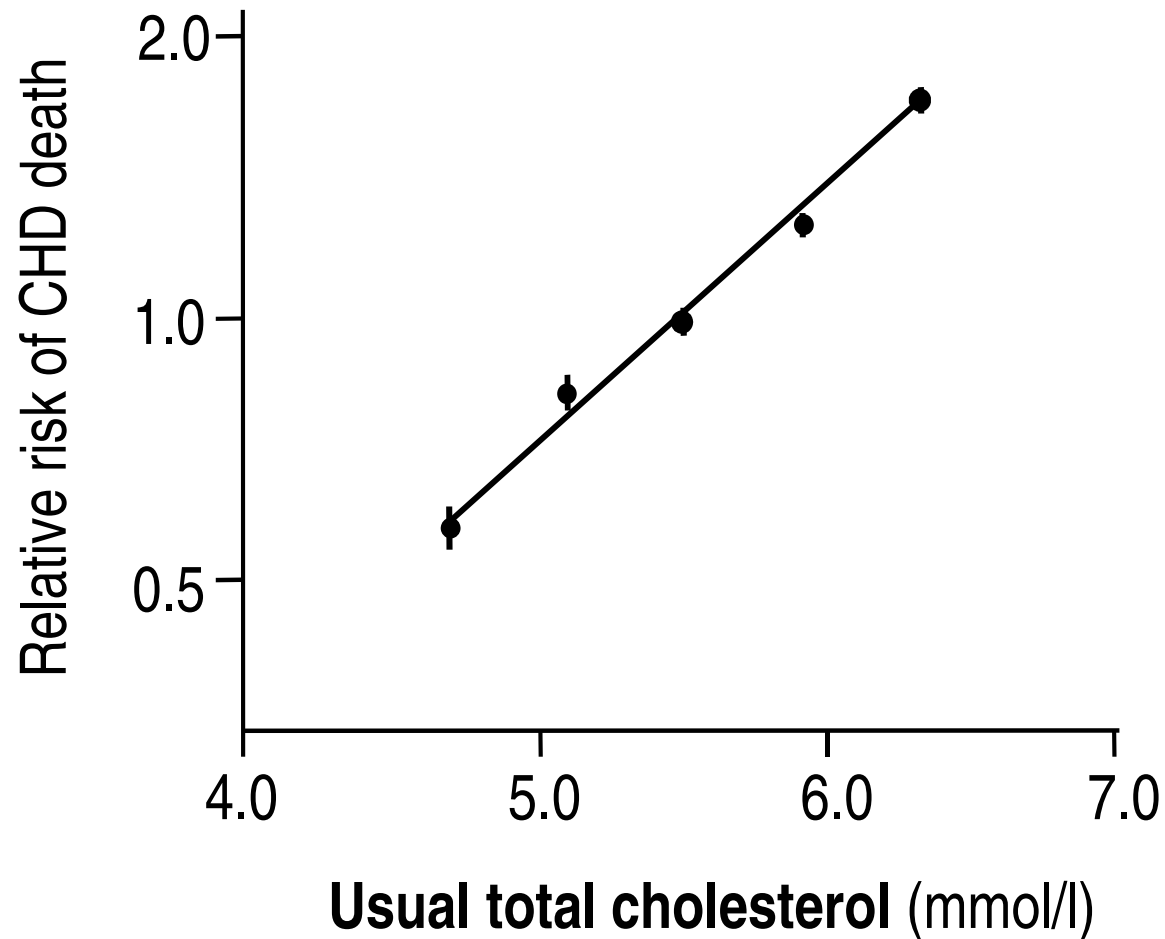
Endpoint:

Nonfatal Myocardial Infarction
Nonfatal Stroke
Death from a CV cause



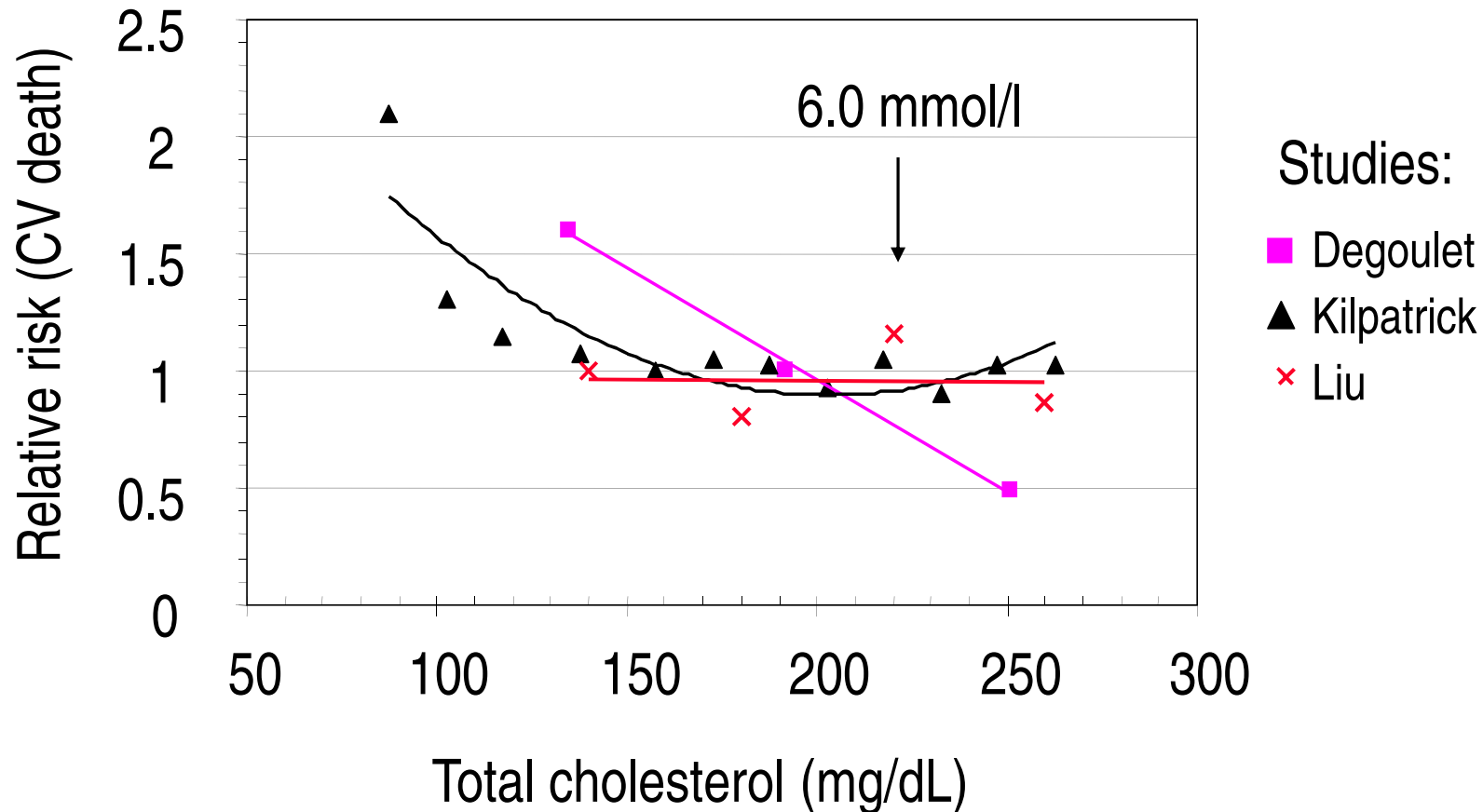
Kjekshus et al NEJM 2008;357:2248-61

Total Cholesterol and Cardiovascular Mortality among 350,000 men: MRFIT Prospective Study



Martin et al, Lancet 1986;2(8513):933-936

Association between cholesterol and CV death in 3 prospective studies



Baigent, Landray & Wheeler, Semin Dial 2007;20:498-503

The Evidence

Statin RCTs involving CKD patients

1. Trials of statins in patients with CV disease (or at high risk) in which CKD patients have been included
2. Trials that have specifically enrolled CKD patients randomised to statin and placebo.

Trials of statins in CKD patients not receiving dialysis

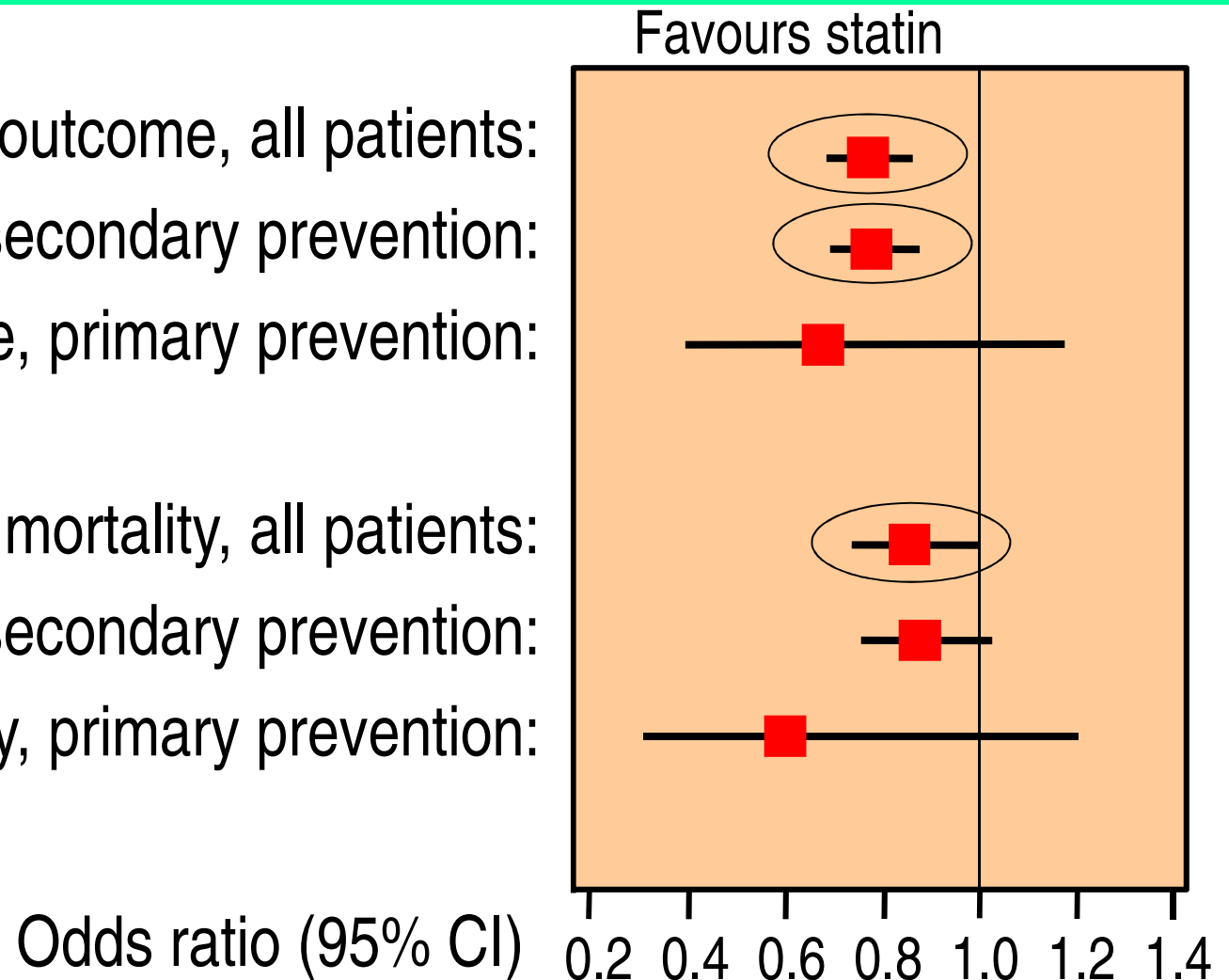
Post hoc subgroup analysis of data from Pravastatin Pooling Project (PPP)

- 3 double blind RCTs (pravastatin 40 mg vs placebo)
 - CARE – secondary prevention
 - LIPID – secondary prevention
 - WOSCOPS – primary prevention
- CKD classified based on K/DOQI criteria:
 - GFR >60 ml/min/1.73 m² (n=15,209)
 - GFR 30–59.9 ml/min/1.73 m² (n=4491)

Pravastatin reduced CVD events and total mortality in stage 3 CKD (eGFR 30-59.9 ml/min)

- Primary outcome, all patients:
- Primary outcome, secondary prevention:
- Primary outcome, primary prevention:

- Total mortality, all patients:
- Total mortality, secondary prevention:
- Total mortality, primary prevention:

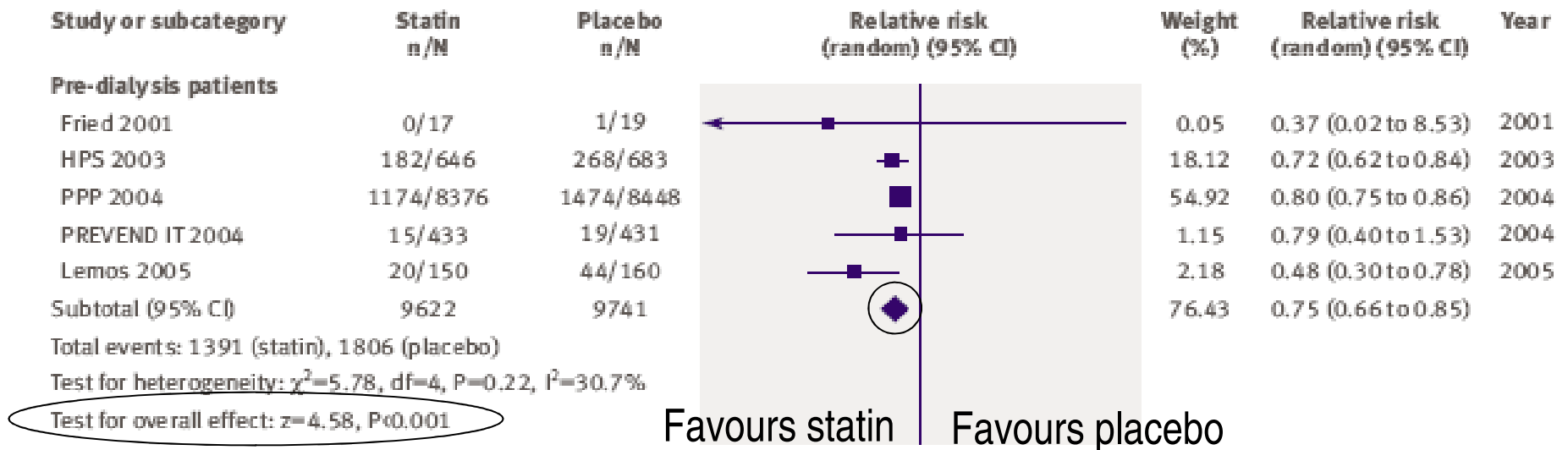


Tonelli et al, *Circulation* 2004;110:1557-1563

BMJ Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials

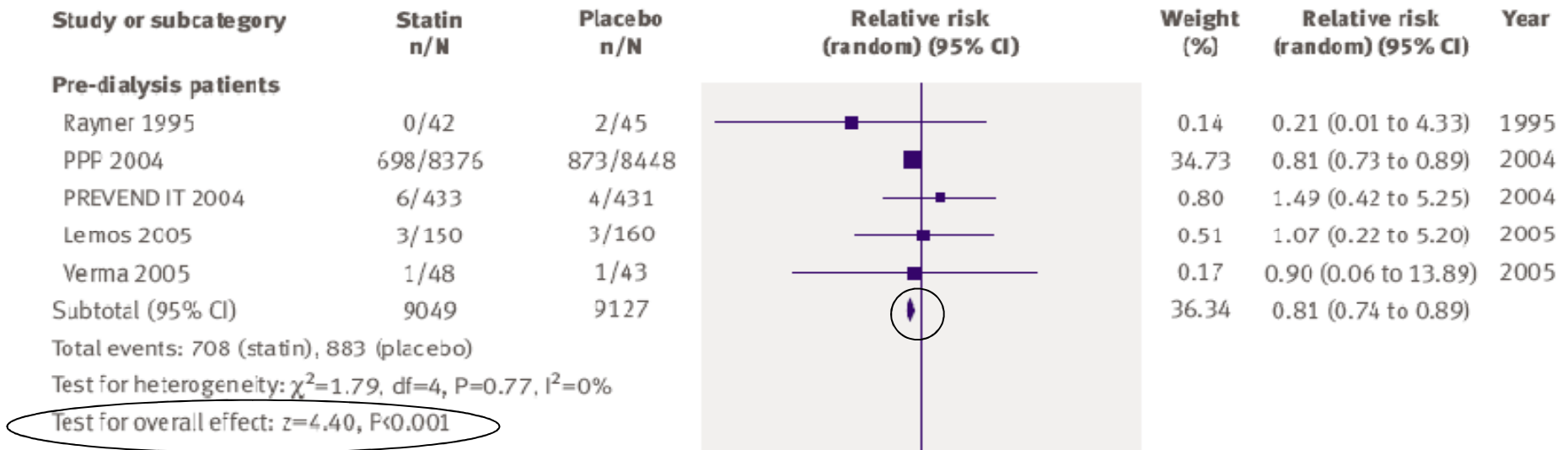
Giovanni F M Strippoli, Sankar D Navaneethan, David W Johnson, Vlado Perkovic, Fabio Pellegrini, Antonio Nicolucci and Jonathan C Craig

Effect of statins on cardiovascular events in stage 1-5 CKD

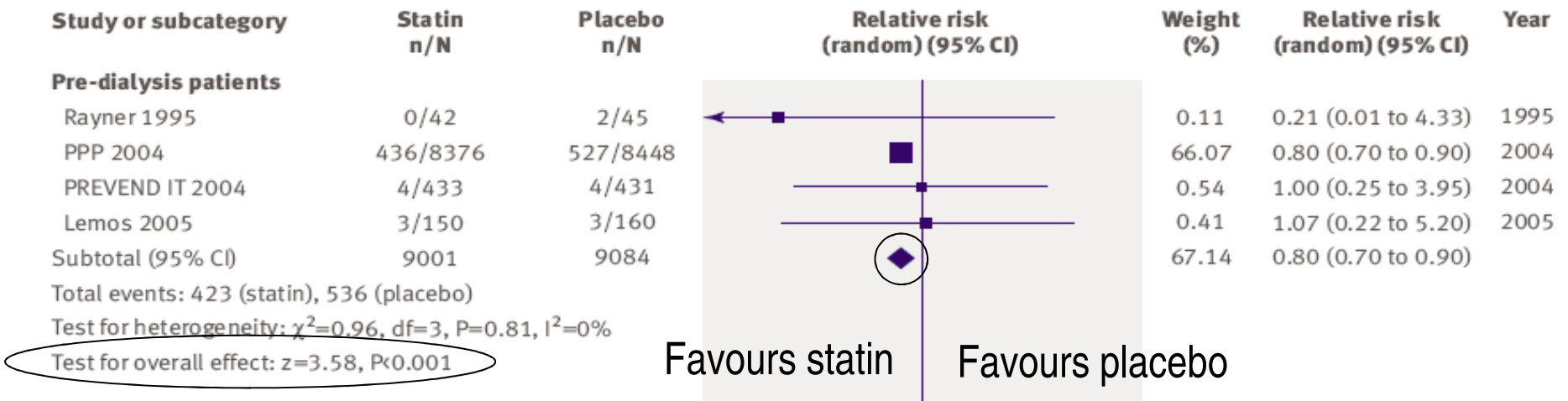


BMJ 2008;336:645-651

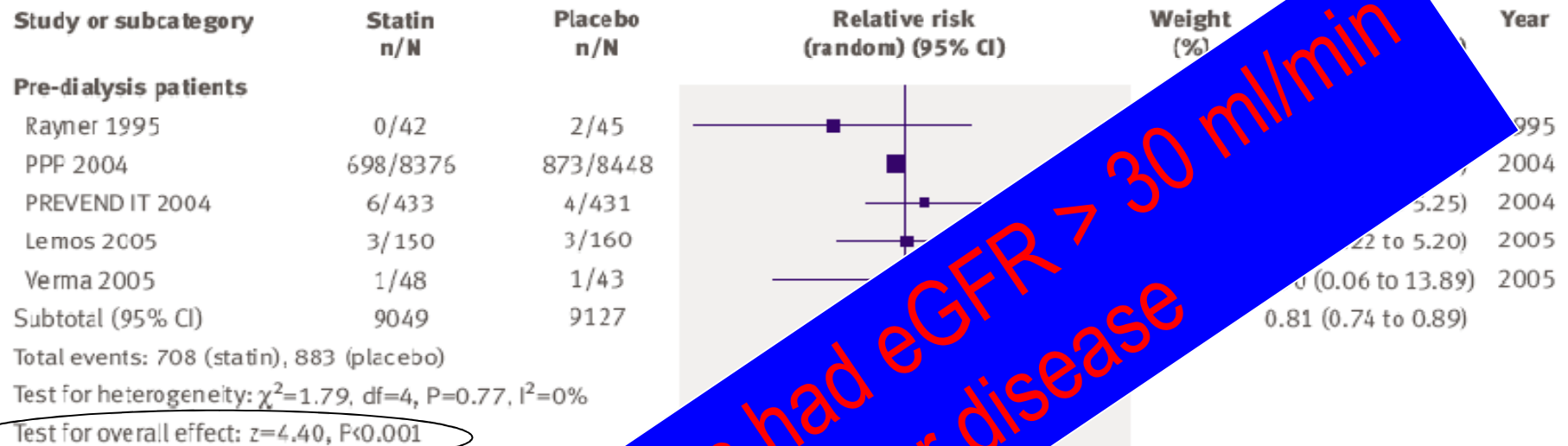
Effect of statins on all cause mortality in stage 1-5 CKD



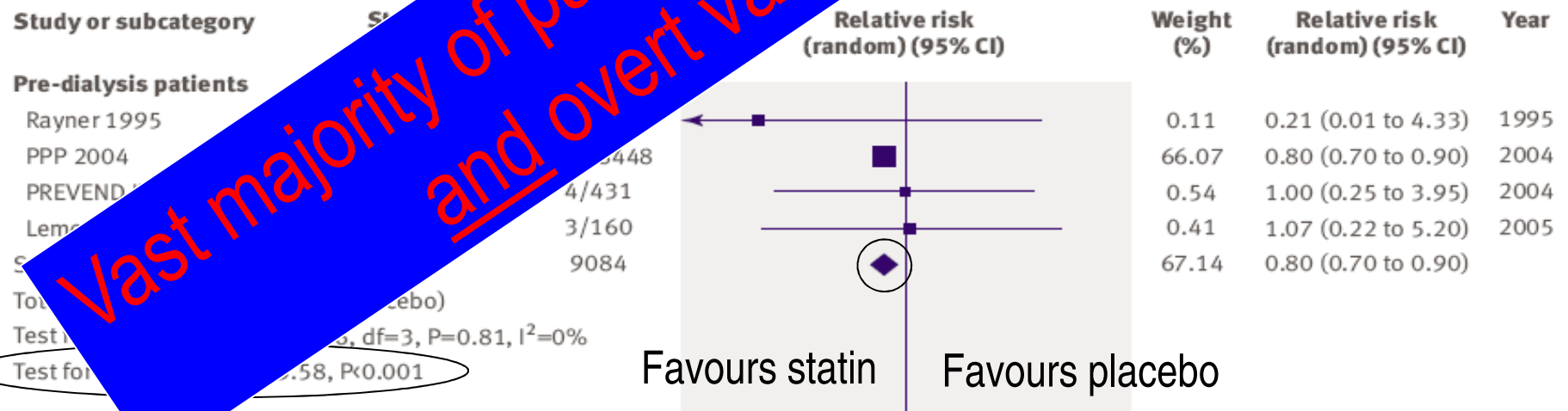
Effect of statins on CV mortality in stage 1-5 CKD



Effect of statins on all cause mortality in stage 1-5 CKD

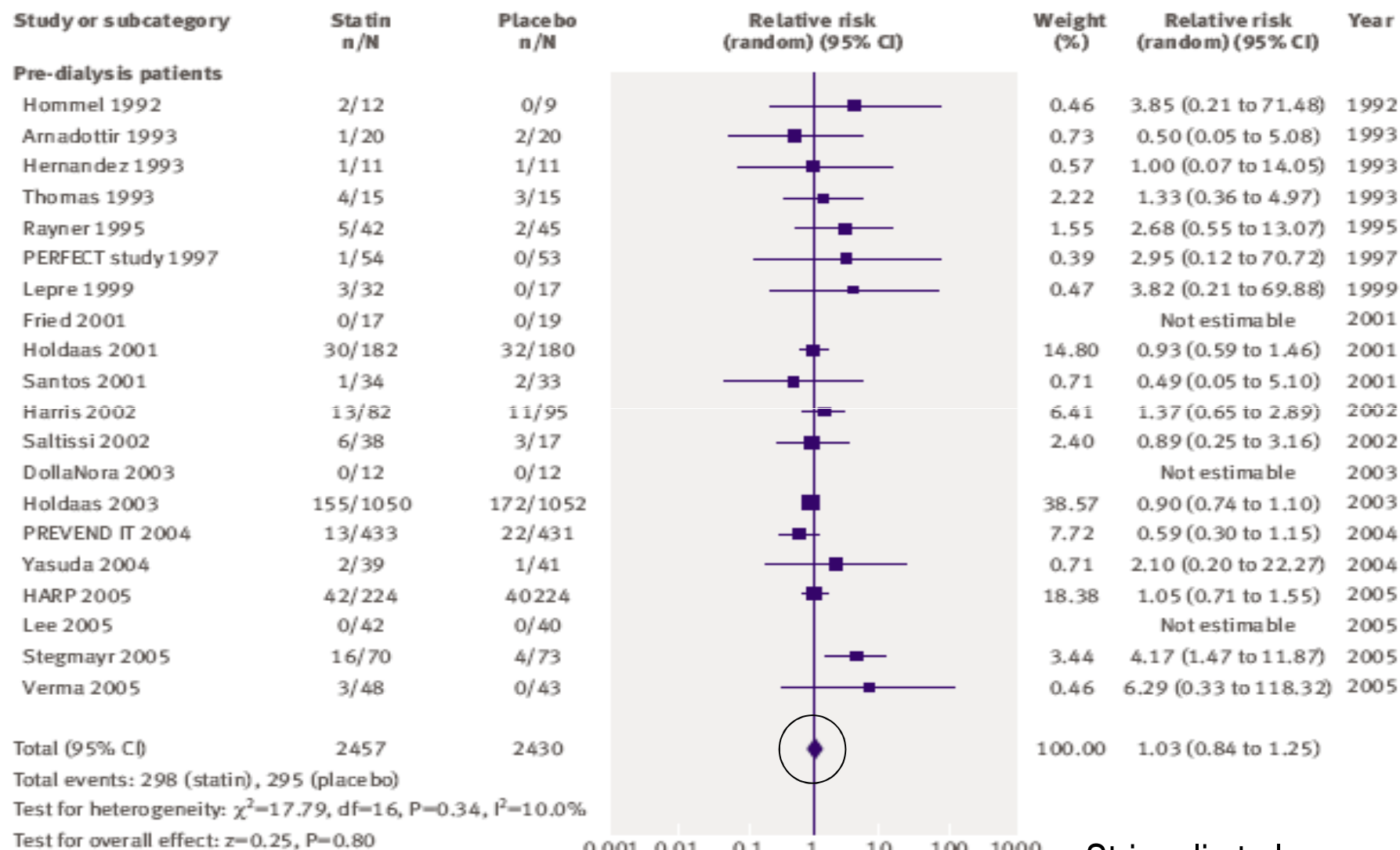


Effect of statins on cardiovascular mortality in stage 1-5 CKD



Vast majority of patients had eGFR > 30 ml/min and overt vascular disease

No excess withdrawals in statin-treated patients



0.001 0.01 0.1 1 10 100 1000
 Favours statin Favours placebo

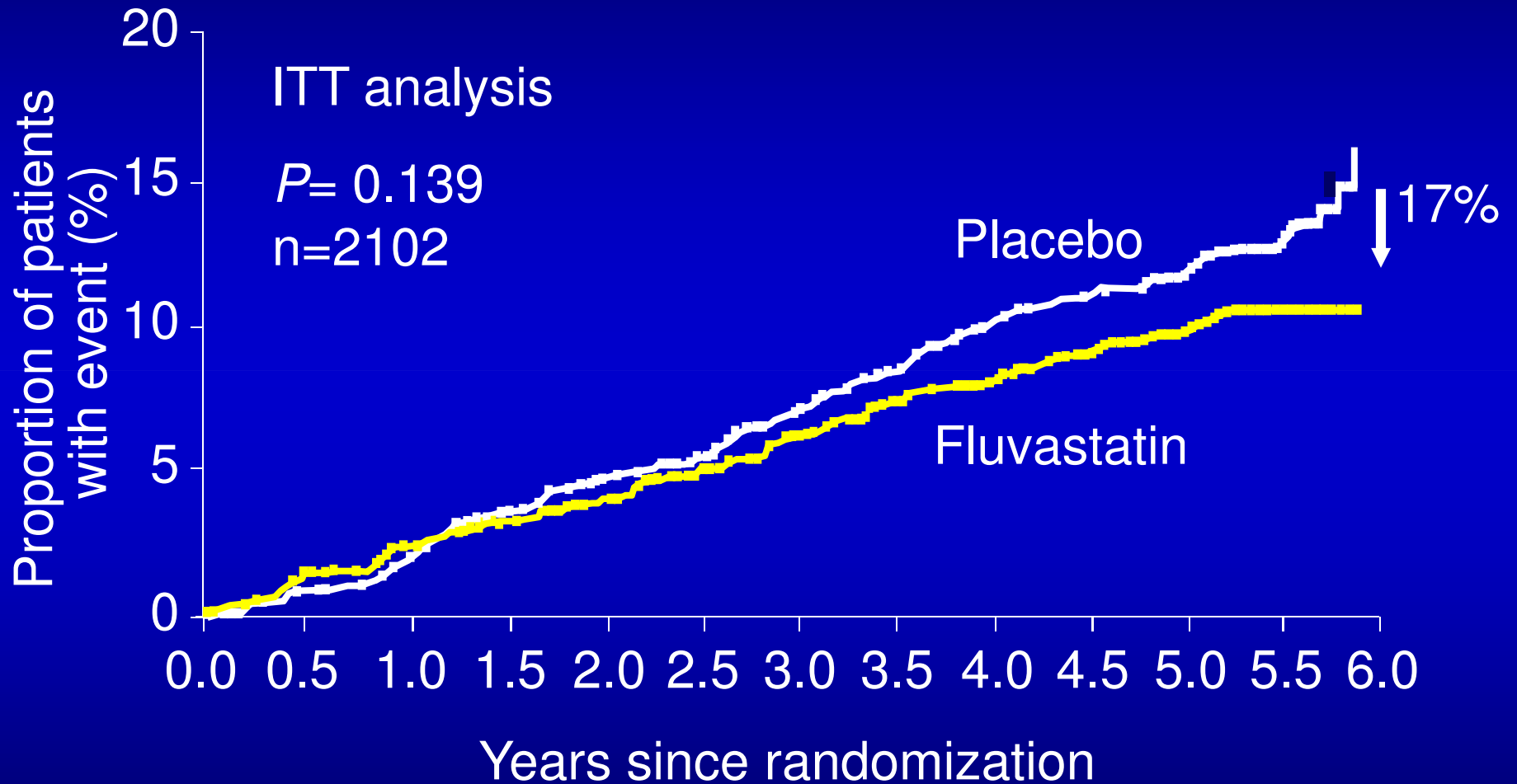
Strippoli et al
 BMJ 2008;336:645-651

**Trials of statins in
CKD patients following kidney
transplantation**

RCTs of statins in kidney transplant recipients examining CV events or death

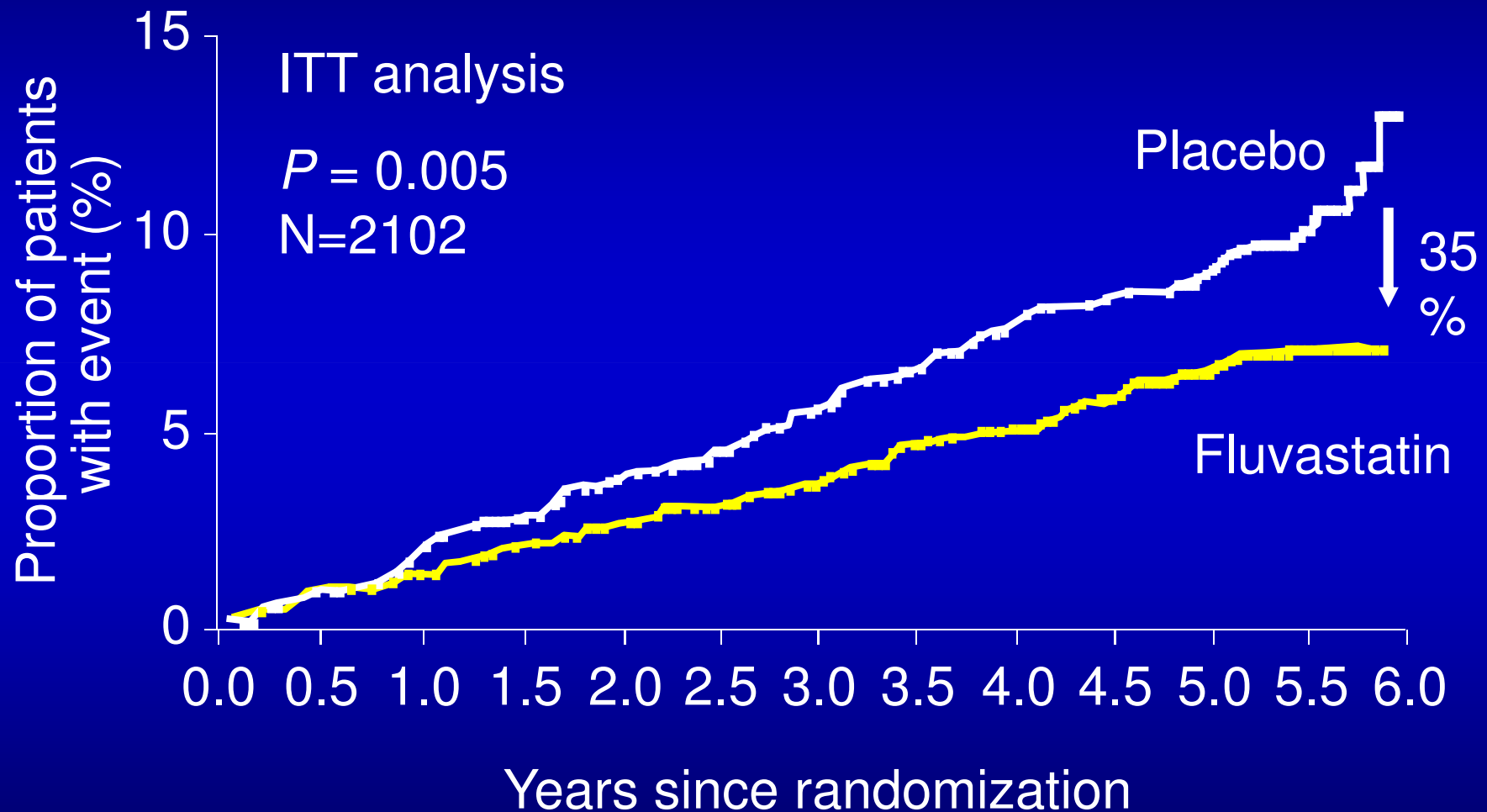
Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambühl P, Olsson AG, Hartmann A, Solbu DO, Pedersen TR; Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet.* 2003 Jun 14;361:2024-31.

ALERT: Cumulative Incidence of Major Adverse Cardiac Events



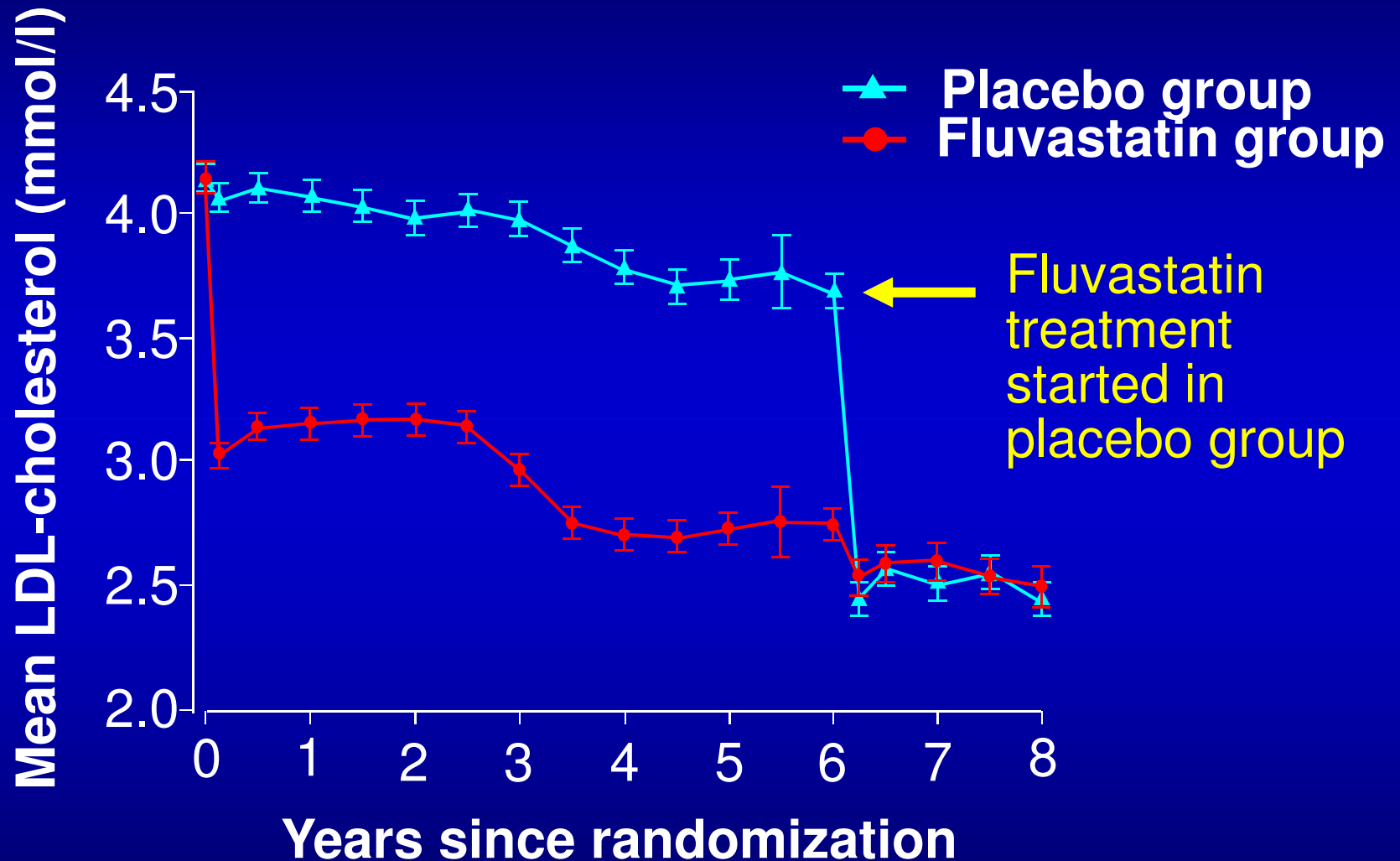
Holdaas et al Lancet 2003;361:2024

ALERT: Cumulative Incidence of Cardiac Death or Nonfatal definite MI



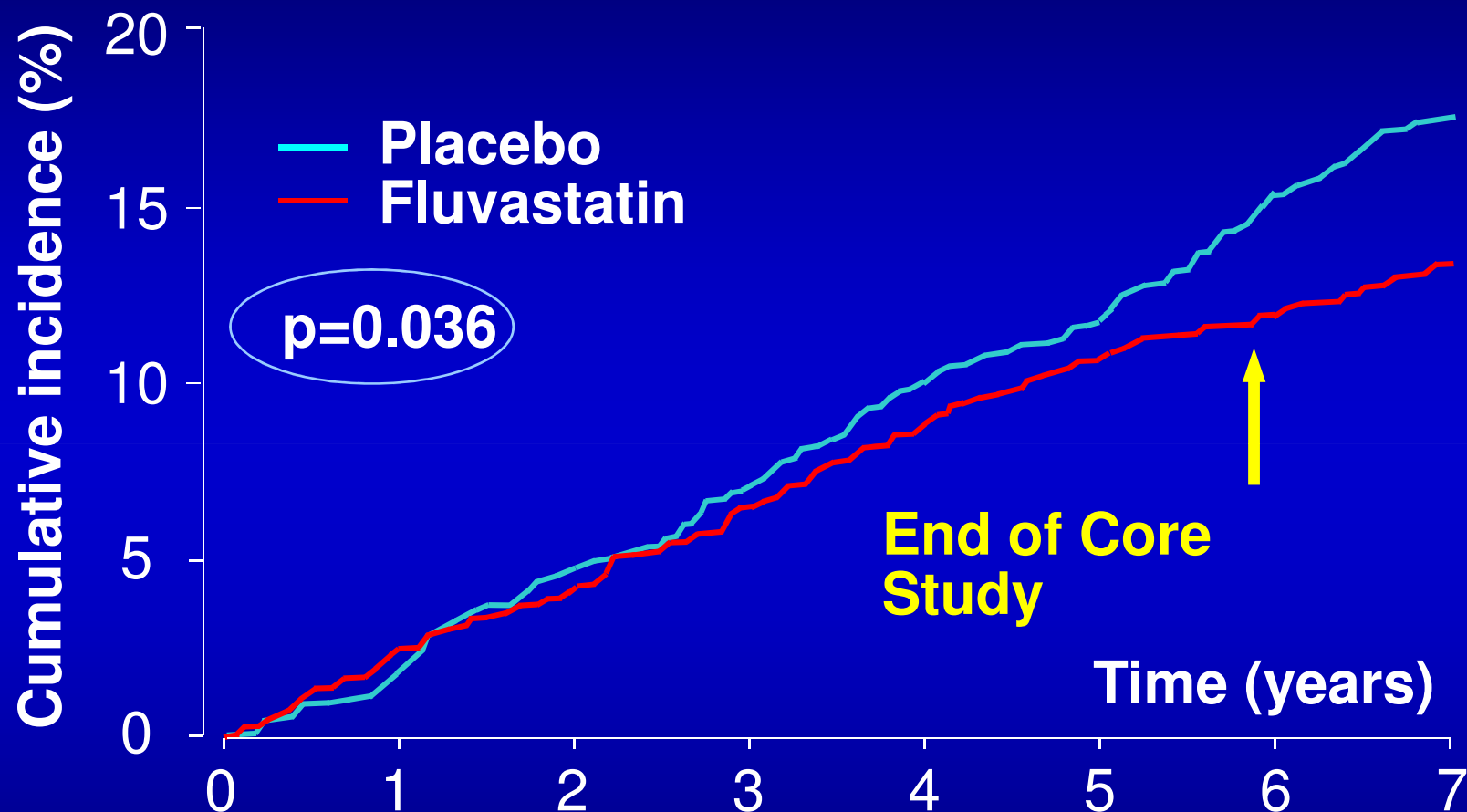
Holdaas et al Lancet 2003;361:2024

ALERT study LDL-cholesterol



Holdaas et al Lancet 2003;361:2024

ALERT+extension: Occurrence of MACE



Fluvastatin	1050	1009	974	930	885	836	755	691
Placebo	1052	1018	972	929	878	846	743	679

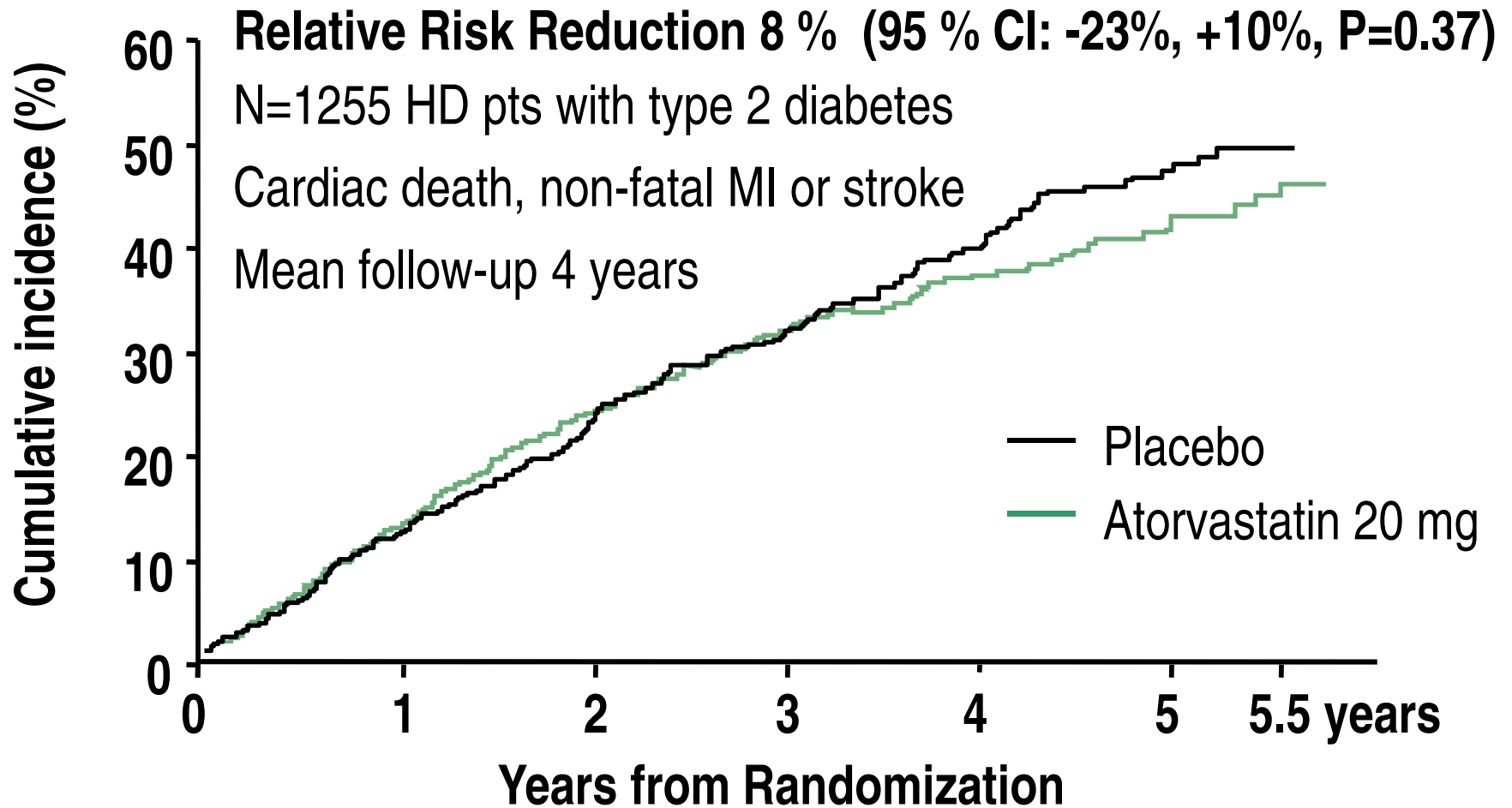
Trials of statins in CKD patients receiving dialysis

RCTs of statins in dialysis patients examining CV events or death

Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E, German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med.* 2005 Jul 21;353:238-48.

Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med.* 2009 Apr 2;360(14):1395-407.

4D Study: Primary composite endpoint



Placebo	636	532	383	252	136	51	29
Atorvastatin	619	515	378	252	136	58	19

Wanner et al NEJM 2005;353:238-48.

ESRF patients have the “wrong” CVD

Cause of death	4D	(USRDS)	CTT
CHD	9%	11%	42%
Other cardiac	35%	32%	7%
Stroke	6%	5%	7%
Non-vascular	50%	52%	44%

Baigent, Landray and Wheeler, Semin Dial 2007;20:498-503

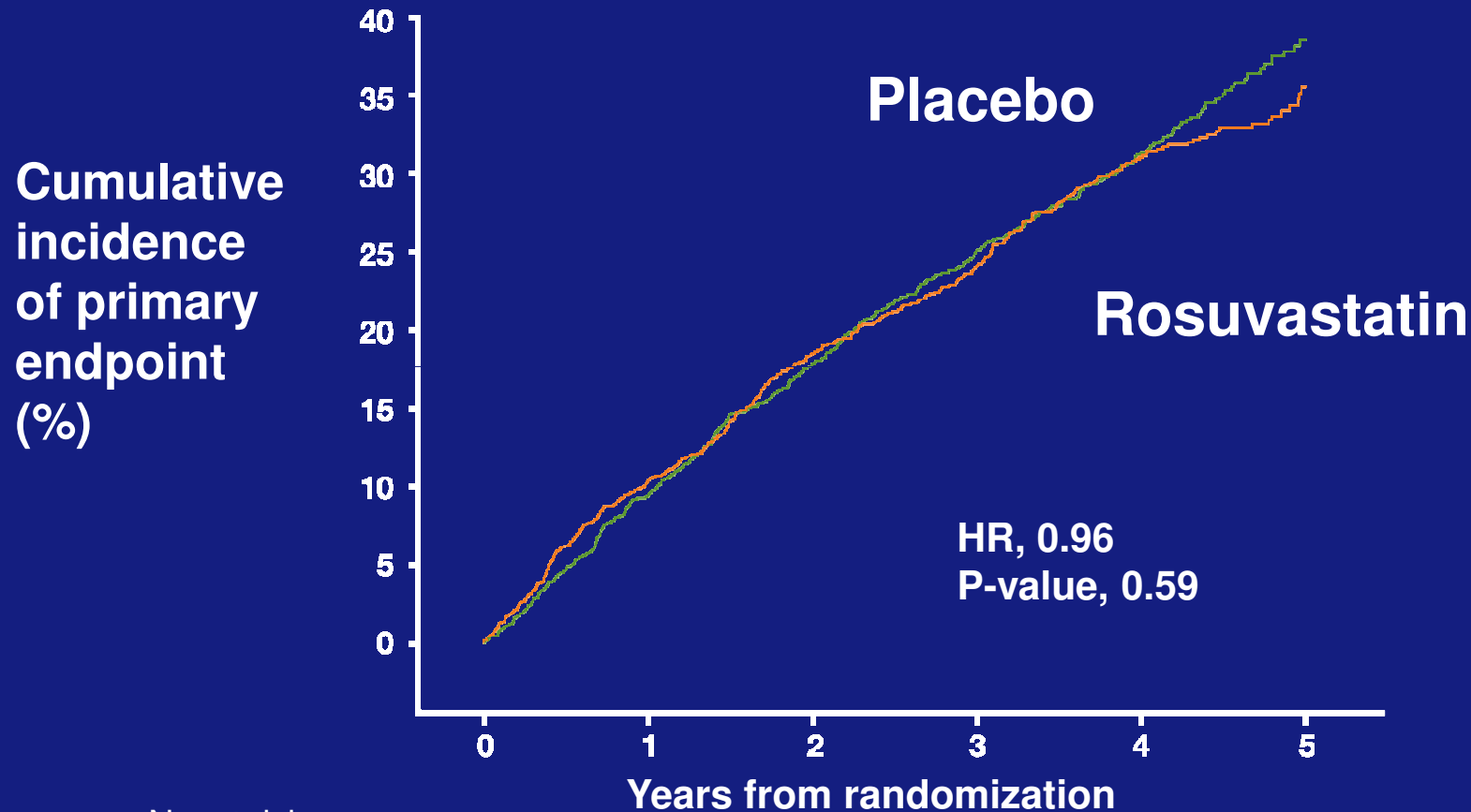
Risk reductions in 4D were predictable

Outcome	Predicted† RR	Observed RR (95% CI)
Primary endpoint	0.83	0.92 (0.77-1.10)
Cardiac events	0.84	0.82 (0.68-0.99)
Stroke	0.75	1.33 (0.90-1.97)
All-cause mortality	0.93	0.93 (0.79-1.08)

†Rate ratio predicted based on a difference of ~1.0 mmol/L at 1 year after randomization in the 4D trial, as derived from the results of the Cholesterol Treatment Trialists' (CTT) meta-analysis.

AURORA: primary endpoint

Kaplan-Meier estimate of time to first major CV event



No. at risk:

Rosuvastatin

1390

1152

962

826

551

148

Placebo

1384

1163

952

809

534

153

Why were 4D and AURORA negative?

1. Lack of powered
2. Excluded the highest-risk patients
3. High drop-out rates
4. Statins don't work in dialysis patients
 - A. "Different" cardiovascular disease
 - B. "Statin resistance"

Stripolli GF, Craig JC NEJM 2009;360:1455-1457

Statins in CKD patients

Summary of the current evidence

CKD Stage	Cardioprotection
Stage 1	Yes*
Stage 2	Yes*
Stage 3	Yes*
Stage 4	?
Stage 5	??
Dialysis	No clear benefit
Transplant	Probably yes

* Post hoc analysis among patients with vascular disease

Statins in CKD patients: Summary of the current evidence

CKD Stage	Cardioprotection
Stage 1	Yes*
Stage 2	Yes*
Stage 3	Yes*
Stage 4	?
Stage 5	??
Dialysis	No clear benefit
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SHARP

* Post hoc analysis among patients with vascular disease

Ongoing statin studies in CKD patients

- **Study of Heart and Renal Protection (SHARP)**
 - 9438 CKD patients without overt CVD
 - 6408 patients with stage 3-5 CKD not on dialysis
 - Ezetimibe 10 mg/simvastatin 20 mg vs. placebo



Ongoing statin studies in CKD patients

- **Study of Heart and Renal Protection (SHARP)**
 - 9438 CKD patients with a history of CVD
 - 6408 patients with CKD not on dialysis
 - Ezetimibe 10 mg + statin 20 mg vs. placebo

Results to be presented at ASN
Saturday 20th November 12:05 hrs



Who should get statins?

- Patients with CKD stage 1-3 who have overt cardiovascular disease or who are at high risk based on exposure to conventional CV risk factor.
- Patients who have received a kidney transplant.

Spare slides

JUPITER: New territory for statins

Inclusion criteria:

LDL < 3.4 mmol/l

CRP ≥ 2.0 mg/l

Intervention:

Rosuvastatin 20mg

vs. placebo

Endpoint:

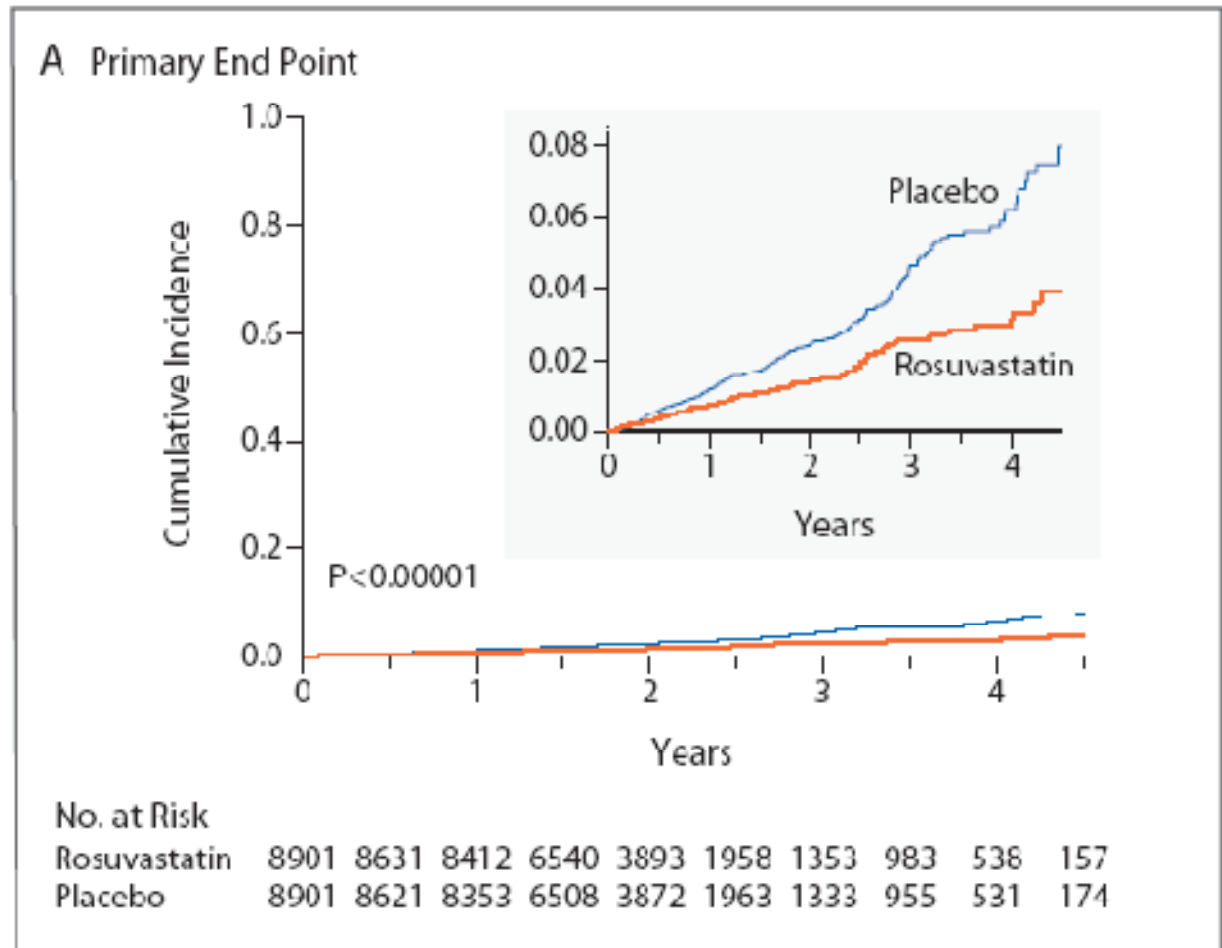
Myocardial Infarction

Stroke

Revascularisation

Hospitalized for angina

Death from CV causes



HR = 0.56 (0.46-0.69) $p < 0.00001$

Ridker et al New Engl J Med 2008;359:2195-2207

Treatment thresholds for dyslipidemia in chronic kidney disease (stage 5)

- Triglycerides \geq 500 mg/dl (5.65 mmol/l)
- LDL cholesterol \geq 100 mg/dl (2.59 mmol/l)
- LDL cholesterol \leq 100 mg/dl (2.59 mmol/l), Triglycerides \geq 200 mg/dl (2.26 mmol/l) and non-HDL chol \geq 130 mg/dl (3.36 mmol/l)

Kidney Disease Outcomes Quality Initiative (K/DOQI) taskforce
Am J Kidney Dis, April 2003;41(suppl 3):S1-S92