Controversies Conference: Diabetic Kidney Disease

Statins

Christoph Wanner

Endpoints: Renal

THE LANCET

Hypothesis:

LIPID NEPHROTOXICITY IN CHRONIC PROGRESSIVE GLOMERULAR AND TUBULO-INTERSTITIAL DISEASE

J.F. Moorhead , M. El-Nahas , M.K. Chan , Z. Varghese

Abstract

It is hypothesised that chronic progressive kidney disease may be mediated by abnormalities of lipid metabolism. A series of

1982;320:1309-1311

Endpoints: Renal

THE LANCET

Hypothesis:

LIPID NEPHROTOXICITY IN CHRC
AND TUBULO-INTERSTITIAL DISE

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1982;320:1309-1311

Cardiovascular and Renal

THE LANCET

Volume 377 · Number 9784 · Pages 2151–2248 · June 25–July 1, 2011 www.thelancet.com

Randomized:

"Lowering LDL cholesterol with the combination of simvastatin plus ezetimibe safely reduces the risk of major atherosclerotic events in a wide range of patients with chronic kidney disease."

See Articles page 2181

2011;377:2181-2192

Cholesterol Treatment Trialist's CTT Collaboration

Articles

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Lancet 2008; 371: 117–25

Cholesterol Treatment Trialist's CTT Collaboration

Articles

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

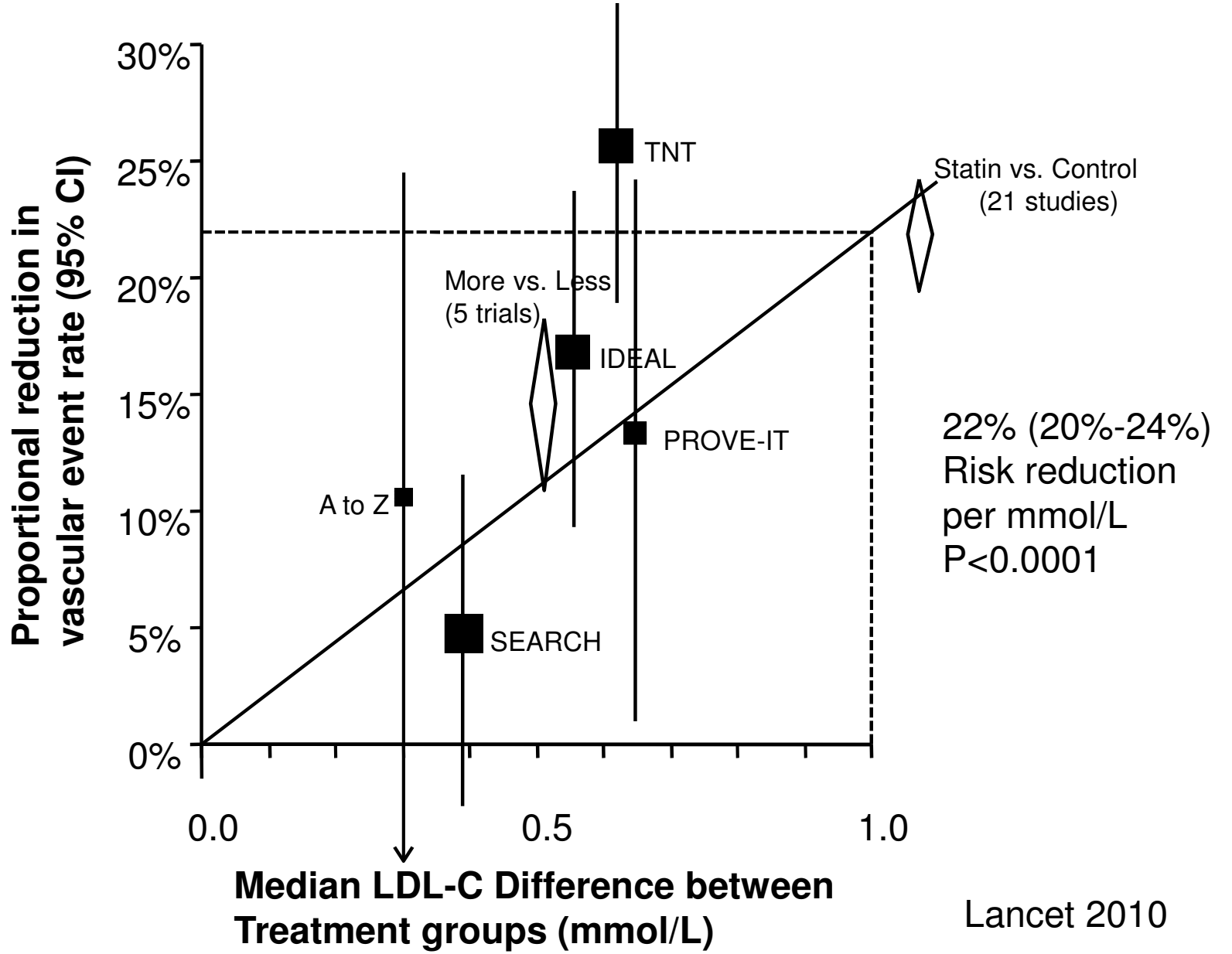
*Cholesterol Treatment Trialists' (CTT) Collaboration**

Lancet 2010; 376: 1670–81

More versus less statin		
PROVE–IT	4162	A80 *vs* P40
A to Z	4497	S40 then S80 *vs* placebo then S20
TNT		
IDEAL		
SEARCH		
ASCOT–LLA	10 305	A10 *vs* placebo
ALERT	2102	F40 *vs* placebo
CARDS	2838	A10 *vs* placebo
ALLIANCE**	2442	A10–80 *vs* usual care
4D**	1255	A20 *vs* placebo
ASPEN**	2410	A10 *vs* placebo
MEGA**††	8214	P10–20 *vs* usual care
JUPITER**	17 802	R20 *vs* placebo
GISSI–HF**	4574	R10 *vs* placebo
AURORA**	2773	R10 *vs* placebo

Lancet 2010

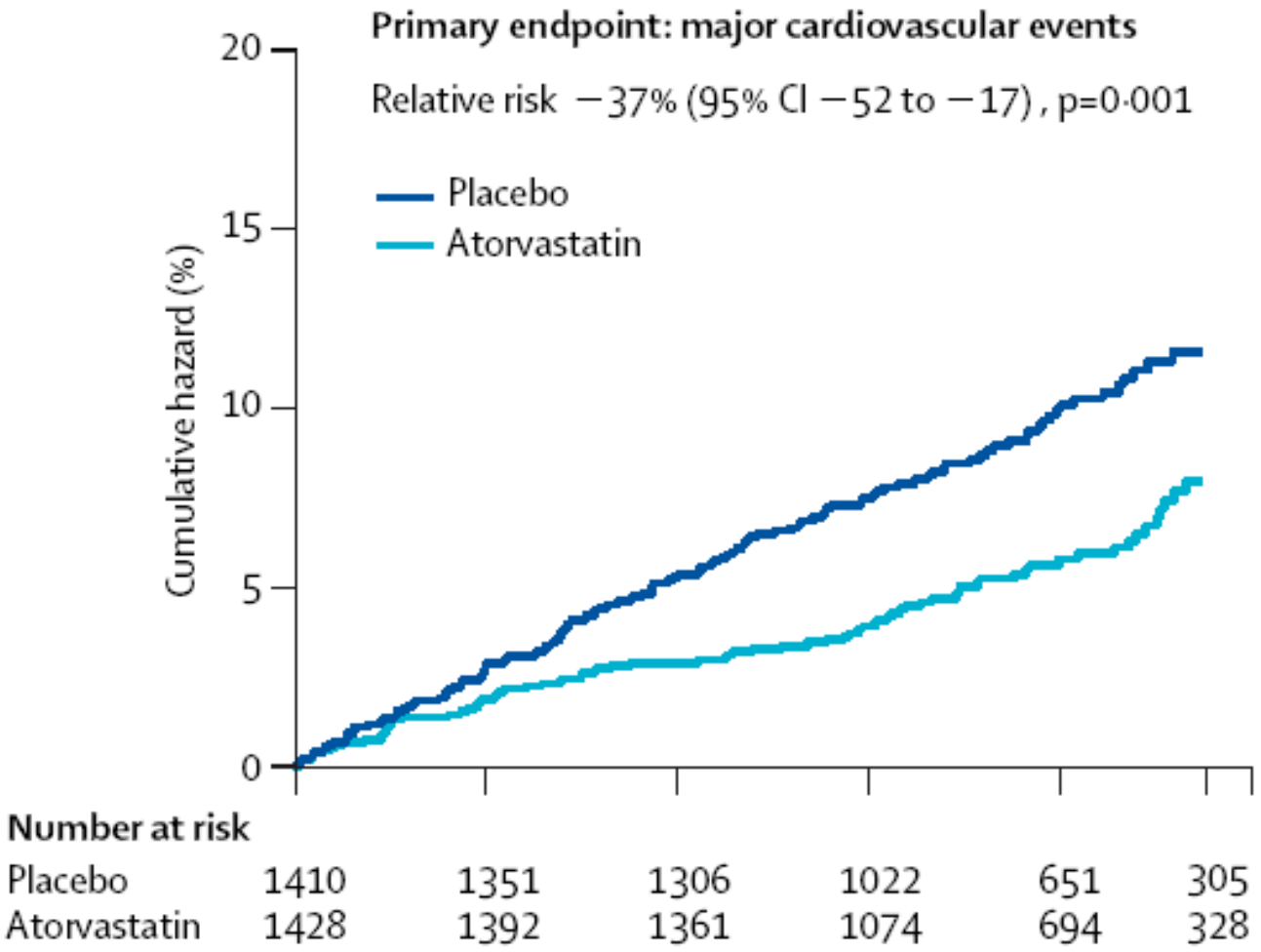
CTT Metaanalysis: Proportional Reduction of MAJOR VASCULAR EVENTS versus absolute LDL-C Reduction



22% (20%-24%)
Risk reduction
per mmol/L
P<0.0001

Lancet 2010

Statins prevent first CV event in T2DM
CARDS study



Colhoun H et al, Lancet 2004; 364: 685-96

CARDS Study

Definition of kidney impairment	eGFR < 60 ml/min/1.73m2
Randomized statin	Atorvastatin 10 mg/d
# treated / # with DM and CKD	482 / 970
CVD outcome vs P	All cause mortality 5.6 vs 6.1 % Stroke 1.2 vs 3.1% Unstable Angina, ACS or revascularization 1.04 vs 3.07%
Kidney outcome vs P	20.5% regression from micro to normoalbuminuria vs 19.4%

Coronary Heart Disease

Effect of Pravastatin on Cardiovascular Events in People With Chronic Kidney Disease

Marcello Tonelli, MD, SM; Chris Isles, MD; Gary C. Curhan, MD, ScD; Andrew Tonkin, MD; Marc A. Pfeffer, MD, PhD; James Shepherd, MD; Frank M. Sacks, MD; Curt Furberg, MD; Stuart M. Cobbe, MD; John Simes, MD, MSc; Timothy Craven, MSPH; Malcolm West

Meta-analysis of data from the **Pravastatin Pooling Project (PPP)**

- WOSCOPS (Primary Prevention)
- LIPID (Secondary Prevention)
- CARE (Secondary Prevention)

Circulation 2004;110:1557-1563

JASN 2005;16:3748-3754

Coronary Heart Disease

Effect of Pravastatin on Cardiovascular Events in People With Chronic Kidney Disease

Effect of Pravastatin in People with Diabetes and Chronic Kidney Disease

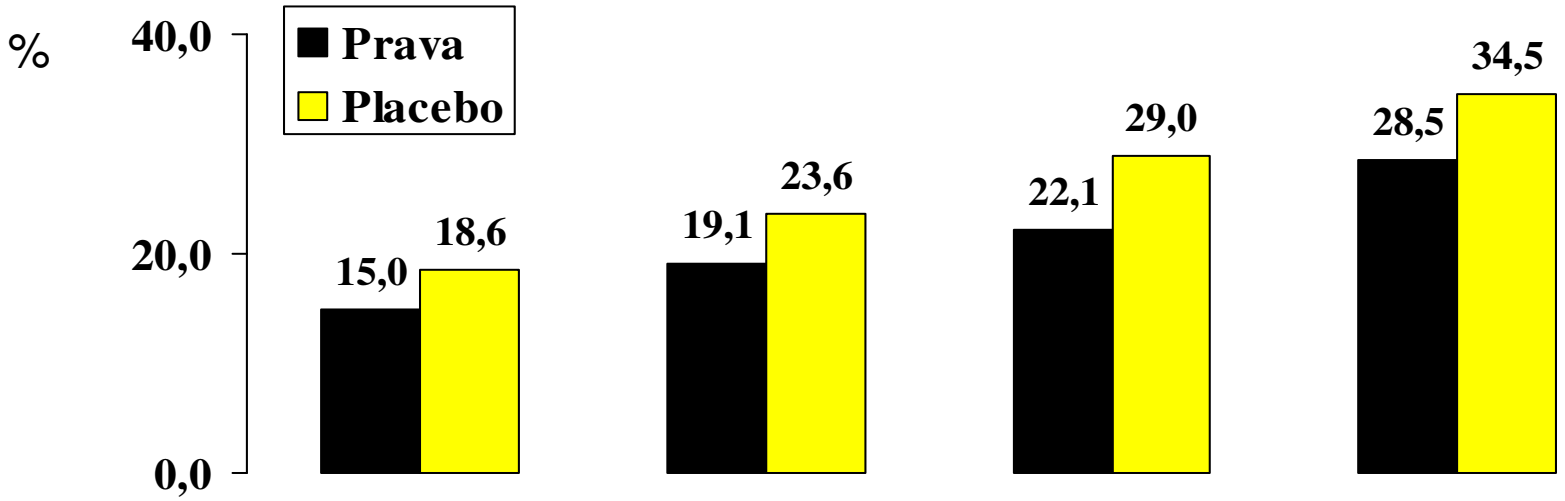
Marcello Tonelli,[*†‡] Anthony Keech,[§] Jim Shepherd,[‖] Frank Sacks,[¶] Andrew Tonkin,[#] Chris Packard,[**] Marc Pfeffer,[††] John Simes,[§] Chris Isles,[‡‡] Curt Furberg,[§§] Malcolm West,[‖‖] Tim Craven,[§§] and Gary Curhan[¶¶##]

Divisions of [*]Nephrology and [†]Critical Care Medicine, University of Alberta, Edmonton, Alberta, Canada; [‡]Institute of Health Economics, Edmonton, Alberta, Canada; [§]NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; [‖]University of Glasgow, Glasgow, Scotland, United Kingdom; Departments of [¶]Nutrition and [¶¶]Epidemiology, Harvard School of Public Health, Boston, Massachusetts; [#]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; [**]Department of Pathological Biochemistry, Glasgow Royal Infirmary, Glasgow, Scotland, United Kingdom; [††]Cardiovascular Division and [##]Renal Division and Channing Laboratory, Brigham and Women's Hospital, Boston, Massachusetts; [‡‡]Department of Medicine, Dumfries and Galloway Royal Infirmary, Dumfries, Scotland, United Kingdom; and [§§]Wake Forest University School of Medicine, Winston-Salem, North Carolina; [‖‖]Department of Medicine, University of Queensland, Brisbane, Australia

JASN 2005;16:3748-3754

Primary Endpoint (extended)

Fatal CVD, non-fatal MI, Revascularisations & (stroke)



DM	-	-	+	+
CKD St. 2+3	-	+	-	+
Subjects	14108	4185	854	590
ARR	3.6	4.5	6.9	5.9

Statins in ESRD

ORIGINAL ARTICLE

Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

Christoph Wanner, M.D., Vera Krane, M.D., Winfried März, M.D., Manfred Olschewski, M.Sc., Johannes F.E. Mann, M.D., Günther Ruf, M.D., and Eberhard Ritz, M.D., for the German Diabetes and Dialysis Study Investigators*

NEJM 2005;353:238-248

ORIGINAL ARTICLE

Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

Bengt C. Fellström, M.D., Ph.D., Alan G. Jardine, M.D., Roland E. Schmieder, M.D., Hallvard Holdaas, M.D., Ph.D., Kym Bannister, M.D., Jaap Beutler, M.D., Ph.D., Dong-Wan Chae, M.D., Ph.D., Alejandro Chevaile, M.D., Stuart M. Cobbe, M.D., Carola Grönhagen-Riska, M.D., Ph.D., José J. De Lima, M.D., Ph.D., Robert Lins, M.D., Ph.D., Gert Mayer, M.D., Alan W. McMahon, M.D., Hans-Henrik Parving, M.D., D.M.Sc., Giuseppe Remuzzi, M.D., Ola Samuelsson, M.D., Ph.D., Sandor Sonkodi, M.D., Ph.D., D. Sci., Gultekin Süleymanlar, M.D., Dimitrios Tsakiris, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Vasil Todorov, M.D., Ph.D., Andrzej Wiecek, M.D., Ph.D., Rudolf P. Wüthrich, M.D., Mattis Gottlow, M.Sc., Eva Johnsson, M.D., Ph.D., and Faiez Zannad, M.D., Ph.D., for the AURORA Study Group*

NEJM 2009;360:1395-1407

SHARP
STUDY OF HEART AND RENAL PROTECTION

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

Lancet 2011;377:2181-2192

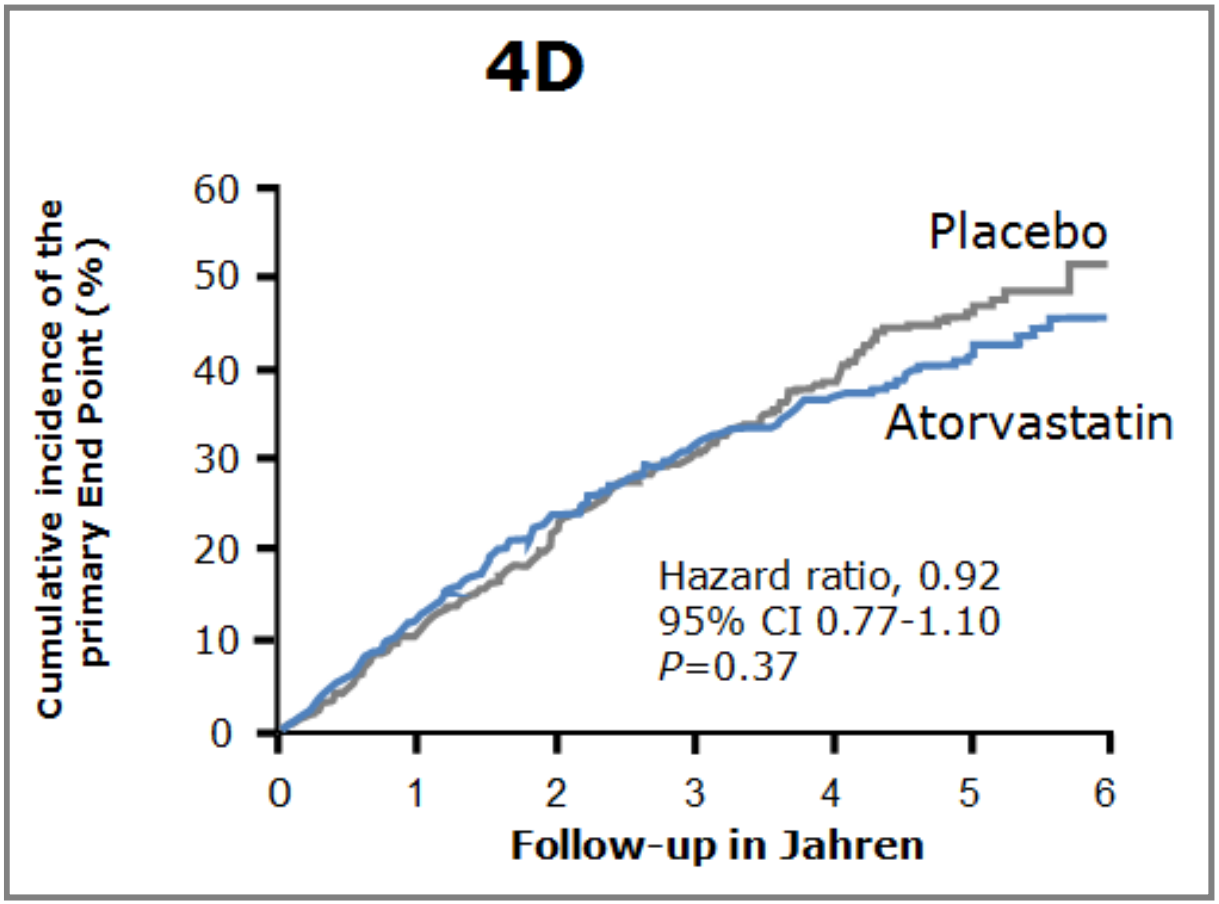
n=9.052

Hämodialysis	2.527
Peritonealdialysis	496
CKD	6.029
CKD3b	1.853
CKD4	2.565
CKD5	1.221

20 mg Simvastatin / 10 mg Ezetimibe

versus placebo, median follow-up 4.9 years

Patients: 62 years, 37% women, 23% diabetics,
eGFR 27 ml/min/1,73m^2 in CKD stages 3-5



„Secondary Prevention“

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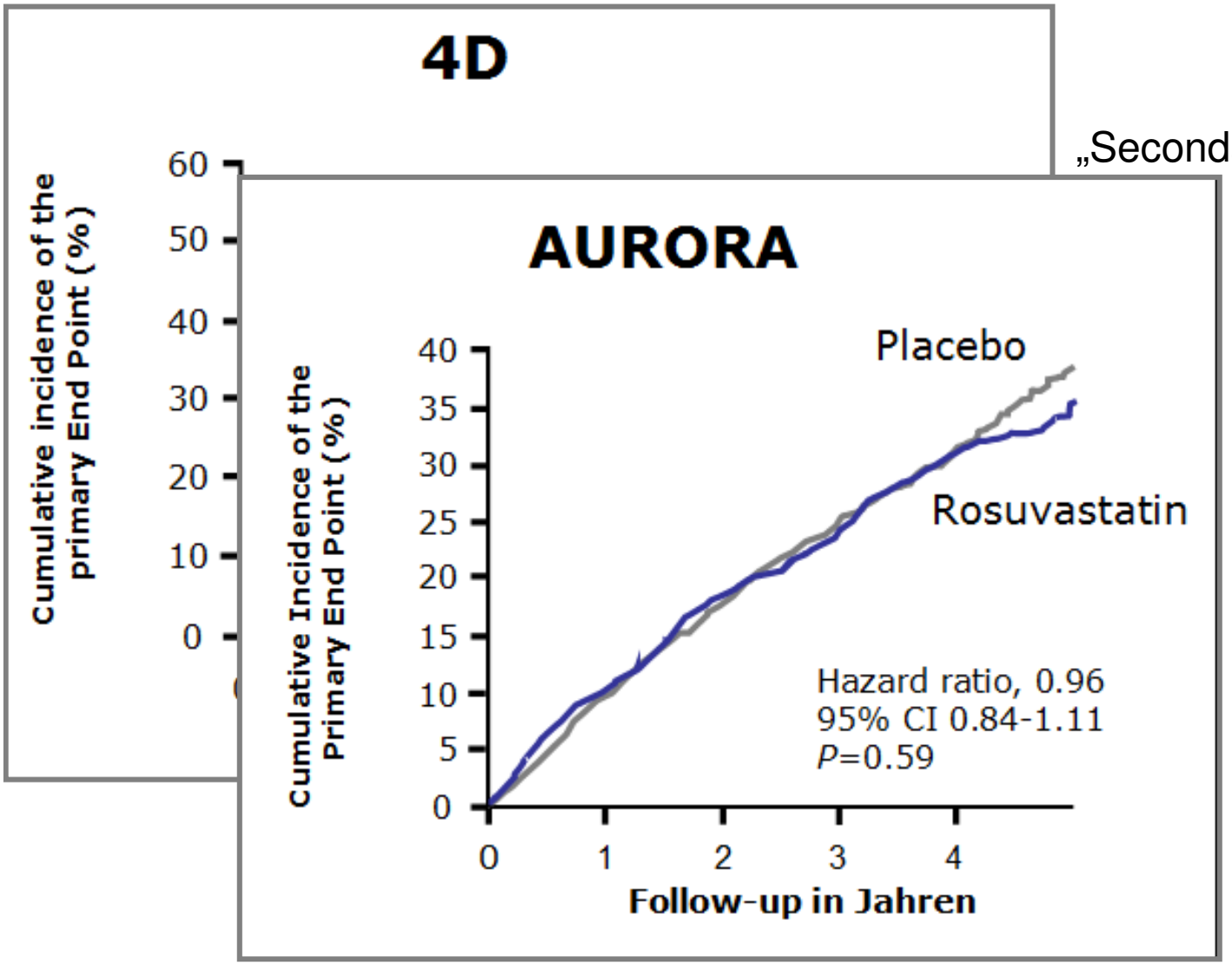
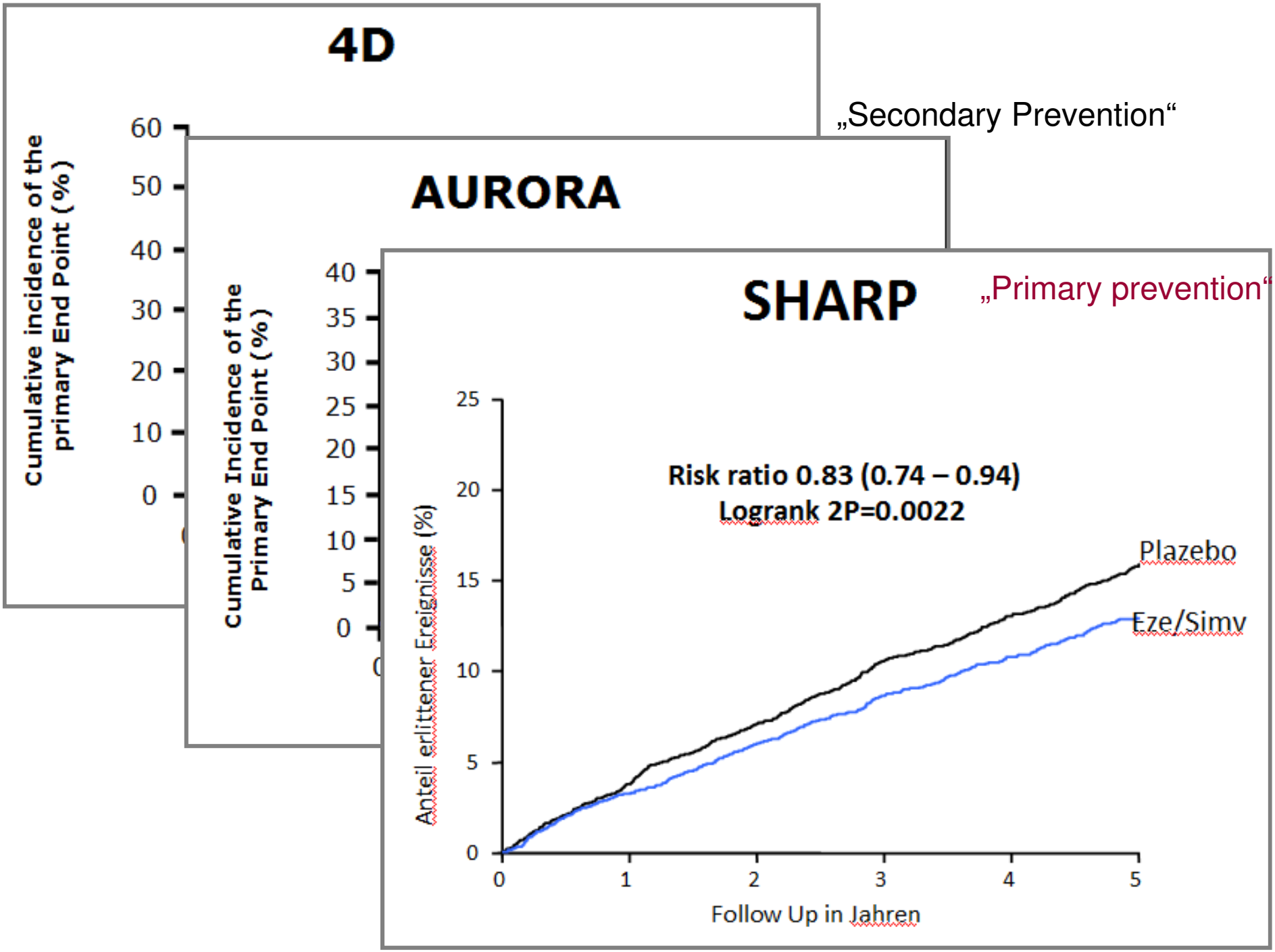


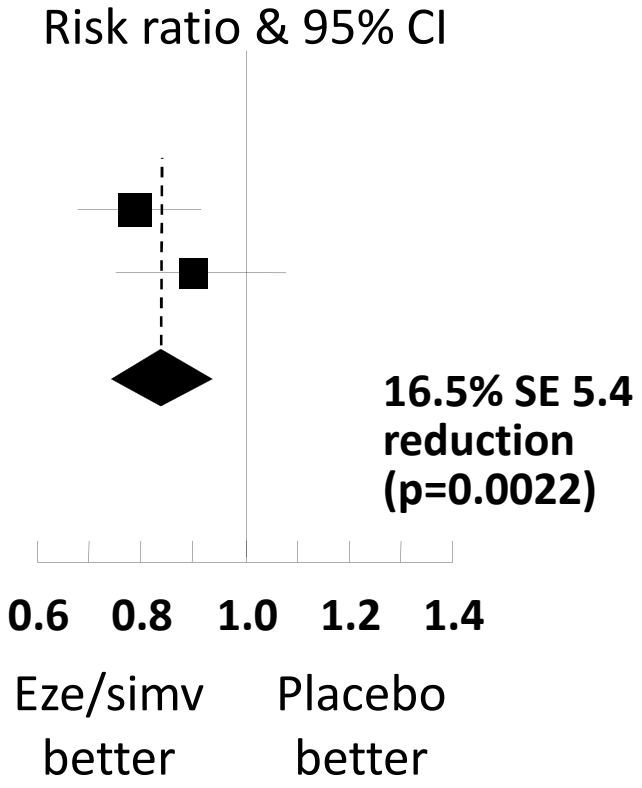
„Secondary Prevention“



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%)
Any patient	**526 (11.3%)**	**619 (13.4%)**

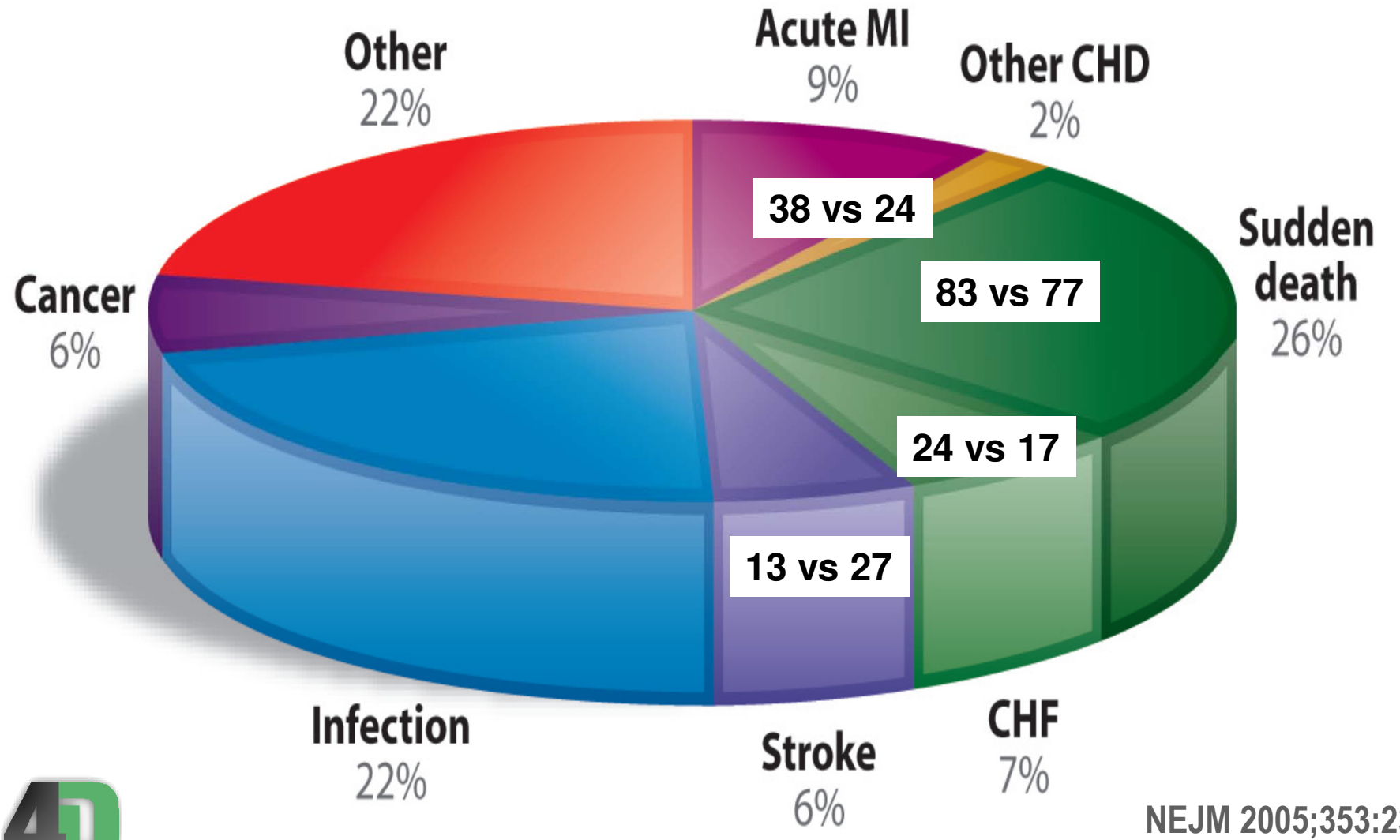
No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)



Proportional mortality in statin trials

	USRDS	4D	AURORA	SHARP	CTT
Coronary Heart Disease	6	9	23	9	42
Other cardiac	33	35	14	16	15
Other vascular	10	9	7	11	
All vascular	49	50	44	37	57
Non-vascular	51	50	56	63	43
Unknown				10	
	AJKD 2005	NEJM 2005	NEJM 2009	Lancet 2011	Lancet 2005/2010

Causes of Death in T2DM on Dialysis



NEJM 2005;353:238
JASN 2008;19:1065

Primary endpoints

4D - cardiovascular:

death from cardiac causes,
nonfatal myocardial infarction
stroke

AURORA - cardiovascular:

death from cardiovascular causes,
nonfatal myocardial infarction,
nonfatal stroke

SHARP - atherosclerotic:

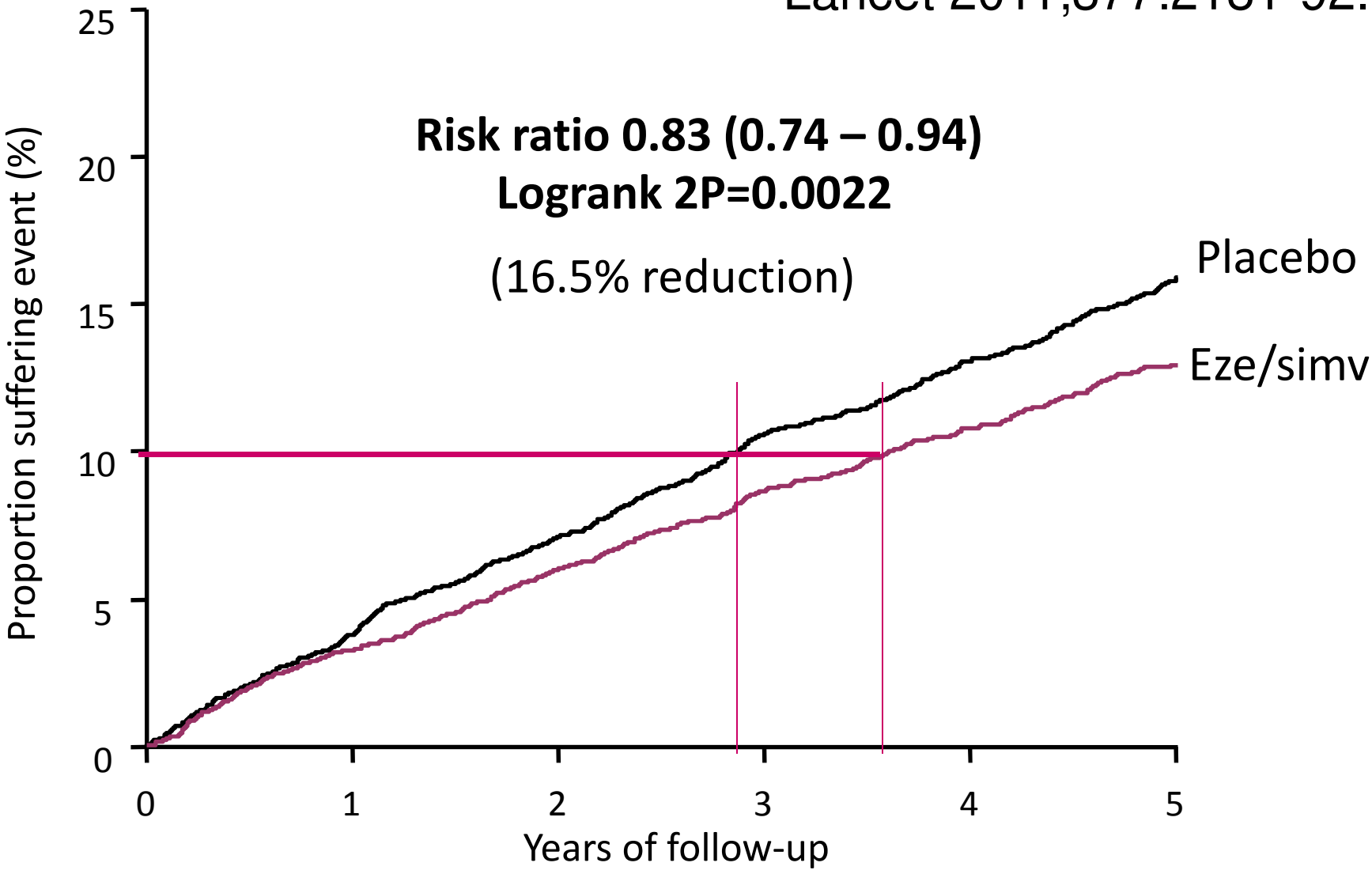
major coronary event
non-haemorrhagic stroke
any revascularization

SHARP: Public health impact of findings

Intention-to-treat analyses indicate that 21 per 1000 fewer patients had MAE over about 5 years (NNT=48)

SHARP: Major Atherosclerotic Events

Lancet 2011;377:2181-92.



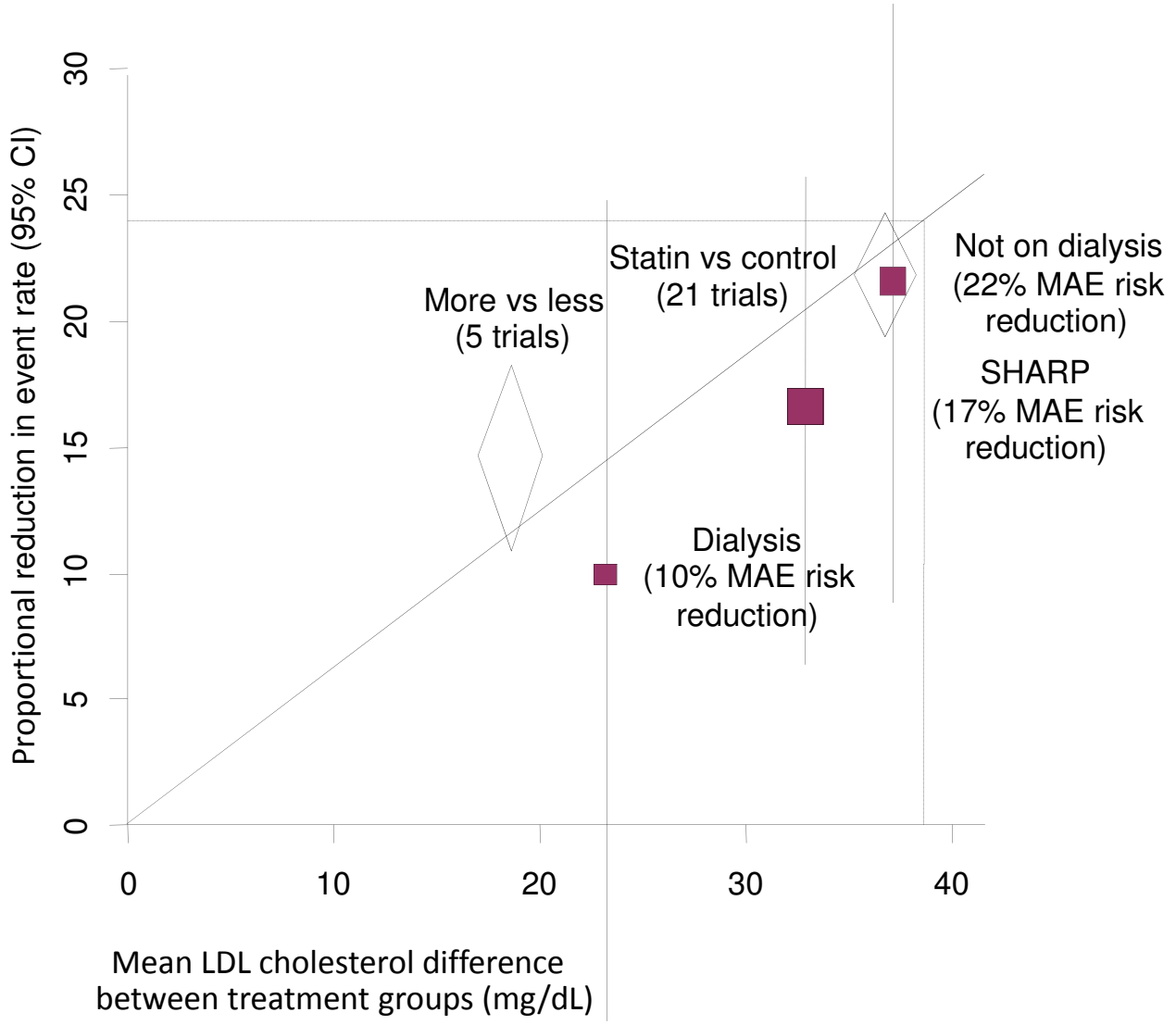
Compliance

Impact of Study medication-compliance on lowering LDL-C over time

Time period	LDL- lowering drug use			LDL-C Difference (mg/dL)		
	Eze/ Simva	Placebo	Netto Compliance	Eze/ Simva	Placebo	Absolute Difference
~ 1 year	77%	3%	74%	-42	+1	-42
~ 2.5 y	71%	9%	61%	-39	-6	-33
~ 4 years	68%	14%	55%	-32	-3	-30

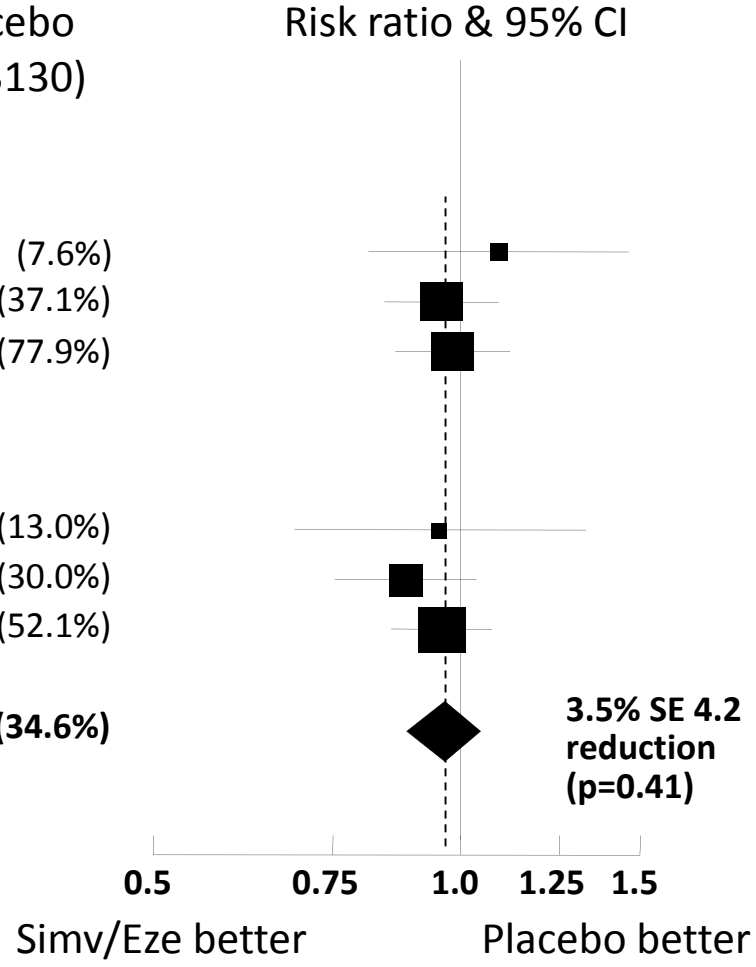
Netto Compliance = at least 80% use of study medication

CTT: Effect on major vascular/atherosclerotic events by trial-midpoint LDL-C reduction



SHARP: renal outcomes by subgroup end-stage renal disease

	Simv/Eze (n=3117)		Placebo (n=3130)	
MDRD estimated GFR (mL/min/1.73m²)				
≥30	96	(8.4%)	83	(7.6%)
≥15 and <30	454	(36.4%)	489	(37.1%)
<15	471	(76.7%)	473	(77.9%)
Urinary Albumin:Creatinine Ratio (mg/g)				
<30	68	(12.5%)	73	(13.0%)
≤30 and <300	281	(27.2%)	323	(30.0%)
≥300	621	(51.6%)	602	(52.1%)
All patients	**1057**	**(33.9%)**	**1084**	**(34.6%)**



SHARP
STUDY OF HEART AND RENAL PROTECTION

What needs to be done

patients on dialysis. In our view, comprehensive trial-level meta-analyses or meta-analyses of individual patient data are now required to evaluate definitively the existing evidence for statins in patients with differing stages of kidney disease.

Palmer and Strippoli *Nat. Rev. Nephrol*. **7**, 609–611 (2011)

Thank you for your attention !