

VYTORIN[®] (ezetimibe/simvastatin) and ZETIA[®] (ezetimibe) in Patients with Chronic Kidney Disease

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The SHARP Study

Study of Heart and Renal Protection

Agenda

- *Dr. J. Tucker, Merck Regulatory Affairs*
 - Introduction
- *Prof. C. Baigent, University of Oxford*
 - Background and Rationale
 - Study Results
- *Prof. R. Collins, University of Oxford*
 - Key Design Points
- *Dr. T. Musliner, Merck Clinical Research*
 - Merck's Perspective on SHARP

The SHARP Study

Study of Heart and Renal Protection

- SHARP was designed and implemented by the Clinical Trial Service Unit (CTSU) at the University of Oxford
- SHARP study was funded by a joint venture of Merck and Schering-Plough
- University of Oxford was the regulatory sponsor
- SHARP data are proprietary to the CTSU and are responsible for the conduct of all analyses
- CTSU and SHARP Steering Committee (SC) also had responsibility for the Statistical Analysis Plan (SAP)

SHARP Study: Rationale

- Patients with chronic kidney disease (CKD) are at a greatly increased risk of cardiovascular (CV) morbidity and mortality
- CKD patients have largely been excluded from statin outcome trials
 - Concerns about reduced elimination of statins and consequently higher risk of adverse effects
 - Doubts about the ability of lipid-lowering treatments to affect major components of the CV disease of CKD patients
- SHARP was designed to address the question of whether a substantial reduction of LDL-C can reduce CV risk in patients with CKD

The SHARP Study

- Placebo-controlled, double-blind
- Multicenter
 - 380 sites
- Multinational
 - 18 countries
- Large study population
 - 9438 patients with CKD

SHARP Study: Main Comparisons

- Primary comparison in the original protocol
 - Major vascular event (MVE)
 - Non-fatal MI or cardiac death
 - Non-fatal or fatal stroke
 - Revascularization procedure
- Key outcome in SAP approved by Steering Committee
 - Major atherosclerotic event (MAE)
 - Non-fatal MI or coronary death
 - Ischemic stroke
 - Revascularization procedure

SHARP Study: Main Comparisons

- SHARP SC blind to the effect of study treatment recommended changing the protocol-defined primary outcome
 - Minimize dilution of a potential benefit on atherosclerotic outcomes by a lack of benefit on non-atherosclerotic components
 - Primary analysis to include all patients allocated to ezetimibe/simvastatin 10/20 mg or placebo at any time point in the study
- Although Merck believed the change was justified on scientific merit, Merck decided not to support the change based on the timing of the proposed changes
- SC recommendations were incorporated into the SAP, before study completion and unblinding
- Results for MVE and MAE are very consistent

The SHARP Study

- Results of SHARP show that in patients with chronic kidney disease ezetimibe/simvastatin 10/20 mg clearly reduces the risk of major cardiovascular events
- Safety profile of ezetimibe/simvastatin 10/20 mg was consistent with the currently approved US product circular for VYTORIN[®] and ZETIA[®]
 - Very few cases of myopathy or rhabdomyolysis, no excess of liver disease, or gallstone complications, and no new adverse effects were found with ezetimibe/simvastatin
 - No increase in cancer incidence or mortality, overall or at any site, even with prolonged follow-up
- Ezetimibe/simvastatin 10/20 mg is thus a well tolerated treatment to reduce the high risk of major cardiovascular events in CKD patients

Proposed New Indications VYTORIN[®] and ZETIA[®]

Prevention of Major Cardiovascular Events in CKD

- VYTORIN is indicated to reduce the risk of major cardiovascular events in patients with chronic kidney disease
- The combination of ZETIA and simvastatin is indicated to reduce the risk of major cardiovascular events in patients with chronic kidney disease

Oxford

- *Sir Rory Collins - Chair, SHARP Steering Committee*
Professor of Medicine and Epidemiology
University of Oxford, Oxford, England
- *Dr. Colin Baigent - SHARP Chief Investigator*
Professor of Epidemiology
University of Oxford, Oxford, England
- *Dr. Martin Landray – SHARP Co-principal Investigator*
Reader in Epidemiology
University of Oxford, Oxford, England

Consultants

- *Thomas P. Bersot, MD, PhD*
Professor of Medicine
University of California, San Francisco
- *W. Virgil Brown, MD*
Professor Emeritus
Emory University School of Medicine, Atlanta
- *Charles Herzog, MD*
Director, Cardiovascular Special Studies Center, US Renal Data System
Professor of Medicine
University of Minnesota, Minneapolis
- *Adeera Levin, MD, FRCPC FACP*
Head, Division of Nephrology
Professor of Medicine
University of British Columbia
Executive Director BC Provincial Renal Agency

Study of Heart and Renal Protection (SHARP):
Safety and efficacy of ezetimibe/simvastatin in
patients with Chronic Kidney Disease (CKD)

Colin Baigent

University of Oxford, UK

SHARP Chief Investigator

Outline of SHARP presentation

- Background and rationale
- Study design
- 1 year safety of ezetimibe
- 5 year safety of ezetimibe/simvastatin
- 5 year efficacy of ezetimibe/simvastatin
- Context of previous statin trials
- Efficacy in patient subgroups

CKD is common in the US population

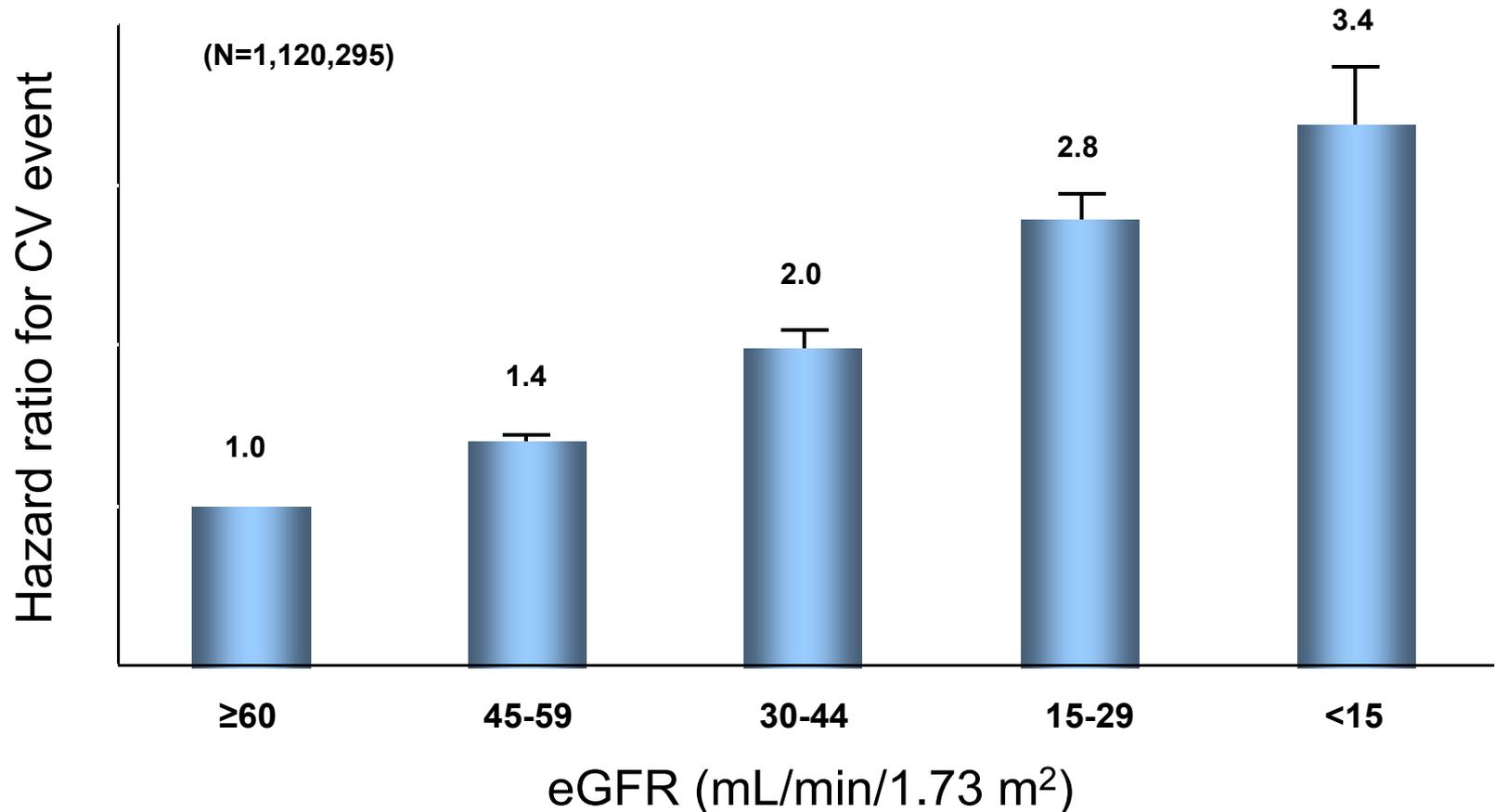
Stage	Description	GFR, mL/min/1.73 m ²	Percentage of US population	Numbers in US population
1	Albuminuria > 30 mg/g with normal or increased GFR	≥90	1.78%	4.0 M
2	Albuminuria > 30 mg/g with mildly decreased GFR	60-89	3.24%	7.3 M
3	Moderately decreased GFR	30-59	7.69%	17.3 M
4	Severely decreased GFR	15-29	0.35%	0.8 M
5	Kidney failure	<15	0.18%	0.6 M

Stages 1-4 from Coresh *JAMA* 2007

Stage 5 from USRDS 2010 Annual Data Report

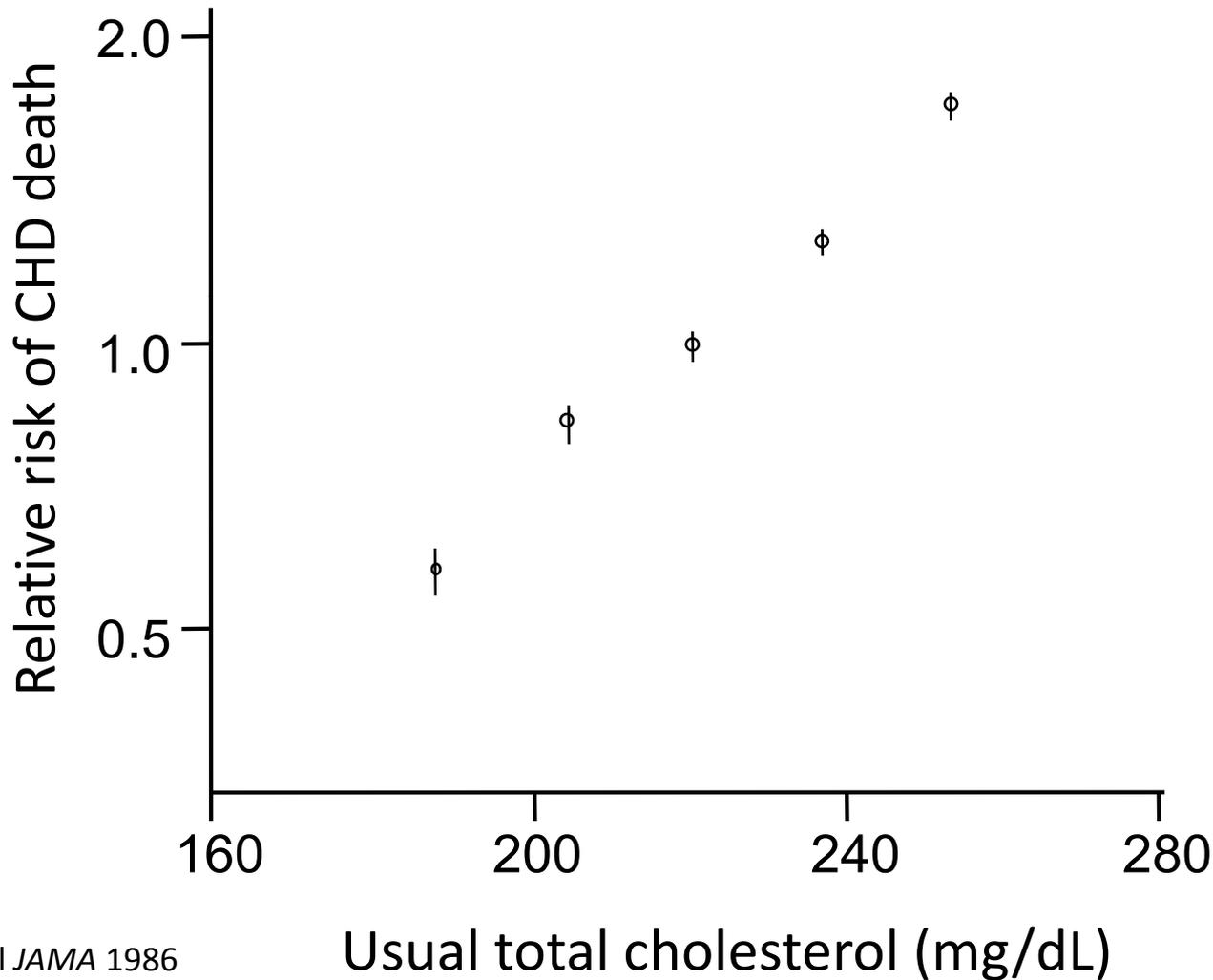
US population: estimated from US Census 2010

Kaiser Permanente Renal Registry: Reduced kidney function is associated with higher risk of CV events



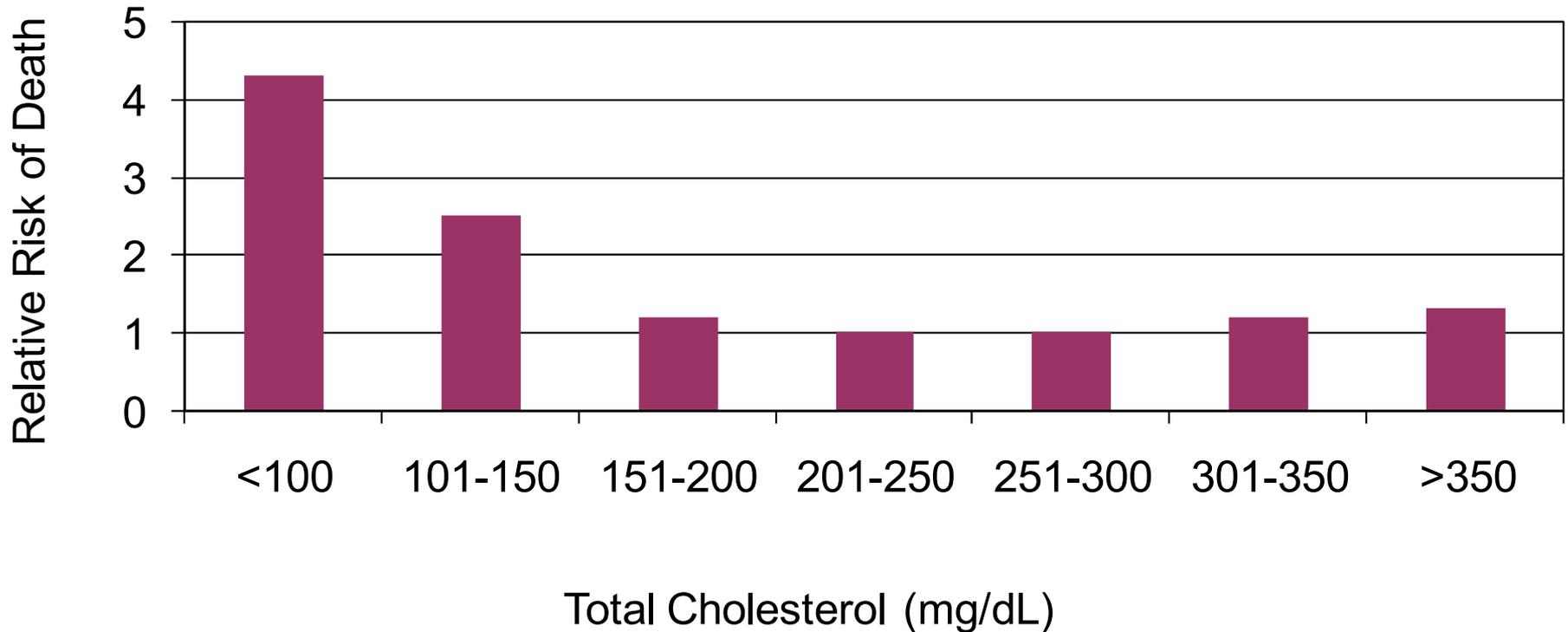
Go et al *N Engl J Med* 2004

MRFIT prospective study: CHD mortality vs total cholesterol among 350,000 US men



Stamler et al *JAMA* 1986

All-cause mortality versus total cholesterol among 12,000 hemodialysis patients

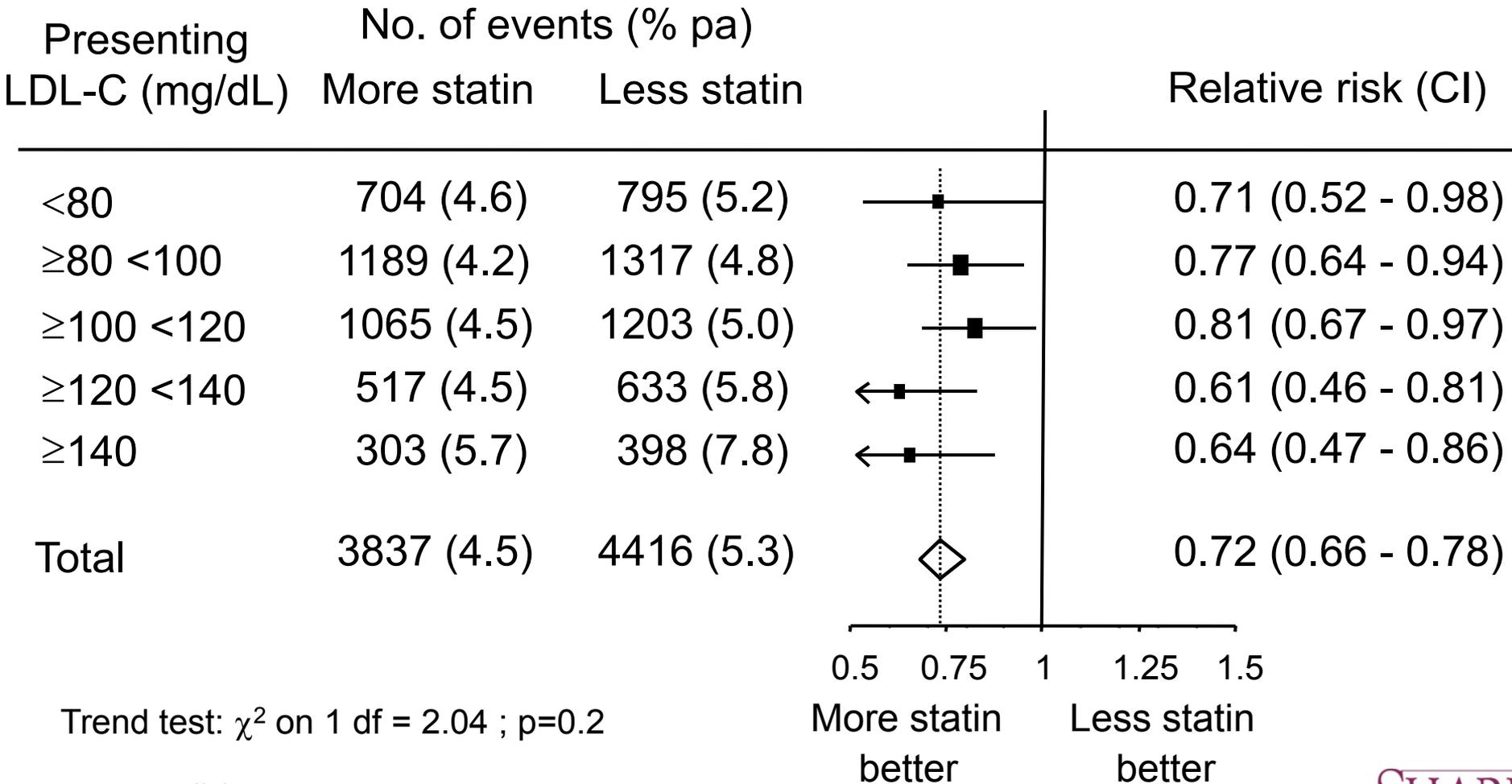


Lowrie & Lew *Am J Kidney Dis* 1990

Cholesterol Treatment Trialists (CTT) Collaboration

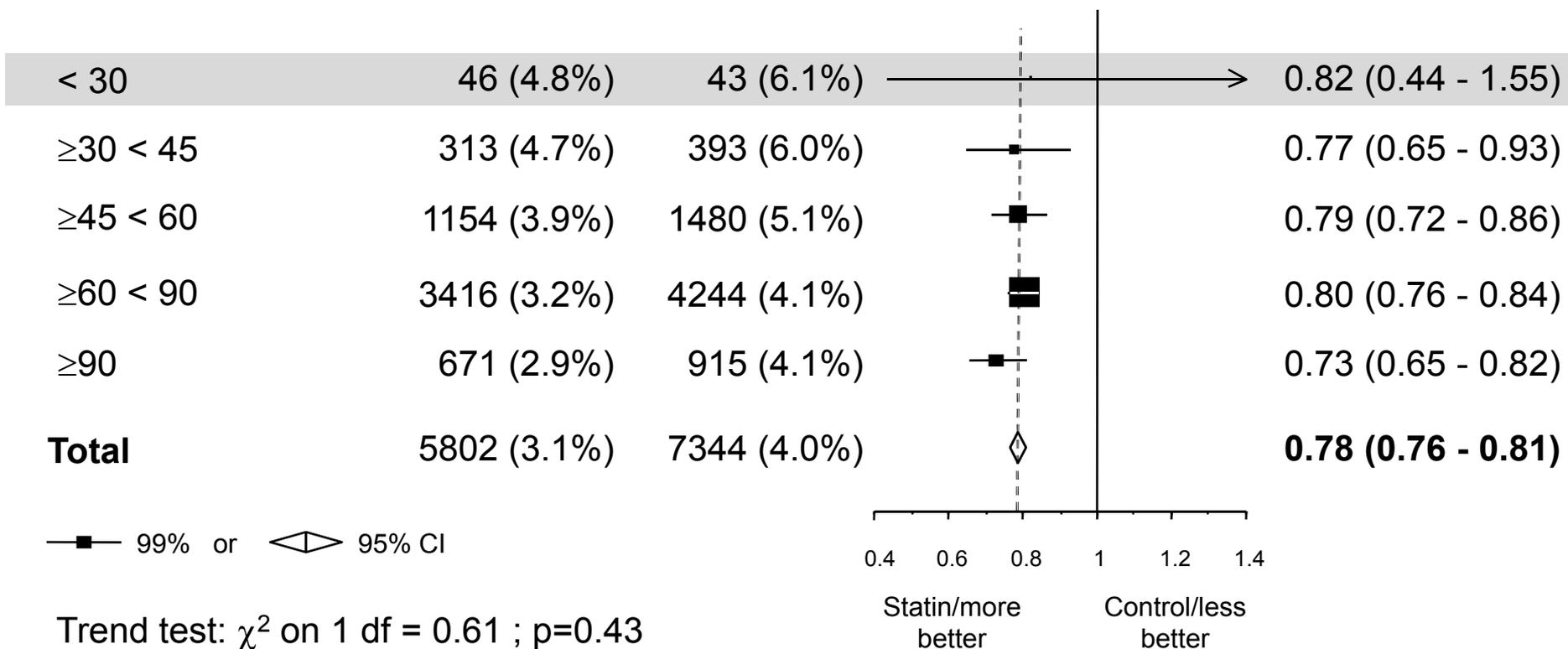
- Collaborative meta-analysis of individual participant data from randomized trials of LDL-cholesterol (LDL-C) lowering therapy
- Allows detailed analyses of effects of statins:
 - Efficacy outcomes: Major vascular events (major coronary events, stroke, or coronary revascularization); vascular mortality
 - Safety outcomes: Cancer (site-specific); non-vascular mortality
 - Major subgroups: Efficacy and safety in different types of patients (eg, by baseline LDL cholesterol, or by stage of kidney disease)
 - By follow-up time (eg, with more prolonged treatment)
- Current cycle:
 - 21 trials of statin versus control
 - 5 trials of more versus less intensive statin
 - 24,000 major vascular events among 170,000 participants

CTT: Similar relative reductions in MVE risk per 40 mg/dL LDL-C reduction, irrespective of presenting LDL-C



CTT: Previous lack of evidence for reduction in MVE risk in people with eGFR below 30 mL/min/1.73m²

Estimated GFR (mL/min/1.73m ²)	No. of events		Relative risk (CI)
	Statin	Control	



Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for dyslipidemia in CKD

Stages 1-4 CKD recommendation

“There are reasonable doubts as to whether trial results from the general population are applicable to all patients with CKD.”

Am J Kidney Disease 2003

HENCE: definitive trials in CKD were required

4D trial: Inconclusive evidence about the benefits of statin therapy in CKD patients

Study population:	1255 hemodialysis patients with Type 2 diabetes
Treatment:	Atorvastatin 20mg vs placebo
LDL-C difference:	1.0 mmol/L (39 mg/dL)
Follow-up:	4 years
Primary endpoint:	Composite of: <ul style="list-style-type: none">- Non-fatal MI or cardiac death; and- Non-fatal or fatal stroke

RR 0.92 (95% CI 0.77 to 1.10); P=0.37

AURORA trial: Inconclusive evidence about the benefits of statin therapy in CKD patients

Study population:	2766 hemodialysis patients
Treatment:	Rosuvastatin 10 mg vs placebo
LDL-C difference:	1.1 mmol/L (43 mg/dL)
Follow-up:	3.8 years
Primary endpoint:	Composite of: <ul style="list-style-type: none">- Non-fatal MI or cardiac death;- Non-fatal or fatal stroke; and- Other vascular death

RR 0.96; 95% CI 0.84 to 1.11; P = 0.59

Persisting uncertainty after AURORA

“The benefits of LDL cholesterol reduction are not transferable directly from the general population to patients undergoing hemodialysis, in whom the causal pathway and disease spectrum are very different.”

Strippoli GFM, Craig JC (Editorial)

N Engl J Med 2009

SHARP fills a gap in the evidence on lowering LDL-C in CKD patients

- Does LDL-lowering therapy reduce risk of atherosclerotic disease in CKD patients?
 - Exclusion of CKD patients from most statin trials
 - Previous statin trials in CKD patients inconclusive
- Can such a reduction be achieved safely?
 - Concerns about safety of statins in CKD patients
 - Combination of ezetimibe with moderate statin dose intended to minimize side-effects

Cardio-renal phenotype: Reasons the effects of LDL-lowering may differ in CKD patients

Arteries

- Atherosclerosis
- Increased wall thickness
- Arterial stiffness
- Endothelial dysfunction
- Arterial calcification
- Systolic hypertension

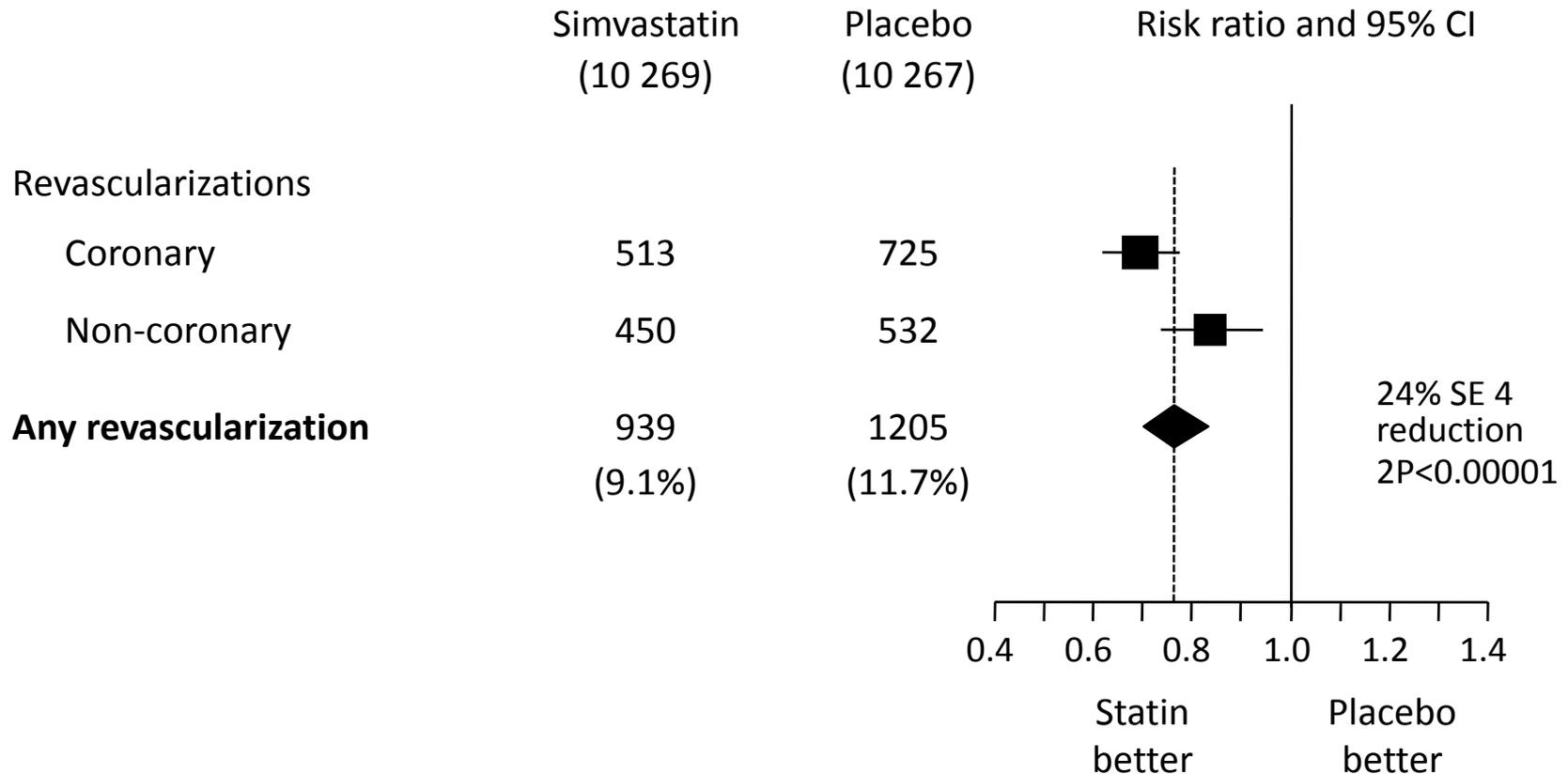
Heart

- Structural disease (ie, ventricular re-modelling)
- Ultrastructural disease (ie, myocyte hypertrophy and capillary reduction)
- Reduced left ventricular function
- Valvular diseases (hyper-calcific mitral/aortic sclerosis or stenosis)
- Conduction defects and arrhythmias

SHARP: Sensitive to potential benefits

- Emphasis on detecting effects on **ATHEROSCLEROTIC** outcomes
 - INCLUSION of coronary and non-coronary revascularization procedures
 - EXCLUSION of hemorrhagic stroke and non-coronary cardiac death from key outcome

Heart Protection Study: Statins prevent both coronary and non-coronary revascularizations

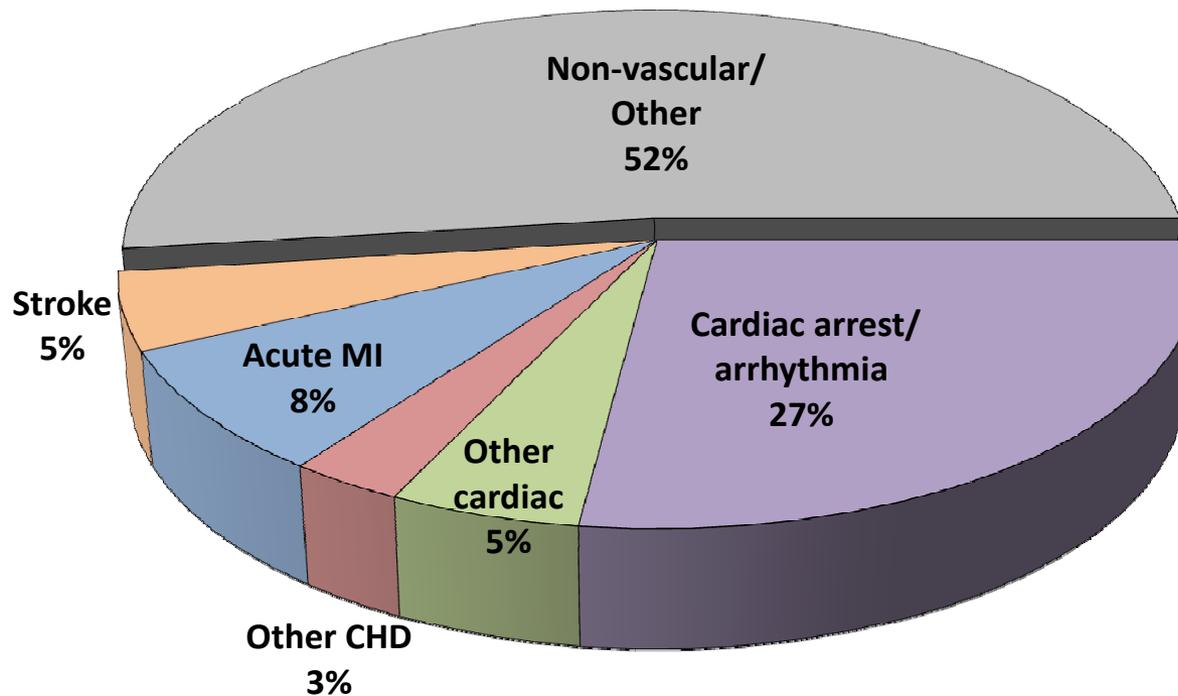


Heart Protection Study Collaborative Group *Lancet* 2002

SHARP: Sensitive to potential benefits

- Emphasis on detecting effects on **ATHEROSCLEROTIC** outcomes
 - INCLUSION of coronary and non-coronary revascularization procedures
 - EXCLUSION of non-coronary cardiac death and hemorrhagic stroke from key outcome

Dialysis patients: Small minority of vascular deaths are atherosclerotic



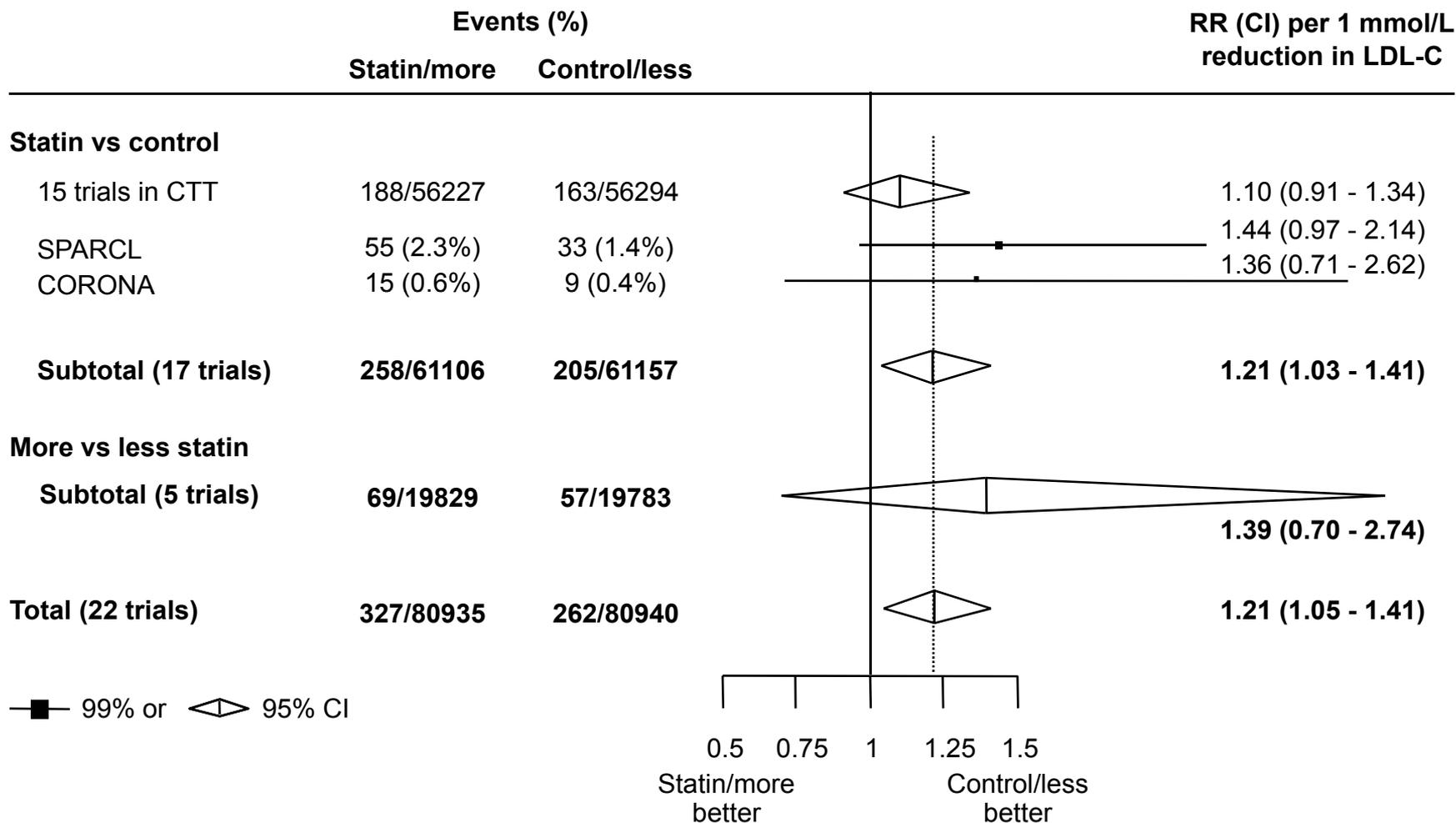
USRDS 2005 Annual Data Report

Statins do not prevent non-coronary cardiac deaths: Evidence from two large trials in heart failure

Causes of death	CORONA ¹		GISSI-HF ²	
	Rosuvastatin	Placebo	Rosuvastatin	Placebo
Any vascular	581	593	478	488
Sudden/ Arrhythmic	316	327	198	182
Worsening heart failure	193	191	203	231
Myocardial infarction	15	9	10	15
Other vascular	57	66	67	60
Non-vascular or unknown	147	166	179	156
Any death	728	759	657	644

¹ CORONA Investigators *N Engl J Med* 2007; ² GISSI-HF Investigators *Lancet* 2008

CTT: No reduction in hemorrhagic stroke



CTT Collaboration *Lancet* 2010

SHARP: Sensitive to potential benefits

- Emphasis on detecting effects on **ATHEROSCLEROTIC** outcomes
 - INCLUSION of coronary and non-coronary revascularization procedures
 - EXCLUSION of non-coronary cardiac death and hemorrhagic stroke from key outcome
- Large number of relevant outcomes and long duration of treatment to maximize power

SHARP: Much larger, longer duration, and key focus on atherosclerotic outcomes

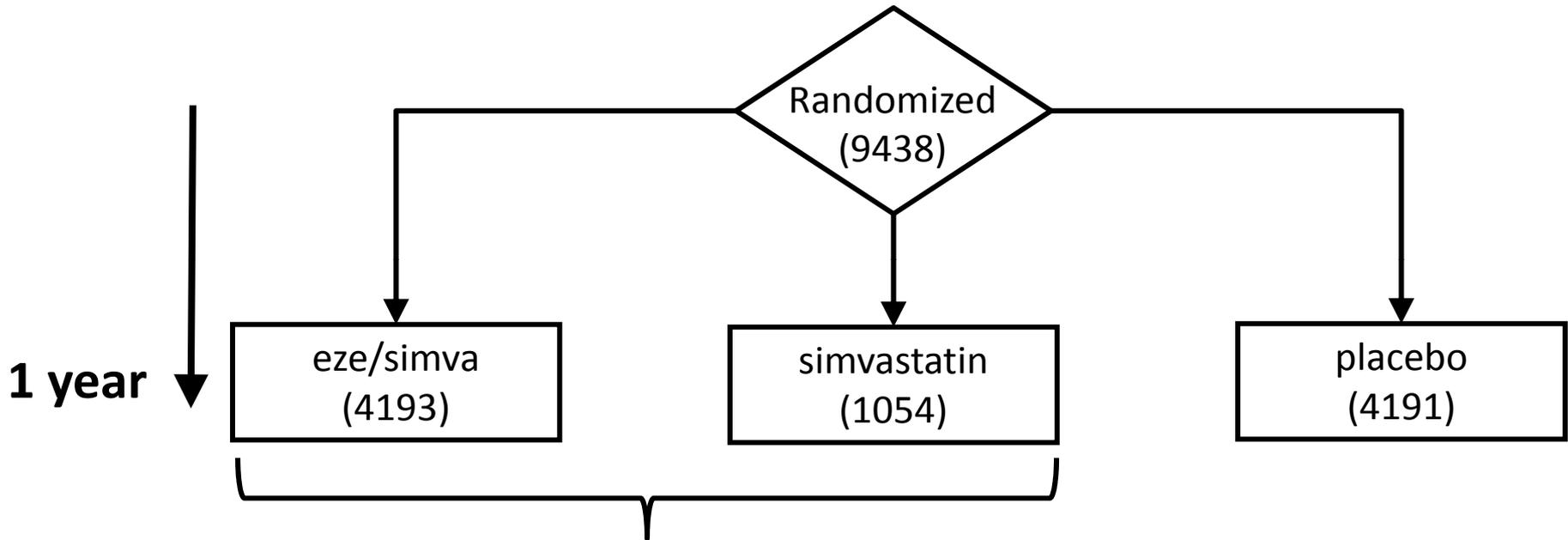
	4D	AURORA	SHARP
Sample size	1255	2776	9270
Duration (years)	4	4	5
Atherosclerotic outcomes			
Major coronary events	127	507	384
Non-hemorrhagic stroke	85	115	277
Any revascularization	-	-	484
Non-atherosclerotic outcomes			
Hemorrhagic stroke	12	41	-
Non-CHD cardiac death	182	64	-
Other vascular death		77	-
Primary/key outcome	469	804	1145

STUDY DESIGN

SHARP: Wide inclusion criteria

- History of chronic kidney disease (CKD)
 - Not on dialysis: elevated creatinine on 2 occasions
 - Men: ≥ 1.7 mg/dL (150 $\mu\text{mol/L}$)
 - Women: ≥ 1.5 mg/dL (130 $\mu\text{mol/L}$)
 - On dialysis: hemodialysis or peritoneal dialysis
- Age ≥ 40 years
- No history of myocardial infarction or coronary revascularization

SHARP: Initial randomization



Effects of ezetimibe on:

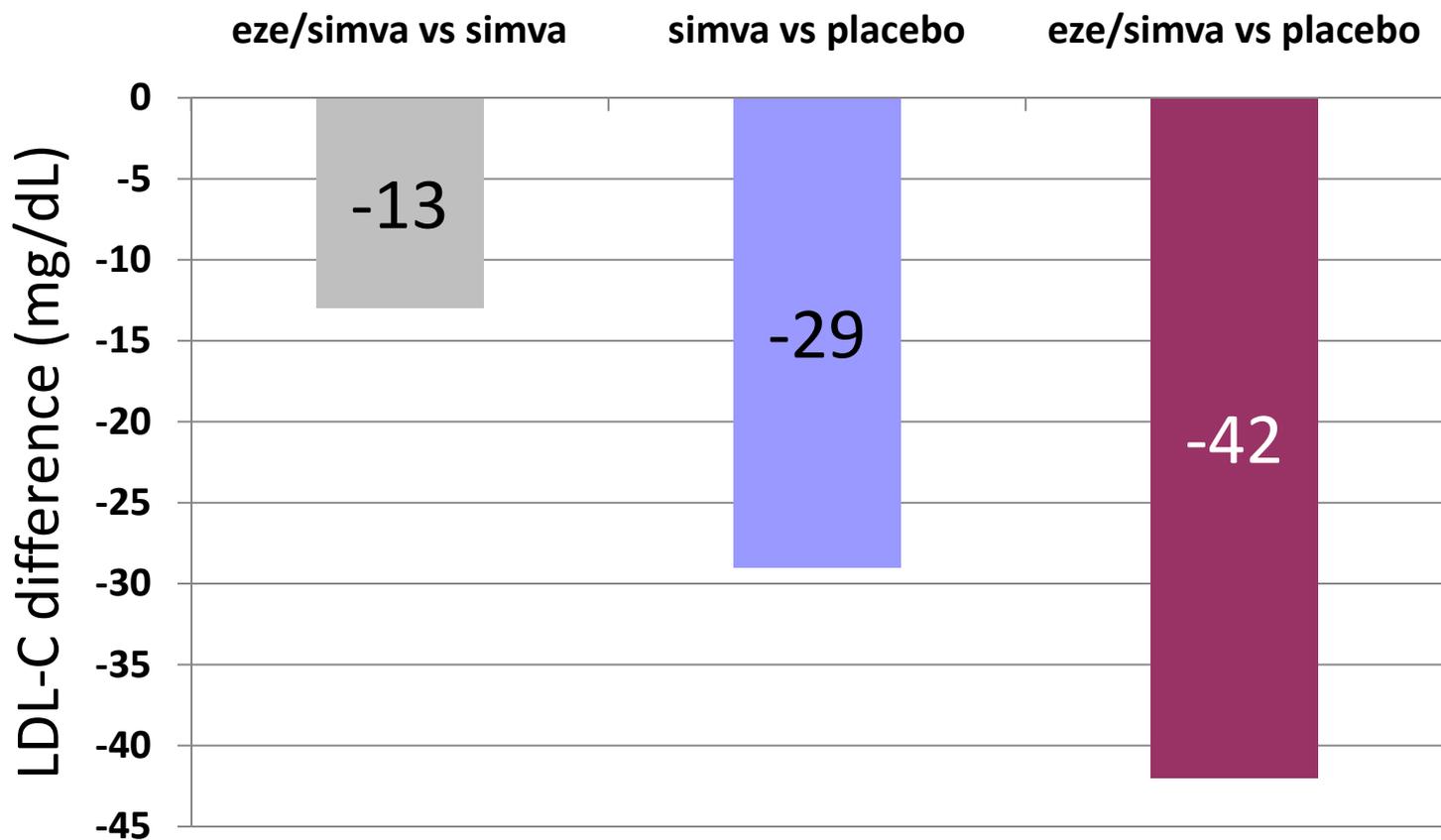
- Safety outcomes
- Lipid profile

1 YEAR SAFETY AND LIPID DIFFERENCES

SHARP: 1 year safety

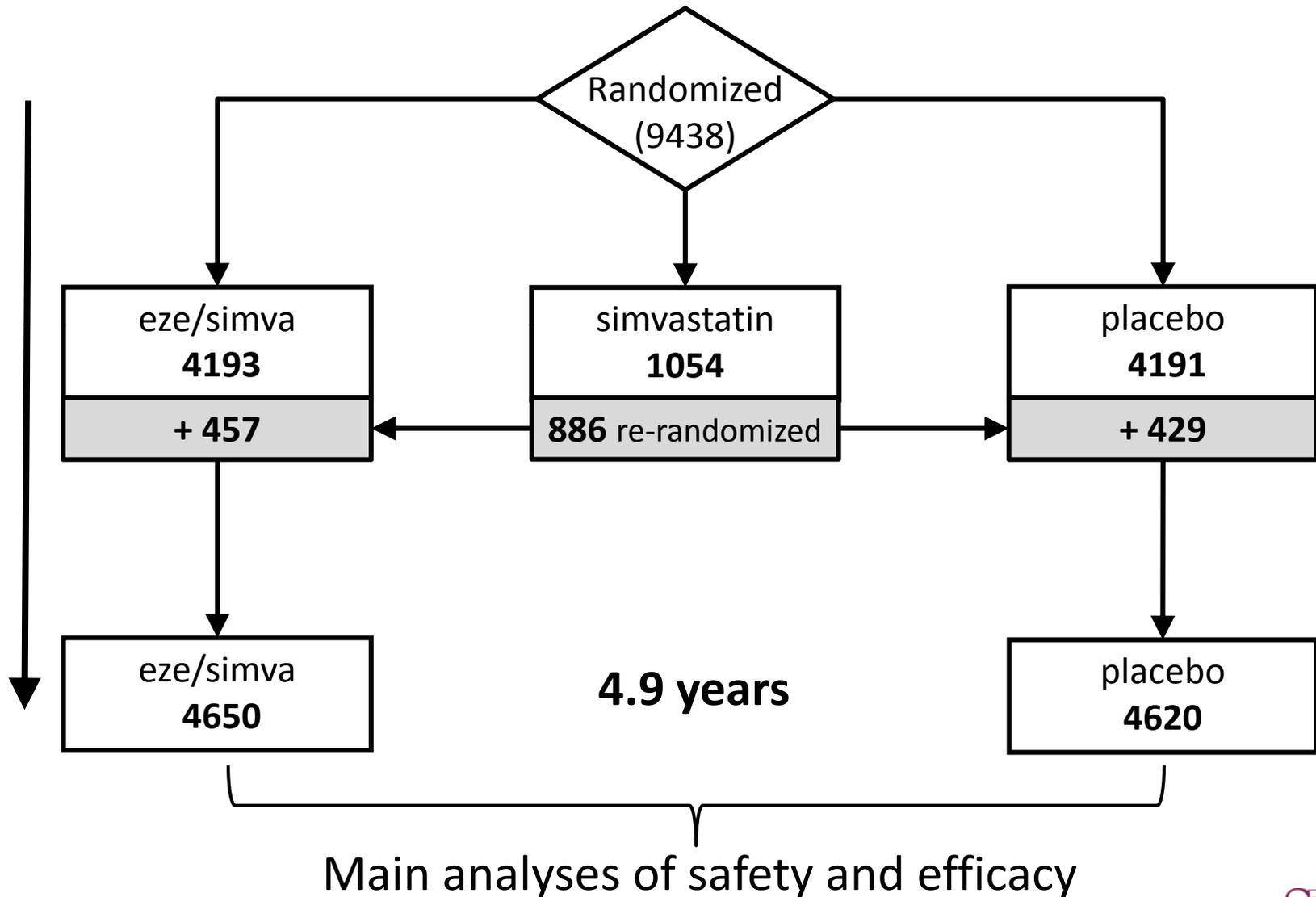
	eze/simva (n=4193)	simva (n=1054)	placebo (n=4191)
Creatine kinase elevations			
>10 x ≤40 x ULN	0.1%	0.1%	0.1%
>40 x ULN	0.0%	0.0%	0.0%
Hepatitis	0.2%	0.2%	0.2%
ALT/AST persistently >3x ULN	0.2%	0.0%	0.1%
Complications of gallstones	0.5%	0.3%	0.5%
Other gallstone hospitalization	0.0%	0.4%	0.1%
Pancreatitis without gallstones	0.0%	0.1%	0.2%

Effect on LDL-cholesterol (LDL-C) at 1 year of three-quarters compliance with eze/simva



**MAIN COMPARISON: ALL
PARTICIPANTS RANDOMIZED
EZE/SIMVA VS PLACEBO**

SHARP: Randomization structure



Sex and age at randomization

	Number	Percent
Sex		
Male	5800	63%
Female	3470	37%
Age (years)		
40-49	1876	20%
50-59	2310	25%
60-69	2472	27%
≥70	2612	28%
ALL PATIENTS	9270	100%

Numbers randomized in each region

Region	Number	Percent
Europe	5152	56%
Asia	1928	21%
Australia & New Zealand	1312	14%
North America	878	9%
ALL REGIONS	9270	100%

Vascular disease and diabetes at randomization

	Number	Percent
Angina	311	3%
Peripheral arterial disease	604	7%
Cerebrovascular disease	651	7%
Any vascular disease	1393	15%
None	7877	85%
Diabetes	2094	23%
ALL PATIENTS	9270	100%

Renal status at randomization

		Number	Percent
Pre-dialysis	eGFR*		
Stages 1/2	≥60	88	1%
Stage 3A	45-59	302	3%
Stage 3B	30-44	1853	20%
Stage 4	15-29	2565	28%
Stage 5	<15	1221	13%
Subtotal: pre-dialysis		6029	67%
Hemodialysis		2527	28%
Peritoneal dialysis		496	5%
Subtotal: dialysis		3023	33%
ALL PATIENTS		9052	100%

*eGFR in mL/min/1.73m²

Lipid profile (mg/dL) at randomization

	Number	Percent
Total-C (mean 189 mg/dL)		
<174	3434	39%
≥174 <212	3049	34%
≥213	2410	27%
LDL-C (mean 108 mg/dL)		
<97	3483	39%
≥97 <116	2096	24%
≥116	3313	37%

Effect of eze/simva on lipid profile at approximate study midpoint (mg/dL)

Biochemical parameter	eze/simva	placebo	Absolute difference	Percentage difference
Total-C	142	183	-41	-23%
LDL-C	70	103	-33	-32%
HDL cholesterol	44	44	1	2%
Non-HDL-C	97	139	-42	-30%
Triglycerides	163	188	-25	-13%
Apolipoprotein B	70	93	-23	-24%
Apolipoprotein A ₁	145	143	2	1%

Impact of net compliance with study treatment on achieved LDL-C differences during the trial

Time period	LDL- lowering drug use		
	eze/ simva	placebo	Net compliance
~ 1 year	77%	3%	74%
~ 2.5 years	71%	9%	61%
~ 4 years	68%	14%	55%

Net compliance is defined as the difference between groups in the proportion that were taking at least 80% of study treatment or a non-study statin

Impact of net compliance with study treatment on achieved LDL-C differences during the trial

Time period	LDL- lowering drug use			LDL-C difference (mg/dL)		
	eze/ simva	placebo	Net compliance	eze/ simva	placebo	Absolute difference
~ 1 year	77%	3%	74%	-42	+1	-42
~ 2.5 years	71%	9%	61%	-39	-6	-33
~ 4 years	68%	14%	55%	-32	-3	-30

Net compliance is defined as the difference between groups in the proportion that were taking at least 80% of study treatment or a non-study statin

Reasons for stopping study treatment

	eze/simva (n=4650)		placebo (n=4620)	
Suspected SAR*	17	(0.4%)	12	(0.3%)
Other serious adverse event	303	(6.5%)	310	(6.7%)
Non-serious adverse event	165	(3.5%)	131	(2.8%)
Other reason	946	(20.3%)	1126	(24.4%)
Contraindicated treatment	248	(5.3%)	449	(9.7%)
Patient wishes	417	(9.0%)	409	(8.9%)
None of the above	91	(2.0%)	79	(1.7%)
TOTAL	1522	(32.7%)	1658	(35.9%)

*Suspected serious adverse reaction: 4 more patients (3 allocated eze/simva and 1 allocated placebo) had a SSAR but continued to take study medication

Reasons for stopping study treatment: Use of contraindicated treatment

	eze/simva (n=4650)	placebo (n=4620)
Statin	162 (3.5%)	365 (7.9%)
Other lipid lowering	14 (0.3%)	31 (0.7%)
Ciclosporin	78 (1.7%)	67 (1.5%)
Azole or macrolide antimicrobial	5 (0.1%)	6 (0.1%)
Type of treatment not recorded	11 (0.2%)	16 (0.3%)
ANY	248 (5.3%)	449 (9.7%)

Completeness of follow-up at study end

Follow-up	eze/simba (n=4650)	placebo (n=4620)
Completed	3407 (73.3%)	3402 (73.6%)
Died	1142 (24.6%)	1115 (24.1%)
< 4 years	101 (2.2%)	103 (2.2%)

STATISTICAL ANALYSIS PLAN

Statistical Analysis Plan: Key analyses

- Key outcome is major atherosclerotic events (MAE):
 - Non-fatal MI or coronary death;
 - Non-hemorrhagic stroke; or
 - revascularization(i.e. exclude non-CHD cardiac death and hemorrhagic stroke)

among ALL randomized patients allocated eze/simva vs placebo (including those re-randomized after one year on simvastatin alone)

Statistical Analysis Plan: Subsidiary analyses

- Subsidiary analyses:
 - Original protocol-defined primary outcome of major vascular events (MVE: non-fatal MI or cardiac death, any stroke, or any revascularization) among patients initially allocated to eze/simva versus placebo
 - Separate components of major atherosclerotic events
 - Major coronary events (coronary death or non-fatal MI)
 - Ischemic stroke
 - Coronary or non-coronary revascularization
 - End-stage renal disease (ESRD): progression to long-term dialysis or transplantation among patients not on dialysis at randomization

SHARP: Statistical power for detecting expected effects on specific outcomes

Outcome	Number	Expected* relative risk reduction	Power (at p=0.05)	Sample size (80% power at p=0.05)
Major atherosclerotic events	1145	18%	94%	6,000
Major coronary events	443	20%	65%	13,000
Ischemic stroke	305	18%	39%	24,500
Any revascularization	636	17%	67%	12,600
Vascular mortality	749	6%	13%	94,000
All cause mortality	2257	2%	8%	240,000

*Based on data from CTT Collaboration *Lancet* 2010

Statistical Analysis Plan: Tertiary analyses

- MAEs in subgroups (including baseline renal function)
- Mortality: overall, and subdivided by cause
- Cancers, subdivided by site
- Stroke: overall, and by subtype
- Transient ischemic attacks
- Hospital admission for angina
- Hospital admission for heart failure
- New diabetes mellitus
- Revision of vascular access for dialysis
- ESRD or death from any cause; ESRD or creatinine doubling (among those not on dialysis at randomization)

Statistical Analysis Plan: Safety outcomes

- Muscle-related outcomes
 - Muscle pain or weakness
 - CK elevations: $> 5 \leq 10 \times \text{ULN}$; $> 10 \leq 40 \times \text{ULN}$; and $\geq 40 \times \text{ULN}$; subdivided by symptoms and presence of end-organ damage
- Liver-related outcomes
 - Hepatitis, subdivided by infective, non-infective, no known cause
 - Persistently elevated liver transaminases
- Complications of gallstones
 - Acute pancreatitis with gallstones, cholelithiasis requiring admission, other gallstone complications
- Pancreatitis without gallstones, acute and chronic separately

Event adjudication procedures

- Documentation sought on pre-specified SAEs (including vascular outcomes, renal events, deaths, cancer and safety outcomes)
- Redaction of text relating to lipids and treatment allocation, and material scanned
- Doctors adjudicated using standard procedures
 - Blind to treatment allocation
 - Further information sought if necessary
 - Quality control with independent re-adjudication
- 12,453 events required adjudication
 - Only 1% could not be adjudicated

MAIN COMPARISON: SAFETY DATA

SHARP: Muscle safety

	eze/simva (n=4650)	placebo (n=4620)
CK >10 x ≤40 x ULN (ITT)	17 (0.4%)	16 (0.3%)
CK >40 x ULN (ITT)	4 (0.1%)	5 (0.1%)
Myopathy* (ITT)	9 (0.2%)	5 (0.1%)
Myopathy* (on treatment)	8 (0.2%)	3 (0.1%)
Rhabdomyolysis (ITT)†	4 (0.1%)	1 (0.0%)
Rhabdomyolysis (on treatment)†	4 (0.1%)	0 (0.0%)

ITT = randomised “intention-to-treat” comparison

*Myopathy defined as CK > 10 x ULN with muscle symptoms

†Rhabdomyolysis defined as myopathy with CK > 40 x ULN

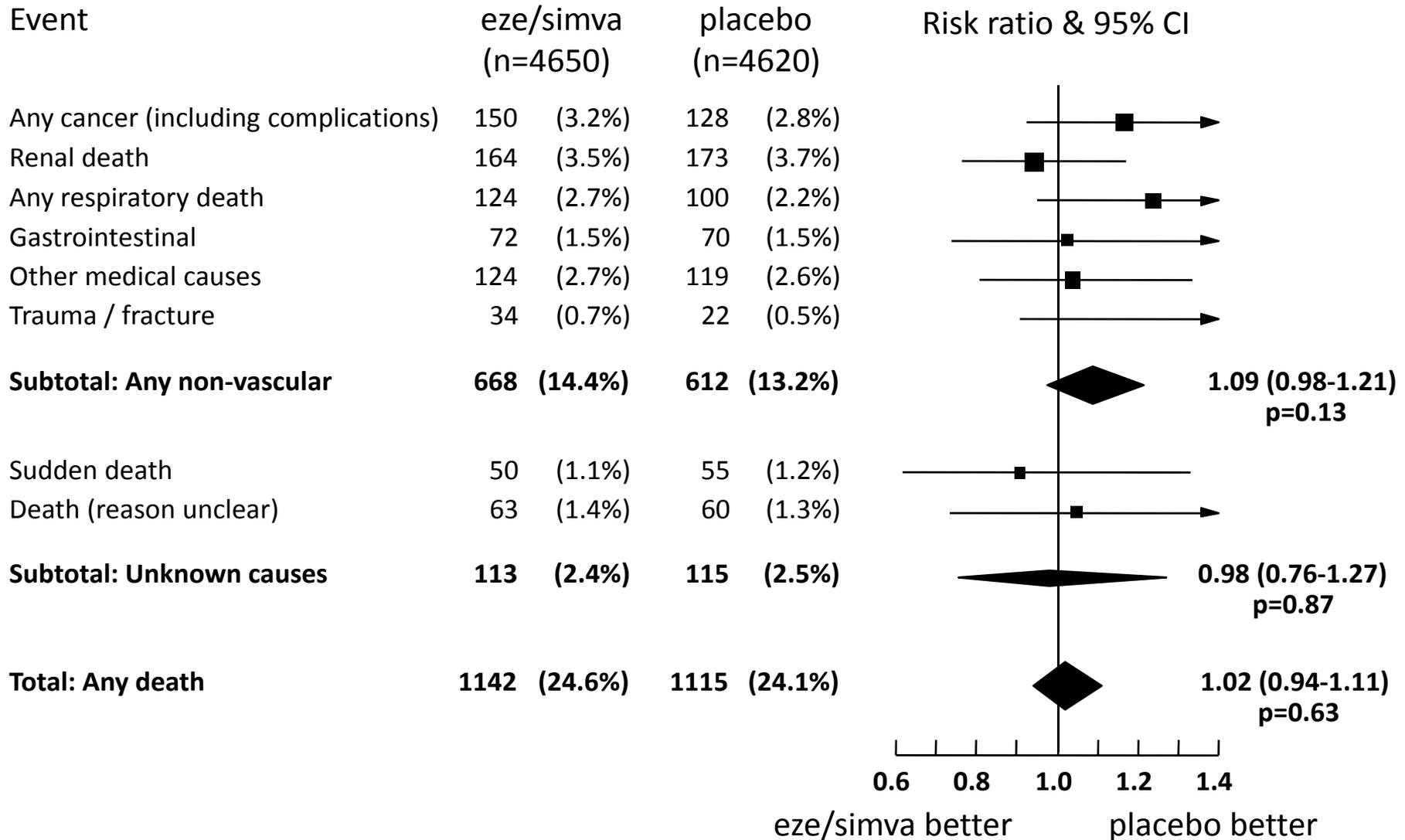
SHARP: Liver safety

	eze/simva (n=4650)	placebo (n=4620)
Hepatitis		
Infective	12 (0.3%)	12 (0.3%)
Non-infective	6 (0.1%)	4 (0.1%)
No cause identified	3 (0.1%)	3 (0.1%)
Any hepatitis	21 (0.5%)	18 (0.4%)
ALT/AST persistently >3x ULN	30 (0.6%)	26 (0.6%)

SHARP: Pancreatic and biliary safety

	eze/simba (n=4650)	placebo (n=4620)
Complications of gallstones	85 (1.8%)	76 (1.6%)
Other gallstone hospitalizations	21 (0.5%)	30 (0.6%)
Pancreatitis without gallstones	12 (0.3%)	27 (0.6%)
New diabetes mellitus	172 (4.8%)	162 (4.5%)

SHARP: Non-vascular mortality



SHARP: Other non-fatal SAEs*

	eze/simva (n=4650)	placebo (n=4620)	RR (95% CI)
Other cardiac	526 (11.3%)	557 (12.1%)	0.94 (0.83 – 1.05)
Other vascular (excl. cardiac)	324 (7.0%)	367 (7.9%)	0.88 (0.76 – 1.02)
Cancer (not incident)	73 (1.6%)	63 (1.4%)	1.15 (0.82 – 1.61)
Other renal	1958 (42.1%)	1966 (42.6%)	0.98 (0.92 – 1.04)
Respiratory	654 (14.1%)	666 (14.4%)	0.98 (0.88 – 1.09)
Liver/Pancreas/Biliary	82 (1.8%)	76 (1.6%)	1.08 (0.79 – 1.47)
Gastrointestinal	957 (20.6%)	988 (21.4%)	0.96 (0.87 – 1.04)
Skin	238 (5.1%)	240 (5.2%)	0.99 (0.82 – 1.18)
Genital & breast	176 (3.8%)	185 (4.0%)	0.94 (0.77 – 1.16)
Psychiatric	68 (1.5%)	62 (1.3%)	1.09 (0.78 – 1.54)
Neurological	220 (4.7%)	222 (4.8%)	0.99 (0.82 – 1.19)
Musculoskeletal	483 (10.4%)	471 (10.2%)	1.02 (0.90 – 1.16)
Hematological	224 (4.8%)	200 (4.3%)	1.12 (0.92 – 1.35)
Eye	184 (4.0%)	179 (3.9%)	1.02 (0.83 – 1.25)
Ear, Nose, Throat	72 (1.5%)	82 (1.8%)	0.87 (0.64 – 1.20)
Endocrine	58 (1.2%)	39 (0.8%)	1.47 (0.99 – 2.19)
Other medical	891 (19.2%)	896 (19.4%)	0.99 (0.90 – 1.09)
Non-medical	340 (7.3%)	333 (7.2%)	1.02 (0.88 – 1.19)
ANY OF ABOVE	3258 (70.1%)	3270 (70.8%)	0.98 (0.93 – 1.03)

*Excludes: MVEs, incident cancer, TIA, hospitalization with angina or heart failure, dialysis access revision, diabetes and hypoglycaemia, dialysis or renal transplantation, pancreatitis, hepatitis, gallstone events, myopathy and rhabdomyolysis

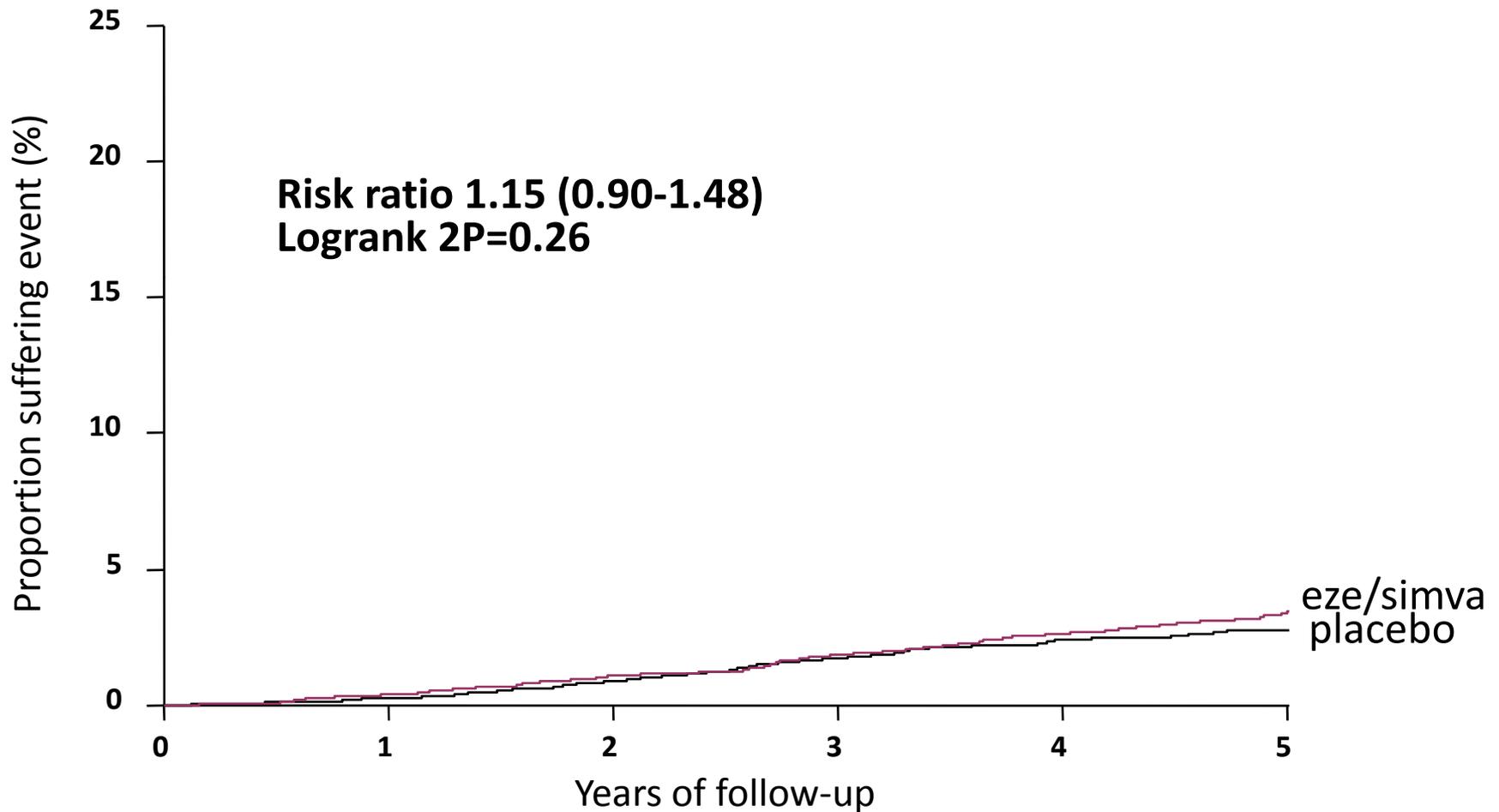
SHARP: Non-fatal respiratory SAEs

	eze/simba (n=4650)	placebo (n=4620)	RR (95% CI)
Pneumonia/Bronchitis	424 (9.1%)	397 (8.6%)	1.07 (0.93-1.23)
Other chest infection	90 (1.9%)	77 (1.7%)	1.16 (0.86-1.58)
COPD/Asthma	60 (1.3%)	59 (1.3%)	1.01 (0.71-1.45)
Other respiratory disease	103 (2.2%)	115 (2.5%)	0.89 (0.68-1.16)
Symptoms/investigations/surgery	132 (2.8%)	144 (3.1%)	0.91 (0.72-1.15)
ANY RESPIRATORY	654 (14.1%)	666 (14.4%)	0.98 (0.88-1.09)

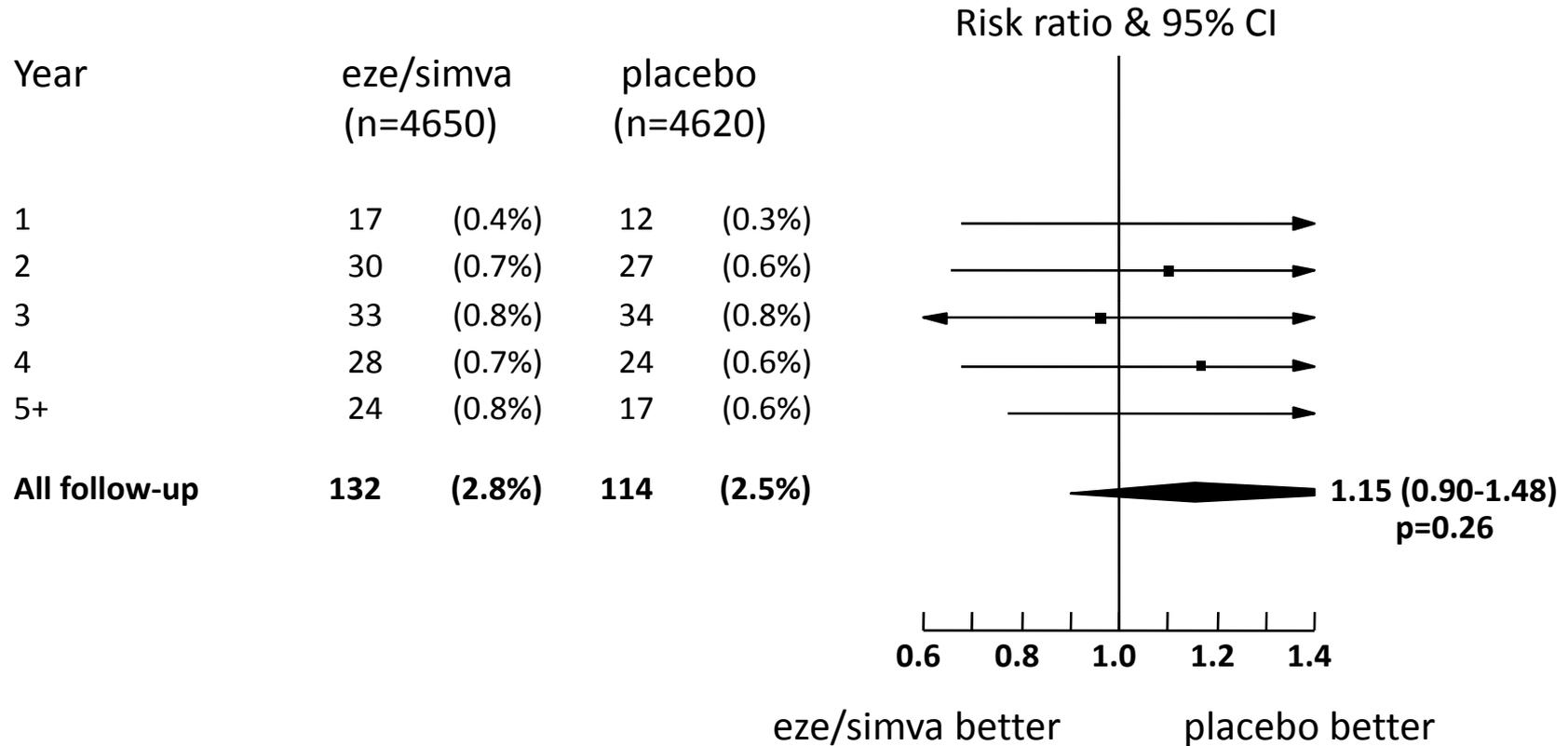
Hypothesis-generating result in SEAS trial, and hypothesis-testing in SHARP and IMPROVE-IT

- In SEAS, an apparent excess of about 50% was observed in the incidence of any new cancer (101 vs. 65: RR=1.55; 95% CI 1.13 to 2.12; $p=0.006$)
- This hypothesis was tested in an independent, much larger, data set by unblinding interim cancer data from two ongoing ezetimibe trials (SHARP and IMPROVE-IT)
- In SHARP and IMPROVE-IT, there were about 5 times as many cancers as in SEAS, but no support for an excess (313 [1.7%] vs 326 [1.8%]: RR 0.96; 95% CI 0.82-1.12)
- SHARP now provides even larger numbers of cancers and even longer duration of treatment to assess risk

SHARP: Cancer mortality



SHARP: Cancer mortality by year

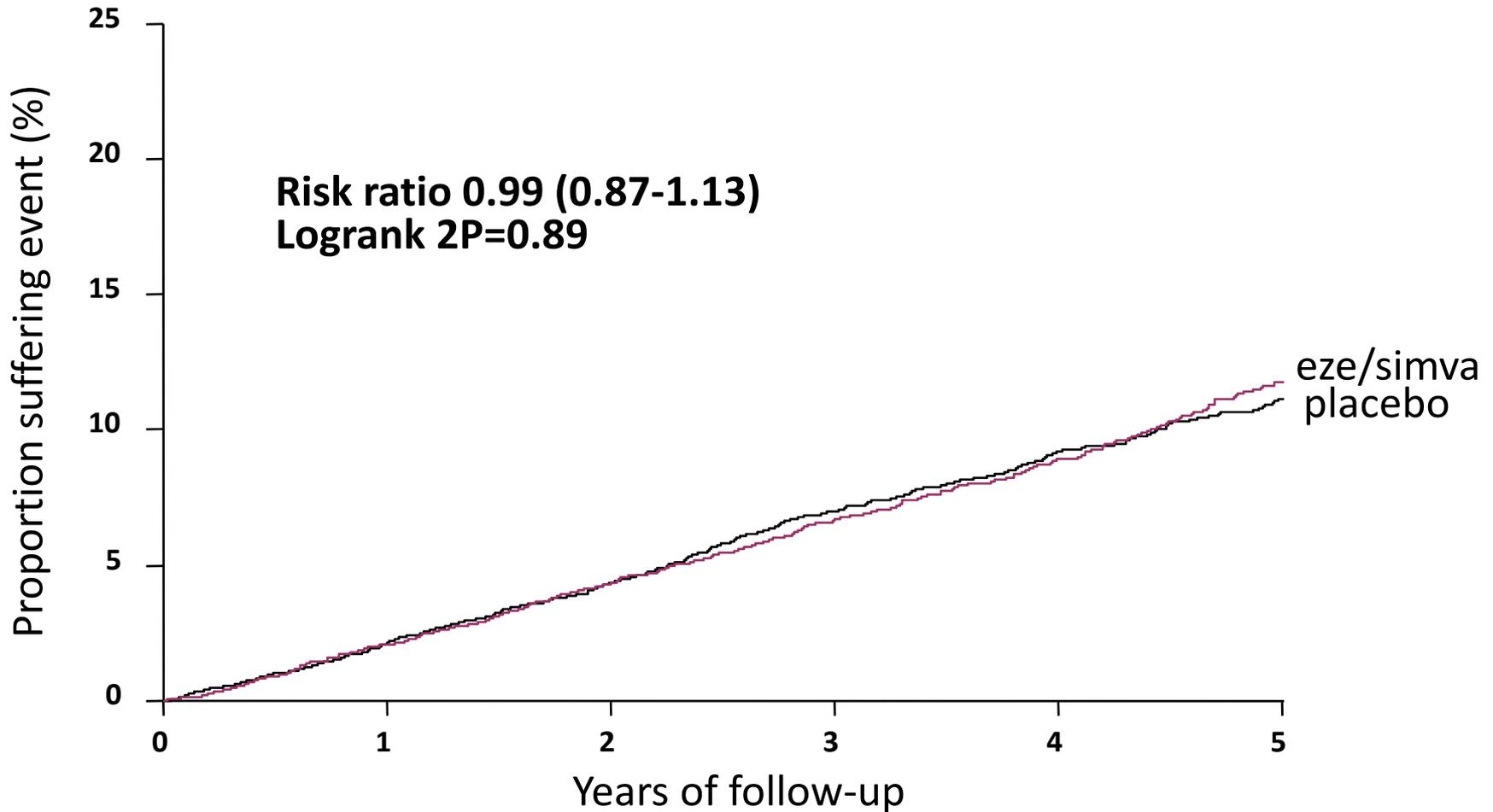


No excess cancer mortality at any individual site

Site	eze/simva (n=4650)	placebo (n=4620)	Nominal P-value
Oropharynx/esophagus	9	8	0.82
Stomach	10	11	0.83
Bowel	20	15	0.40
Pancreas	7	10	0.46
Hepatobiliary	4	4	0.72
Lung	32	22	0.18
Other respiratory	2	3	0.65
Skin	4	4	0.91
Breast	1	1	1.00
Prostate	6	2	0.15
Kidney	5	1	0.10
Bladder & urinary tract	8	7	0.80
Genital	4	2	0.42
Hematological	6	14	0.07
Other known site	3	5	0.47
Unspecified site	11	5	0.14
Any cancer death*	132	114	0.26

* Excludes 18 vs 14 deaths from cancer diagnosed before randomization

SHARP: Cancer incidence

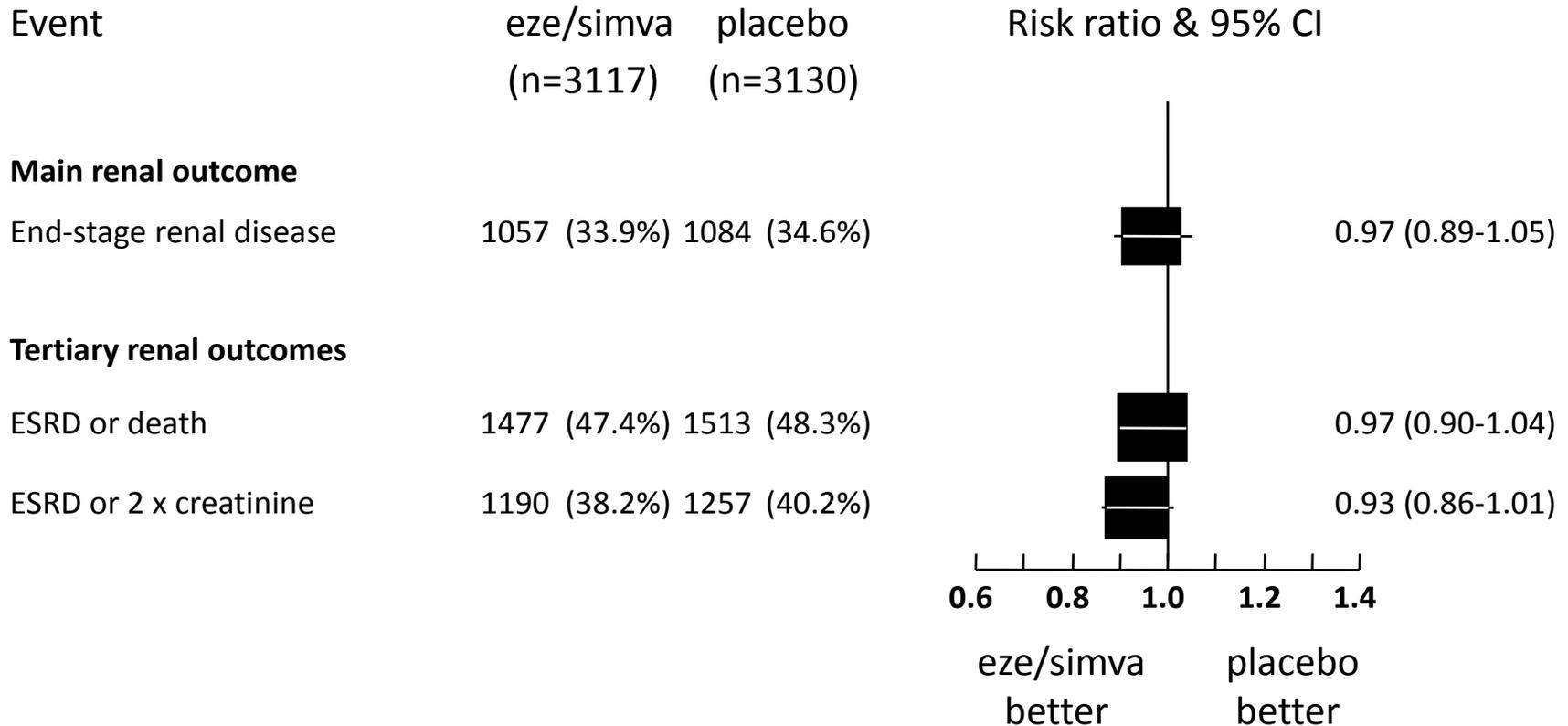


No excess cancer incidence at any individual site

Site	eze/simva (n=4650)	placebo (n=4620)	Nominal p-value
Oropharynx/esophagus	14	16	0.70
Stomach	11	14	0.54
Bowel	53	35	0.06
Pancreas	9	10	0.81
Hepatobiliary	8	4	0.25
Lung	42	35	0.44
Other respiratory	3	4	0.70
Skin	136	153	0.29
Breast	29	21	0.26
Prostate	39	52	0.16
Kidney	31	23	0.28
Bladder & urinary tract	26	32	0.42
Genital	12	14	0.69
Hematological	26	27	0.88
Other known site	9	12	0.50
Unspecified site	13	7	0.18
Any incident cancer	438	439	0.89

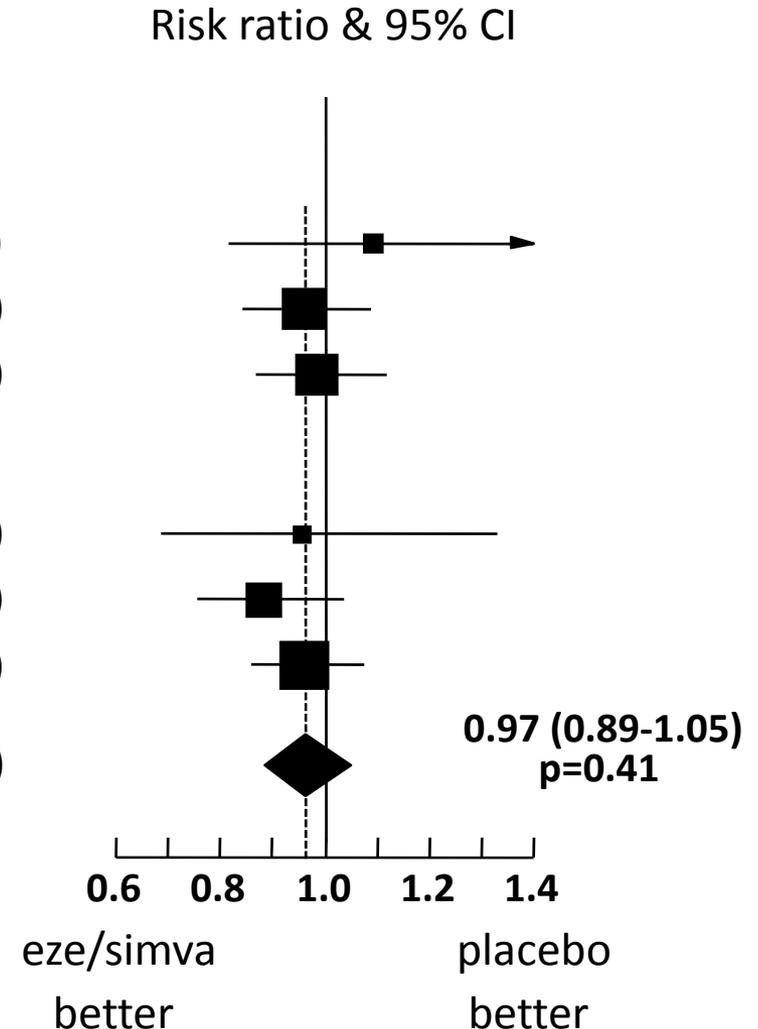
RENAL OUTCOMES

No beneficial (or adverse) effect on pre-specified renal outcomes



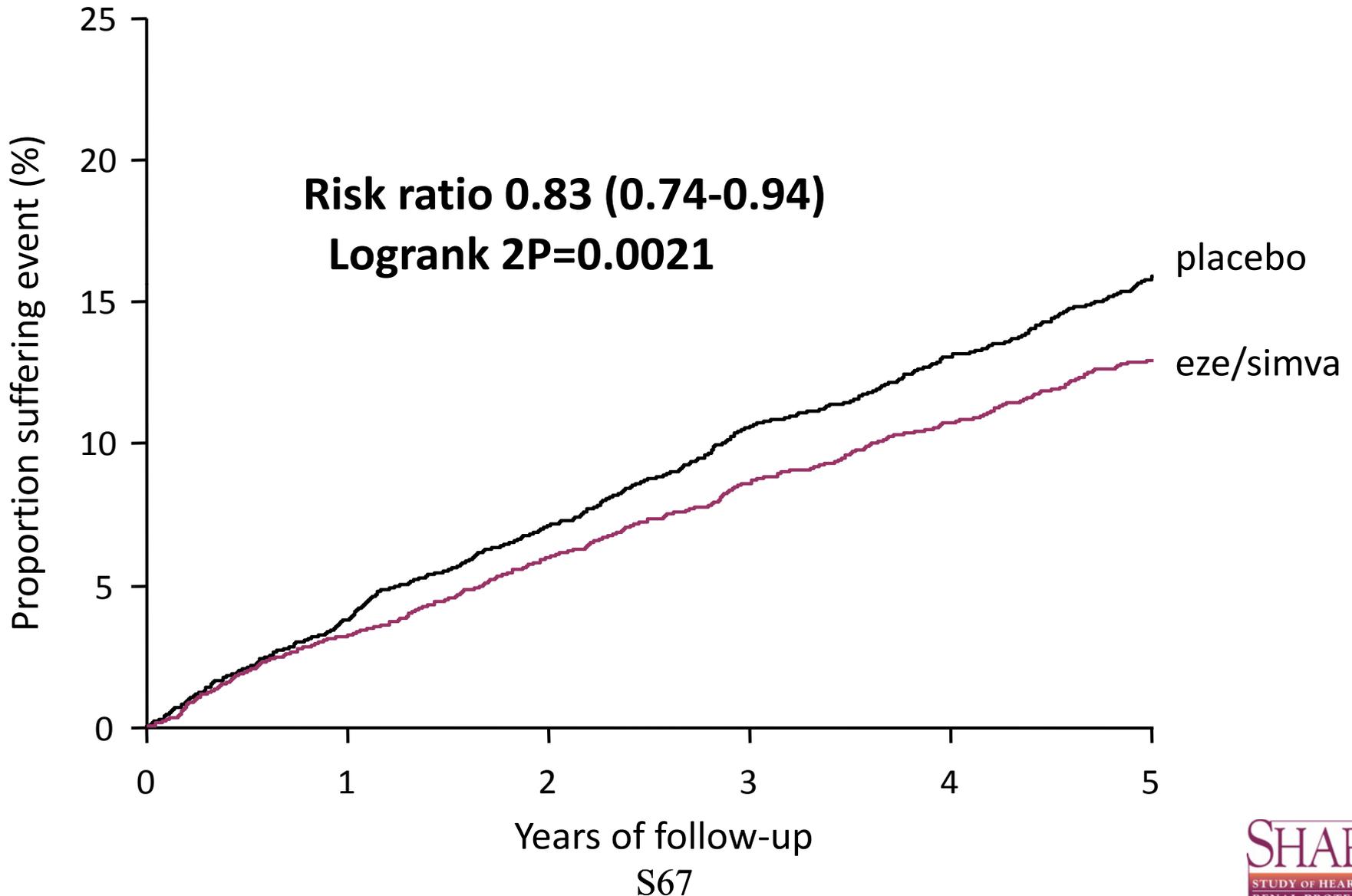
Lack of effect on progression to end-stage renal disease subdivided by disease stage at start

Event	eze/simva (n=3117)	placebo (n=3130)
MDRD estimated GFR (mL/min/1.73m²)		
≥30 (stage 2-3)	96 (8.4%)	83 (7.6%)
≥15 and <30 (stage 4)	454 (36.4%)	489 (37.1%)
<15 (stage 5)	471 (76.7%)	473 (77.9%)
Urinary ACR (mg/g)		
<30 (normo)	68 (12.5%)	73 (13.0%)
≥30 and <300 (micro)	281 (27.2%)	323 (30.0%)
≥300 (macro)	621 (51.6%)	602 (52.1%)
All patients	1057 (33.9%)	1084 (34.6%)



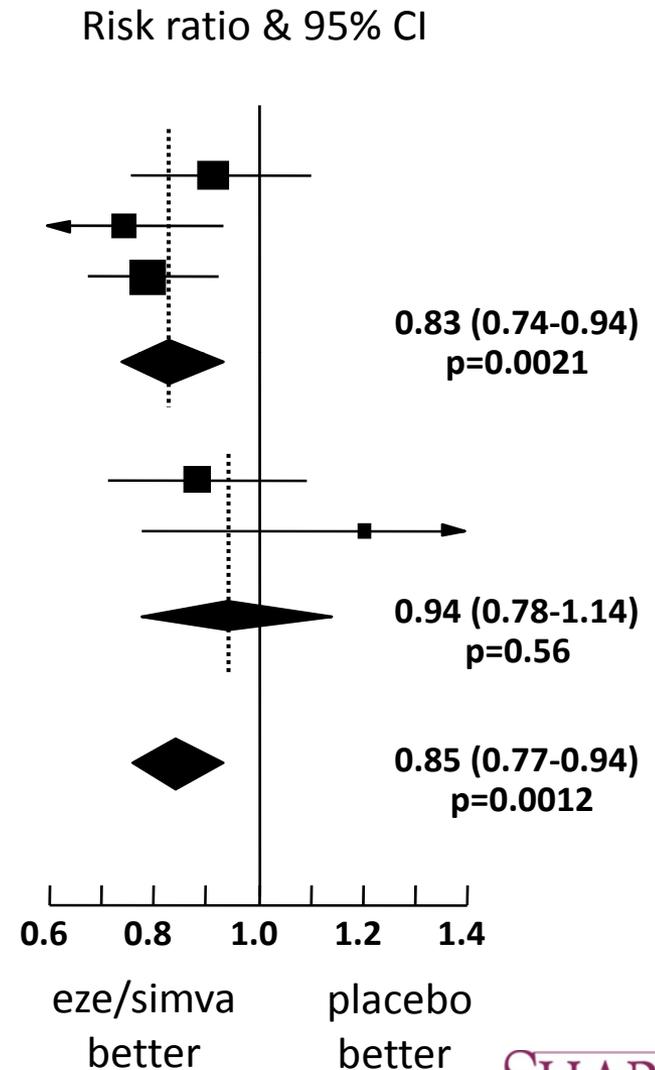
EFFICACY OUTCOMES

Key outcome: Major Atherosclerotic Events

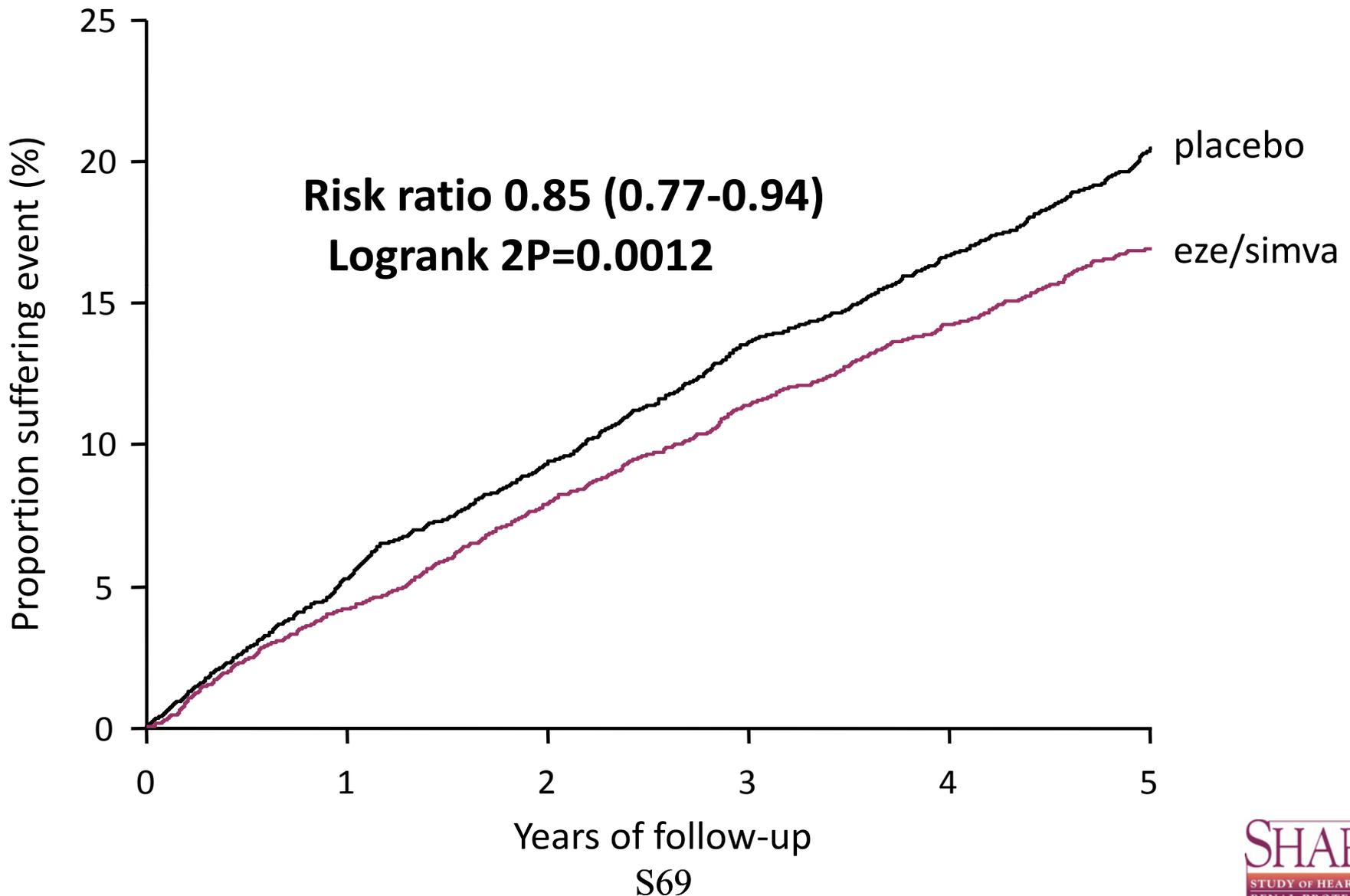


Benefit for both MAEs and MVEs

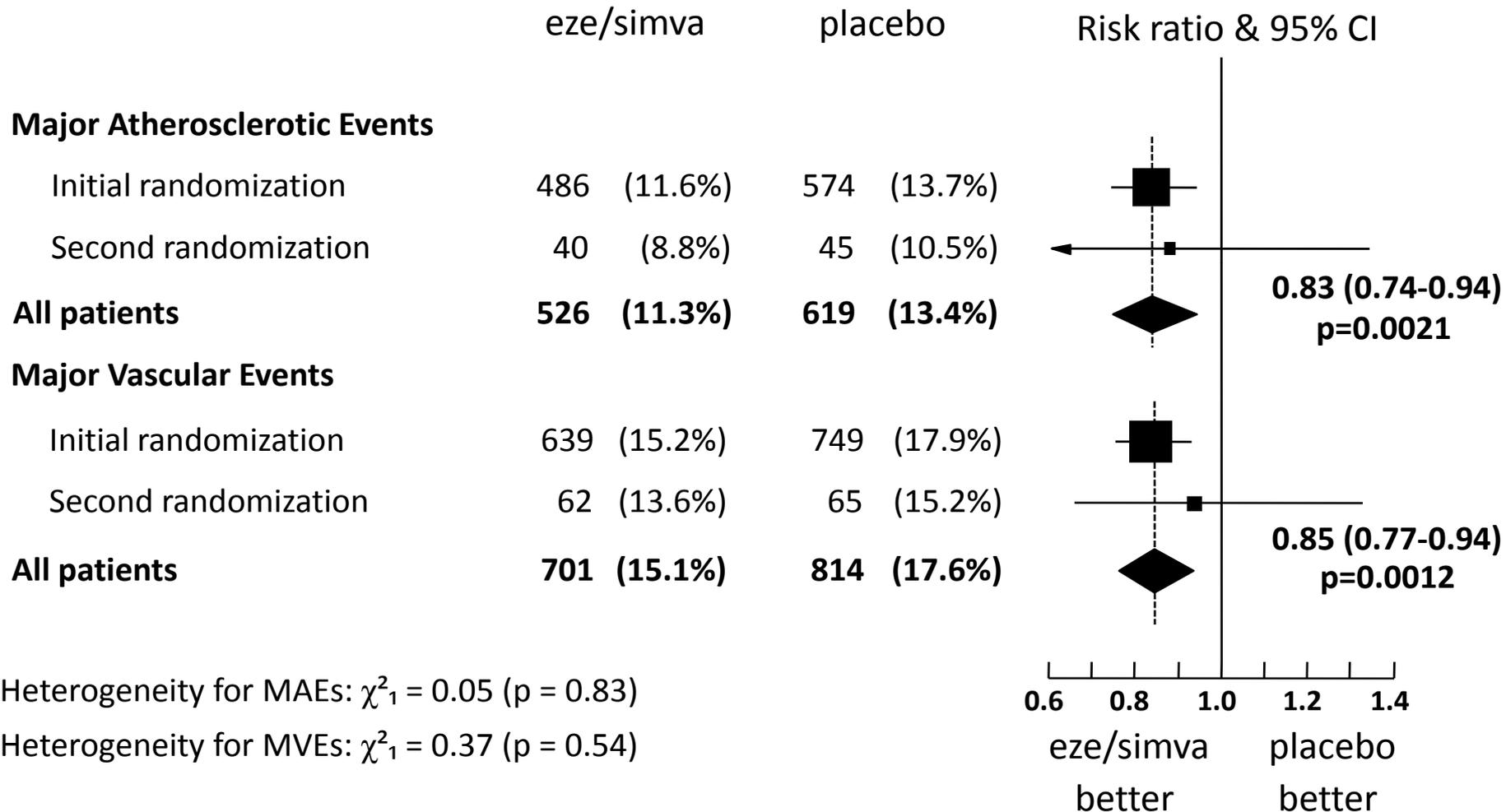
Event	eze/simva (n=4650)		placebo (n=4620)	
Major coronary event	213	(4.6%)	230	(5.0%)
Non-hemorrhagic stroke	131	(2.8%)	174	(3.8%)
Any revascularization procedure	284	(6.1%)	352	(7.6%)
Major Atherosclerotic Event	526	(11.3%)	619	(13.4%)
Other cardiac death	162	(3.5%)	182	(3.9%)
Hemorrhagic stroke	45	(1.0%)	37	(0.8%)
Other Major Vascular Events	207	(4.5%)	218	(4.7%)
Major Vascular Event	701	(15.1%)	814	(17.6%)



SHARP: Major Vascular Events



SHARP: MVEs and MAEs by timing of randomization to eze/simva vs placebo



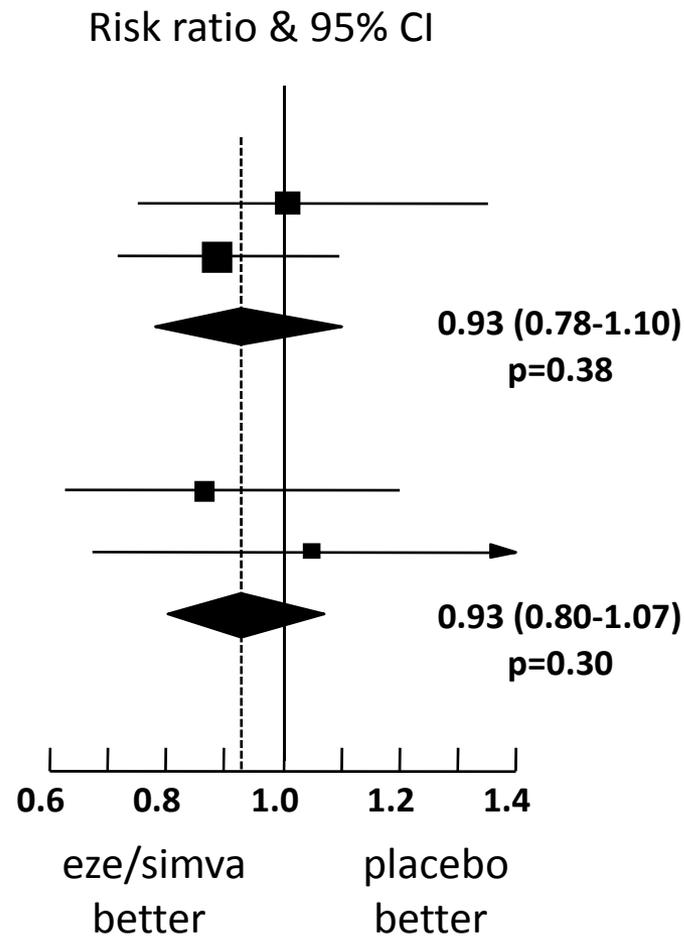
SHARP: Statistical power for detecting expected effects on specific outcomes

Outcome	Number	Expected* relative risk reduction	Power (at p=0.05)	Sample size (80% power at p=0.05)
Major atherosclerotic events	1145	18%	94%	6,000
Major coronary events	443	20%	65%	13,000
Ischemic stroke	305	18%	39%	24,500
Any revascularization	636	17%	67%	12,600
Vascular mortality	749	6%	13%	94,000
All cause mortality	2257	2%	8%	240,000

*Based on data from CTT Collaboration *Lancet* 2010

SHARP: Vascular mortality

Event	eze/simva (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%)

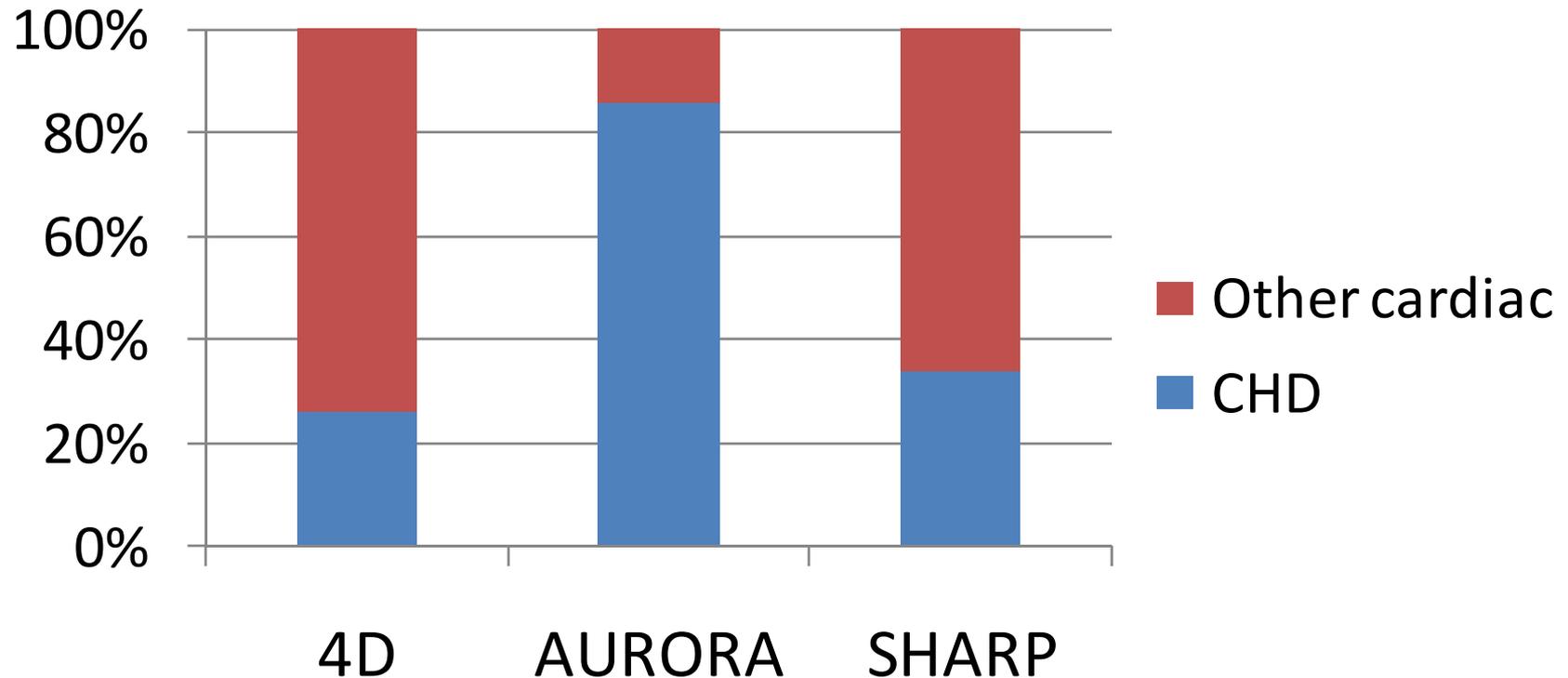


SHARP CONSISTENT WITH 4D AND AURORA TRIALS IN DIALYSIS PATIENTS

Comparing 4D, AURORA and SHARP: methodological considerations

- Meta-analyses of patient-level data from CTT
- Primary endpoints differed importantly:
 - SHARP did not include non-coronary cardiac deaths or hemorrhagic stroke, whereas 4D and AURORA did
 - Only SHARP included revascularization procedures
- In AURORA, almost all of the cardiac deaths were coded as being coronary in nature

AURORA: Adjudication rules coded almost all cardiac deaths as coronary

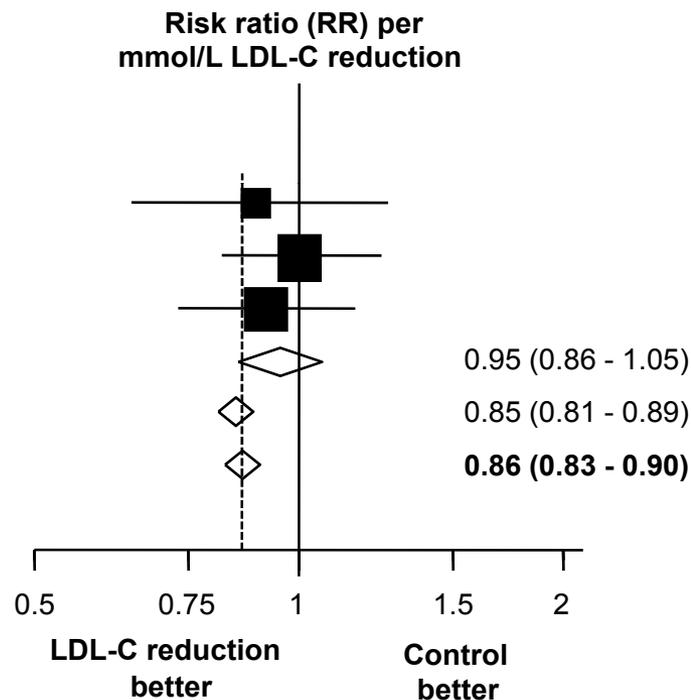


Comparing 4D, AURORA and SHARP: methodological considerations

- Meta-analyses of patient-level data from CTT
- Primary endpoints differed importantly:
 - SHARP did not include non-coronary cardiac deaths or hemorrhagic stroke, whereas 4D and AURORA did
 - Only SHARP included revascularization procedures
- In AURORA, almost all of the cardiac deaths were coded as being coronary in nature
- Hence, comparisons most valid for endpoints that were defined similarly in the 3 trials (ie, vascular death; MI; stroke; and coronary revascularization)

4D, AURORA and SHARP: Vascular death

	Events (% pa)		
	Allocated LDL-C reduction	Allocated control	Risk ratio (RR) per mmol/L LDL-C reduction
Vascular death			
4D	151 (8.52)	167 (9.36)	
AURORA	324 (6.87)	324 (6.86)	
SHARP	361 (1.82)	388 (1.97)	
Subtotal: 3 trials	836 (3.18)	879 (3.35)	0.95 (0.86 - 1.05)
Other 24 trials	3745 (1.05)	4303 (1.21)	0.85 (0.81 - 0.89)
All trials	4581 (1.20)	5182 (1.36)	0.86 (0.83 - 0.90)



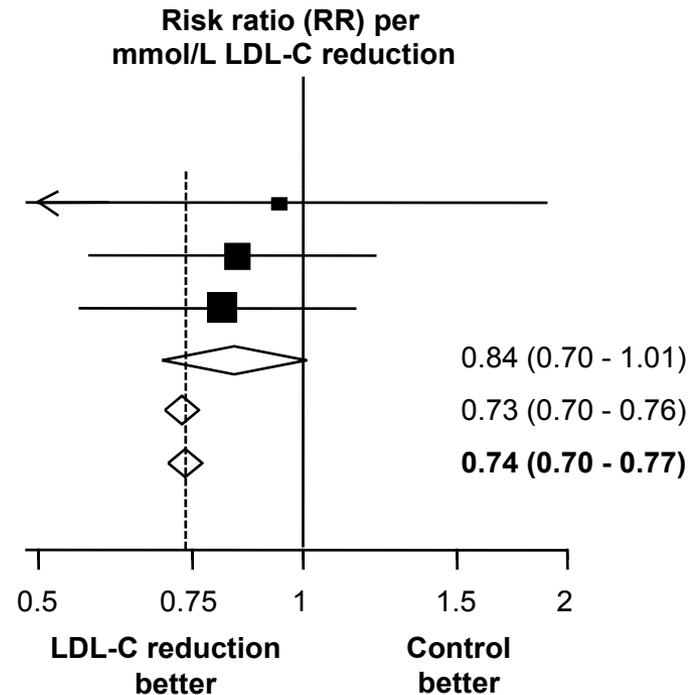
■ 99% or ◇ 95% CI

Heterogeneity between renal trials: $\chi^2 = 0.8$ ($p = 0.65$)

Difference between renal and non-renal trials: $\chi^2 = 3.8$ ($p = 0.05$)

4D, AURORA and SHARP: Non-fatal MI

	Events (% pa)		Risk ratio (RR) per mmol/L LDL-C reduction
	Allocated LDL-C reduction	Allocated control	
Non-fatal MI			
4D	33 (1.91)	35 (2.02)	
AURORA	91 (1.97)	107 (2.33)	
SHARP	134 (0.71)	159 (0.85)	
Subtotal: 3 trials	258 (1.02)	301 (1.20)	0.84 (0.70 - 1.01)
Other 24 trials	3361 (0.97)	4451 (1.29)	0.73 (0.70 - 0.76)
All trials	3619 (0.97)	4752 (1.29)	0.74 (0.70 - 0.77)



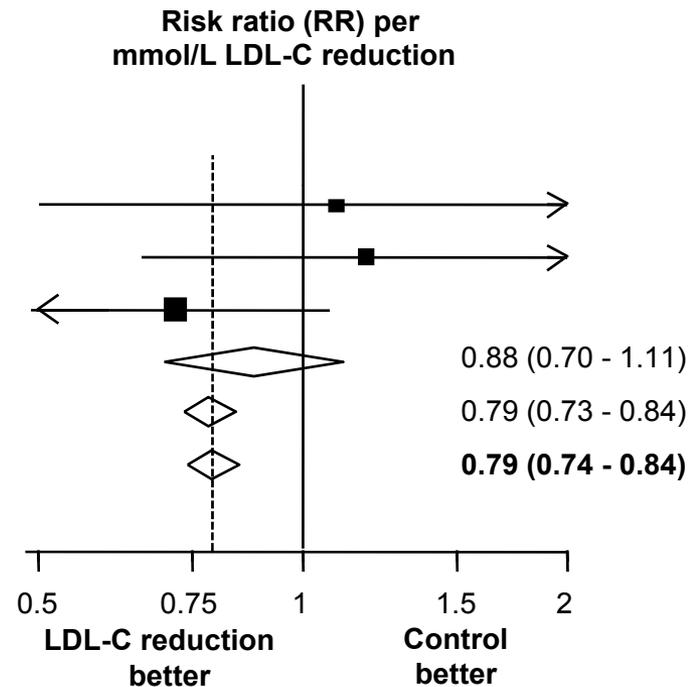
■ 99% or ◇ 95% CI

Heterogeneity between renal trials: $\chi^2 = 0.2$ ($p = 0.89$)

Difference between renal and non-renal trials: $\chi^2_1 = 2.1$ ($p = 0.15$)

4D, AURORA and SHARP: Non-fatal presumed ischemic stroke

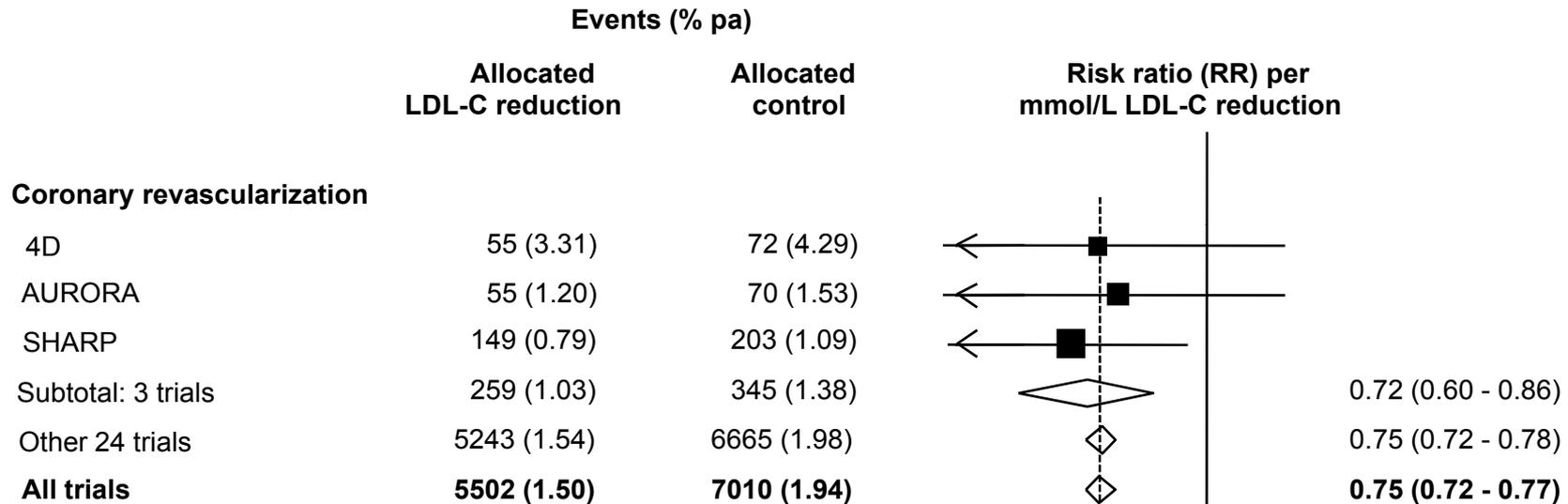
	Events (% pa)	
	Allocated LDL-C reduction	Allocated control
Non-fatal presumed ischemic stroke		
4D	31 (1.80)	29 (1.67)
AURORA	46 (0.99)	39 (0.84)
SHARP	97 (0.51)	128 (0.68)
Subtotal: 3 trials	174 (0.68)	196 (0.77)
Other 24 trials	1675 (0.48)	2092 (0.61)
All trials	1849 (0.50)	2288 (0.62)



Heterogeneity between renal trials: $\chi^2 = 4.1$ ($p = 0.13$)

Difference between renal and non-renal trials: $\chi^2_1 = 1.0$ ($p = 0.33$)

4D, AURORA and SHARP: Coronary revascularization

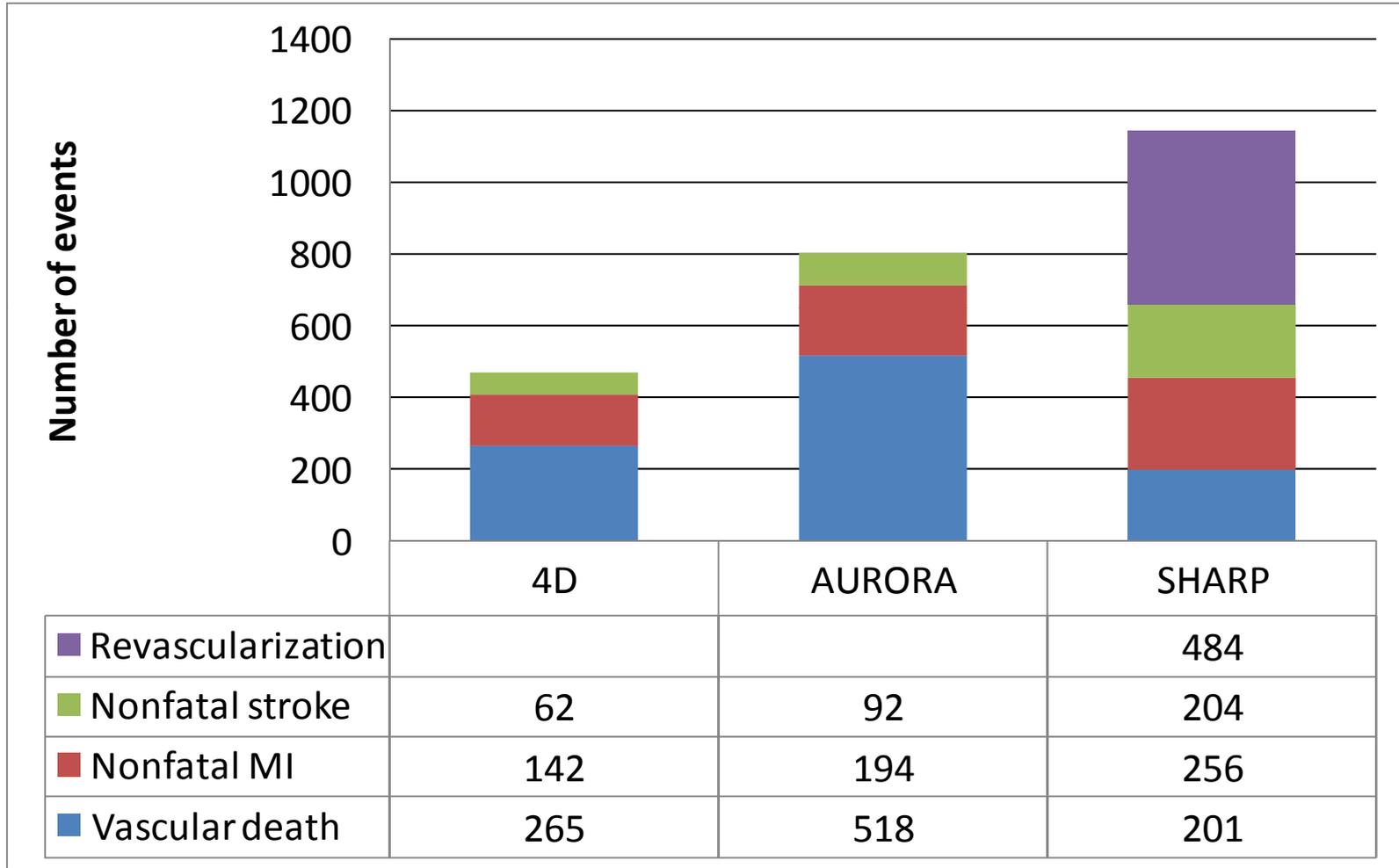


■ 99% or ◊ 95% CI

Heterogeneity between renal trials: $\chi^2 = 0.4$ ($p = 0.82$)

Difference between renal and non-renal trials: $\chi^2_1 = 0.1$ ($p = 0.72$)

4D, AURORA and SHARP: Comparison of outcomes



MAJOR ATHEROSCLEROTIC EVENTS BY SUBGROUPS

SHARP Data Analysis Plan: Published strategy for interpreting results in subgroups

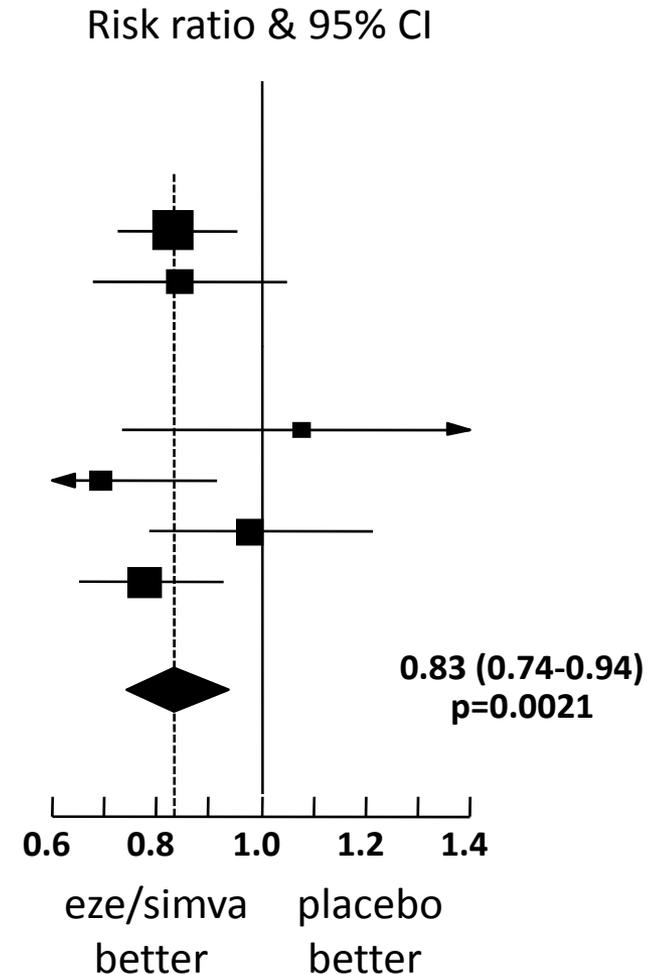
- Chance alone can lead to misleading apparent lack of effect in particular subgroups
- Proportional effects in subgroups may be best estimated by overall effect seen in all patients
- Pre-specified strategy for subgroups:
 - Tests for heterogeneity “*with allowance for multiple comparisons and other differences between subgroups*”
 - Test for trend where an ordering is more appropriate

Major Atherosclerotic Events by subgroups

- No significant heterogeneity between subgroups
- Broadly similar percentage reductions in MAEs produced by given absolute reduction in LDL-C irrespective of:
 - Age
 - Sex
 - History of vascular disease
 - Diabetes
 - Presenting lipid profile
 - Severity of renal disease

SHARP: Major Atherosclerotic Events by sex and age

	eze/simva (n=4650)	placebo (n=4620)
Sex		
Male	376 (12.9%)	445 (15.4%)
Female	150 (8.6%)	174 (10.0%)
Age at randomization (years)		
40-49	56 (5.8%)	50 (5.5%)
50-59	85 (7.3%)	119 (10.4%)
60-69	163 (13.3%)	171 (13.7%)
70+	222 (17.1%)	279 (21.2%)
Major Atherosclerotic Event	526 (11.3%)	619 (13.4%)

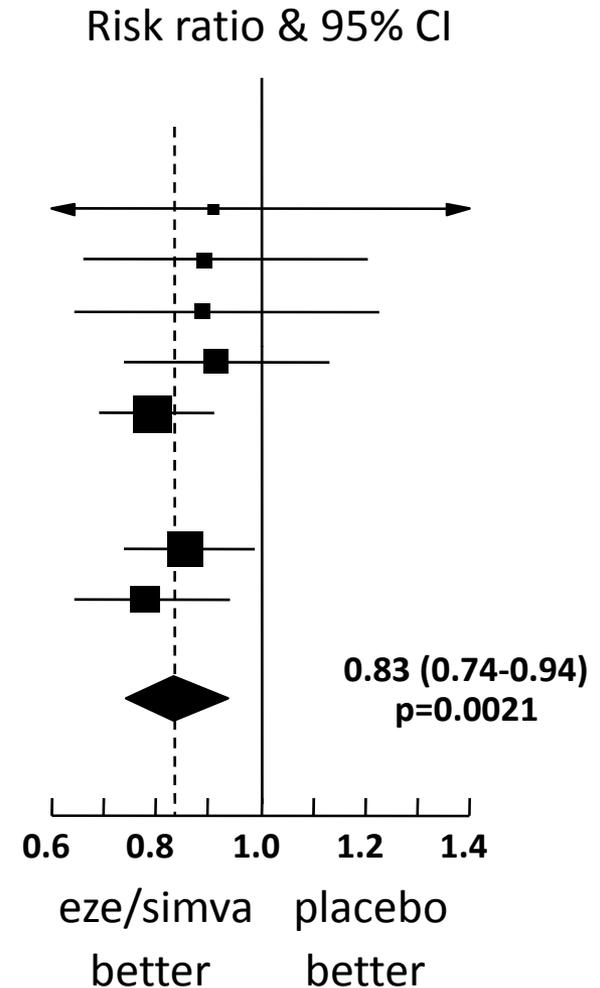


No significant heterogeneity:

- (i) by sex (p=0.9)
- (ii) by age (p=0.44)

SHARP: Major Atherosclerotic Events by prior vascular disease or diabetes

	eze/simva (n=4650)	placebo (n=4620)
Prior vascular disease		
Coronary disease	36 (21.3%)	35 (24.6%)
Peripheral arterial disease	82 (27.0%)	87 (29.0%)
Cerebrovascular disease	74 (22.0%)	77 (24.5%)
At least one of above 3 conditions	167 (23.5%)	172 (25.2%)
None	359 (9.1%)	447 (11.4%)
Diabetes		
No diabetes	333 (9.3%)	385 (10.8%)
Diabetes	193 (18.3%)	234 (22.5%)
Major atherosclerotic event	526 (11.3%)	619 (13.4%)

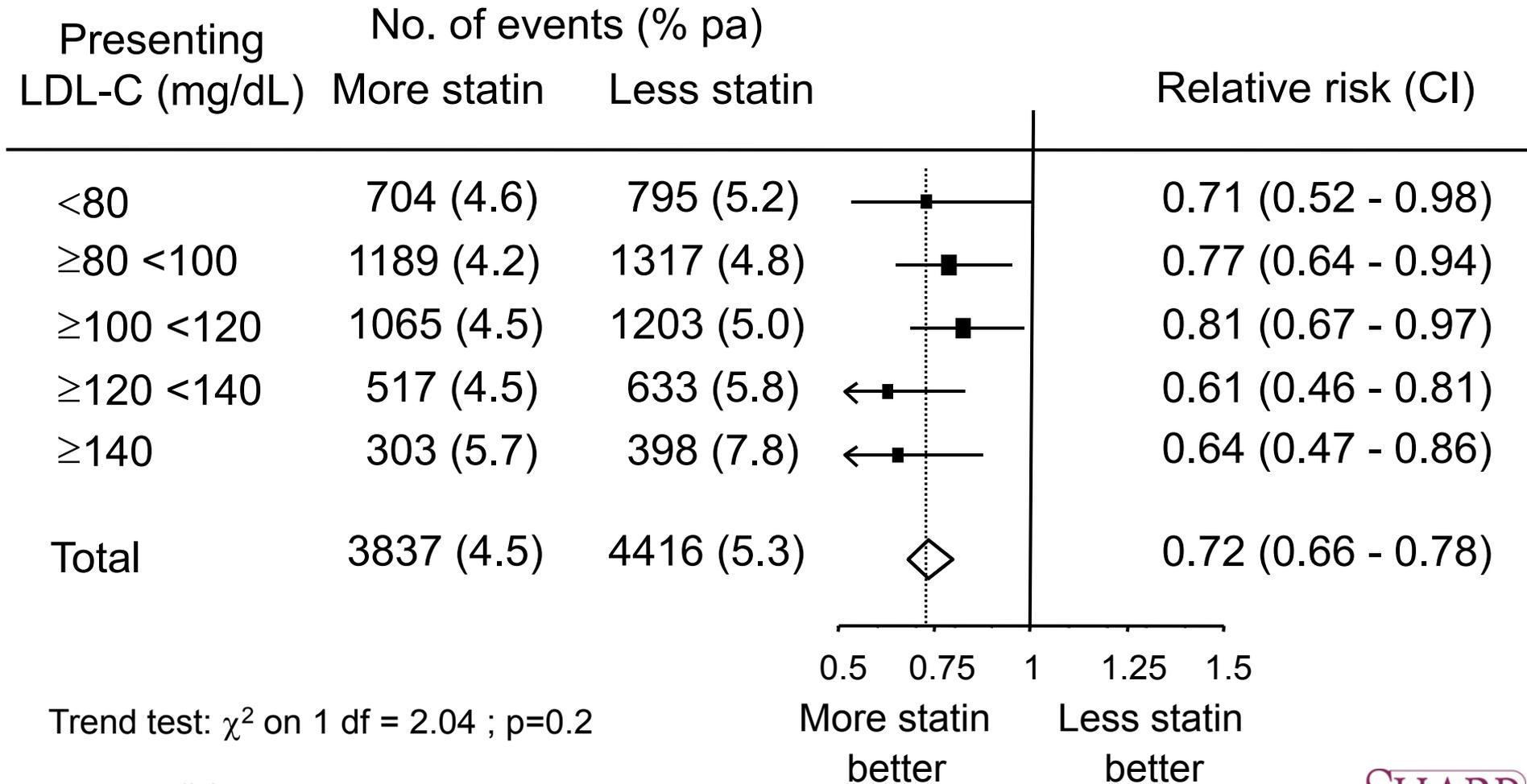


No significant heterogeneity:

(i) by prior vascular disease (p=0.27)

(ii) by history of diabetes (p=0.45)

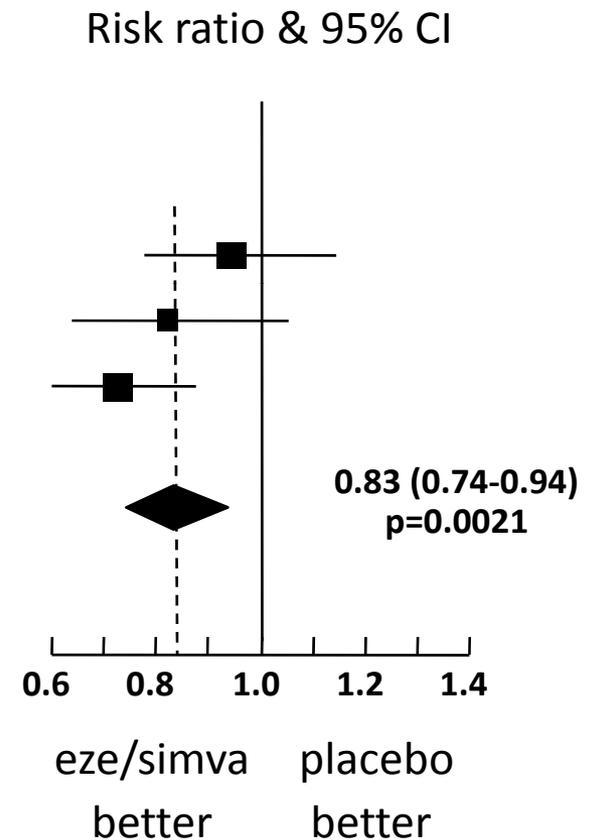
CTT: Similar relative reductions in MVE risk per 40 mg/dL LDL-C reduction, irrespective of presenting LDL-C



SHARP: Major Atherosclerotic Events by presenting LDL cholesterol

	eze/simva (n=4650)	placebo (n=4620)
LDL cholesterol (mg/dL)		
<97	202 (11.4%)	207 (12.1%)
≥97 to <116	115 (10.9%)	135 (13.0%)
≥116	186 (11.4%)	259 (15.4%)
Major atherosclerotic event	526 (11.3%)	619 (13.4%)

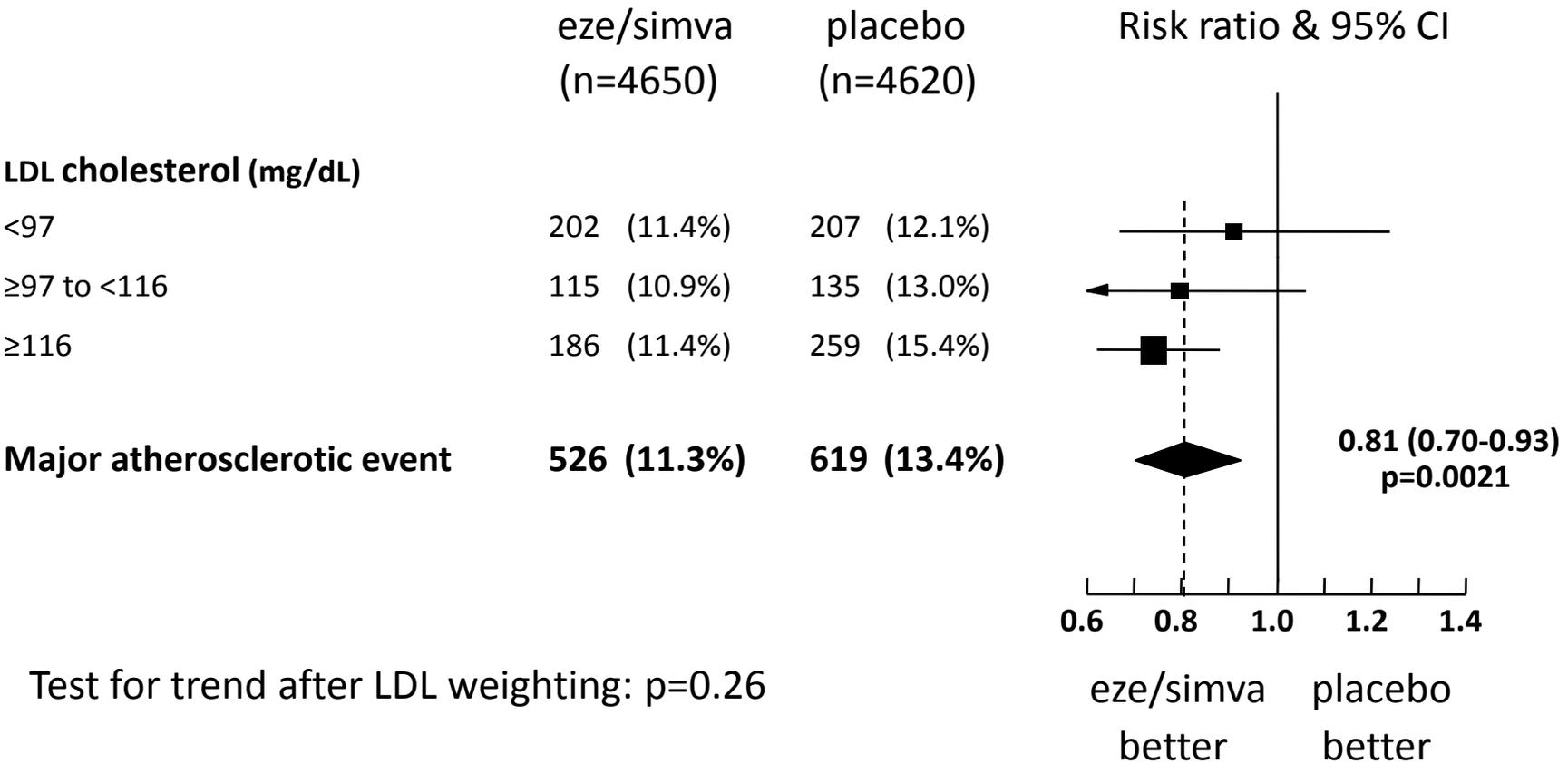
Test for trend: p=0.06



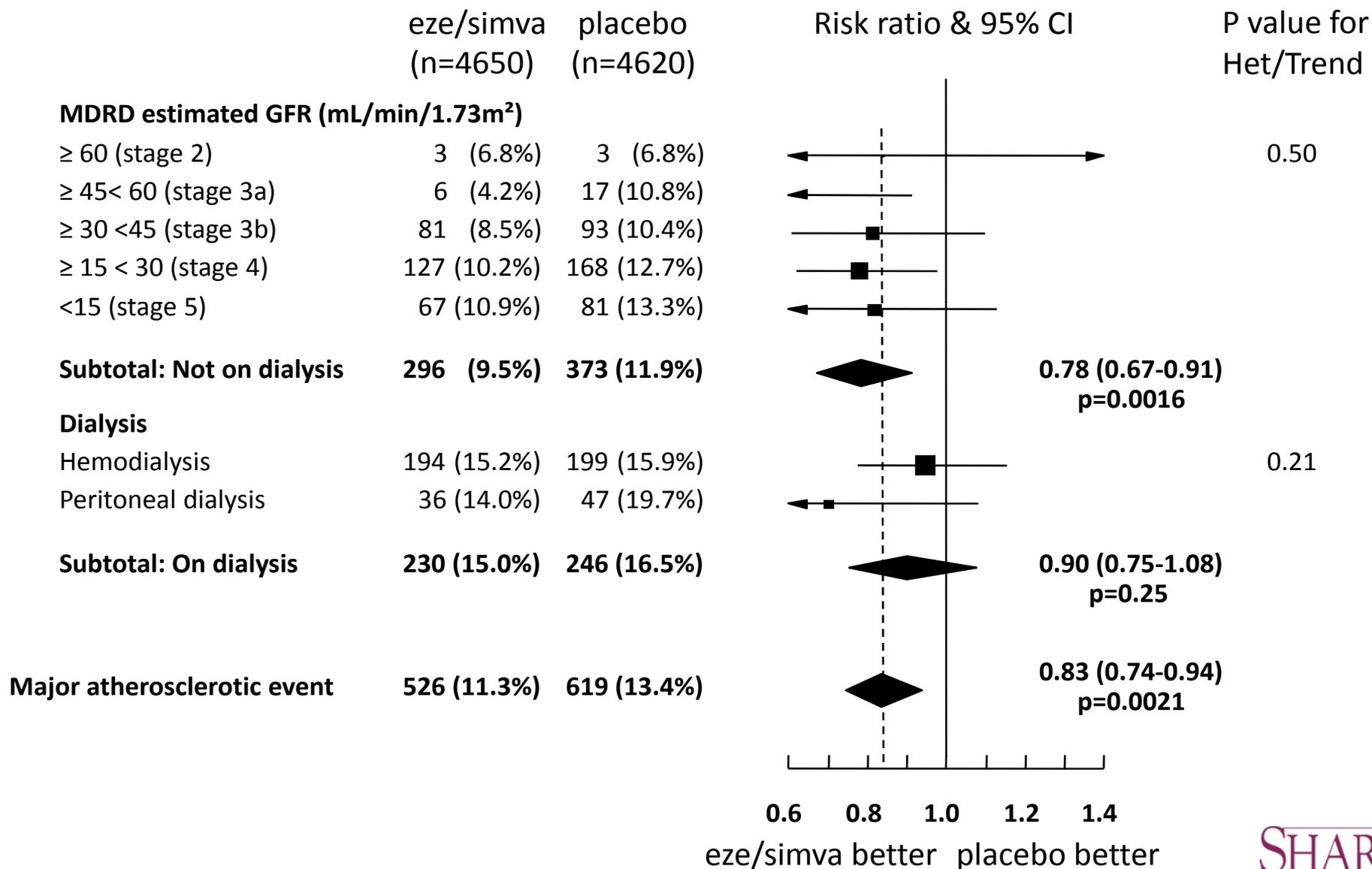
Net compliance and change in LDL-C at study midpoint, by presenting LDL-C

LDL cholesterol (mg/dL)	LDL- lowering drug use			LDL-C difference (mg/dL)		
	eze/ simva	placebo	Net compliance	eze/ simva	placebo	Absolute difference
< 97	67%	7%	60%	-20	5	24
≥97 <116	73%	7%	66%	-37	-4	33
≥116	73%	13%	61%	-58	-17	41
All patients	71%	9%	61%	-39	-6	33

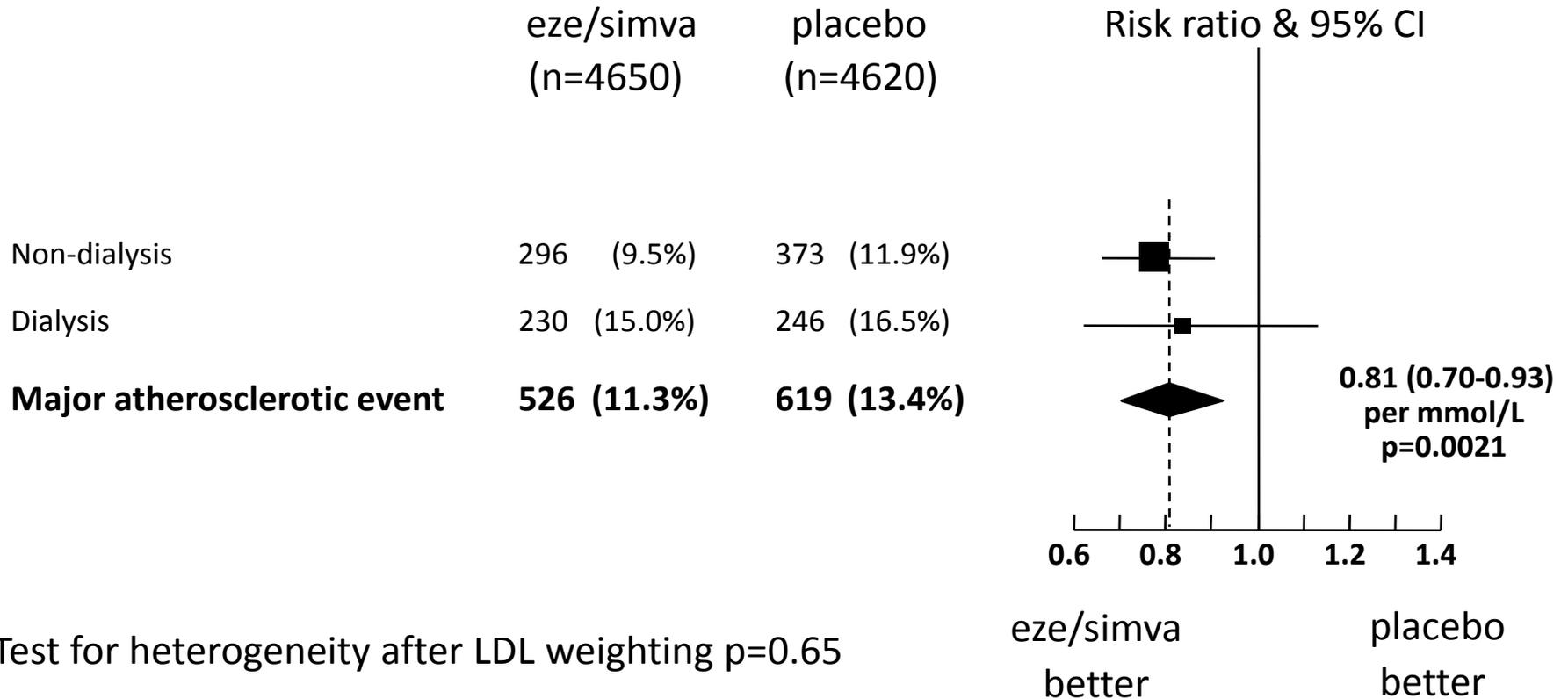
SHARP: Effects on Major Atherosclerotic Events (per 40 mg/dL LDL-C reduction) by presenting LDL-C



SHARP: Major Atherosclerotic Events by CKD stage



SHARP: Effects on Major Atherosclerotic Events (per 40 mg/dL LDL-C reduction) by renal status



Test for heterogeneity after LDL weighting p=0.65

Study of Heart and Renal Protection (SHARP): Design points and Conclusions

Rory Collins

University of Oxford, UK

Chair, SHARP Steering Committee

SHARP: Organisational structure

- Trial sponsor was University of Oxford, UK
- Coordination of 380 sites by 7 regional centres
- Independent Steering Committee
 - Representatives from each of 18 countries
 - 2 non-voting representatives from funder
- Independent Data Monitoring Committee
 - 6-monthly review of unblinded data report
 - No recommendation made to stop during trial
- Principal funder was Merck/Schering-Plough

Rationale for randomization structure

- 3-way randomization for first year only
 - Simvastatin vs placebo
 - LDL-lowering effects of simvastatin
 - Eze/simva vs simvastatin
 - Additional LDL-lowering effects of ezetimibe
 - Early safety of adding ezetimibe to simvastatin
- 2-way randomization of eze/simva vs placebo
 - 5-year effects of eze/simva on clinical outcomes
 - Simvastatin-allocated patients re-randomized to maximize power for assessment of eze/simva

SHARP: Sensitive to potential benefits

- Emphasis on detecting effects of eze/simva on ATHEROSCLEROTIC outcomes
 - INCLUSION of coronary and non-coronary revascularization procedures
 - EXCLUSION of non-coronary cardiac death and hemorrhagic stroke from key outcome
- Large number of relevant outcomes and long duration of treatment to maximize power

Importance of considering external and internal evidence regarding study power during trials

“The primary variable [outcome] ...should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial”

Section 2.2.2 in Statistical Principles
for Clinical Trials (ICH E9)

Steering Committee's blinded decision to emphasize “key outcome” of Major Atherosclerotic Events

- Original primary: “major vascular event” (MVE: non-fatal MI or cardiac death, any stroke, or any revascularization)
- October 2009 meeting of Steering Committee:
 - LDL difference lower than expected (33 vs 39 mg/dL)
 - 1/3 of MVEs adjudicated as non-coronary cardiac deaths or hemorrhagic strokes
- Steering Committee decided to change primary outcome to “major atherosclerotic event” (MAE: non-fatal MI or coronary death, non-hemorrhagic stroke, or any revascularization)
- Statistical Analysis Plan published with MAE as “key outcome” (but protocol could not be changed without funder approval)

SHARP: Estimated difference in power for expected effects on MVE and MAE

Outcome (and risk reduction)	Patients	Expected result	Power at $p=0.01$
MVE (13%)	8400	737 vs 845	66%
MAE (18%)	8400	525 vs 639	84%
	9438	576 vs 701	88%

SHARP: Special features of design

- Largest randomized trial in kidney patients
- Non-restrictive inclusion criteria yield widely generalizable results for CKD populations
- Included CKD patients in stages 3-5 (both pre-dialysis and dialysis)
- Focus on outcomes that are sensitive to LDL lowering (ie, major atherosclerotic events)
- Combination of moderate-dose statin plus ezetimibe yielded large LDL-C reduction, but it was also well-tolerated by CKD patients

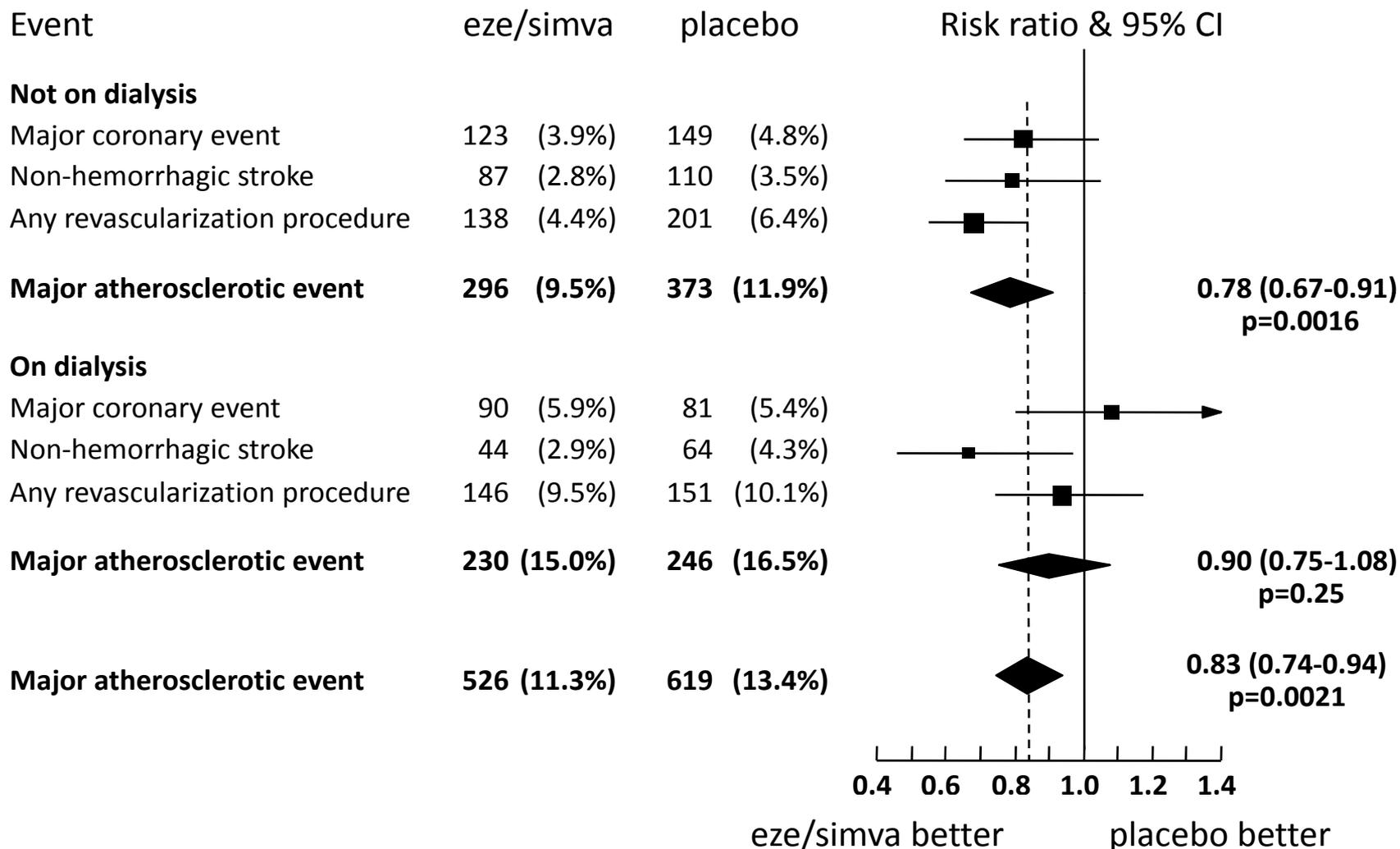
Interpretation of subgroup analyses of effects in dialysis and non-dialysis patients

- SHARP was not designed to have power to assess effects on MAE or MVE in different subgroups considered separately
- Instead, pre-specified approach involved testing for differences between observed effects, with allowance made for:
 - multiple subgroup comparisons; and
 - other differences between subgroups
- Allocated study treatment produced smaller LDL-C reduction in dialysis (23mg/dL) versus non-dialysis (37mg/dL) patients
- After allowance for this difference in LDL-C reduction, similar MAE and MVE reduction in non-dialysis and dialysis patients (with no significant evidence of heterogeneity)
- Dialysis patients have higher absolute risk of vascular events, so absolute benefit may be larger than in non-dialysis patients

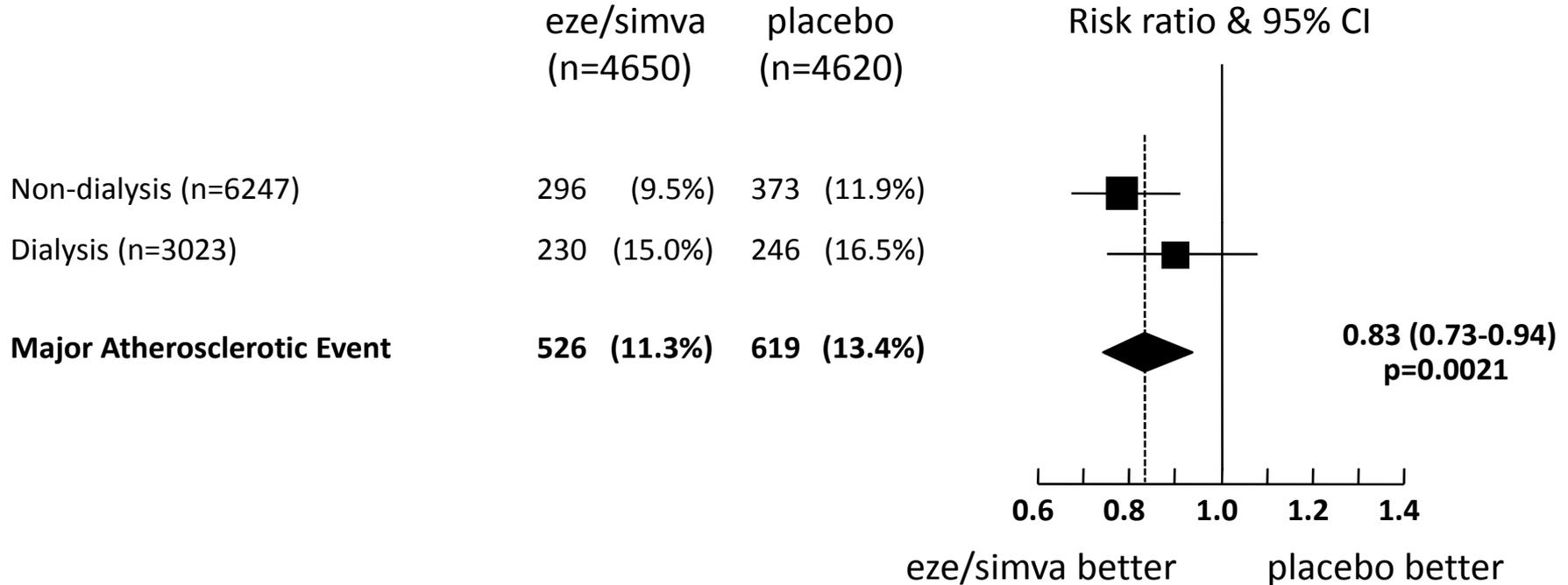
Net compliance and LDL reduction differed between non-dialysis and dialysis patients

eGFR	LDL-lowering drug use			Mean LDL difference (mg/dL)		
	eze/ simva	placebo	Absolute difference	eze/ simva	placebo	Absolute difference
Not on dialysis	73%	8%	65%	-43	-6	37
Dialysis	65%	11%	54%	-29	-6	23
All patients	71%	9%	61%	-39	-6	33

SHARP: Major Atherosclerotic Events by dialysis status

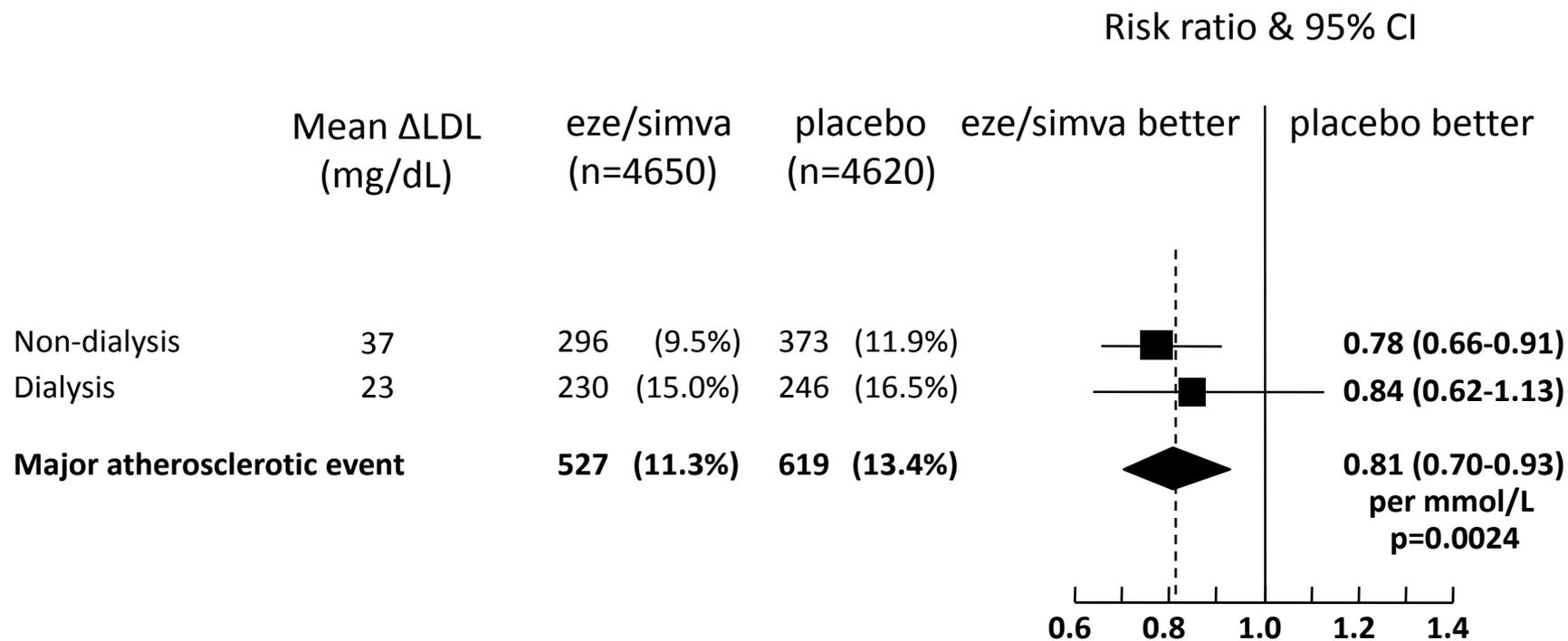


SHARP: Effects on Major Atherosclerotic Events by renal status (not adjusted for LDL-C reduction)



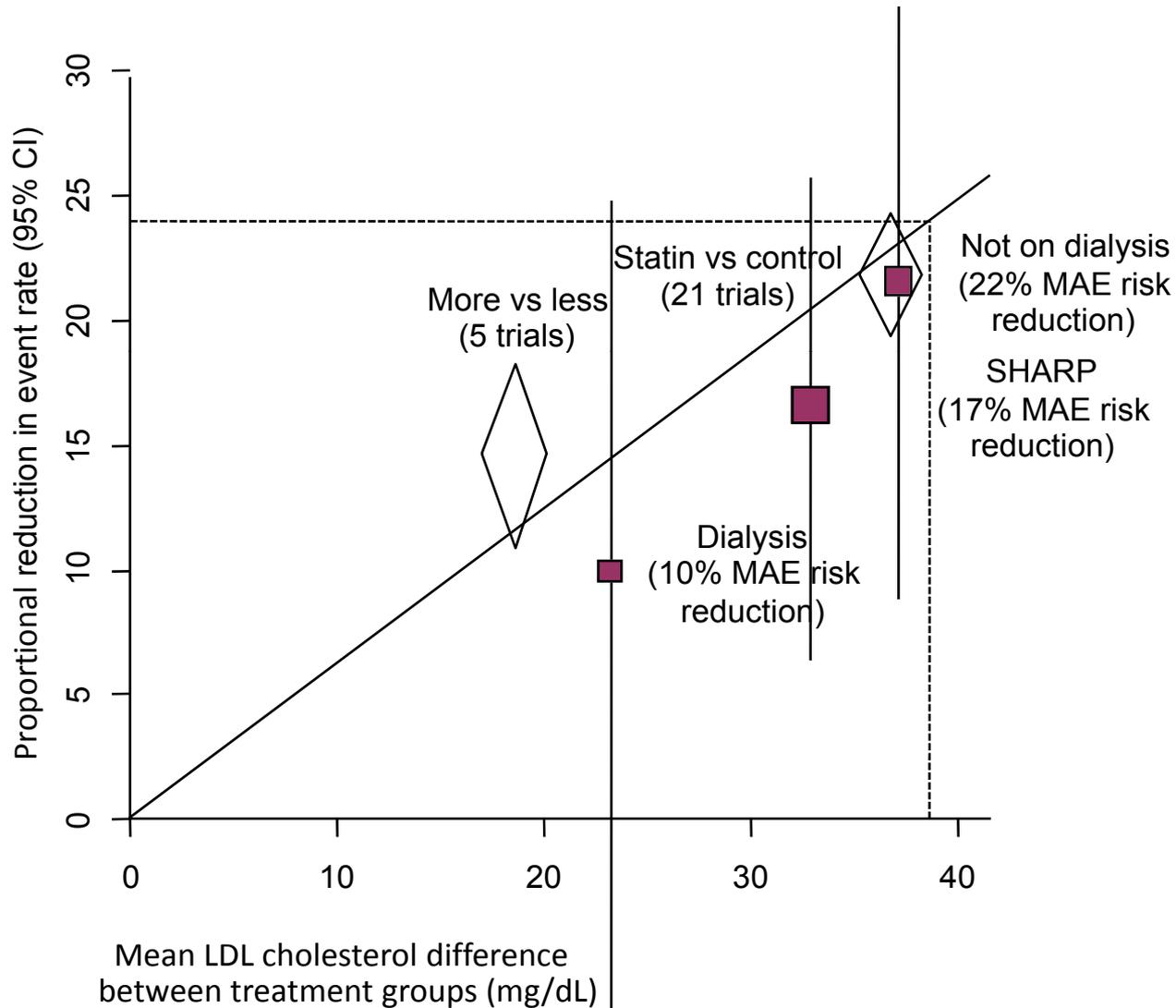
Heterogeneity test between non-dialysis and dialysis patients: p=0.25

SHARP: Effects on Major Atherosclerotic Events by renal status (per 40 mg/dL LDL-C reduction)

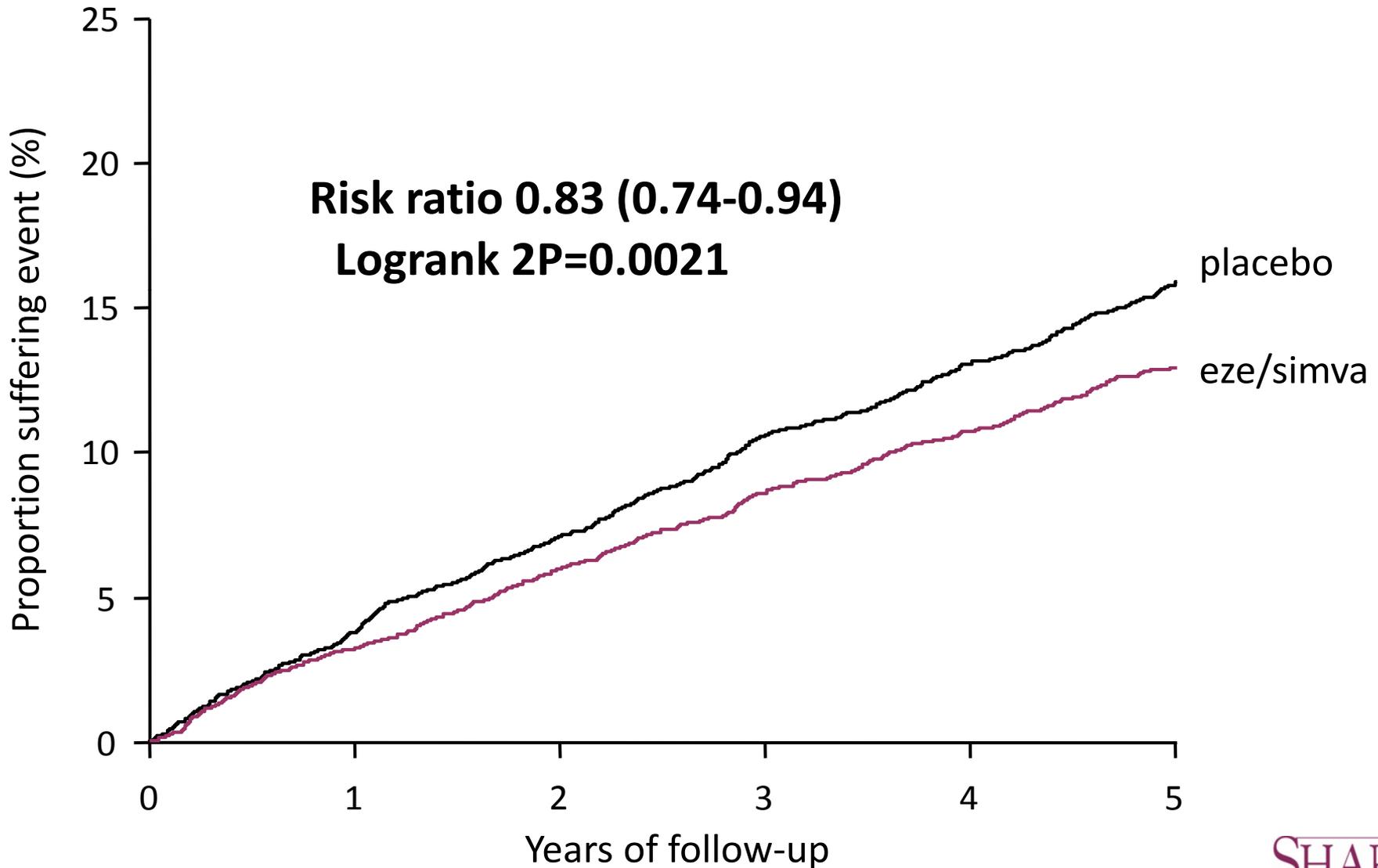


Heterogeneity test between non-dialysis and dialysis patients: p=0.65

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

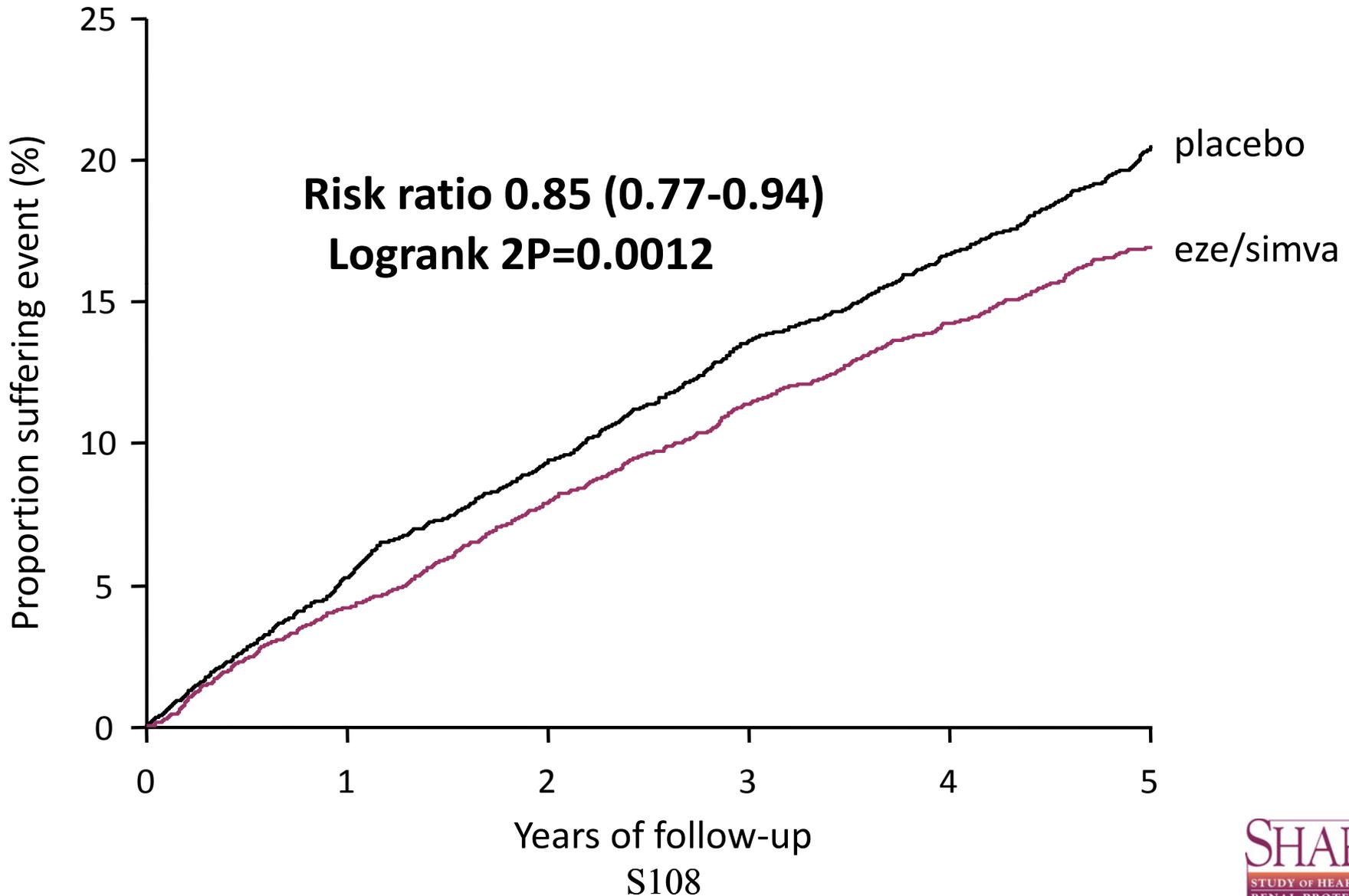


SHARP: More prolonged treatment produces bigger reduction in MAE risk



S107

SHARP: More prolonged treatment produces bigger reduction in MVE risk



Better compliance produces bigger LDL-C reductions

Time period	LDL- lowering drug use			LDL-C difference (mg/dL)		
	eze/ simva	placebo	Net compliance	eze/ simva	placebo	Absolute difference
~ 1 year	77%	3%	74%	-42	+1	-42
~ 2.5 years	71%	9%	61%	-39	-6	-33
~ 4 years	68%	14%	55%	-32	-3	-30

Net compliance is defined as the difference between groups in the proportion that were taking at least 80% of study treatment or a non-study statin

SHARP: Summary of findings

- Allocation to eze/simba produced:
 - mean study LDL-C reduction of 33mg/dL
 - 17% reduction in major atherosclerotic events
- Similar, and significant, reductions in both:
 - Major atherosclerotic events (p=0.0021)
 - Major vascular events (p=0.0012)
- Longer treatment, and better compliance, would be expected to lead to larger benefits
- No evidence of serious adverse effects with eze/simba in vulnerable CKD patient population

SHARP: Public health impact of findings

- 19 million Americans currently have stage 3-5 CKD
- Intention-to-treat analyses indicate that 21 per 1000 fewer patients had MAE over about 5 years (NNT=48)
- Or, more appropriately, SHARP indicates that 21,000 fewer per million would have had MAE over 5 years
- Benefits are similar to those seen with LDL-lowering therapy in other high-risk groups (eg, diabetic patients)
- Observed benefit is an underestimate of actual use:
 - Longer treatment and better compliance would be expected to yield even larger reductions in absolute risk of events
 - SHARP excluded highest risk patients (eg, those with CHD)

Merck's Perspective on SHARP

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Background

- CKD patients are at greatly increased CV risk
- CV risk in CKD patients represents a significant unmet need
- Prior to SHARP, the CV benefit and safety of LDL-C lowering in patients with moderate to advanced CKD had not been demonstrated

SHARP: Outcomes Efficacy

- SHARP demonstrated that reduction in LDL-C with ezetimibe/simvastatin 10/20 mg translates into CV risk reduction in a broad spectrum of CKD patients
 - ~1/3 of the LDL-C lowering in SHARP was attributable to ezetimibe
 - Although SHARP was powered only for the composite endpoint;
 - ezetimibe/simvastatin was numerically superior for each major component of MVE and MAE
 - statistically significant treatment effects were achieved for revascularization and stroke
 - Effects of ezetimibe/simvastatin were consistent across subgroups, supporting general use in moderate to severe CKD patients

SHARP: Safety

- Treatment with ezetimibe/simvastatin 10/20 mg over a median follow-up of ~5 years resulted in generally similar rates compared with placebo in all of the pre-specified safety categories, including:
 - Serious adverse events
 - Adverse events leading to discontinuation
 - Myopathy/CK elevations
 - Hepatitis, gallstones, or pancreatitis
 - Cancer
- The safety profile of ezetimibe/simvastatin 10/20 mg in SHARP was consistent with current labeling, with no new adverse effects identified

Conclusions

- SHARP, a large, robust study of ezetimibe/simvastatin 10/20 mg, is the first study to successfully demonstrate that a specific lipid-lowering treatment can reduce CV risk in patients with moderate to severe CKD
- The combination of ezetimibe/simvastatin 10/20 mg is generally safe and well tolerated in this vulnerable population
- The SHARP results represent an important advance for the treatment of a very high-risk population with a significant unmet medical need

Proposed New Indications

- The SHARP study results support the proposed new indication for VYTORIN[®] to:
 - reduce the risk of major cardiovascular events in patients with chronic kidney disease
- The SHARP study results support the proposed new indication for ZETIA[®] to:
 - reduce the risk of major cardiovascular events in patients with chronic kidney disease in combination with simvastatin