The results of the Study of Heart and Renal Protection (SHARP)

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on behalf of the SHARP Investigators
Australia/New Zealand/SE Asia
Regional Coordination.

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SHARP: Rationale

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

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SHARP: Eligibility

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

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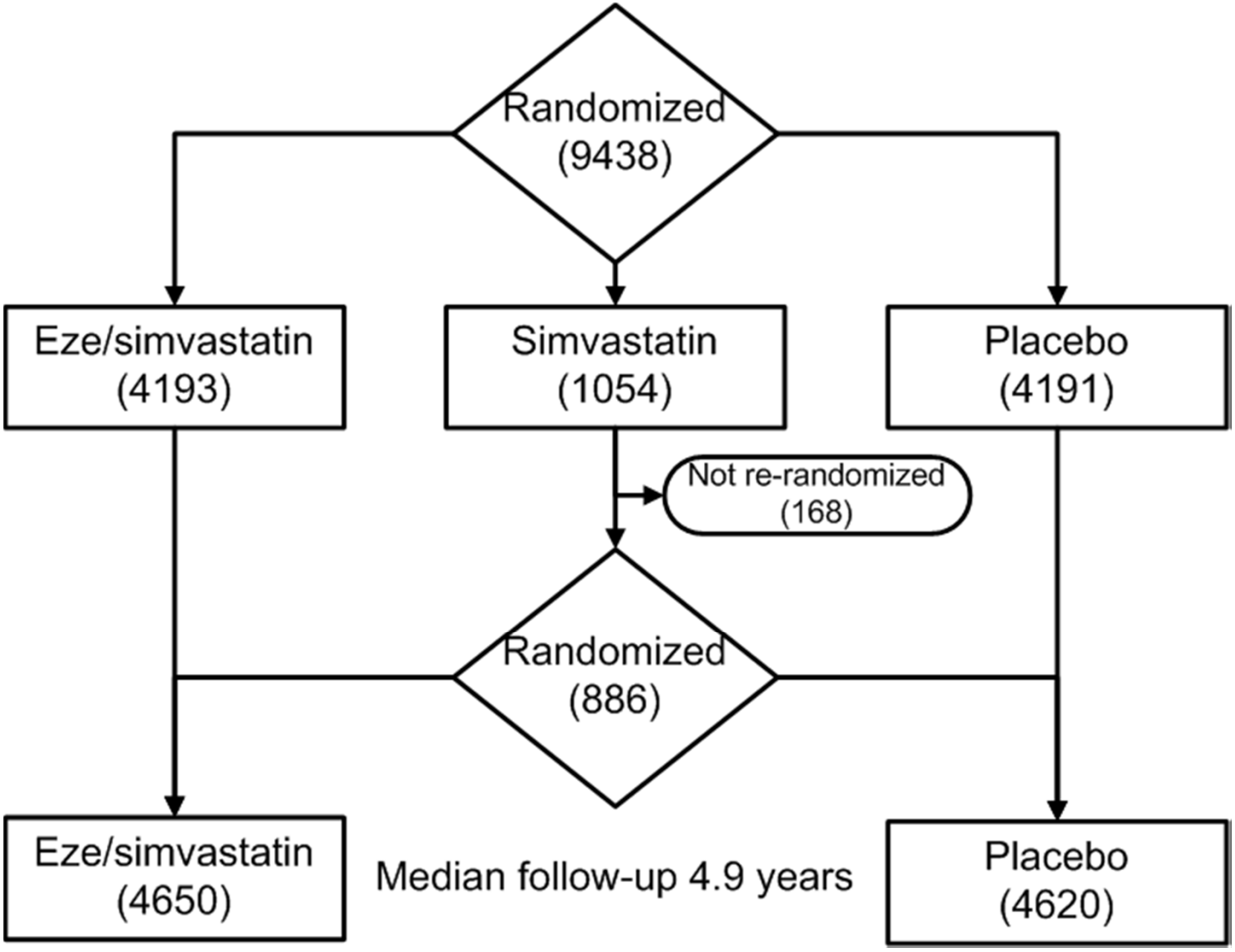
SHARP: Assessment of LDL-lowering



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SHARP: Baseline characteristics

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

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SHARP: Compliance and LDL-C reduction at study midpoint

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

~2/3 compliance

LDL-C reduction of 0.83mmol/l (32 mg/dL) with 2/3 compliance,
equivalent to 1.3mmol/l (50 mg/dL) with full compliance

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SHARP: Baseline paper and Data Analysis Plan

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

SHARP Collaborative Group

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

- 1-year LDL-C reduction of 0.78mmol/l (30 mg/dL) with simvastatin 20 mg alone and of 1.1 mmol/l (43 mg/dL) with eze/simv 10/20mg
- Confirmation of safety of ezetimibe when added to simvastatin (1-year results)
- Revised data analysis plan published as an appendix before unblinding of main results

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SHARP: Main outcomes

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

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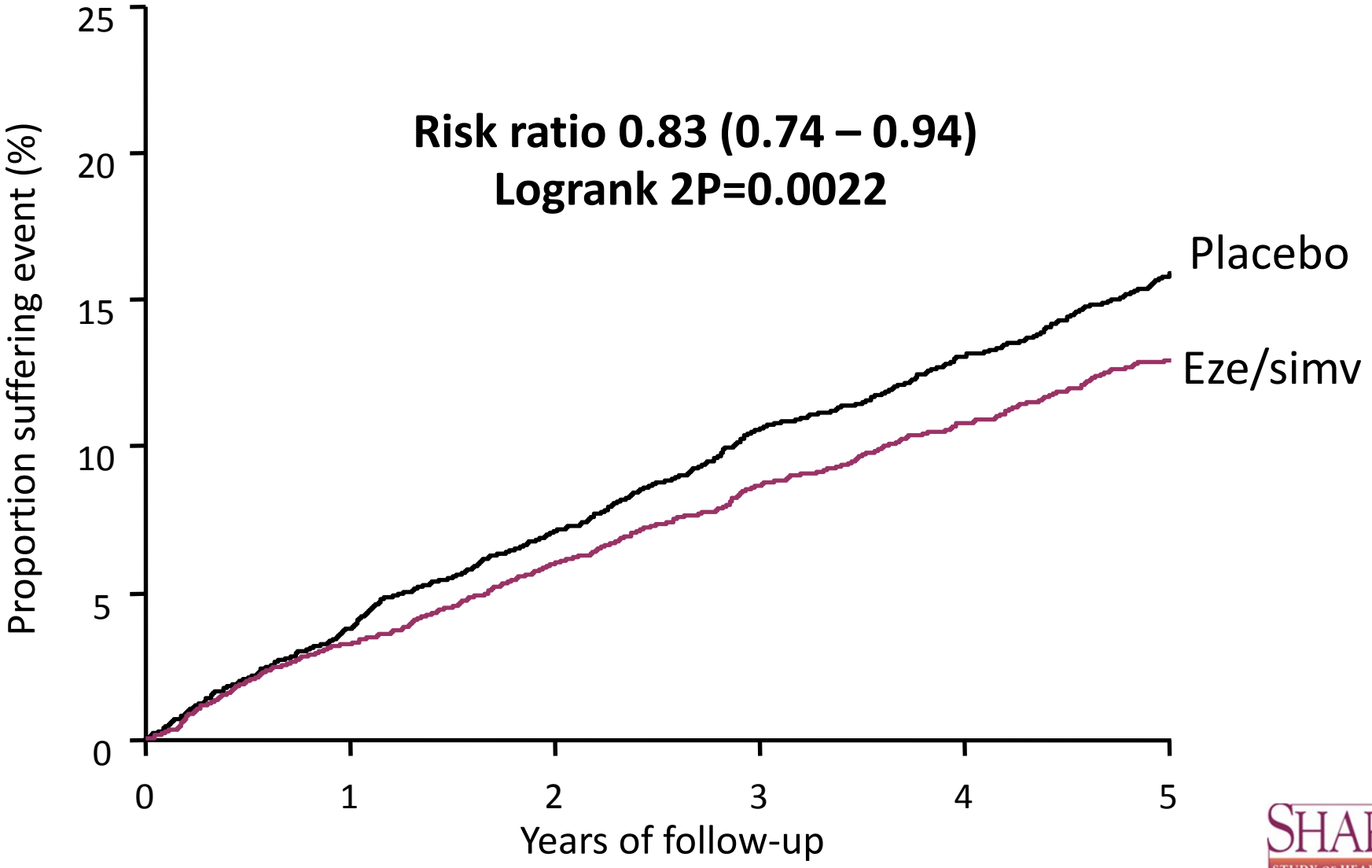
SHARP: Major Atherosclerotic Events



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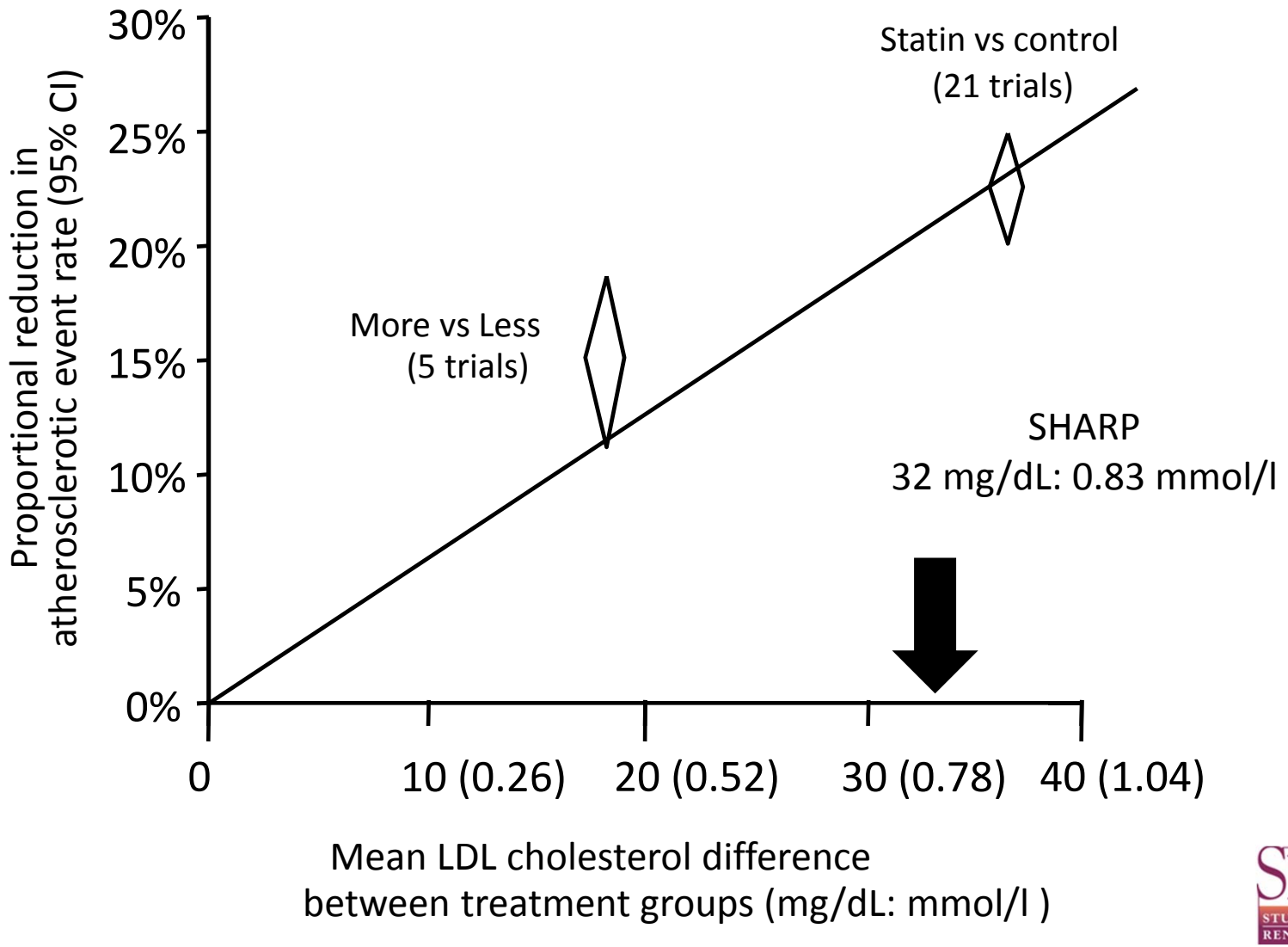
CTT: Effects on Major Atherosclerotic Events



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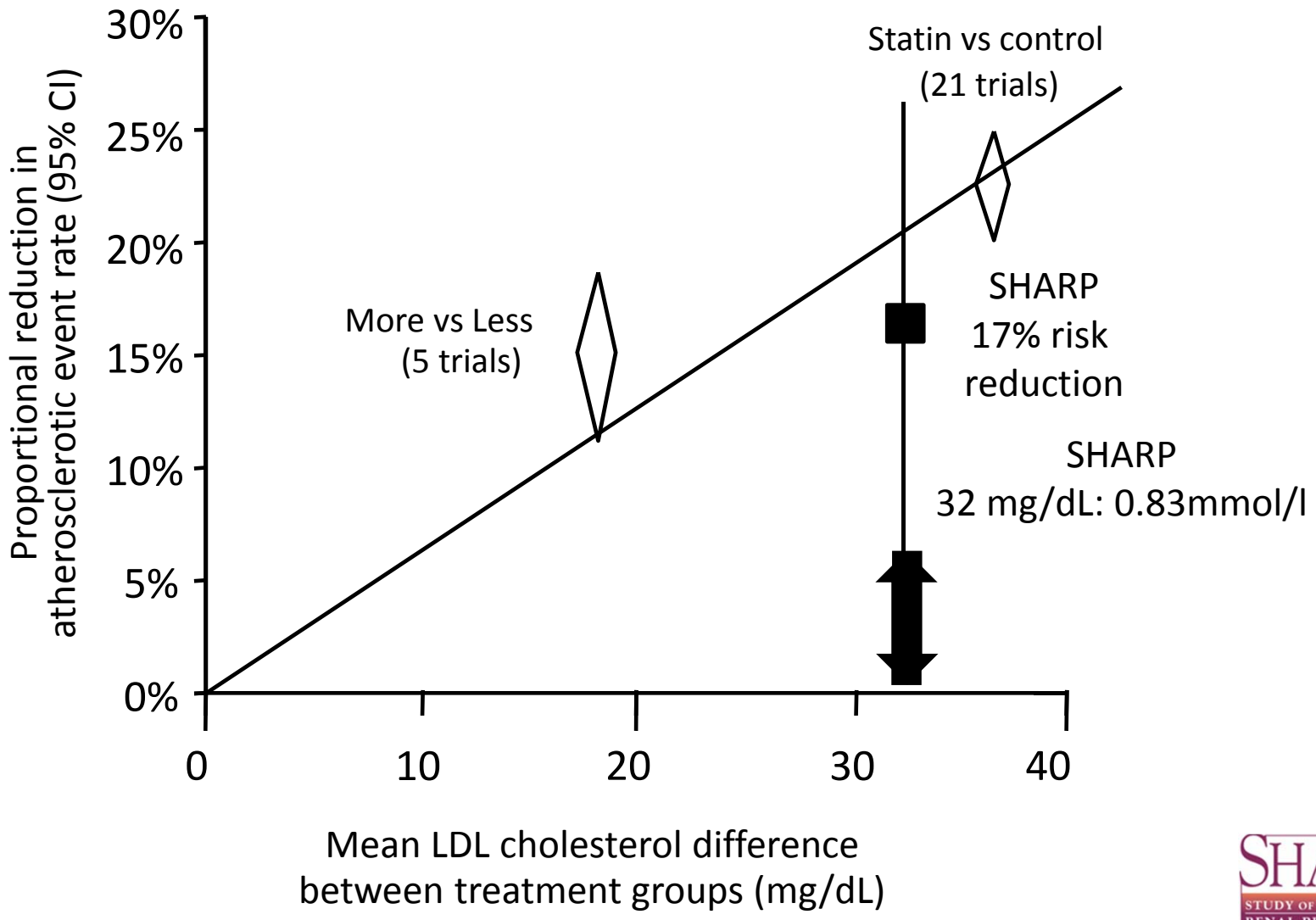
CTT: Effects on Major Atherosclerotic Events



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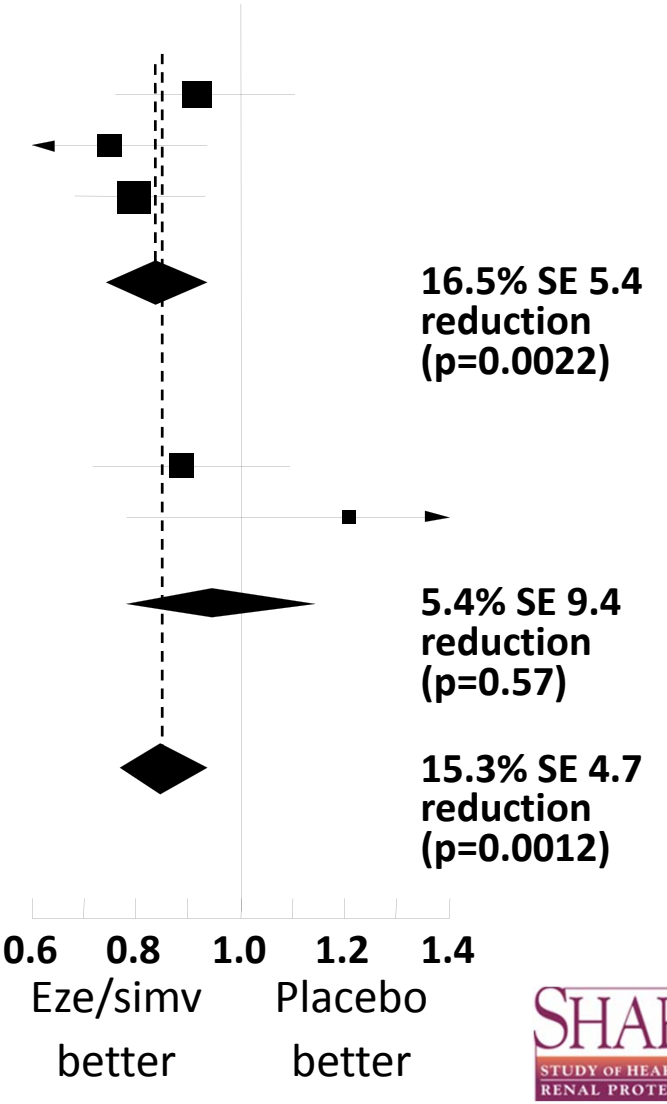
SHARP: Major Atherosclerotic Events

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



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SHARP: Effects in subgroups

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

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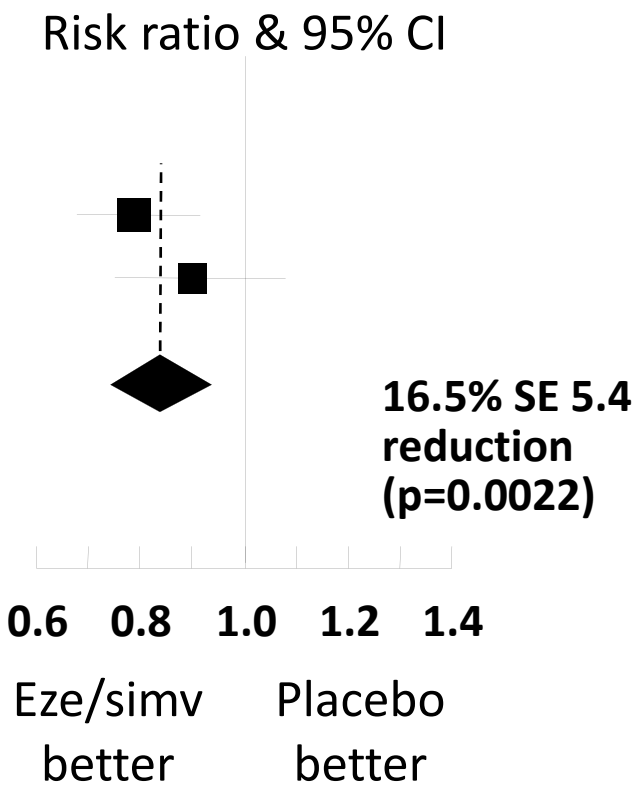
SHARP: Major Atherosclerotic Events by renal status at randomization

	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)



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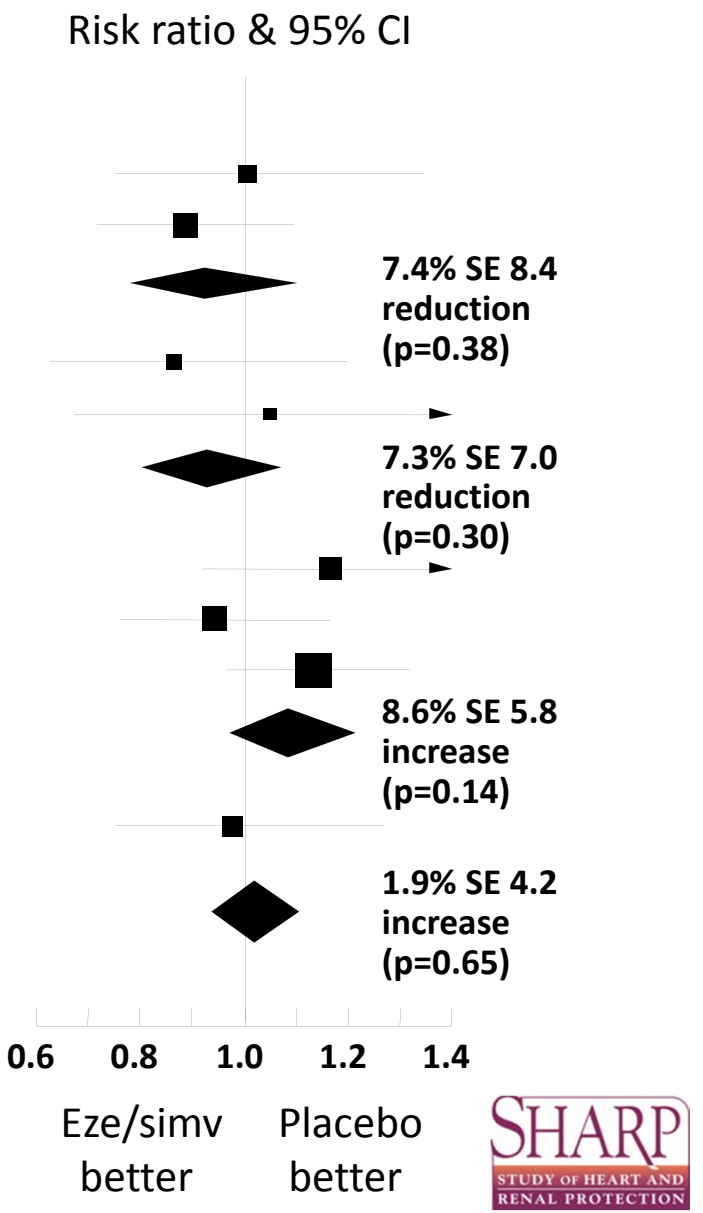
SHARP: Cause-specific mortality

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



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SHARP: Renal outcomes

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

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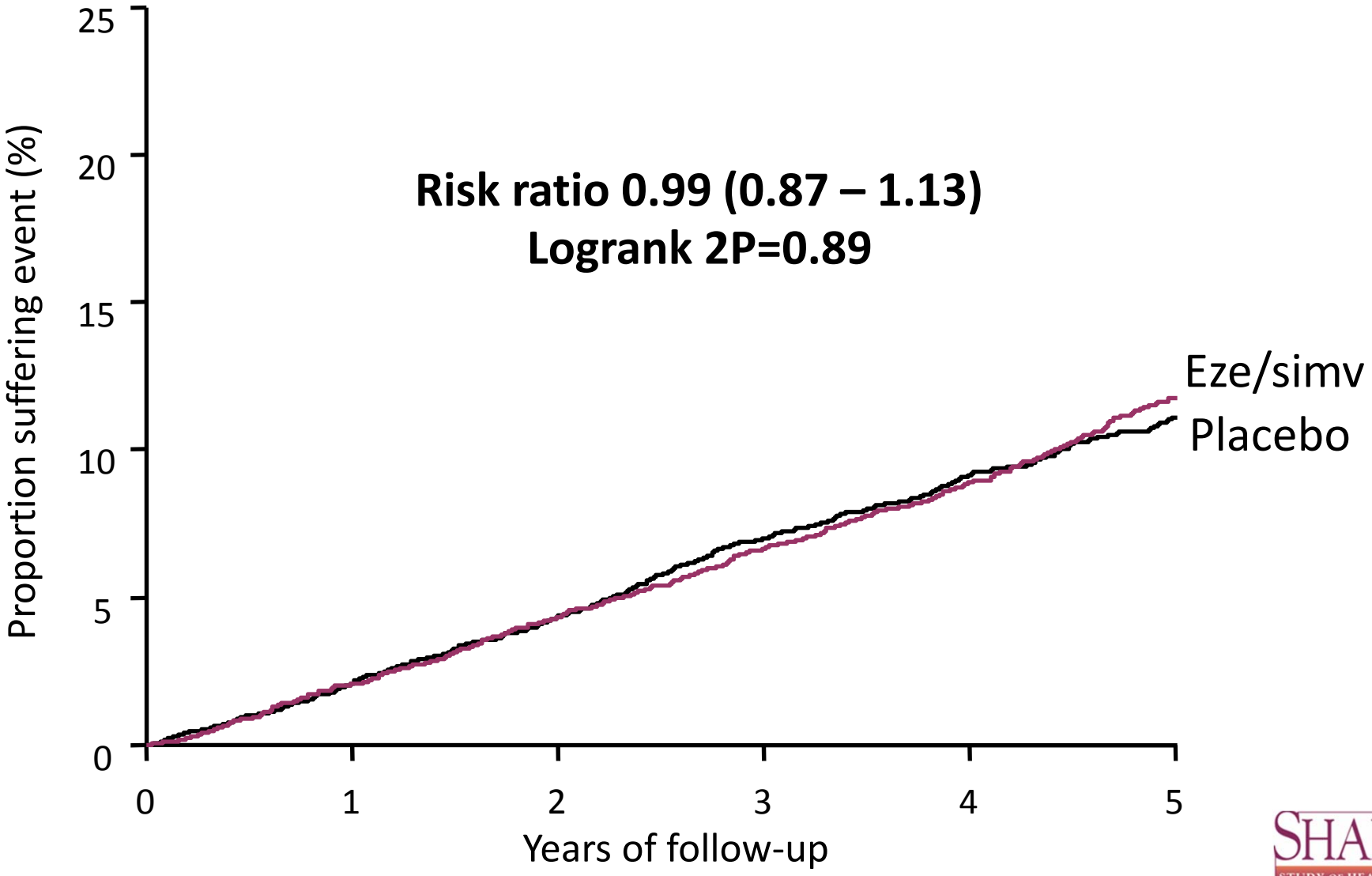
SHARP: Cancer incidence



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SHARP: Cancer incidence by site

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

No significant differences

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SHARP: Safety

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

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SHARP: Conclusions

- No increase in risk of myopathy, liver and biliary disorders, cancer, or nonvascular mortality
- No substantial effect on kidney disease progression
- Two-thirds compliance with eze/simv reduced the risk of major atherosclerotic events by 17% (consistent with meta-analysis of previous statin trials)
- Similar proportional reductions in all subgroups (including among dialysis and non-dialysis patients)
- Full compliance would reduce the risk of major atherosclerotic events by one quarter, avoiding 30–40 events per 1000 treated for 5 years

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SHARP (ER)

- Proposal:
- extend the follow up of SHARP Study participants a further 5 years beyond their final study visit.
- Using patient visits, telephone contact, hospital record review and linkage to national data registries, this extended follow up will provide unique data on:

SHARP (ER)

- The long-term effects of cholesterol-lowering treatment in patients with CKD and ESKD;
- Factors that determine the progression of CKD in a large pre-dialysis cohort;
- The long-term effects of cholesterol lowering upon cancer risk; and
- The economic and social impact of CKD on patients and families.

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