Cholesterol-lowering in kidney disease and/or diabetes: Is it safe and efficient?

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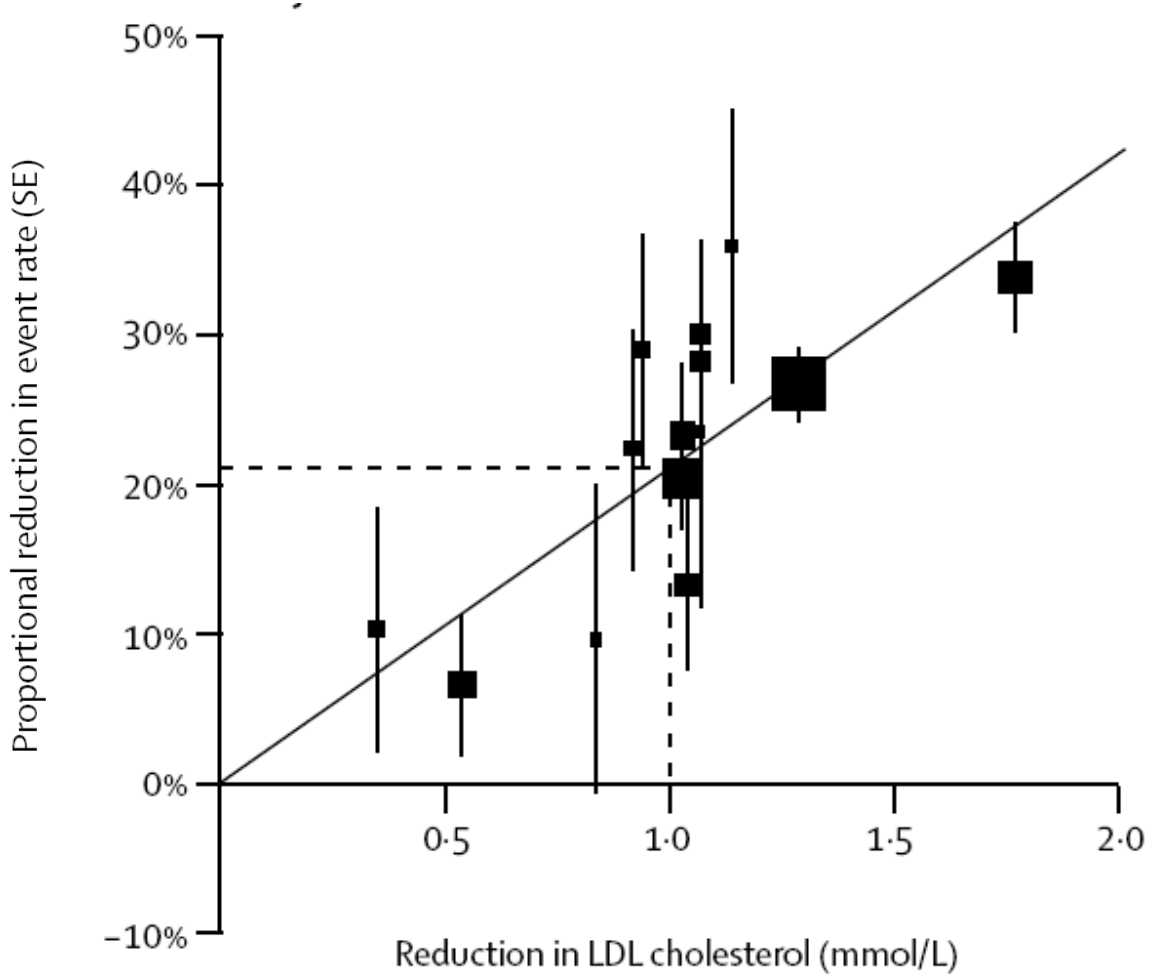
Disclosure

I am the CI of the SHARP trial, which was funded by a grant from Merck

First CTT cycle: Relation between the proportional reduction in MAJOR VASCULAR EVENTS and mean absolute LDL-C reduction at 1 year in 14 statin trials



Lancet 2005; 366: 1267–78

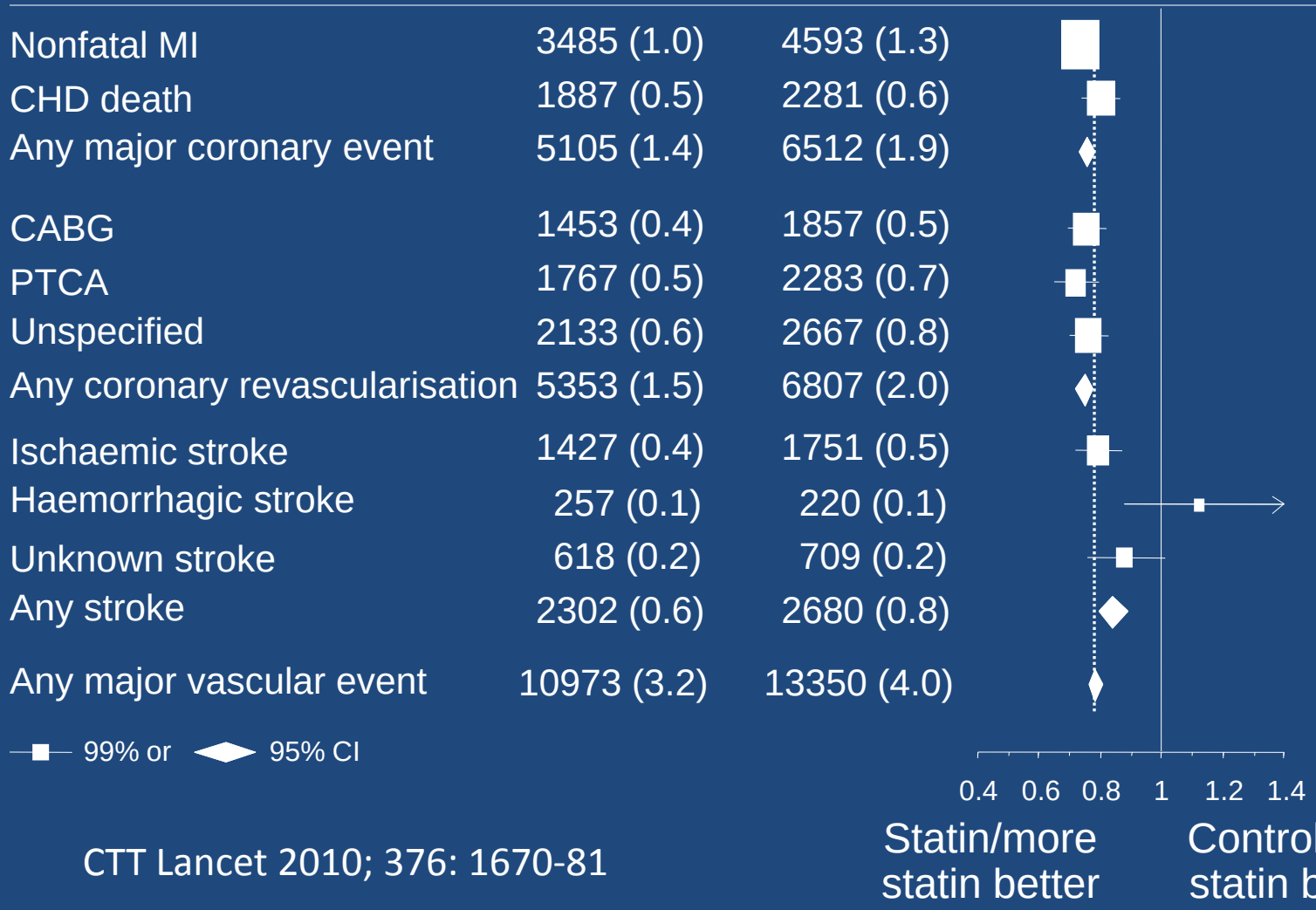
Cholesterol Treatment Trialists (CTT) Collaboration

- 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 Collaboration *Lancet* 2010

Proportional effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol

	No. of events (% pa) Statin/ More statin	Control/ Less statin	Relative risk (CI)
Nonfatal MI	3485 (1.0)	4593 (1.3)	0.73 (0.69 - 0.78)
CHD death	1887 (0.5)	2281 (0.6)	0.80 (0.74 - 0.87)
Any major coronary event	5105 (1.4)	6512 (1.9)	0.76 (0.73 - 0.78)
CABG	1453 (0.4)	1857 (0.5)	0.75 (0.69 - 0.82)
PTCA	1767 (0.5)	2283 (0.7)	0.72 (0.65 - 0.80)
Unspecified	2133 (0.6)	2667 (0.8)	0.76 (0.70 - 0.82)
Any coronary revascularisation	5353 (1.5)	6807 (2.0)	0.75 (0.72 - 0.78)
Ischaemic stroke	1427 (0.4)	1751 (0.5)	0.79 (0.72 - 0.87)
Haemorrhagic stroke	257 (0.1)	220 (0.1)	1.12 (0.88 - 1.43)
Unknown stroke	618 (0.2)	709 (0.2)	0.88 (0.76 - 1.01)
Any stroke	2302 (0.6)	2680 (0.8)	0.84 (0.79 - 0.89)
Any major vascular event	10973 (3.2)	13350 (4.0)	0.78 (0.76 - 0.80)



CTT Lancet 2010; 376: 1670-81

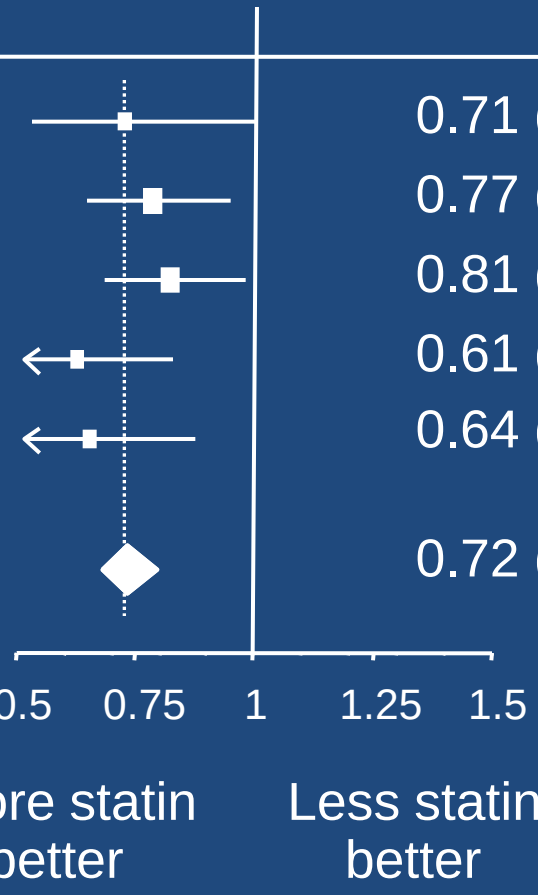
Effects on MAJOR VASCULAR EVENTS among participants with diabetes*

Major vascular event and prior diabetes	Events (%) Treatment	Control	RR (CI)
Major coronary event			
Diabetes	776 (8·3)	979 (10·5)	0·78 (0·69 - 0·87)
No diabetes	2561 (7·2)	3441 (9·6)	0·77 (0·73 - 0·81)
Any major coronary event	**3337 (7·4)**	**4420 (9·8)**	**0·77 (0·74 - 0·80)**
Coronary revascularization			
Diabetes	491 (5·2)	627 (6·7)	0·75 (0·64 - 0·88)
No diabetes	2129 (6·0)	2807 (7·9)	0·76 (0·72 - 0·81)
Any coronary revascularization	**2620 (5·8)**	**3434 (7·6)**	**0·76 (0·73 - 0·80)**
Stroke			
Diabetes	407 (4·4)	501 (5·4)	0·79 (0·67 - 0·93)
No diabetes	933 (2·7)	1116 (3·2)	**0·83 (0·76 - 0·88)**
Any stroke	**1340 (3·0)**	**1617 (3·7)**	
Major vascular event			
Diabetes	1465 (15·6)	1782 (19·2)	0·79 (0·72 - 0·86)
No diabetes	4889 (13·7)	6212 (17·4)	0·79 (0·76 - 0·82)
Any major vascular event	**6354 (14·1)**	**7994 (17·8)**	**0·79 (0·77 - 0·81)**

*Lancet 2008; **371**: 117-125

More vs less trials: Proportional effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by baseline LDL cholesterol

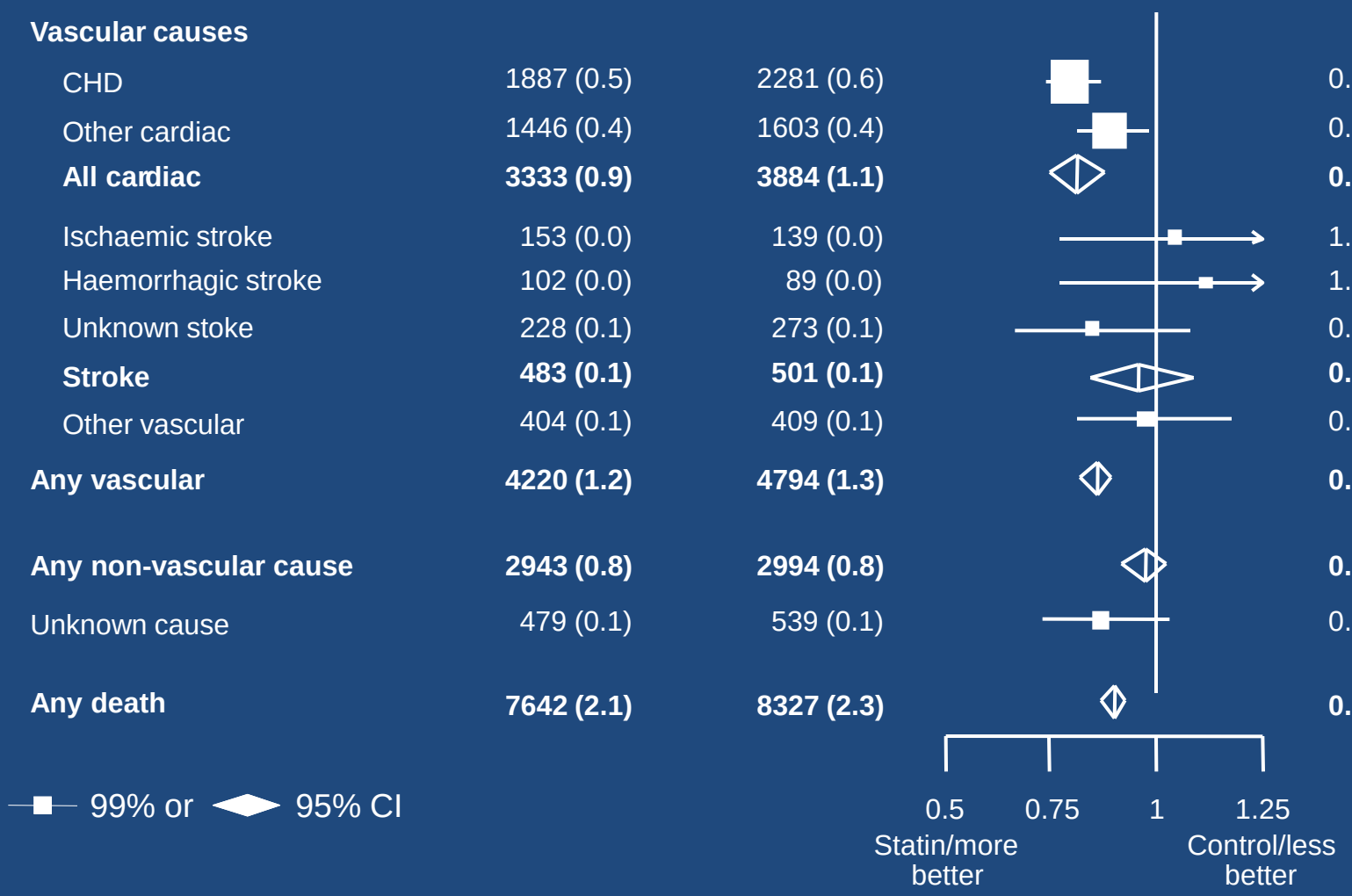
	No. of events (% pa)		Relative risk (CI)
	More statin	Less statin	
<2	704 (4.6)	795 (5.2)	0.71 (0.52 - 0.98)
≥2,<2.5	1189 (4.2)	1317 (4.8)	0.77 (0.64 - 0.94)
≥2.5,<3.0	1065 (4.5)	1203 (5.0)	0.81 (0.67 - 0.97)
≥3,<3.5	517 (4.5)	633 (5.8)	0.61 (0.46 - 0.81)
≥3.5	303 (5.7)	398 (7.8)	0.64 (0.47 - 0.86)
Total	3837 (4.5)	4416 (5.3)	0.72 (0.66 - 0.78)



99% or 95% CI

Proportional effects on CAUSE-SPECIFIC MORTALITY per mmol/L LDL-C reduction

Cause of death	Events (% p.a.) Statin/more	Events (% p.a.) Control/less	RR (CI) per 1 mmol/L reduction in LDL-C
Vascular causes			
CHD	1887 (0.5)	2281 (0.6)	0.80 (0.74 - 0.87)
Other cardiac	1446 (0.4)	1603 (0.4)	0.89 (0.81 - 0.98)
All cardiac	**3333 (0.9)**	**3884 (1.1)**	**0.84 (0.80 - 0.88)**
Ischaemic stroke	153 (0.0)	139 (0.0)	1.04 (0.77 - 1.41)
Haemorrhagic stroke	102 (0.0)	89 (0.0)	1.12 (0.77 - 1.62)
Unknown stoke	228 (0.1)	273 (0.1)	0.85 (0.66 - 1.08)
Stroke	**483 (0.1)**	**501 (0.1)**	**0.96 (0.84 - 1.09)**
Other vascular	404 (0.1)	409 (0.1)	0.98 (0.81 - 1.18)
Any vascular	**4220 (1.2)**	**4794 (1.3)**	**0.86 (0.82 - 0.90)**
Any non-vascular cause	**2943 (0.8)**	**2994 (0.8)**	**0.97 (0.92 - 1.03)**
Unknown cause	479 (0.1)	539 (0.1)	0.87 (0.73 - 1.03)
Any death	**7642 (2.1)**	**8327 (2.3)**	**0.90 (0.87 - 0.93)**



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

Serum Lipid Distribution Across Various Stages of CKD

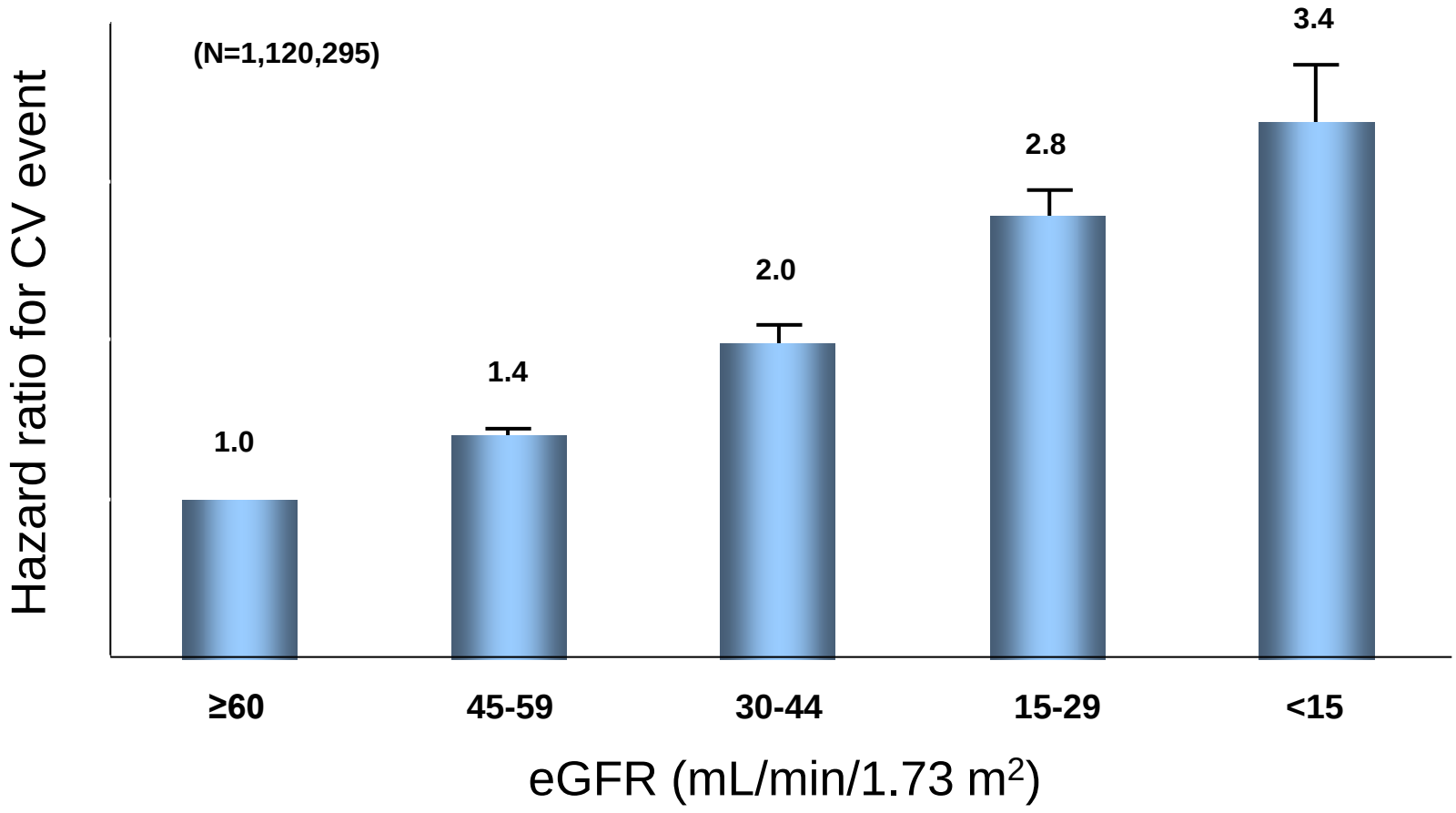
	LDL-C	sdLDL	TRG	HDL-C	Lp(a)
Predialysis CKD (Stages 3-4)	↔ OR ↓	↑	↑	↓	↑*
Nephrotic syndrome (Stages 3-4)	↑	↑	↔ OR ↑	↓ OR ↔ OR ↑	↑
Hemodialysis (Stage 5)	↔ OR ↓	↑	↑	↓	↑
Peritoneal dialysis (Stage 5)	↑	↑	↑	↓	↑
Renal transplantation (Stage 5)	↑	↑	↑	↑	↓*

*Mainly in individuals with high-molecular-weight apolipoprotein(a) phenotypes.

Tsimihodimos V et al. *Am J Nephrol*. 2008;28(6):958 973.

SHARP STUDY OF HEART AND RENAL PROTECTION

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



Go et al *N Engl J Med* 2004

SHARP STUDY OF HEART AND RENAL PROTECTION

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

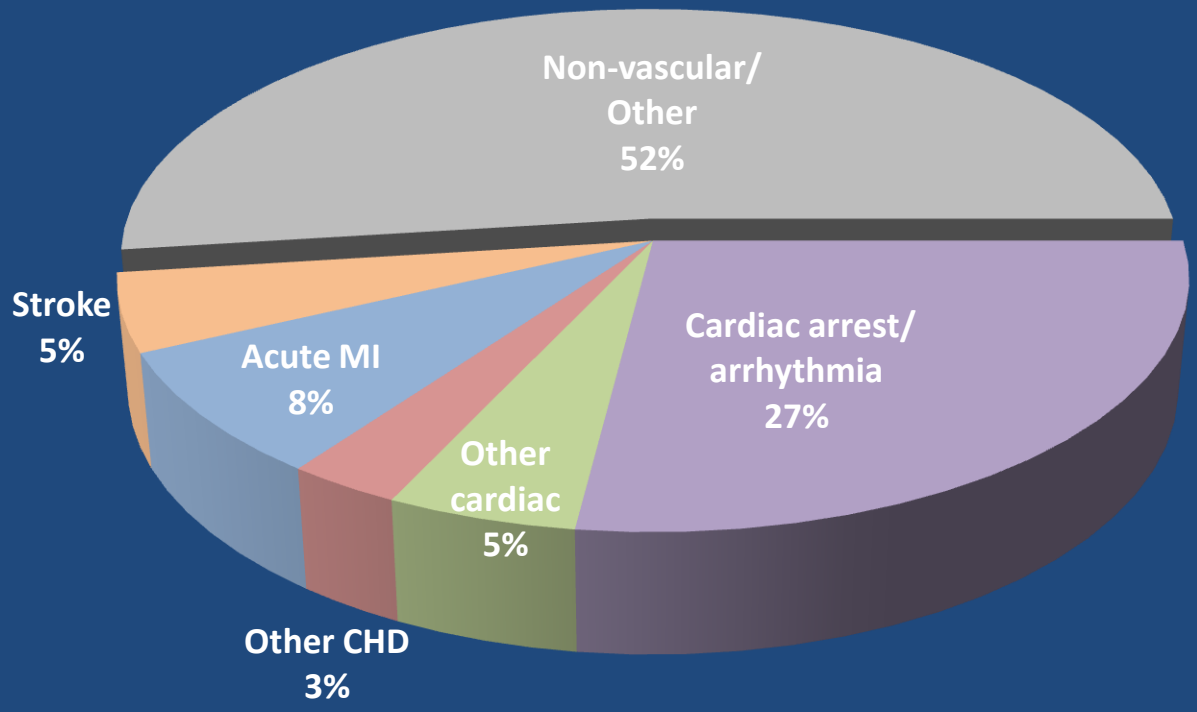
Arteries

- 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

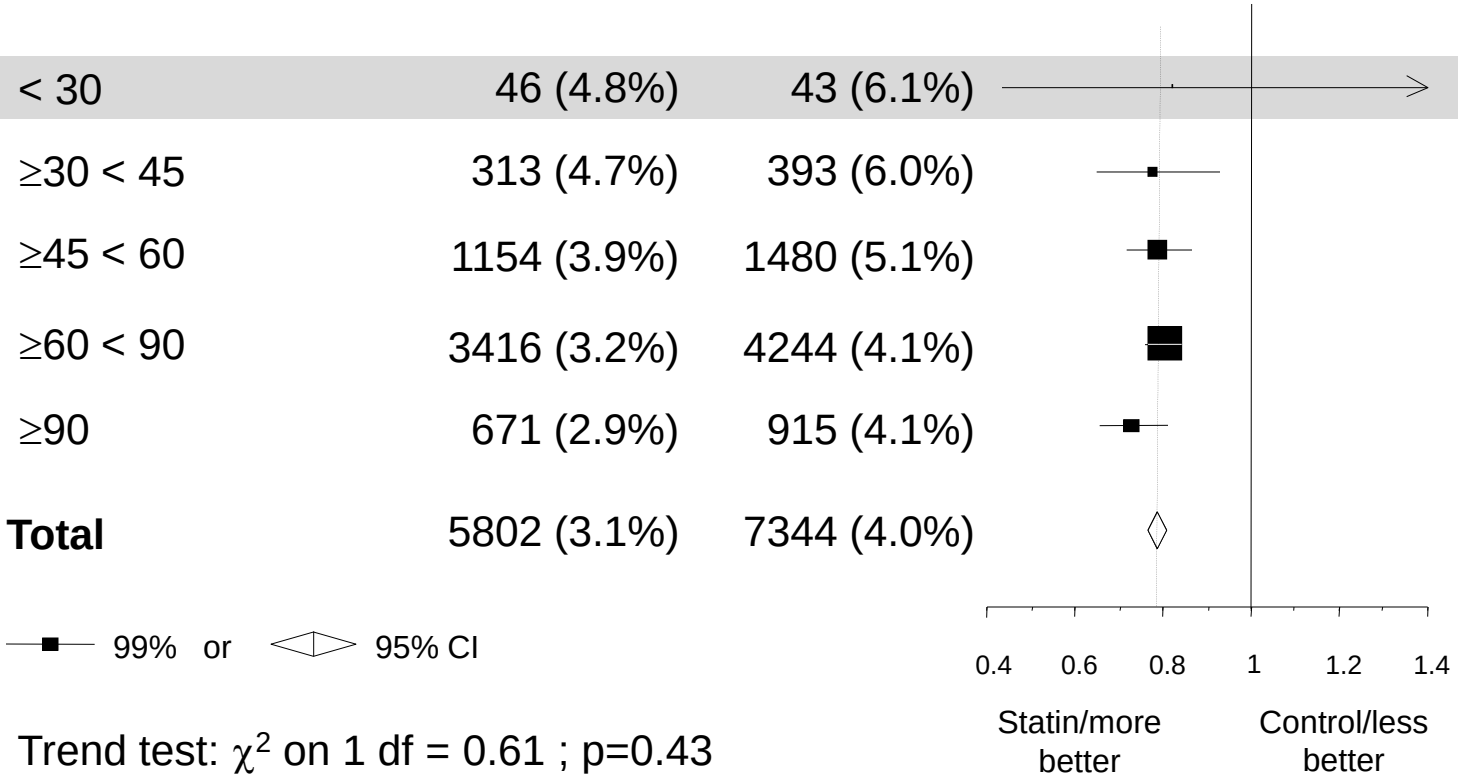
Dialysis patients: Small minority of vascular deaths are atherosclerotic



USRDS 2005 Annual Data Report

CTT: Previous lack of evidence for reduction in MVE risk in people with eGFR below 30 mL/min/1.73m^2

Estimated GFR (mL/min/1.73m^2)	No. of events: Statin	No. of events: Control	Relative risk (CI)
< 30	46 (4.8%)	43 (6.1%)	0.82 (0.44 - 1.55)
≥30 < 45	313 (4.7%)	393 (6.0%)	0.77 (0.65 - 0.93)
≥45 < 60	1154 (3.9%)	1480 (5.1%)	0.79 (0.72 - 0.86)
≥60 < 90	3416 (3.2%)	4244 (4.1%)	0.80 (0.76 - 0.84)
≥90	671 (2.9%)	915 (4.1%)	0.73 (0.65 - 0.82)
Total	5802 (3.1%)	7344 (4.0%)	**0.78 (0.76 - 0.81)**



Trend test: χ^2 on 1 df = 0.61 ; p=0.43

CTT Collaboration *Lancet* 2010

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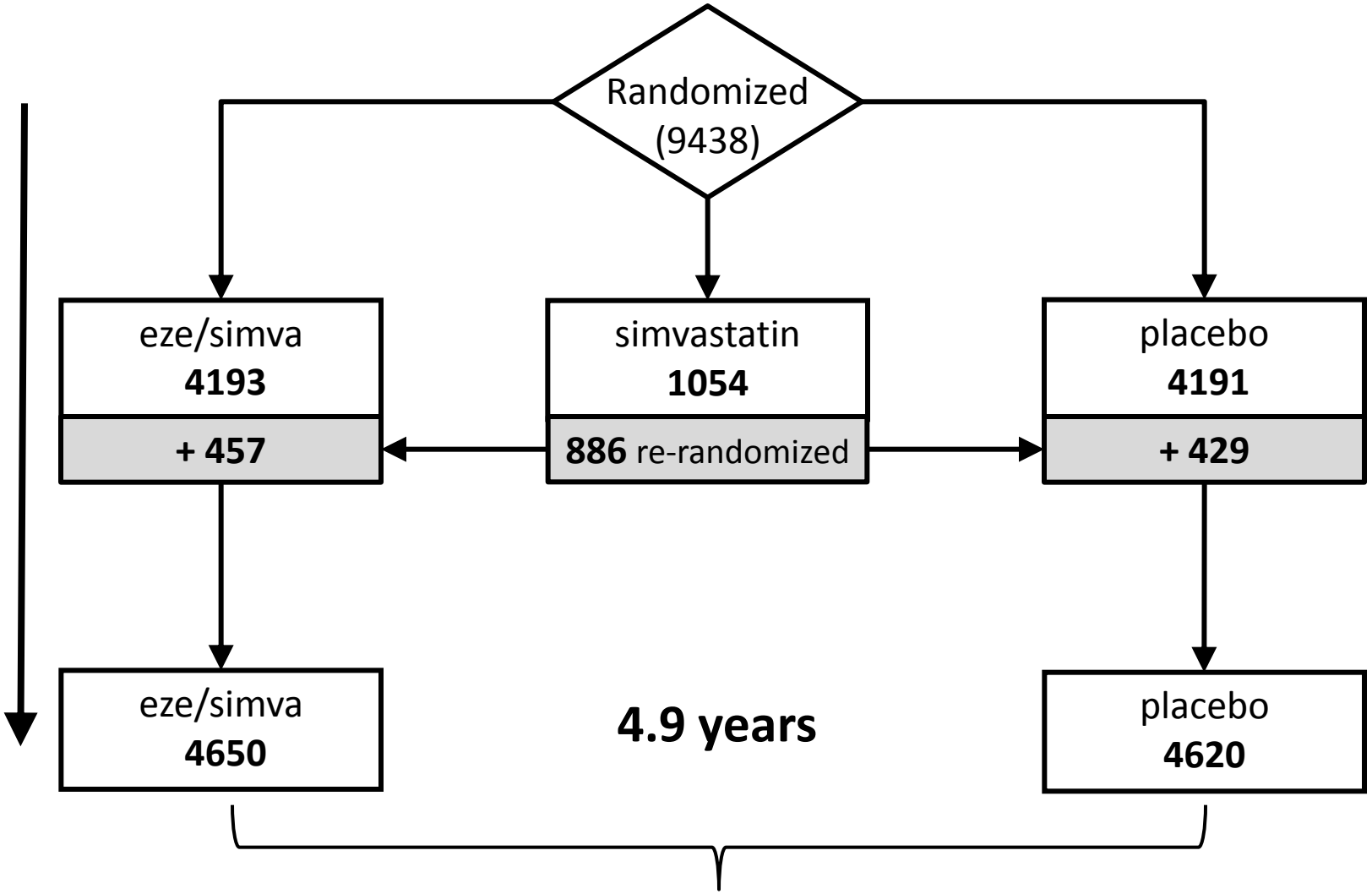
Statin trials in dialysis patients (~1 mmol/L reduction for ~4 years)

	4D (N=1255)	AURORA (N=2776)
Coronary event	0.82 (0.68-0.99)	0.96 (0.81-1.14)
Stroke	1.33 (0.90-1.97)	1.17 (0.79-1.75)
Vascular mortality	0.91 (0.73-1.13)	1.00 (0.85-1.16)
Major vascular events	0.92 (0.77-1.10)	0.96 (0.84-1.11)

SHARP filled 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

SHARP: Randomization structure



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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%

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%

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/1.73m^2

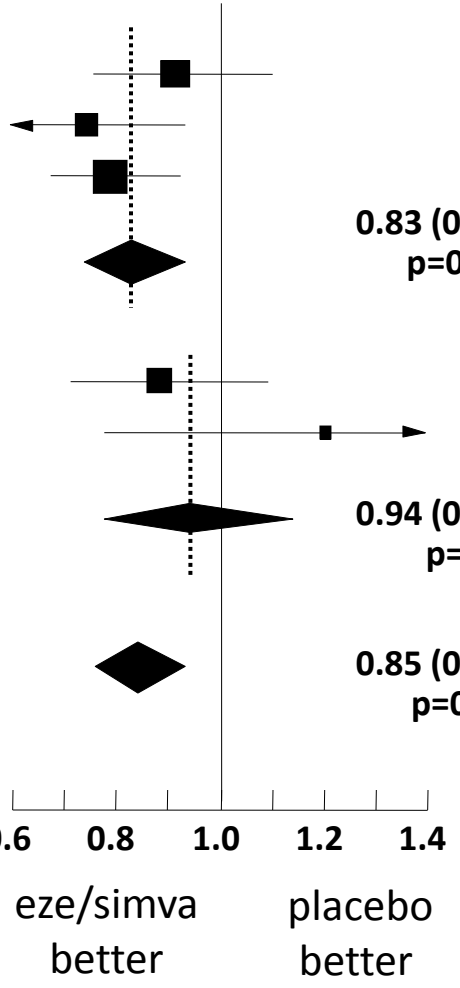
SHARP STUDY OF HEART AND RENAL PROTECTION

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%)

Benefit for both MAEs and MVEs

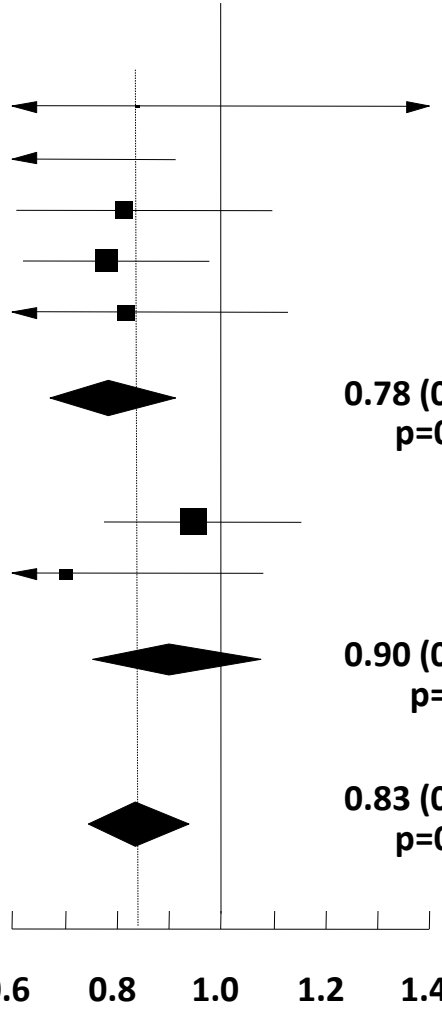
Event	eze/simva (n=4650)		placebo (n=4620)		Risk ratio & 95% CI
Major coronary event	213	(4.6%)	230	(5.0%)	
Non-hemorrhagic stroke	131	(2.8%)	174	(3.8%)	
Any revascularization procedure	284	(6.1%)	352	(7.6%)	
Major Atherosclerotic Event	**526**	**(11.3%)**	**619**	**(13.4%)**	**0.83 (0.74-0.94) p=0.0021**
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%)**	**0.94 (0.78-1.14) p=0.56**
Major Vascular Event	**701**	**(15.1%)**	**814**	**(17.6%)**	**0.85 (0.77-0.94) p=0.0012**



SHARP STUDY OF HEART AND RENAL PROTECTION

SHARP: Major Atherosclerotic Events by CKD stage

	eze/simva (n=4650)	placebo (n=4620)	Risk ratio & 95% CI	P value for Het/Trend
MDRD estimated GFR (mL/min/1.73m²)				
≥ 60 (stage 2)	3 (6.8%)	3 (6.8%)		0.50
≥ 45< 60 (stage 3a)	6 (4.2%)	17 (10.8%)		
≥ 30 <45 (stage 3b)	81 (8.5%)	93 (10.4%)		
≥ 15 < 30 (stage 4)	127 (10.2%)	168 (12.7%)		
<15 (stage 5)	67 (10.9%)	81 (13.3%)		
Subtotal: Not on dialysis	**296 (9.5%)**	**373 (11.9%)**	**0.78 (0.67-0.91) p=0.0016**	
Dialysis				
Hemodialysis	194 (15.2%)	199 (15.9%)		0.21
Peritoneal dialysis	36 (14.0%)	47 (19.7%)		
Subtotal: On dialysis	**230 (15.0%)**	**246 (16.5%)**	**0.90 (0.75-1.08) p=0.25**	
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**	**0.83 (0.74-0.94) p=0.0021**	



SHARP STUDY OF HEART AND RENAL PROTECTION

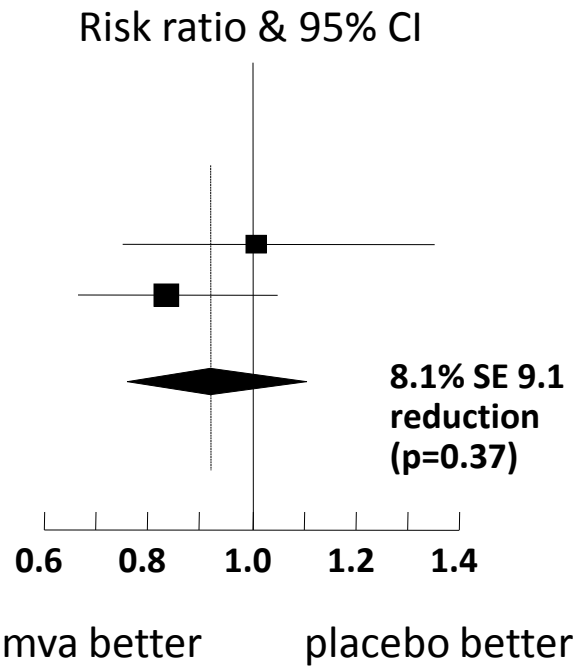
SHARP: Statistical power for detecting expected effects on specific outcomes

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

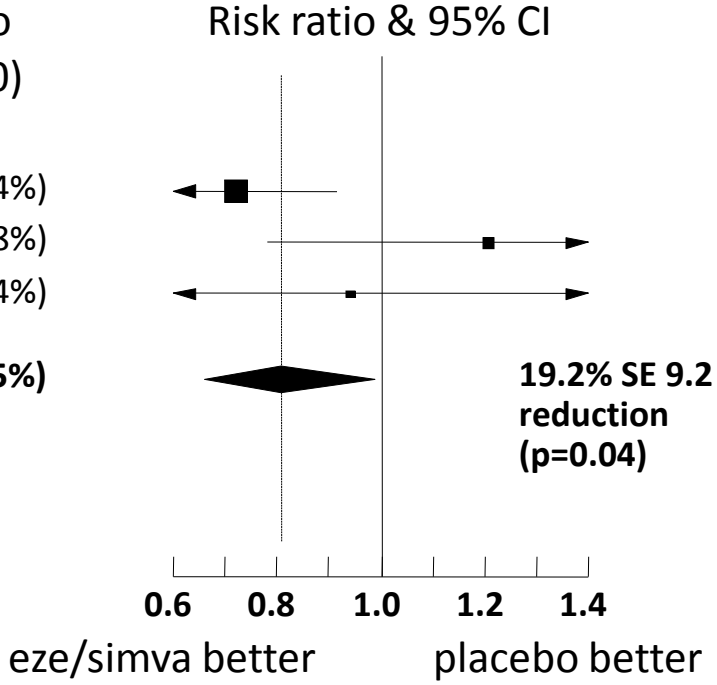
SHARP: Major coronary events

Event	eze/simva (n=4650)		placebo (n=4620)	
Coronary death	91	(2.0%)	90	(1.9%)
Non-fatal myocardial infarction	134	(2.9%)	159	(3.4%)
Major Coronary Event	**213**	**(4.6%)**	**230**	**(5.0%)**



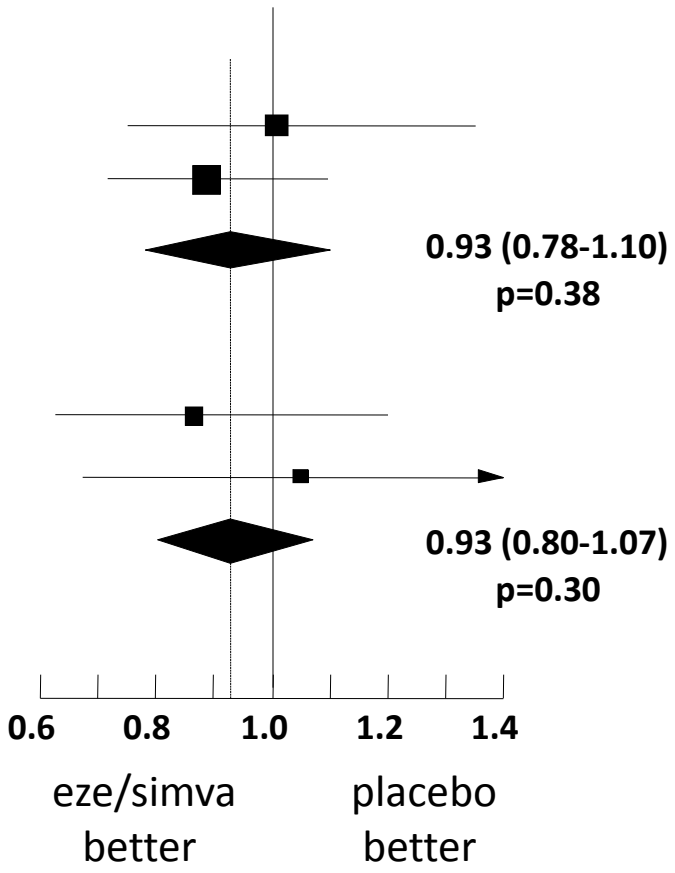
SHARP: Total stroke

Event	eze/simva (n=4650)		placebo (n=4620)	
ischemic stroke	114	(2.5%)	157	(3.4%)
hemorrhagic stroke	45	(1.0%)	37	(0.8%)
Unknown stroke	18	(0.4%)	19	(0.4%)
Stroke (any type)	**171**	**(3.7%)**	**210**	**(4.5%)**



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%)**

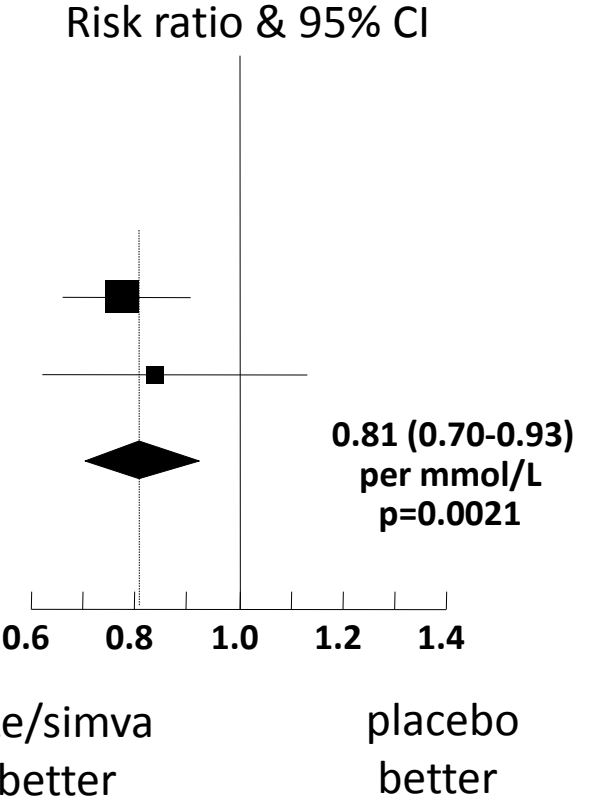


Net compliance and LDL reduction differed between non-dialysis and dialysis patients

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

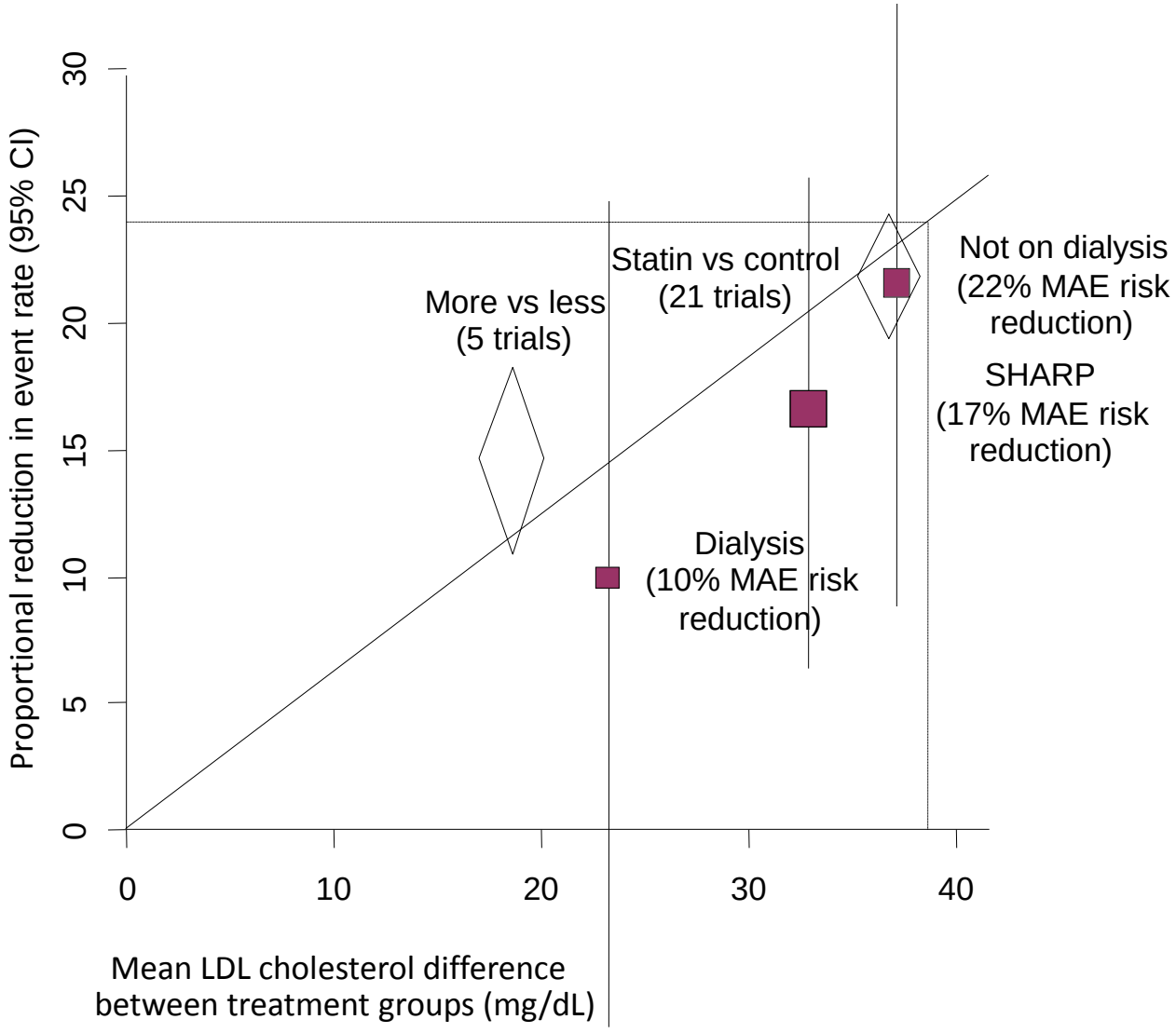
	eze/simva (n=4650)	placebo (n=4620)
Non-dialysis	296 (9.5%)	373 (11.9%)
Dialysis	230 (15.0%)	246 (16.5%)
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**



Test for heterogeneity after LDL weighting p=0.65

SHARP STUDY OF HEART AND RENAL PROTECTION

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



SHARP STUDY OF HEART AND RENAL PROTECTION

SHARP: Summary of findings

- Allocation to eze/simva produced:
  - mean LDL-C reduction 33mg/dL (0.85mmol/L)
  - 17% reduction in major atherosclerotic events
  - No significant protective effect on renal progression
- Proportional reductions in line with LDL reduction in each patient subgroup (eg, dialysis patients), as predicted by trials in non-renal patients
- Longer treatment, and better compliance, would be expected to lead to larger benefits
- No evidence of serious adverse effects with eze/simva in vulnerable CKD patient population