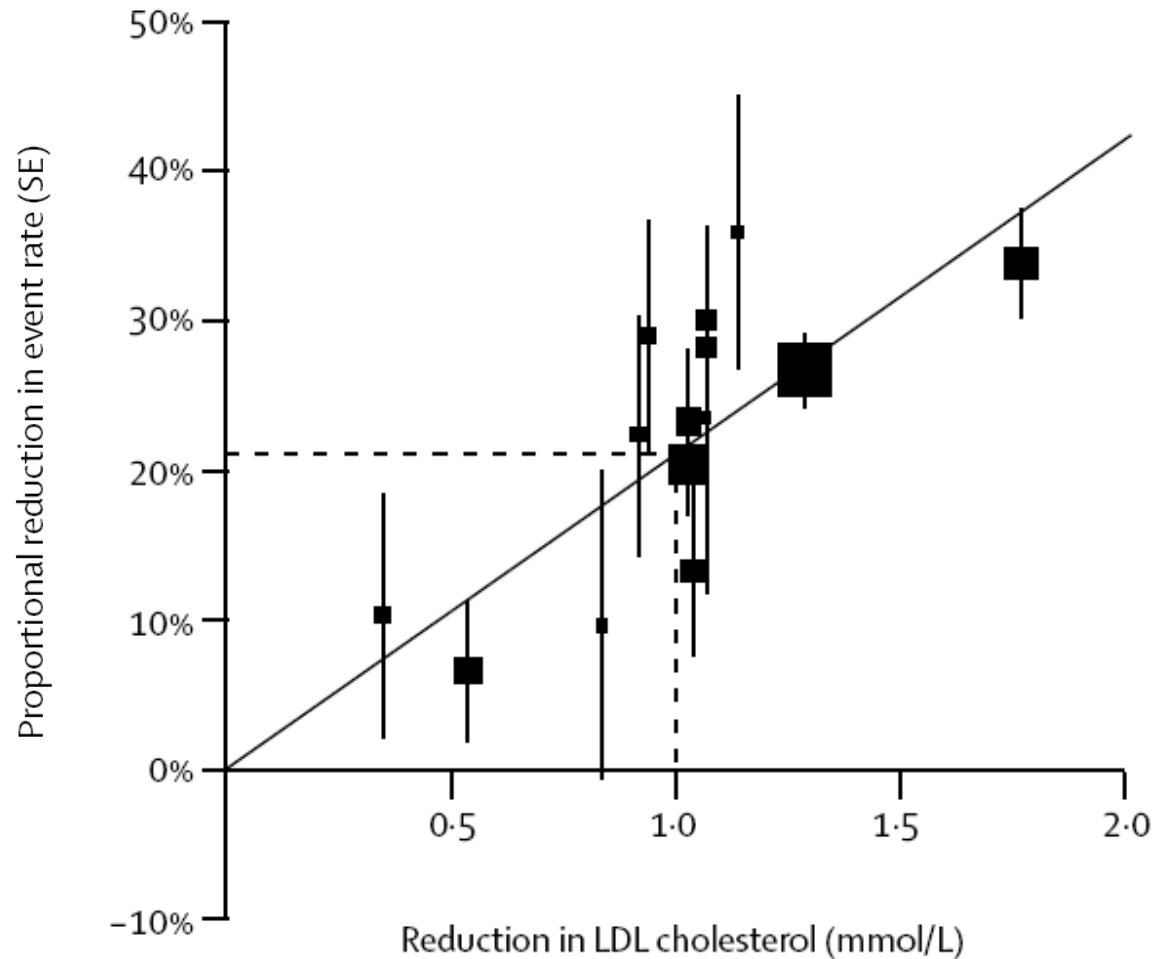


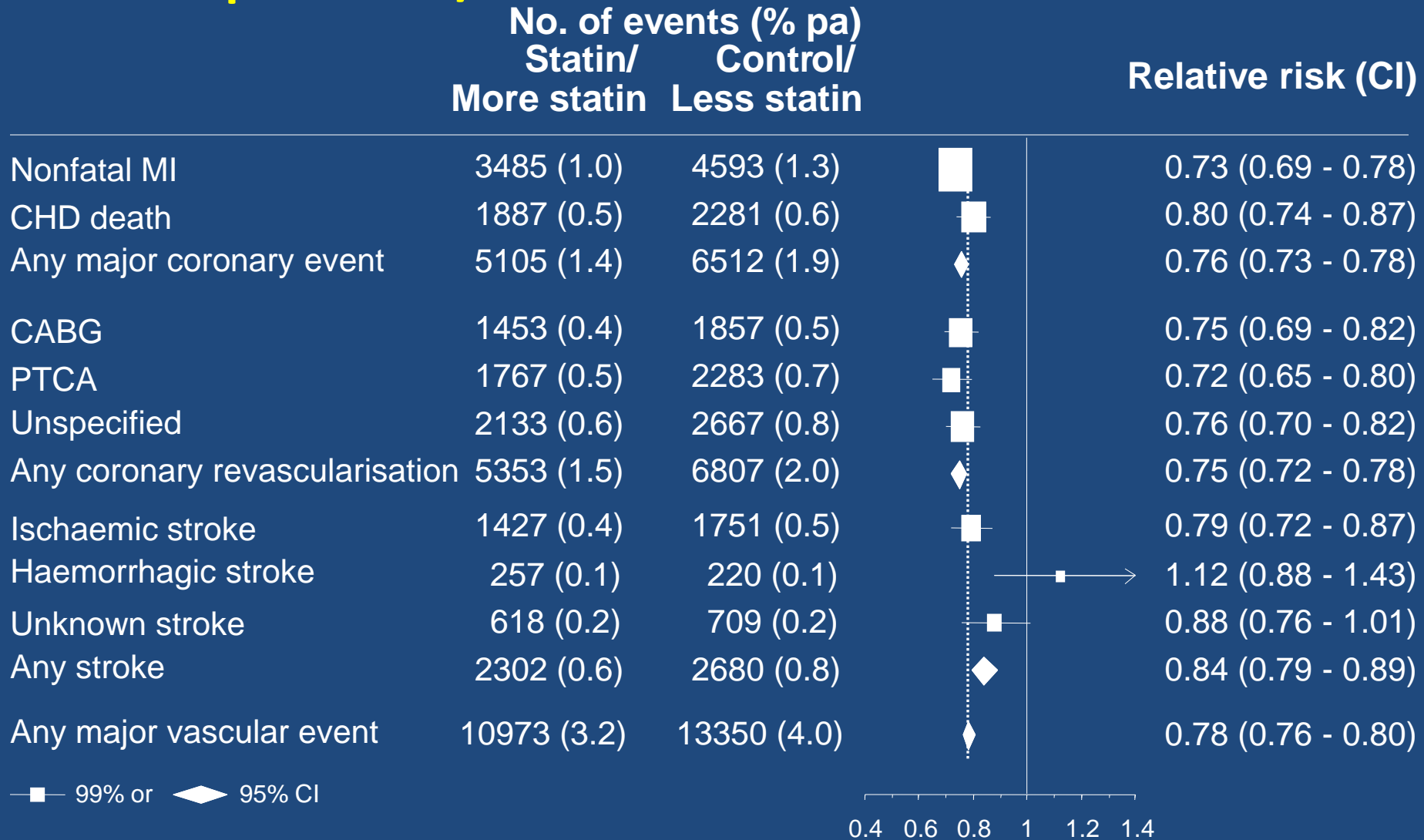
Protecting the heart and kidney: implications from the SHARP trial

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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



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



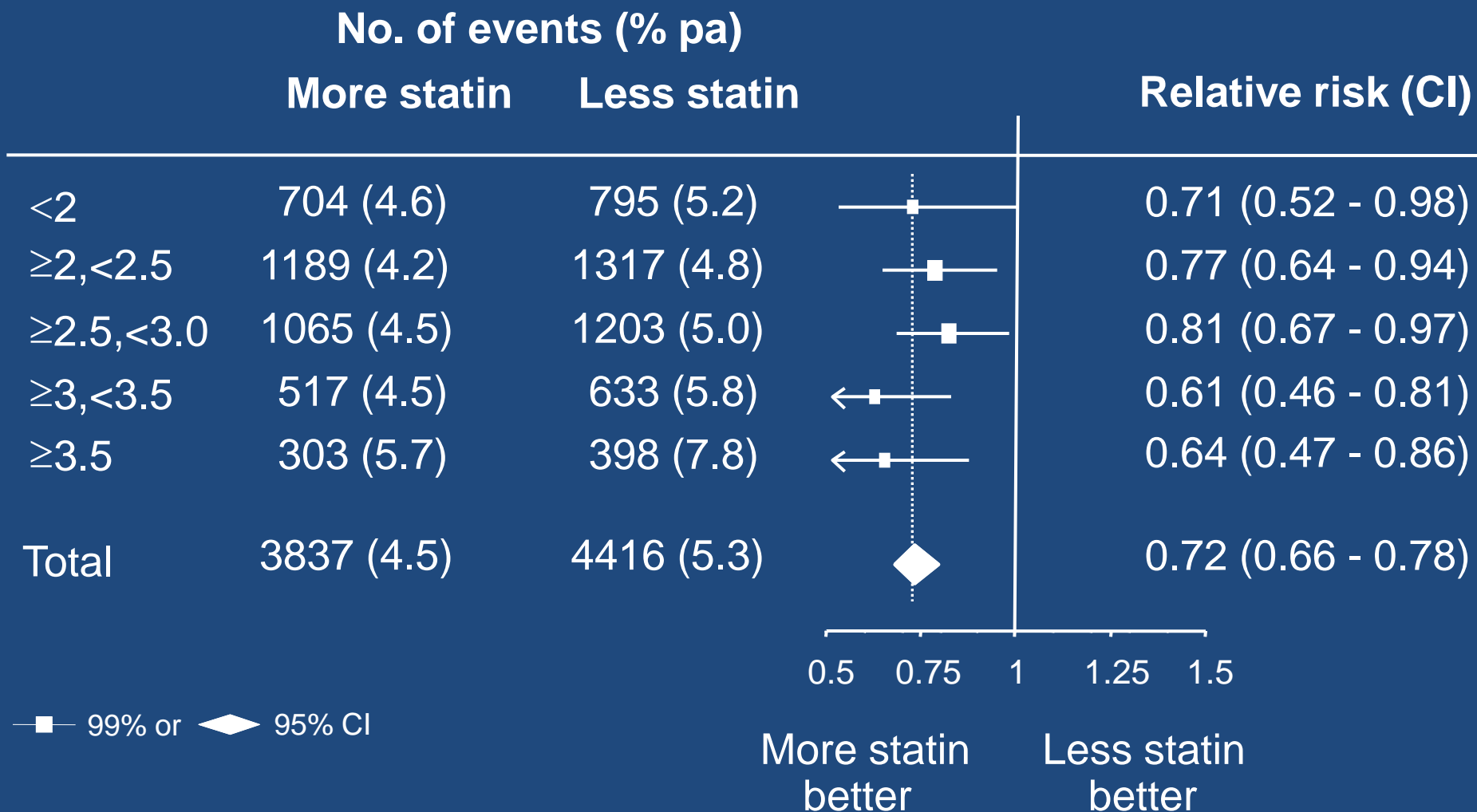
CTT Lancet 2010; 376: 1670-81

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

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



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.

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

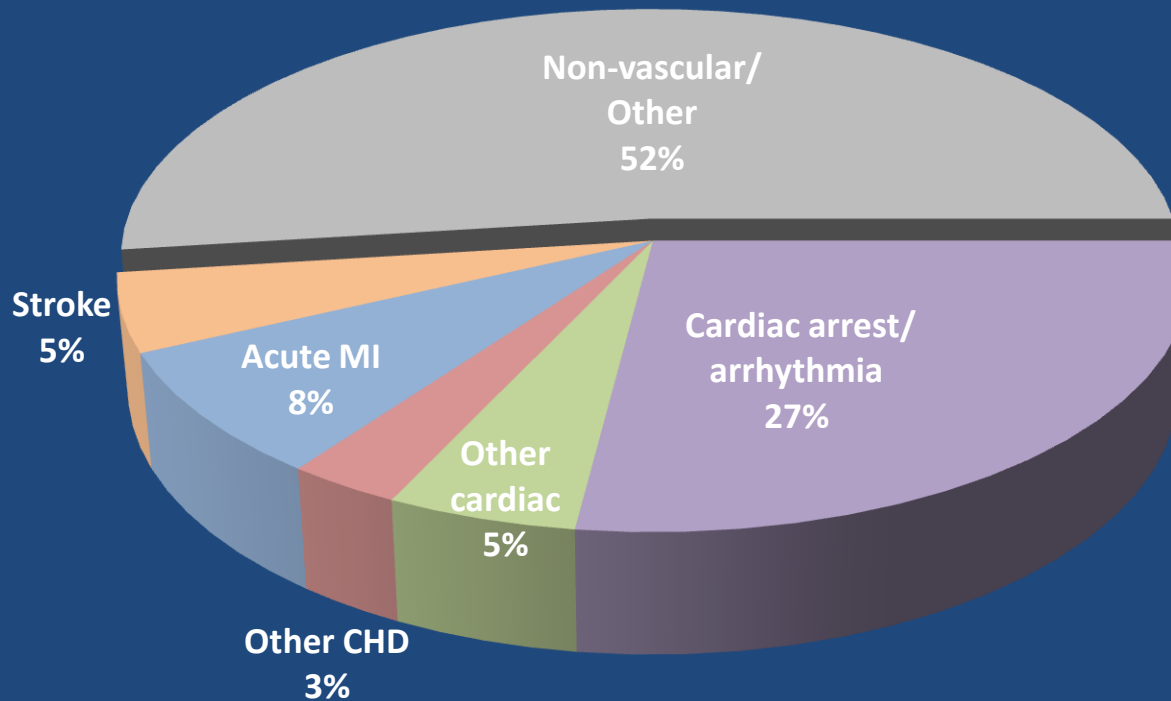
Arteries

- 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

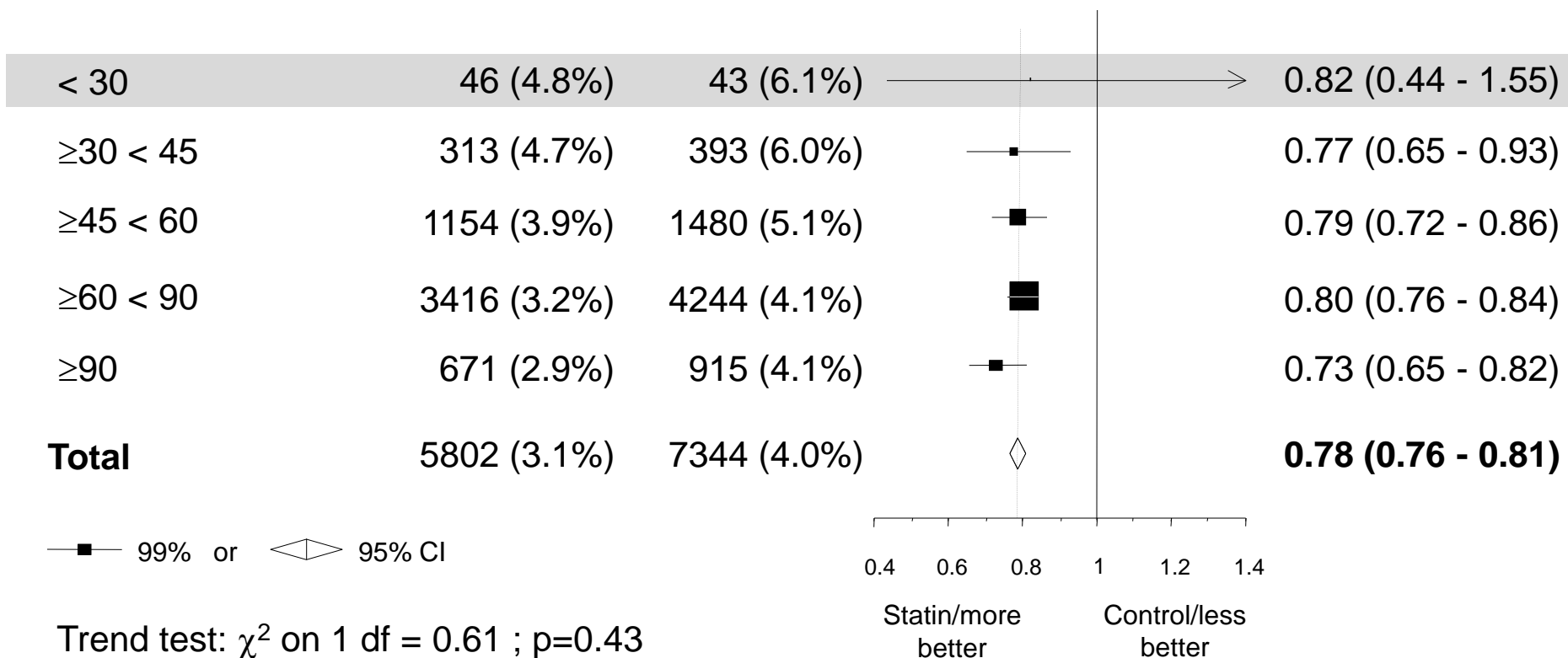


Statin trials in dialysis patients (~1 mmol/L reduction for ~4 years)

| | 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) |

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 | |



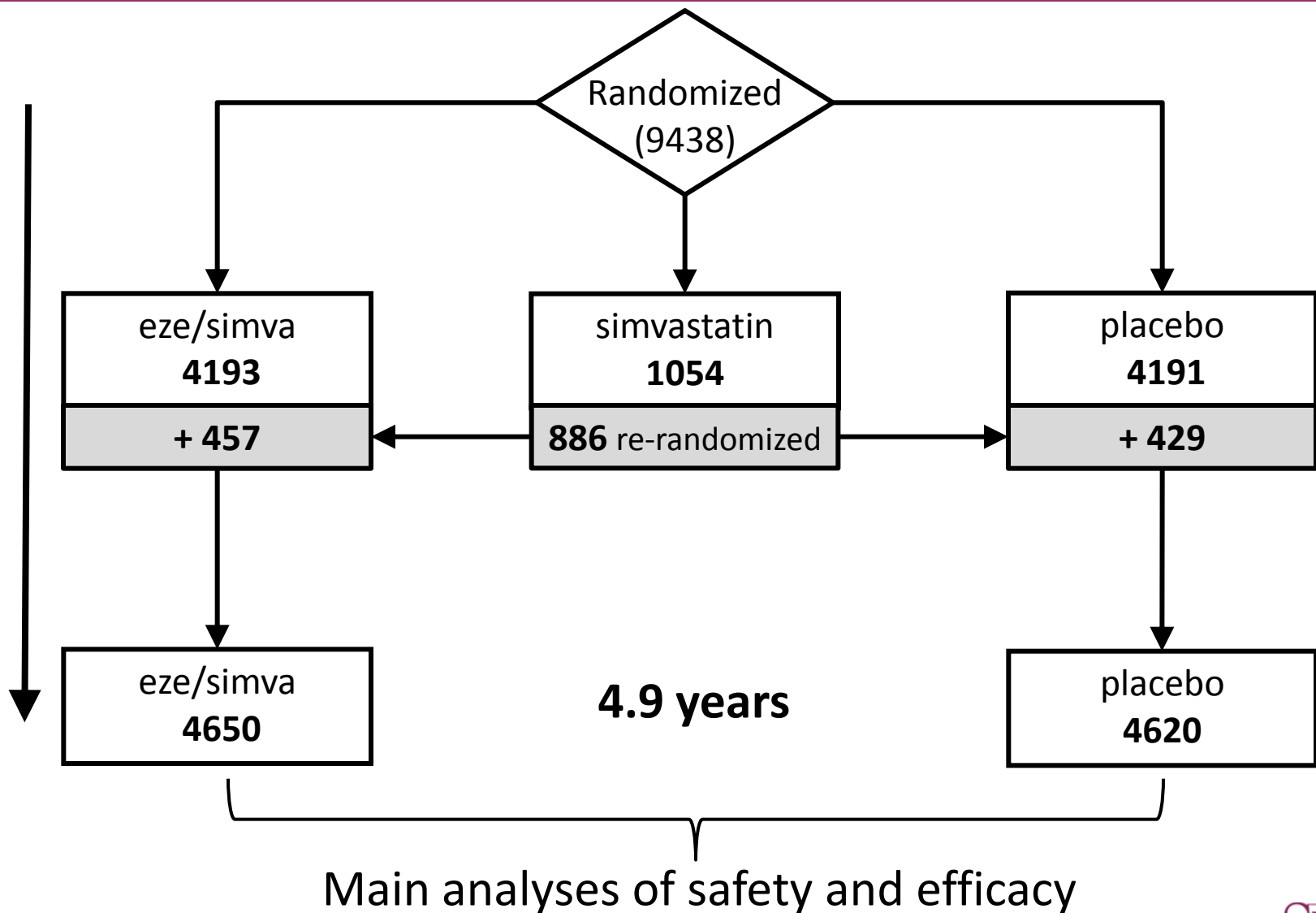
SHARP filled a gap in the evidence on lowering LDL-C in CKD patients

- 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: 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: Randomization structure



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% |

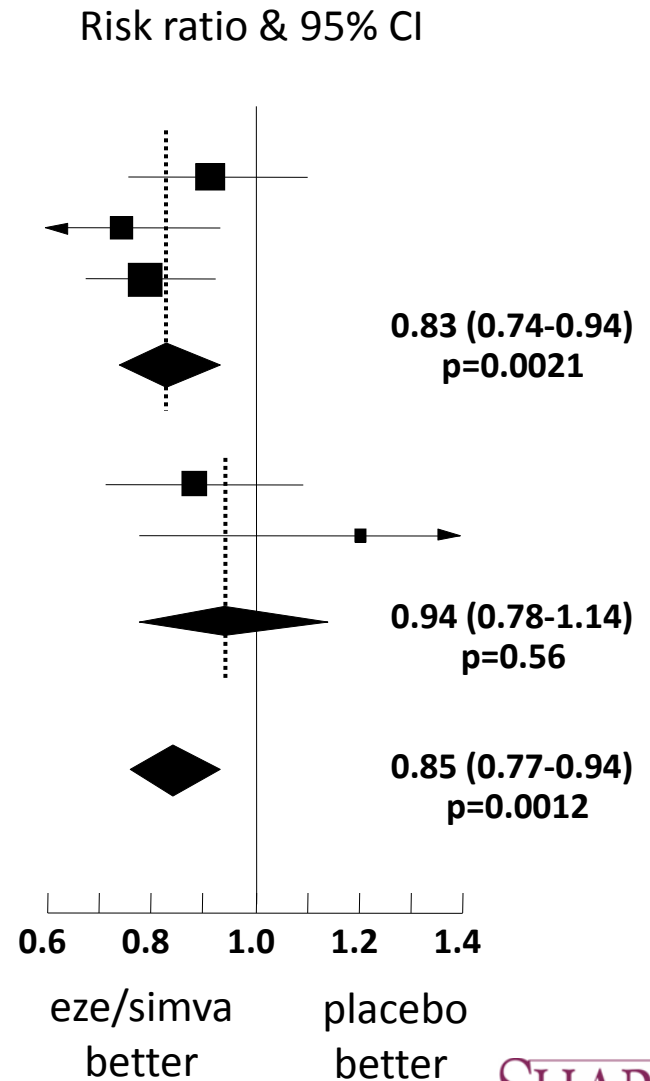
*eGFR in mL/min/1.73m²

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) | |
|------------------------------------|-----------------------|----------------|---------------------|----------------|
| 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%) |



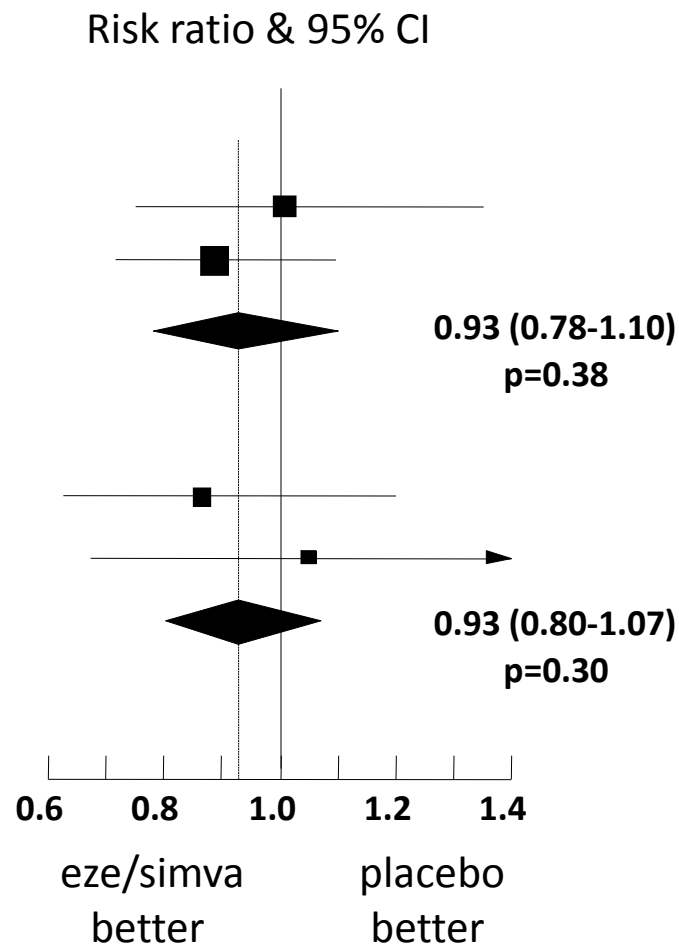
SHARP: Statistical power for detecting expected effects on specific outcomes

| 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 |

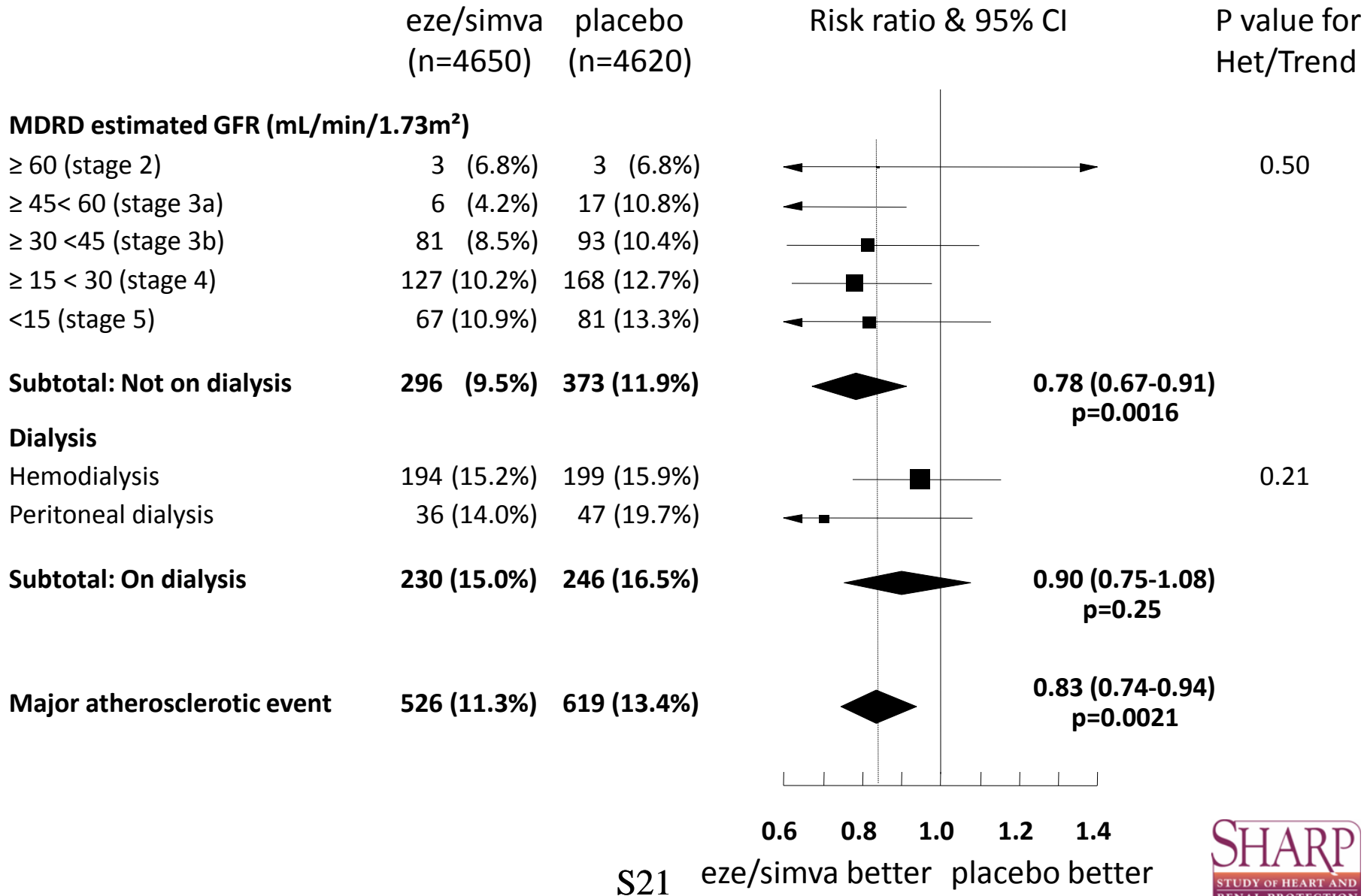
*Based on data from CTT Collaboration *Lancet* 2010

SHARP: Vascular mortality

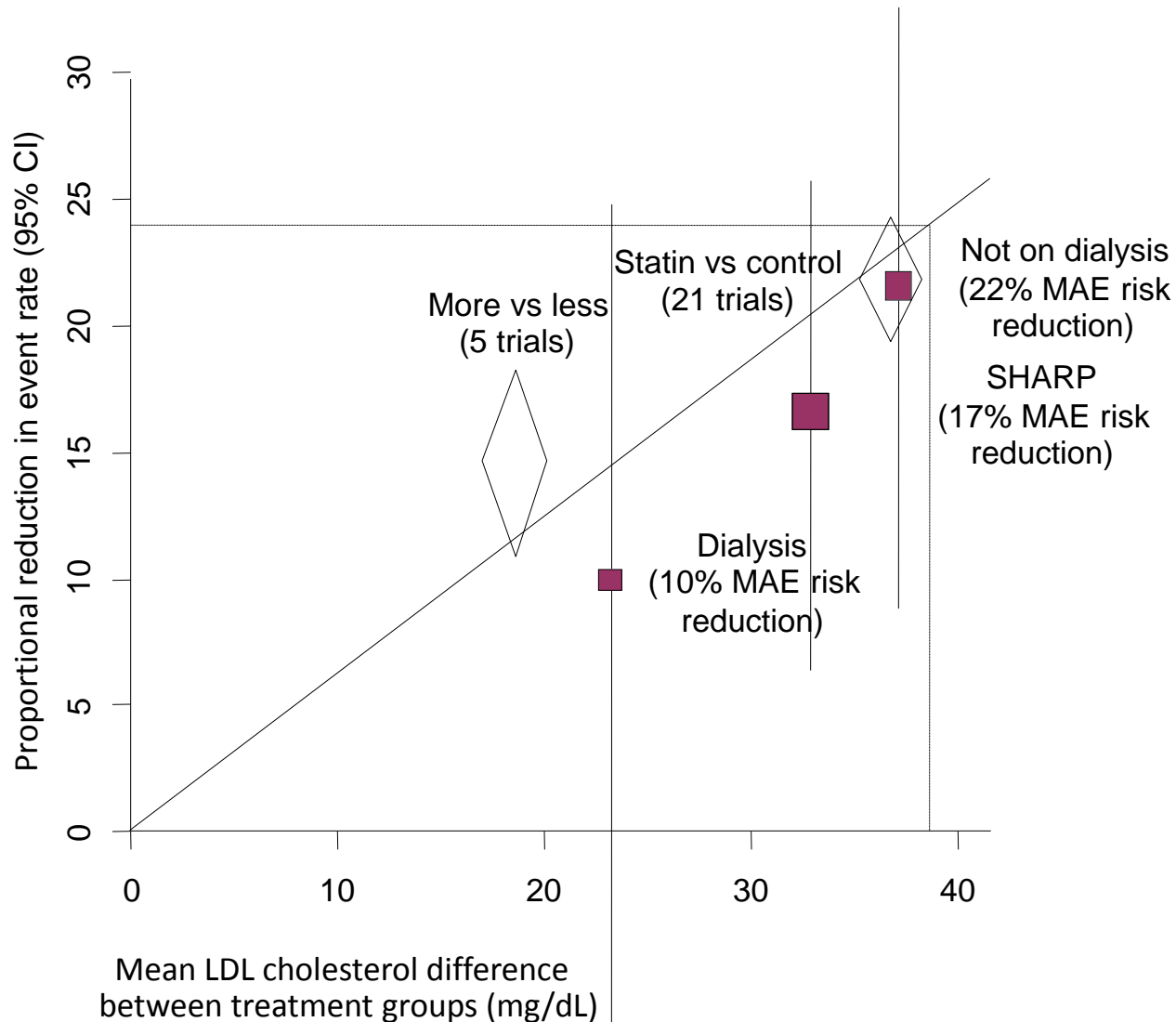
| Event | eze/simva (n=4650) | | placebo (n=4620) | |
|-------------------------------|-----------------------|---------------|---------------------|---------------|
| Coronary | 91 | (2.0%) | 90 | (1.9%) |
| Other cardiac | 162 | (3.5%) | 182 | (3.9%) |
| Subtotal: Any cardiac | 253 | (5.4%) | 272 | (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%) |



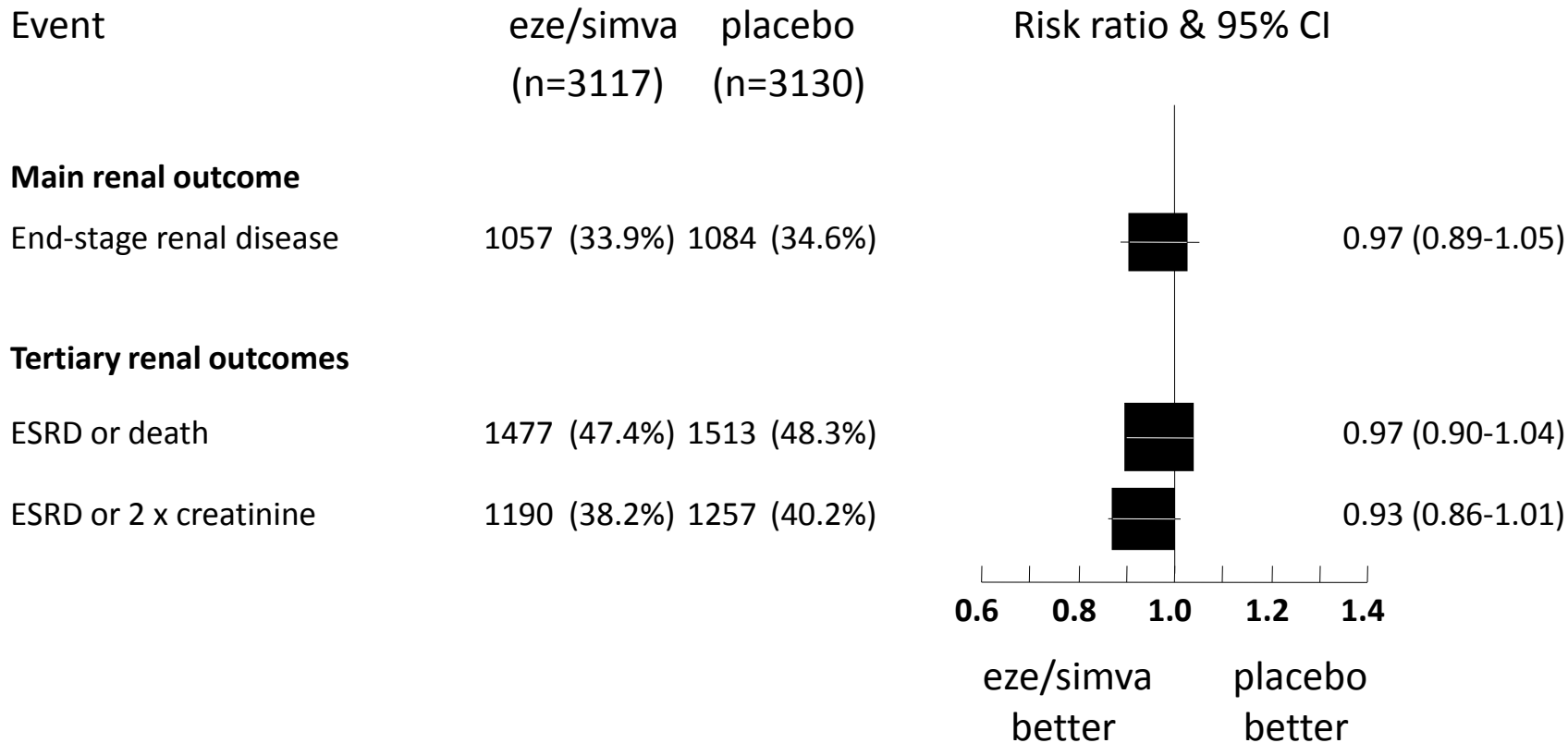
SHARP: Major Atherosclerotic Events by CKD stage



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



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



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