THE LANCET

## Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019; **393:** 407–15.

# Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials


## Cholesterol Treatment Trialists' (CTT) Collaboration


## Supplementary material

**Supplementary Page**

**Webtable 1: Number of participants in each study contributing to categories of age**

| Study | Median follow-up in survivors (years)* | Treatment comparison | Number of participants† | Age (years) at randomisation, n (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | ≤55 | >55, ≤60 | >60, ≤65 | >65, ≤70 | >70, ≤75 | >75 |
| **Statin vs control** | | | | | | | | | |
| SSSS | 5.4 | S20-40 vs. placebo | 4,444 | 1,305 (29%) | 1,095 (25%) | 1,283 (29%) | 760 (17%) | 1 (0%) | 0 (0%) |
| WOSCOPS | 4.8 | P40 vs. placebo | 6,595 | 3,553 (54%) | 1,800 (27%) | 1,242 (19%) | 0 (0%) | 0 (0%) | 0 (0%) |
| CARE | 5.0 | P40 vs. placebo | 4,159 | 1,445 (35%) | 747 (18%) | 851 (20%) | 740 (18%) | 376 (9%) | 0 (0%) |
| Post CABG | 4.3 | L40-80 vs. L2.5-5 | 1,351 | 315 (23%) | 259 (19%) | 362 (27%) | 316 (23%) | 97 (7%) | 2 (0%) |
| AFCAPS/TexCaps | 5.2 | L20-40 vs. placebo | 6,605 | 2,467 (37%) | 1,610 (24%) | 1,322 (20%) | 898 (14%) | 308 (5%) | 0 (0%) |
| LIPID | 6.0 | P40 vs. placebo | 9,014 | 2,349 (26%) | 1,469 (16%) | 2,128 (24%) | 2,135 (24%) | 933 (10%) | 0 (0%) |
| GISSI-P | 2.0 | P20 vs. no treatment | 4,271 | 1,515 (35%) | 730 (17%) | 767 (18%) | 625 (15%) | 410 (10%) | 224 (5%) |
| LIPS | 3.9 | F80 vs. placebo | 1,677 | 546 (33%) | 269 (16%) | 315 (19%) | 277 (17%) | 201 (12%) | 69 (4%) |
| HPS | 5.4 | S40 vs. placebo | 20,536 | 3,860 (19%) | 2,994 (15%) | 4,005 (20%) | 4,898 (24%) | 4,350 (21%) | 429 (2%) |
| PROSPER | 3.3 | P40 vs. placebo | 5,804 | 0 (0%) | 0 (0%) | 0 (0%) | 501 (9%) | 2,948 (51%) | 2,355 (41%) |
| ALLHAT-LLT | 4.9 | P40 vs. usual care | 10,355 | 494 (5%) | 2,022 (20%) | 2,511 (24%) | 2,273 (22%) | 1,635 (16%) | 1,420 (14%) |
| ASCOT-LLA | 3.3 | A10 vs. placebo | 10,305 | 1,604 (16%) | 2,131 (21%) | 2,125 (21%) | 2,029 (20%) | 1,520 (15%) | 896 (9%) |
| ALERT | 5.5 | F40 vs. placebo | 2,102 | 1,418 (67%) | 254 (12%) | 225 (11%) | 150 (7%) | 55 (3%) | 0 (0%) |
| CARDS | 4.1 | A10 vs. placebo | 2,838 | 634 (22%) | 453 (16%) | 622 (22%) | 690 (24%) | 397 (14%) | 42 (1%) |
| ALLIANCE | 4.7 | A10-80 vs. usual care | 2,442 | 662 (27%) | 407 (17%) | 481 (20%) | 495 (20%) | 377 (15%) | 20 (1%) |
| 4D | 4.0 | A20 vs. placebo | 1,255 | 129 (10%) | 177 (14%) | 280 (22%) | 273 (22%) | 249 (20%) | 147 (12%) |
| ASPEN | 4.0 | A10 vs. placebo | 2,410 | 651 (27%) | 436 (18%) | 566 (23%) | 500 (21%) | 252 (10%) | 5 (0%) |
| MEGA†† | 5.0 | P10-20 vs. usual care | 8,214 | 2,849 (35%) | 1,870 (23%) | 1,916 (23%) | 1,496 (18%) | 34 (0%) | 0 (0%) |
| JUPITER | 2.0 | R20 vs. placebo | 17,802 | 1461 (8%) | 3,030 (17%) | 4,050 (23%) | 4,277 (24%) | 2,808 (16%) | 2,176 (12%) |
| GISSI-HF | 4.2 | R10 vs. placebo | 4,574 | 680 (15%) | 399 (9%) | 695 (15%) | 860 (19%) | 885 (19%) | 1,055 (23%) |
| AURORA | 4.6 | R10 vs. placebo | 2,773 | 601 (22%) | 468 (17%) | 428 (15%) | 480 (17%) | 461 (17%) | 335 (12%) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CORONA | 3.0 | R10 vs. placebo | 5,011 | 0 (0%) | 167 (3%) | 760 (15%) | 1,049 (21%) | 1,197 (24%) | 1,838 (37%) |
| HOPE-3 | 5.6 | R10 vs. placebo | 12,705 | 0 (0%) | 2,289 (18%) | 3,770 (30%) | 3,560 (28%) | 1,998 (16%) | 1088 (9%) |
| **Subtotal: All 23 trials** | **4.8** | | **147,242** | **28,538 (19%)** | **25,076 (17%)** | **30,704 (21%)** | **29,282 (20%)** | **21,492 (15%)** | **12,101 (8%)** |
| **More vs less trials** | | | | | | | | | |
| PROVE-IT | 2.1 | A80 vs. P40 | 4,162 | 1,797 (43%) | 669 (16%) | 585 (14%) | 450 (11%) | 355 (9%) | 306 (7%) |
| A to Z | 2.0 | S40 then S80 vs. placebo then S20 | 4,497 | 1,547 (34%) | 641 (14%) | 652 (15%) | 734 (16%) | 643 (14%) | 279 (6%) |
| TNT | 5.0 | A80 vs. A10 | 10,001 | 2,612 (26%) | 1,711 (17%) | 1,869 (19%) | 2,033 (20%) | 1,558 (16%) | 218 (2%) |
| IDEAL | 4.8 | A40-80 vs. S20-40 | 8,888 | 2,419 (27%) | 1,473 (17%) | 1,564 (18%) | 1,615 (18%) | 1,242 (14%) | 575 (6%) |
| SEARCH | 7.0 | S80 vs. S20 | 12,064 | 2,329 (19%) | 1,864 (15%) | 2,390 (20%) | 2,453 (20%) | 2,024 (17%) | 1,004 (8%) |
| **Subtotal: All 5 trials** | **5.1** | | **39,612** | **10,704 (27%)** | **6,358 (16%)** | **7,060 (18%)** | **7,285 (18%)** | **5,822 (15%)** | **2,382 (6%)** |
| **Total: All 28 trials** | **4.9** | | **186,854** | **39,242 (21%)** | **31,434 (17%)** | **37,764 (20%)** | **36,567 (20%)** | **27,314 (15%)** | **14,483 (8%)** |

* Estimated using standard Kaplan-Meier methods with participants censored at their date of death. Median follow-up for trials weighted by trial-specific variances of observed logrank (o-e) for major vascular events. †Includes 50 patients with missing age (49 from MEGA and 1 from A to Z). ††Includes 382 randomised patients who were excluded from the original publication.

SSSS=Scandinavian Simvastatin Survival Study; WOSCOPS=West of Scotland Coronary Prevention Study; CARE=Cholesterol And Recurrent Events; Post-CABG=Post-Coronary Artery Bypass Graft; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; GISSI-P=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; LIPS=Lescol Intervention Prevention Study; HPS=Heart Protection Study; PROSPER=PROspective Study of Pravastatin in the Elderly at Risk; ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ALERT=Assessment of Lescol in Renal Transplantation; CARDS=Collaborative Atorvastatin Diabetes Study; ALLIANCE=Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group; AURORA=A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events; CORONA=Controlled Rosuvastatin Multinational Trial in Heart Failure; HOPE-3=Heart Outcomes Prevention Evaluation-3; PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy; A to Z=Aggrastat to Zocor; TNT=Treating to New Targets; IDEAL=Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group; SEARCH=Study of the effectiveness of additional reductions in cholesterol and homocysteine.

**Webtable 2: Baseline characteristics of participants in all studies by category of age**

| | Age at randomisation, N(%)* | | | | | | All participants |
|---|---|---|---|---|---|---|---|
| | ≤55 | >55, ≤60 | >60, ≤65 | >65, ≤70 | >70, ≤75 | >75 | |
| Number of people | 39,242 | 31,434 | 37,764 | 36,567 | 27,314 | 14,483 | 186,854 |
| Age (years) | 49.5 (4.8) | 57.9 (1.3) | 62.9 (1.3) | 67.8 (1.3) | 72.7 (1.3) | 78.8 (2.8) | 62.9 (9.2) |
| Male | 32,390 (83%) | 24,713 (79%) | 26,675 (71%) | 24,166 (66%) | 17,839 (65%) | 8,476 (59%) | 134,261 (72%) |
| History of vascular disease | 23,334 (59%) | 15,574 (50%) | 19,741 (52%) | 20,671 (57%) | 16,768 (61%) | 8,034 (55%) | 104,124 (56%) |
| History of myocardial infarction | 15,075 (38%) | 9,820 (31%) | 12,451 (33%) | 12,738 (35%) | 9,570 (35%) | 4,210 (29%) | 63,865 (34%) |
| History of other symptomatic coronary heart disease | 15,216 (39%) | 10,023 (32%) | 12,720 (34%) | 13,241 (36%) | 10,567 (39%) | 4,448 (31%) | 66,216 (35%) |
| History of heart failure (NYHA class II-IV)† | 680 (2%) | 566 (2%) | 1,455 (4%) | 1,909 (5%) | 2,082 (8%) | 2,893 (20%) | 9,585 (5%) |
| On dialysis‡ | 730 (2%) | 645 (2%) | 708 (2%) | 753 (2%) | 710 (3%) | 482 (3%) | 4,028 (2%) |
| History of diabetes | 6,444 (16%) | 5,496 (17%) | 7,305 (19%) | 7,356 (20%) | 5,318 (19%) | 2,499 (17%) | 34,418 (18%) |
| Current smokers | 11,142 (28%) | 7,789 (25%) | 7,306 (19%) | 5,636 (15%) | 3,828 (14%) | 1,485 (10%) | 37,186 (20%) |
| Treated hypertension | 15,115 (39%) | 14,125 (45%) | 18,503 (49%) | 19,338 (53%) | 15,132 (55%) | 8,698 (60%) | 90,911 (49%) |
| Systolic blood pressure (mmHg) | 131.5 (18.9) | 136.8 (18.4) | 138.8 (18.4) | 140.9 (19.2) | 143.9 (21.0) | 143.4 (21.4) | 138.5 (19.7) |
| Diastolic blood pressure (mmHg) | 81.5 (11.4) | 82.4 (10.5) | 81.4 (10.0) | 80.6 (10.1) | 79.9 (10.8) | 78.9 (10.8) | 81 (10.6) |
| Body mass index (kg/m$^2$) | 27.1 (24.5-30.2) | 27.3 (24.7-30.4) | 27.2 (24.7-30.2) | 27.1 (24.6-30.1) | 26.8 (24.4-29.6) | 26.3 (23.8-29.1) | 27.1 (24.5-30.1) |
| Total-cholesterol (mmol/L) | 5.5 (1.1) | 5.4 (1.0) | 5.4 (1.0) | 5.3 (0.9) | 5.2 (1) | 5.1 (1.0) | 5.4 (1.0) |
| LDL-cholesterol (mmol/L) | 3.5 (1.0) | 3.4 (0.9) | 3.4 (0.9) | 3.2 (0.8) | 3.2 (0.8) | 3.2 (0.8) | 3.3 (0.9) |
| HDL-cholesterol (mmol/L) | 1.1 (0.3) | 1.1 (0.3) | 1.2 (0.3) | 1.2 (0.3) | 1.2 (0.3) | 1.3 (0.3) | 1.2 (0.3) |
| Triglycerides (mmol/L) | 1.7 (1.2-2.4) | 1.6 (1.2-2.3) | 1.6 (1.1-2.2) | 1.5 (1.1-2.1) | 1.5 (1.1-2.1) | 1.4 (1.0-1.9) | 1.6 (1.1-2.2) |
| Creatinine (µmol/L)§ | 92 (80-106) | 91 (80-106) | 93 (80-106) | 96 (80-108) | 97 (86-114) | 99 (88-117) | 95 (80-106) |

Data presented as number of participants (%), mean (SD) or median (IQR). HOPE-3 participant data for body mass index (mean (SD) among >55, ≤60; >60, ≤65; >65, ≤70; >70, ≤75; >75 year old participants: 27.3 (4.5); 27.4 ( 4.7); 27.2 (4.9); 26.8 (4.9) and 26.1 (4.8)), triglycerides (1.8 (1.3); 1.7 (1.1); 1.7 (1.0); 1.6 (0.8) and 1.6 (0.9), respectively) and creatinine (84 (18); 77 (19); 77 (19); 80 (19) and 82 (20), respectively) not included.

*Excludes 50 participants with missing age (49 from MEGA and 1 from A to Z). †All participants from GISSI-HF and CORONA trials only. ‡All participants from 4D and AURORA trials only. §Excludes participants on dialysis at randomisation (ie, participants from 4D and AURORA).

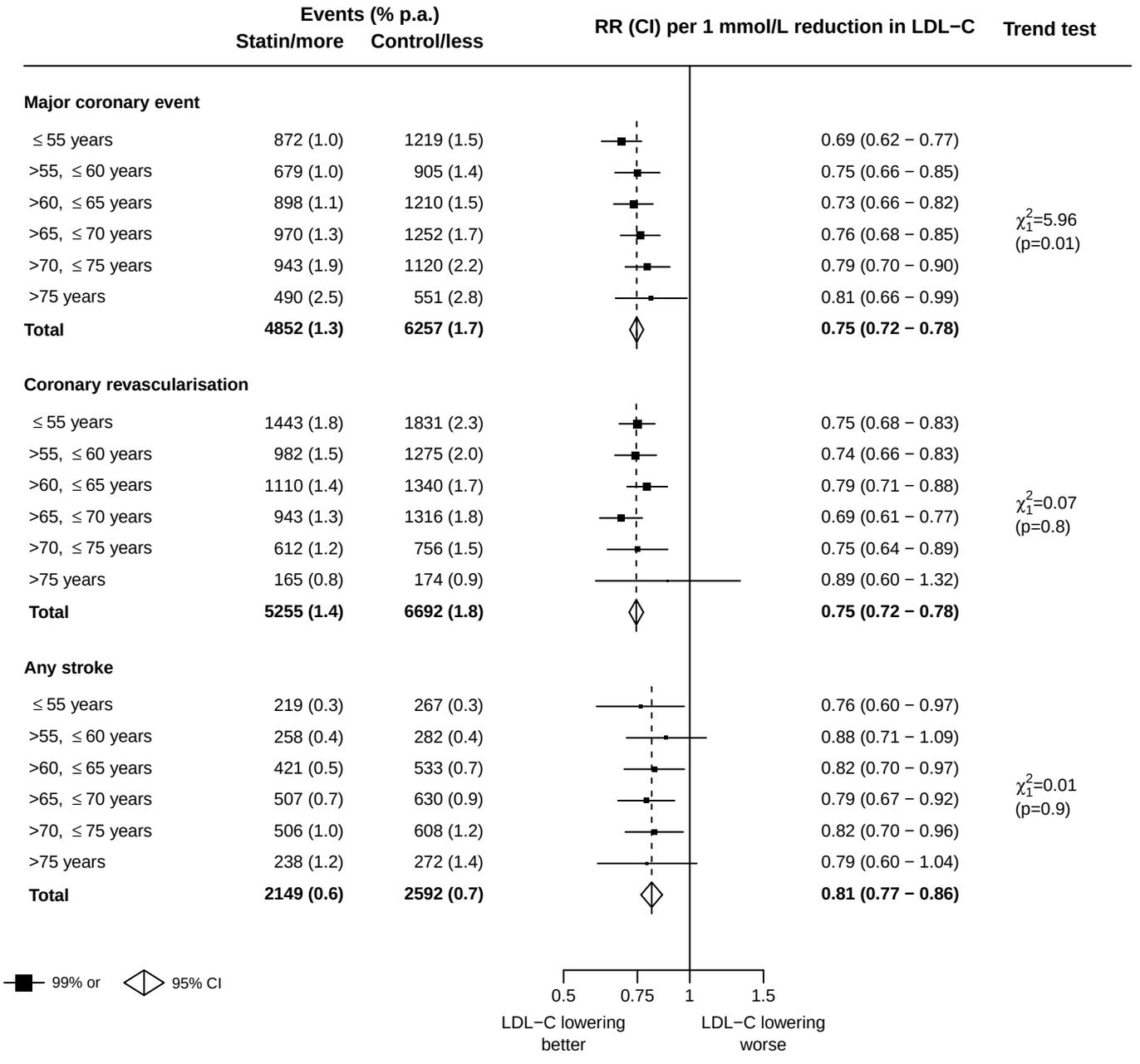
**Webtable 3: Mean plasma lipid concentrations at baseline and mean difference in plasma lipid concentrations at 1 year in participants in all studies, by category of age**

| | Mean plasma lipid concentrations at baseline | | | | Mean difference in plasma lipid concentrations at 1 year | | | |
|---|---|---|---|---|---|---|---|---|
| Age at randomisation | Total cholesterol (mmol/L) | LDL cholesterol (mmol/L) | HDL cholesterol (mmol/L) | Triglycerides (mmol/L) | Total cholesterol (mmol/L) | LDL cholesterol (mmol/L) | HDL cholesterol (mmol/L) | Triglycerides (mmol/L) |
| **Statin vs. control** | | | | | | | | |
| ≤55 | 5.9 | 3.8 | 1.1 | 2.0 | -1.18 | -1.06 | 0.02 | -0.24 |
| >55, ≤60 | 5.7 | 3.6 | 1.2 | 1.8 | -1.24 | -1.10 | 0.06 | -0.27 |
| >60, ≤65 | 5.6 | 3.6 | 1.2 | 1.8 | -1.22 | -1.09 | 0.03 | -0.20 |
| >65, ≤70 | 5.5 | 3.4 | 1.2 | 1.8 | -1.27 | -1.12 | 0.06 | -0.38 |
| >70, ≤75 | 5.5 | 3.4 | 1.2 | 1.7 | -1.31 | -1.10 | 0.01 | -0.17 |
| >75 | 5.3 | 3.3 | 1.3 | 1.6 | -1.01 | -0.97 | 0.07 | -0.24 |
| **Subtotal (23 trials)** | **5.6** | **3.6** | **1.2** | **1.8** | **-1.21** | **-1.08** | **0.04** | **-0.26** |
| **More vs. Less statin** | | | | | | | | |
| ≤55 | 4.5 | 2.6 | 1.1 | 2.0 | -0.68 | -0.56 | -0.01 | -0.26 |
| >55, ≤60 | 4.4 | 2.5 | 1.1 | 1.9 | -0.67 | -0.55 | -0.01 | -0.29 |
| >60, ≤65 | 4.4 | 2.5 | 1.1 | 1.8 | -0.61 | -0.51 | -0.01 | -0.22 |
| >65, ≤70 | 4.3 | 2.5 | 1.2 | 1.7 | -0.58 | -0.48 | -0.00 | -0.21 |
| >70, ≤75 | 4.3 | 2.4 | 1.2 | 1.6 | -0.55 | -0.47 | 0.00 | -0.18 |
| >75 | 4.3 | 2.4 | 1.2 | 1.6 | -0.47 | -0.38 | 0.00 | -0.18 |
| **Subtotal (5 trials)** | **4.4** | **2.5** | **1.1** | **1.8** | **-0.61** | **-0.51** | **-0.01** | **-0.23** |

Lipid differences at 1 year for trial subgroups weighted by trial and age subgroup-specific variances of observed logrank (o-e) for major vascular events.

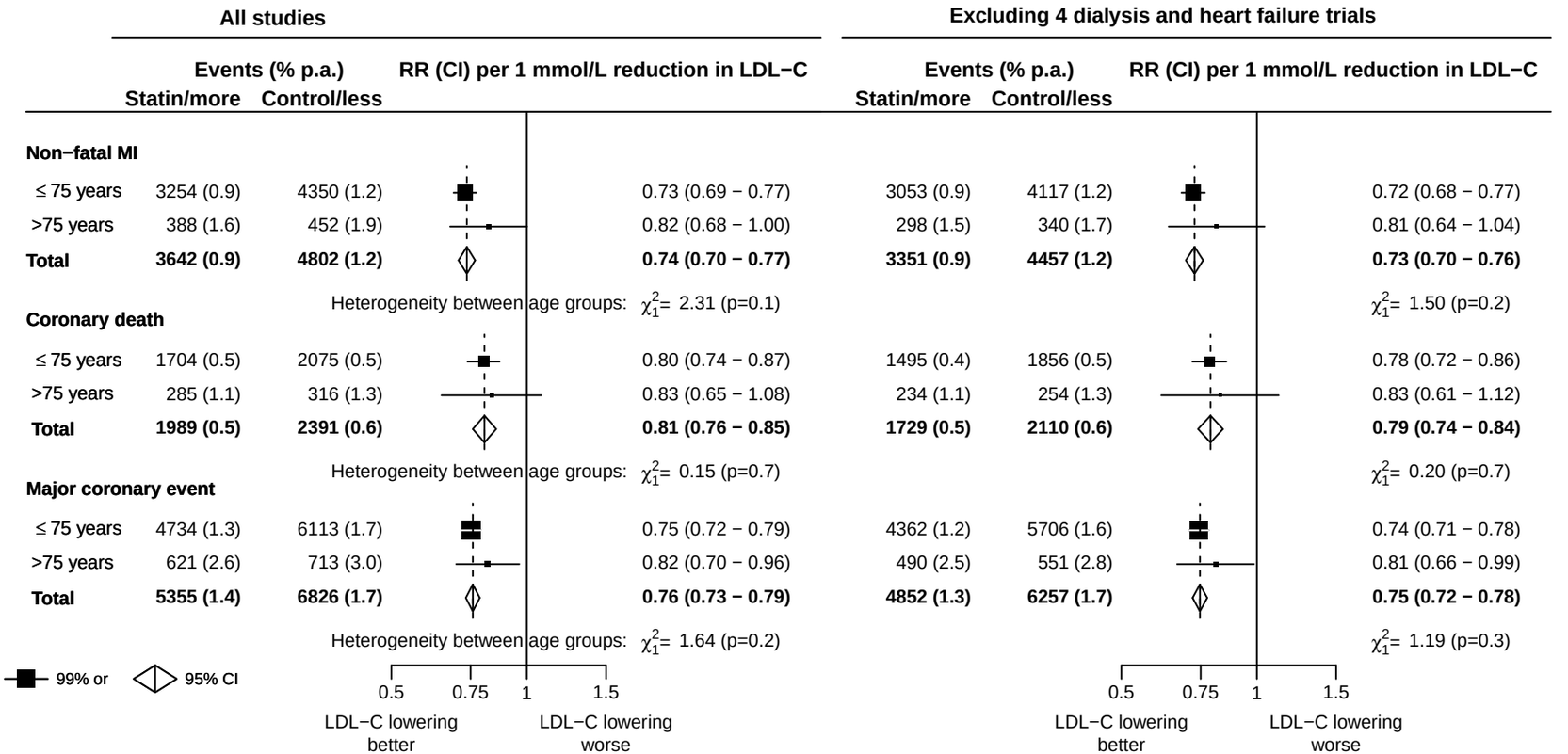
In trials where the LDL-C at 1 year was missing (or >10mmol/L) the baseline value was assigned. In some studies, only a sub-sample of participants had 1 year blood samples: HPS (~4% of trial participants); SEARCH (~3% of participants); HOPE-3 (~12% of participants). In SEARCH, the mean differences in plasma lipid concentrations for each age group were estimated by applying the respective overall proportional reduction at one year to the estimated mean baseline levels among less intensive statin-allocated participants in each age group. In other studies, no samples at 1 year were taken and so other blood samples were used: In A to Z and PROVE-IT, blood samples taken at 8 months were used. In ALLHAT samples taken at 2 years (from a random sample of 10% of participants randomised to pravastatin and 5% of participants randomised to usual care) were used. In ALLIANCE, lipid differences at 1 year in the usual care group were interpolated from those at baseline and final follow-up because the 1 year bloods were assayed in different laboratories depending on treatment allocation. In trials comparing more versus less intensive statin therapy, the relevant baseline lipid values would be those achieved on the less intensive regimen. In three of these trials (A to Z, PROVE-IT and IDEAL), any statin therapy was stopped before randomisation, so their relevant baseline values had to be estimated by multiplying the values at the randomisation visit (ie, off statin treatment) by the mean proportional reduction observed at 1 year among those allocated the less intensive regimen.

**Webfigure 1: Effects on components of MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by age at randomisation, excluding four trials that exclusively included participants with heart failure or on dialysis**

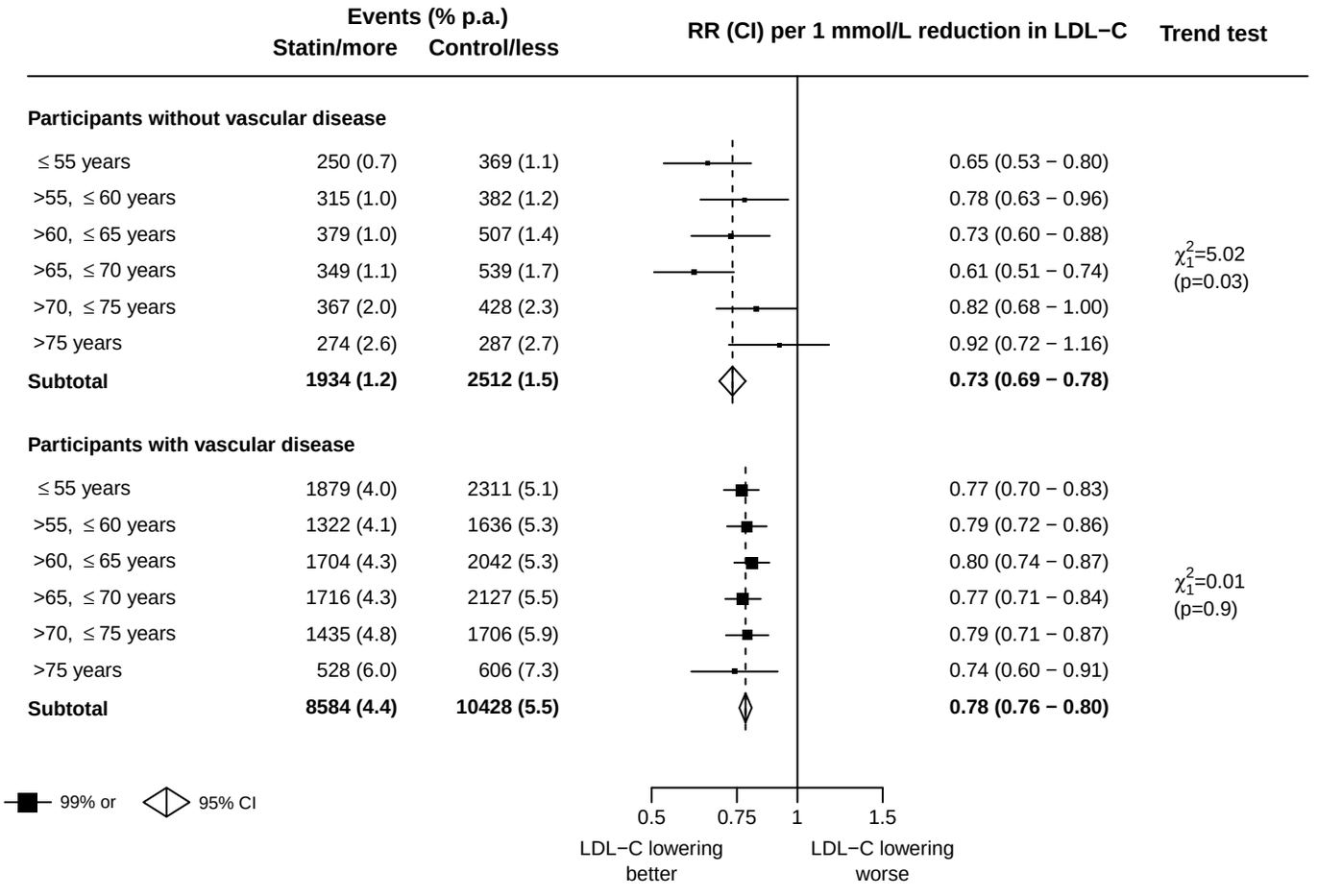



Data on participants with missing baseline data included in totals.

**Webfigure 2: Effects on components of MAJOR CORONARY EVENTS per mmol/L reduction in LDL cholesterol, by age at randomisation**

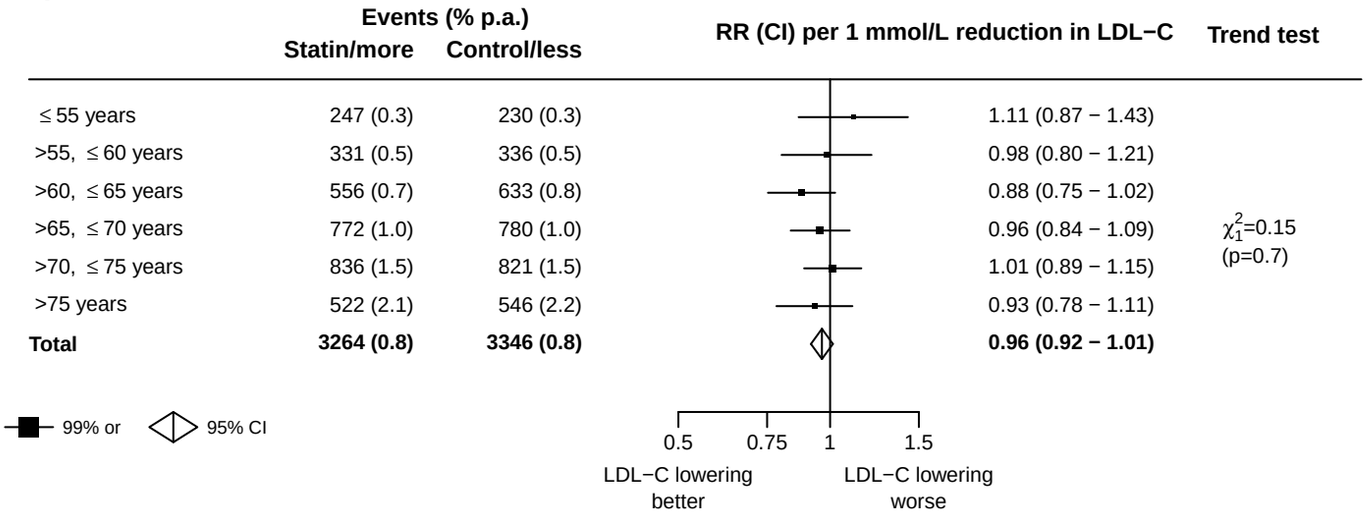


**Webfigure 3: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, subdivided by age at randomisation and by prior vascular disease, excluding four trials that exclusively included participants with heart failure or on dialysis**

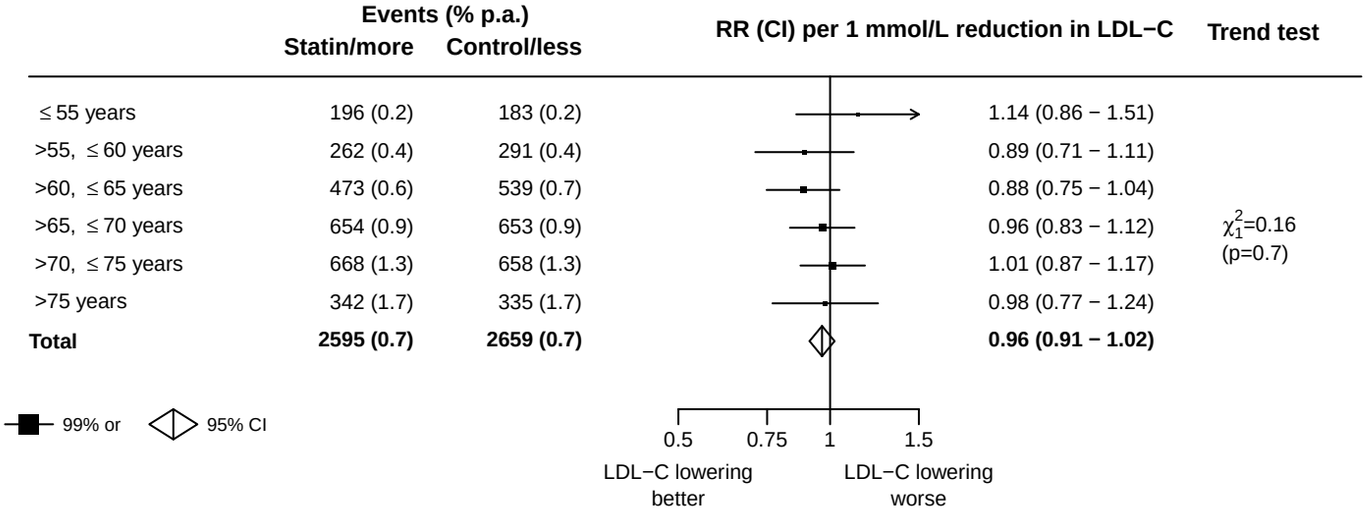


**Webfigure 4: Effects on NONVASCULAR DEATH per mmol/L reduction in LDL cholesterol, by age at randomisation**

**a) All studies**

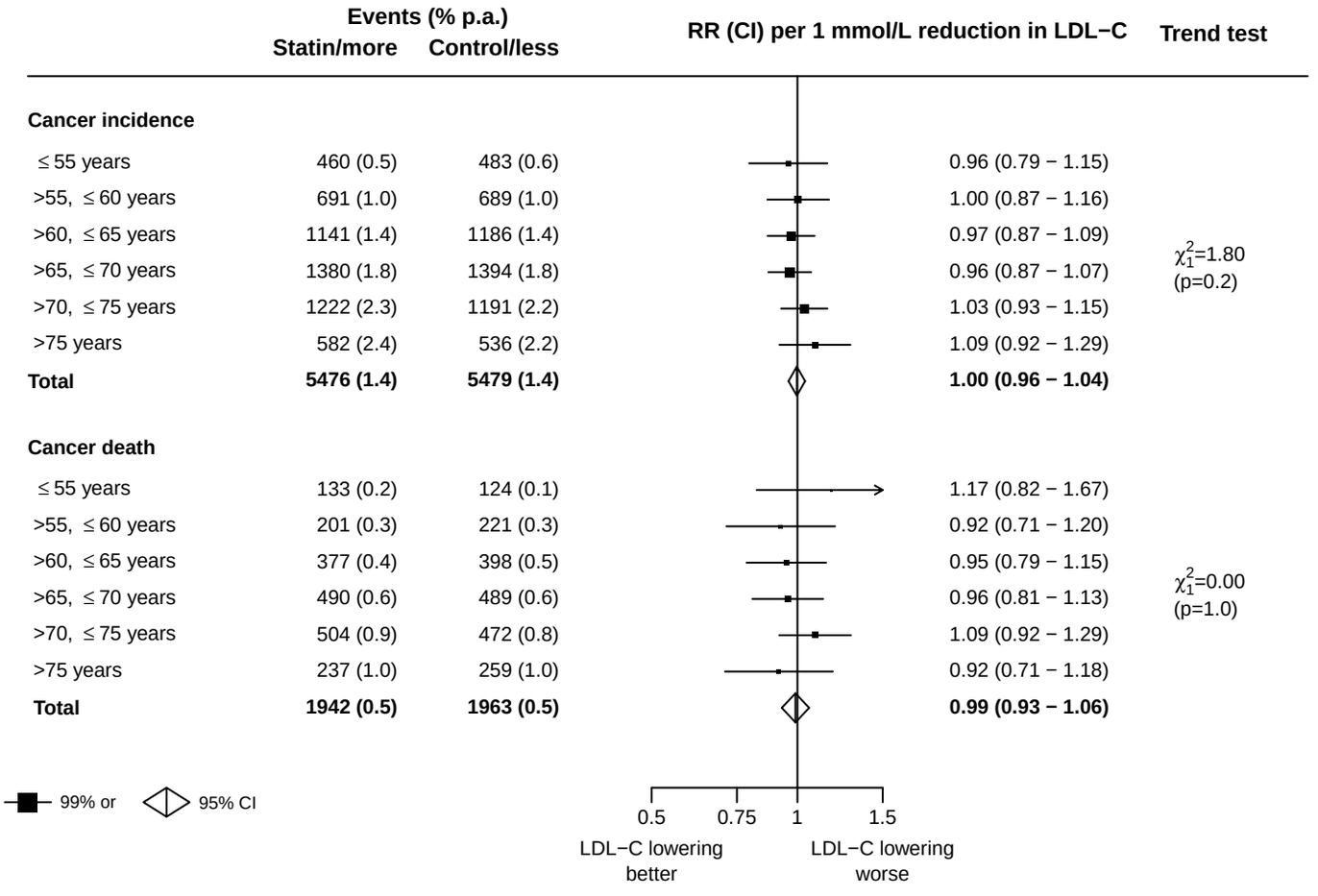



**b) Excluding four trials that exclusively included participants with heart failure or on dialysis**




Data on participants with missing baseline data included in totals.

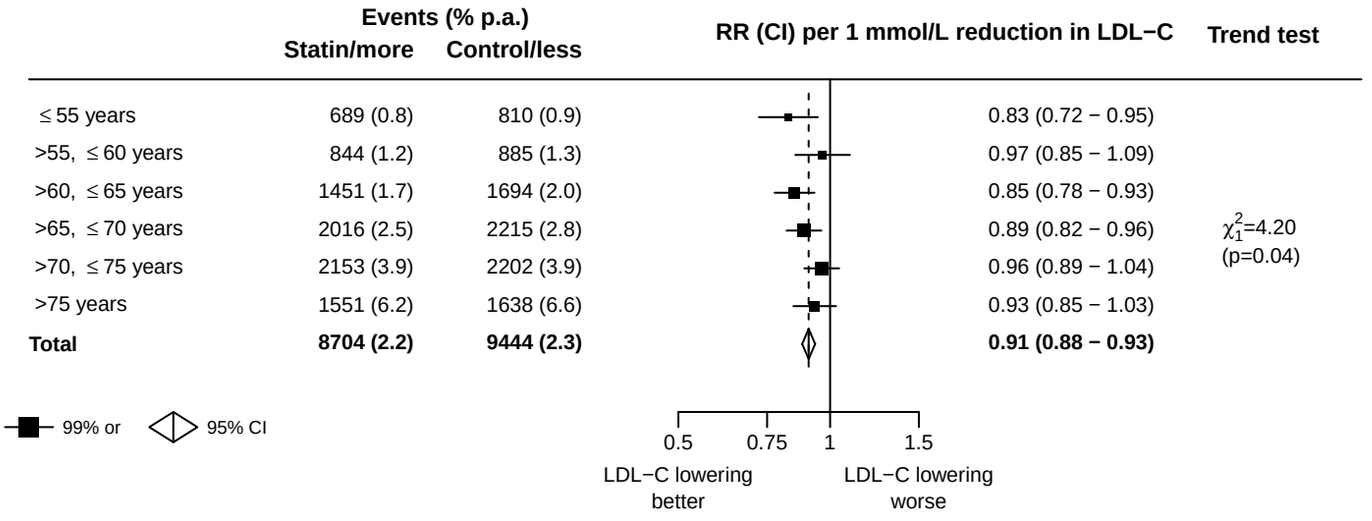
**Webfigure 5: Effects on CANCER INCIDENCE and CANCER DEATH per mmol/L reduction in LDL cholesterol in all studies, by age at randomisation**



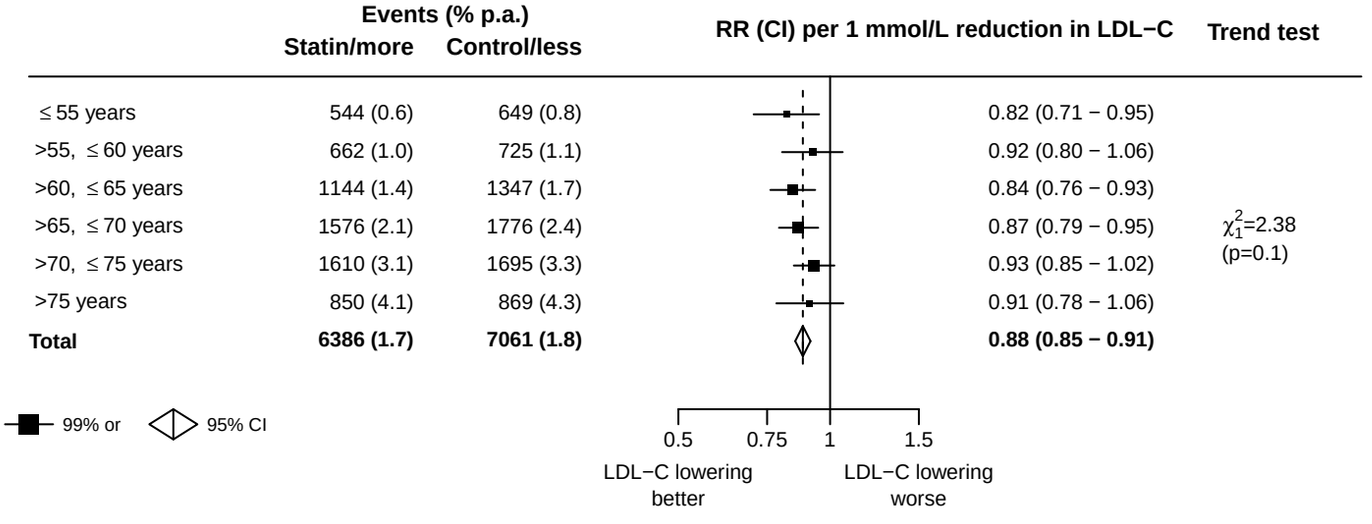

Data on participants with missing baseline data included in totals.

**Webfigure 6: Effects on ANY DEATH per mmol/L reduction in LDL cholesterol, by age at randomisation**

## a) All studies




## b) Excluding four trials that exclusively included participants with heart failure or on dialysis




Data on participants with missing baseline data included in totals.