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' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; published online May 17. DOI:10.1016/S0140-6736(12)60367-5.

Online webappendix

The effects of lowering LDL cholesterol with statin therapy in people at low-risk of vascular disease: meta-analysis of individual data from 27 randomised trials

Webtables

Webfigures

Webtable 1: Cox proportional hazard models predicting the risk of a first major vascular event in participants allocated to control (model 1) or less statin (model 2)

Parameter	Model 1 Statin vs. Control	Model 2 More vs. less statin
	Hazard ratio (95% CI)	**Hazard ratio (95% CI)**
A. Baseline characteristics		
Male gender	1.56 (1.45 - 1.69)	1.07 (0.98 - 1.16)
Current smoker	1.43 (1.28 - 1.60)	1.27 (1.18 - 1.38)
Age (per 10 years) §	1.41 (1.35 - 1.48)	1.12 (1.08 - 1.16)
Natural logarithm of HDL (per 1 lnmmol/L) §	0.69 (0.63 - 0.75)	0.76 (0.68 - 0.86)
LDL (per 1 mmol/L) §	1.14 (1.11 - 1.18)	1.19 (1.13 - 1.25)
Treatment for hypertension	1.23 (1.17 - 1.29)	1.15 (1.08 - 1.22)
Systolic BP (per 20mmHg) §	1.18 (1.13 - 1.23)	
Diastolic BP (per 10mmHg) §	0.95 (0.93 - 0.97)	
Creatinine (per 50μmol/L) §*	1.18 (1.12 - 1.23)	1.19 (1.10 - 1.28)
History of MI	2.50 (2.23 - 2.81)	1.19 (1.07 - 1.32)
History of other CHD, but no MI	1.83 (1.69 - 1.97)	
History of stroke	1.35 (1.25 - 1.46)	1.48 (1.33 - 1.64)
History of PAD	1.24 (1.16 - 1.32)	1.38 (1.24 - 1.54)
Other/nonspecific vascular disease history†	1.22 (1.06 - 1.42)	
History of diabetes mellitus	1.53 (1.45 - 1.62)	1.40 (1.29 - 1.51)
B. Interaction terms #		
Age and history of MI (per 10 years)	0.74 (0.70 - 0.79)	
Age and history of other CHD (per 10 years)	0.77 (0.71 - 0.83)	
Systolic BP and history of MI	0.91 (0.86 - 0.95)	
Systolic BP and other CHD	0.89 (0.84 - 0.94)	
Current smoker and male gender	0.80 (0.71 - 0.9)	
Male gender and history of MI	0.78 (0.70 - 0.87)	
C. Trial-specific terms (to model average risk)		
SSSS	1.95 (1.78 - 2.13)	
WOSCOPS	0.91 (0.79 - 1.04)	
CARE	1.25 (1.13 - 1.39)	
Post-CABG	0.88 (0.72 - 1.07)	
AFCAPS/TexCAPS	0.55 (0.47 - 0.65)	
LIPID	1.06 (0.98 - 1.15)	
GISSI-P	0.74 (0.59 - 0.92)	
ASCOT-LLA	0.65 (0.56 - 0.75)	
PROSPER	2.00 (1.80 - 2.22)	
CARDS	0.67 (0.55 - 0.81)	
ALERT	0.87 (0.73 - 1.04)	
ALLHAT-LLT	1.19 (1.07 - 1.32)	
LIPS	1.11 (0.87 - 1.42)	
ALLIANCE	1.51 (1.33 - 1.73)	
ASPEN	0.81 (0.67 - 0.97)	
4D	1.93 (1.63 - 2.28)	
MEGA	0.32 (0.26 - 0.39)	
JUPITER	0.48 (0.41 - 0.57)	
GISSI-HF	0.47 (0.37 - 0.60)	
AURORA	2.78 (2.46 - 3.14)	

CORONA	0.95 (0.79 - 1.16)	
A to Z		0.59 (0.40 - 0.86)
PROVE-IT		1.76 (1.39 - 2.23)
TNT		1.37 (1.24 - 1.51)
IDEAL		1.21 (1.09 - 1.35)
D. Trial and period-specific terms		
GISSI-P; months 0 to 6	4.27 (3.21 - 5.67)	
LIPS; months 0 to 6	4.00 (2.82 - 5.66)	
LIPS; months 7 to 12	2.96 (1.99 - 4.40)	
GISSI-HF; months 0 to 6	1.75 (1.20 - 2.56)	
A to Z; months 0 to 6		7.77 (5.03 - 12.02)
A to Z; months 7 to 12		2.44 (1.51 - 3.95)
PROVE-IT; months 0 to 6		3.78 (2.77 - 5.16)
PROVE-IT; months 7 to 12		2.02 (1.46 - 2.79)
TNT; months 0 to 6		1.41 (1.11 - 1.80)
IDEAL; months 0 to 6		3.12 (2.48 - 3.93)
IDEAL; months 7 to 12		1.39 (1.10 - 1.75)

HDL= high-density lipoprotein cholesterol. LDL= low-density lipoprotein cholesterol. BP=blood pressure. MI=myocardial infarction. CHD=coronary heart disease. PAD=peripheral arterial disease

* missing creatinine values at randomisation in ASCOT were replaced with creatinine measured at screening; in AFCAPS/TexCAPS, AURORA and 4D creatinine data were either not available (AFCAPS/TexCAPS) or not relevant (dialysis patients in AURORA/4D) and so centred values of 0 were used

§ centred around study mean

†defined as history of myocardial infarction or stroke for ALLHAT; history of heart failure in GISSI-HF and CORONA; carotid artery disease, carotid stenosis ≥50%, carotid endarterectomy and abdominal aortic aneurysm in AURORA

interpretation of the effects of the separate characteristics in these interactions should be based both on relevant main effects (part A) and the interaction effects (part B)

Webtable 2: Comparison of the observed (95% CI) and predicted rates of major vascular events in participating trials

Study	Duration (years)*	Observed MVEs (%) (95% CI)†	Average predicted MVEs (%)
Statin vs. Control			
SSSS	5	33.8% (31.8% - 35.8%)	33.7%
WOSCOPS	5	10.0% (8.9% - 11.1%)	10.1%
CARE	5	27.3% (25.3% - 29.3%)	27.2%
Post-CABG	5	22.9% (15.5% - 30.4%)	17.4%
AFCAPS/TexCAPS	5	5.4% (4.6% - 6.2%)	5.7%
LIPID	5	22.4% (21.2% - 23.7%)	22.9%
GISSI-P	2	11.1% (9.7% - 12.4%)	10.9%
HPS	5	19.5% (18.7% - 20.3%)	19.5%
ASCOT-LLA	4	6.9% (6.1% - 7.8%)	7.3%
PROSPER	4	19.3% (17.6% - 21.0%)	20.2%
CARDS	5	10.9% (8.9% - 12.9%)	11.4%
ALERT	5	12.5% (10.4% - 14.6%)	12.8%
ALLHAT-LLT	5	16.1% (15.0% - 17.2%)	15.8%
LIPS	4	27.3% (23.9% - 30.7%)	26.8%
ALLIANCE	5	28.0% (25.1% - 30.9%)	27.6%
ASPEN	4	12.3% (10.4% - 14.3%)	12.5%
4D	5	39.9% (33.6% - 46.2%)	39.4%
MEGA	5	3.2% (2.7% - 3.8%)	3.2%
JUPITER	5	5.3% (4.2% - 6.5%)	4.9%
GISSI-HF	5	9.4% (7.9% - 10.8%)	10.6%
AURORA	5	33.9% (30.7% - 37.1%)	34.7%
CORONA	3	15.1% (13.5% - 16.7%)	15.3%
More vs. Less statin			
A to Z	2	13.3% (11.8% - 14.8%)	13.3%
PROVE-IT	2	22.6% (20.7% - 24.5%)	22.7%
TNT	5	23.4% (22.2% - 24.6%)	23.4%
IDEAL	5	25.8% (24.4% - 27.1%)	25.7%
SEARCH	5	17.1% (16.2% - 18.1%)	17.2%
Risk categories			
<5%	5	2.8% (2.4% - 3.2%)	3.4%
≥5%, <10%	5	7.4% (6.9% - 7.9%)	7.3%
≥10%, <20%	5	15.9% (15.5% - 16.4%)	15.4%
≥20%, <30%	5	24.7% (24.0% - 25.3%)	24.3%
≥30%	5	38.1% (37.0% - 39.2%)	38.1%

MVE= major vascular event.

*Duration over which rates of major vascular events compared: 5 years or the latest year with available Kaplan-Meier estimate of MVE within 50 days from end of that year.

†Estimated using Kaplan-Meier survival methods among participants allocated to the control or less statin arm, respectively.

Webtable 3: Mean difference in plasma lipid concentrations at 1 year in participants at different levels of risk

Estimated 5-year risk of major vascular event	Total cholesterol (mmol/L*)	LDL cholesterol (mmol/L*)	HDL cholesterol (mmol/L*)	Triglycerides (mmol/L*)
Statin vs. Control				
<5%	-0.94	-0.88	0.034	-0.19
≥5%, <10%	-1.08	-0.96	0.031	-0.25
≥10%, <20%	-1.14	-0.99	0.045	-0.27
≥20%, <30%	-1.26	-1.10	0.032	-0.24
≥30%	-1.31	-1.21	0.034	-0.23
Subtotal (22 trials)	**-1.22**	**-1.08**	**0.038**	**-0.26**
More vs. Less statin				
≥10%, <20%†	-0.52	-0.44	0.006	-0.19
≥20%, <30%	-0.65	-0.53	-0.011	-0.24
≥30%	-0.70	-0.58	-0.013	-0.30
Subtotal (5 trials)	**-0.61**	**-0.51**	**-0.005**	**-0.23**

LDL= low-density lipoprotein cholesterol. HDL= high-density lipoprotein cholesterol.

* To convert values from mmol/L to mg/dL, divide triglycerides by 0.01129 and other lipids by 0.02586.

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 were selected for 1 year blood samples: HPS (~4% of trial participants); SEARCH (~3% of participants). 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.

Average values weighted by the trial and risk category-specific variances of the 'logrank' O minus E statistics for major vascular events.

† Includes 141 participants (48 [4 MVEs] from A to Z and 93 [11 MVEs] from SEARCH) with an estimated 5-year risk of MVE between 5% and 10%

Webtable 4: Eligibility of participants without prior vascular disease in each CTT risk category for statin therapy under current major guidelines

CTT risk category (among participants without prior vascular disease)			Broad eligibility under current guidelines		
Estimated 5-year MVE risk	**Observed MCE event rate (% per annum)***	**Observed vascular death rate (% per annum)***	**ATP-III[1]**	**ESC task force[2]**	**NICE[3]**
<5%	0.2	0.1	×	×	×
≥5%, <10%	0.8	0.3	×	×	×
≥10%, <20%	1.6	1.0	✓	✓	✓
≥20%, <30%	3.2	2.3	✓	✓	✓
≥30%	5.6	5.8	✓	✓	✓

CTT= Cholesterol Treatment Collaboration. MCE= major coronary event, defined as non-fatal myocardial infarction or coronary death. * among placebo-allocated participants

1. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education program in the US recommends considering drug therapy for cholesterol modification for individuals without history of vascular disease but with multiple risk factors that confer a 10-year risk for major coronary events (i.e. myocardial infarction and coronary death) >10% which is considered moderately high or high risk. Observed annual major coronary event rate was less than 1% in those allocated to control intervention in the two lowest risk categories in CTT and therefore these participants are ineligible for statin intervention under ATP III.

   Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486-97.

   Grundy SM, Cleeman JI, Merz CNB et al. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004;110(2):227-39.

2. The Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies on Cardiovascular Disease Prevention in Clinical Practice and the ESC/EAS Guidelines for the management of dyslipidaemias recommend consideration of statin treatment typically for individuals without known vascular disease but at estimated 10-year risk of a fatal atherosclerotic event (including heart attack, stroke, aneurysm of the aorta, or other) of at least 5%. Observed annual vascular death rate was less than 0.5% in those participants without vascular disease allocated to control intervention in the two lowest risk categories in CTT and therefore these participants are ineligible for statin intervention under The Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice.

   Graham I, Atar D, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). European Journal of Cardiovascular Prevention & Rehabilitation 2007;14:Suppl-113.

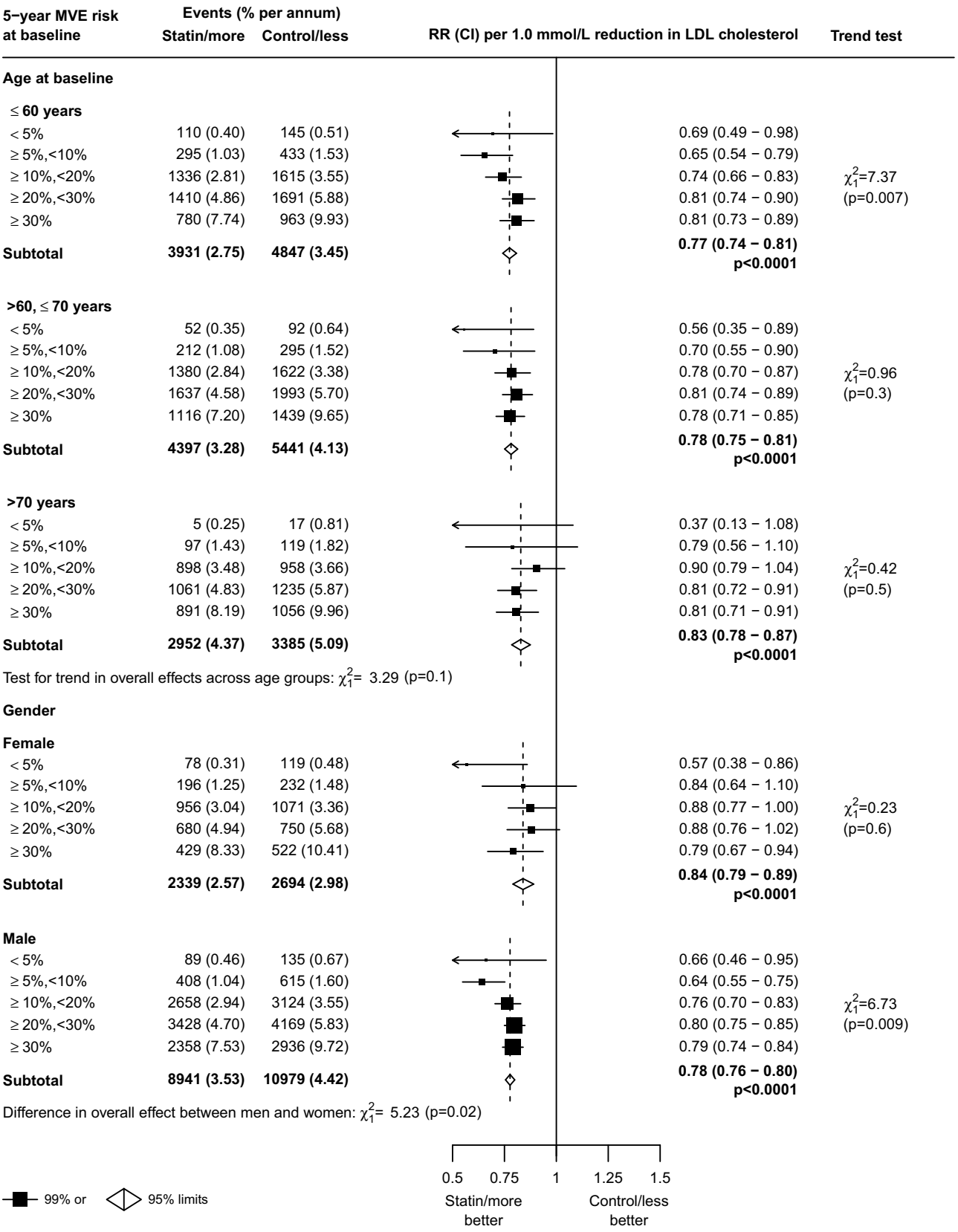
   Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32(14):1769-818.

3. The National Institute for Health and Clinical Excellence (NICE) in the National Health Service (NHS) in England and Wales recommends lipid modification drug therapy for individuals without known cardiovascular disease (CVD) who have 20% or greater 10-year risk of developing CVD (defined as myocardial infarction, CHD death, angina, stroke or transient ischemia). As no total CVD endpoint was available in CTT data, an approximate estimation of risk was carried out to allow interpretation. Total CVD was evaluated by multiplying observed vascular death rates within the risk categories by a factor of 3 to 4 (as indicated by the SCORE data). The total estimated 10-year CVD risk among those allocated to control intervention in the two lowest risk categories in CTT was less than 20% and therefore these participants are ineligible for statin intervention under NICE guidelines.

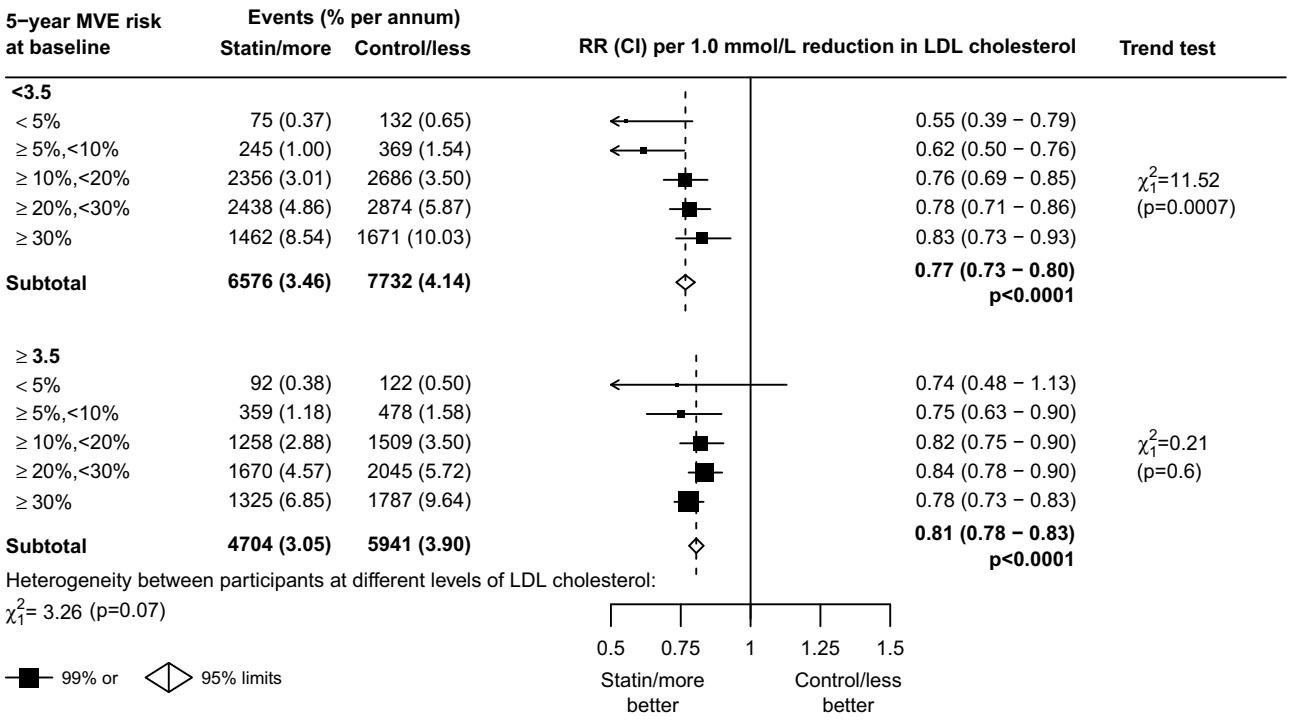
   Cooper A, Nherera L, Calvert N et al. Clinical Guidelines and Evidence Review for Lipid Modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. London:National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2008.

   Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32(14):1769-818.

Webfigure 1: Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk, by baseline age and gender

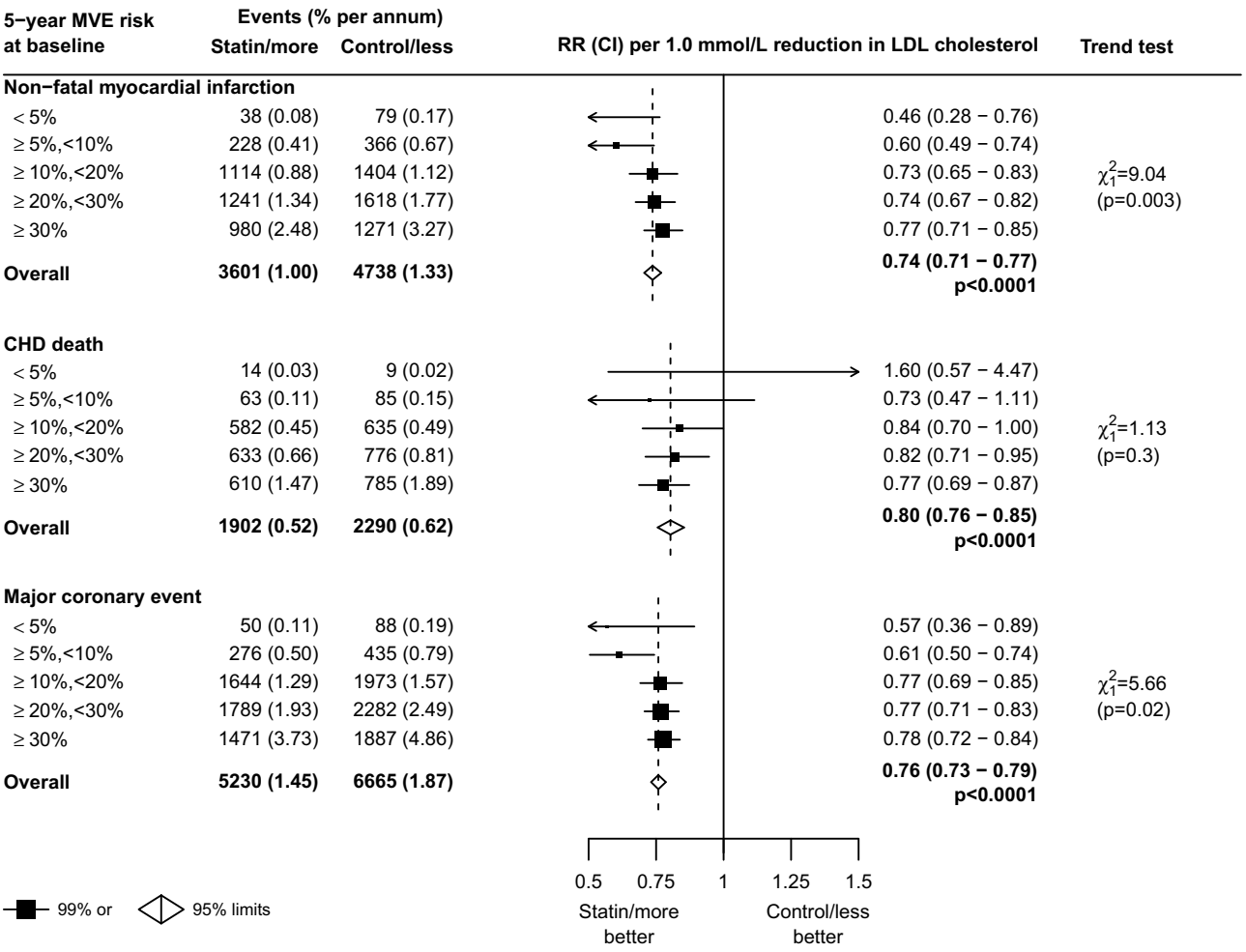


Webfigure 2: Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk, by baseline LDL cholesterol (mmol/L)

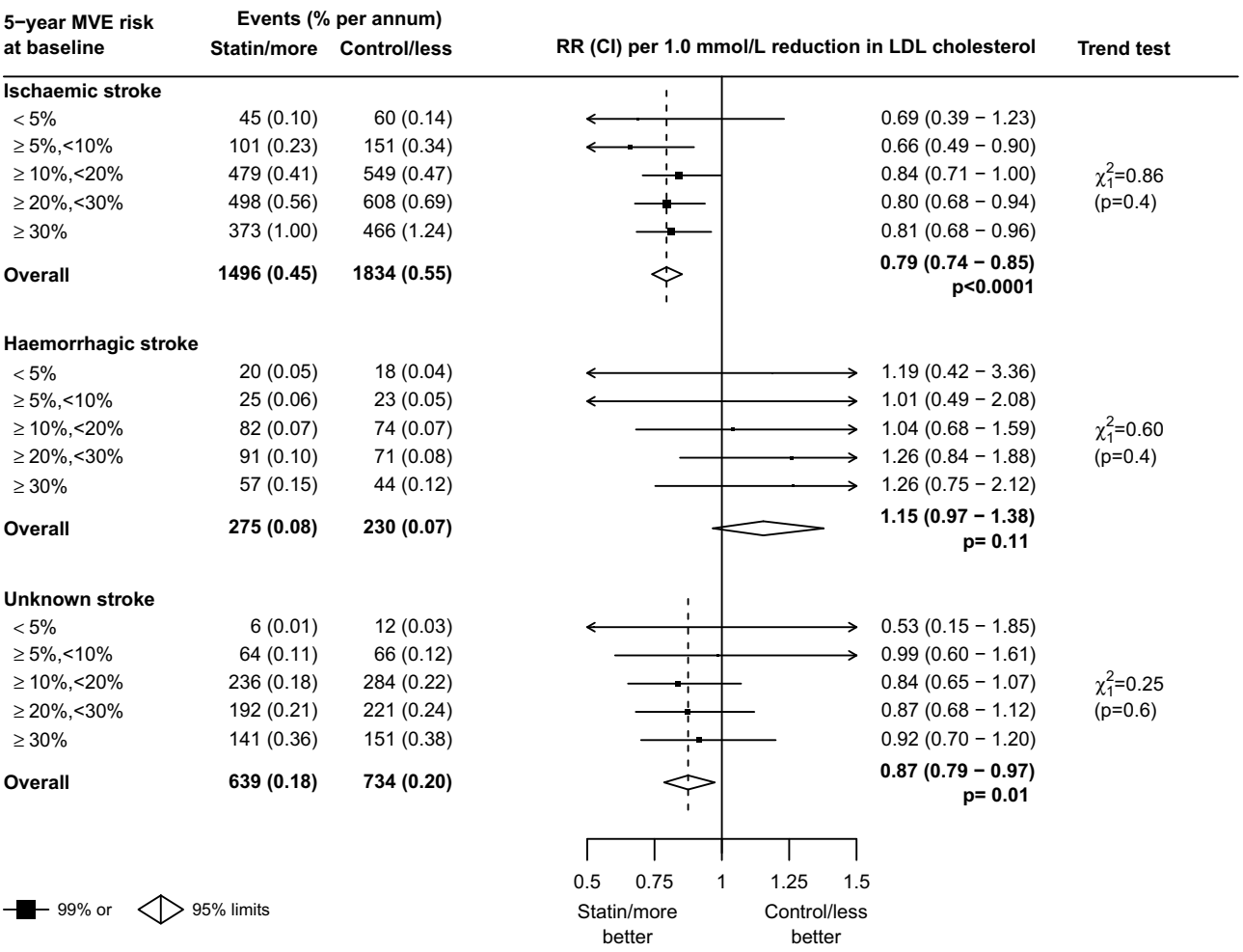


Trial− and LDL subgroup−specific LDL weights used in these subgroup analyses.

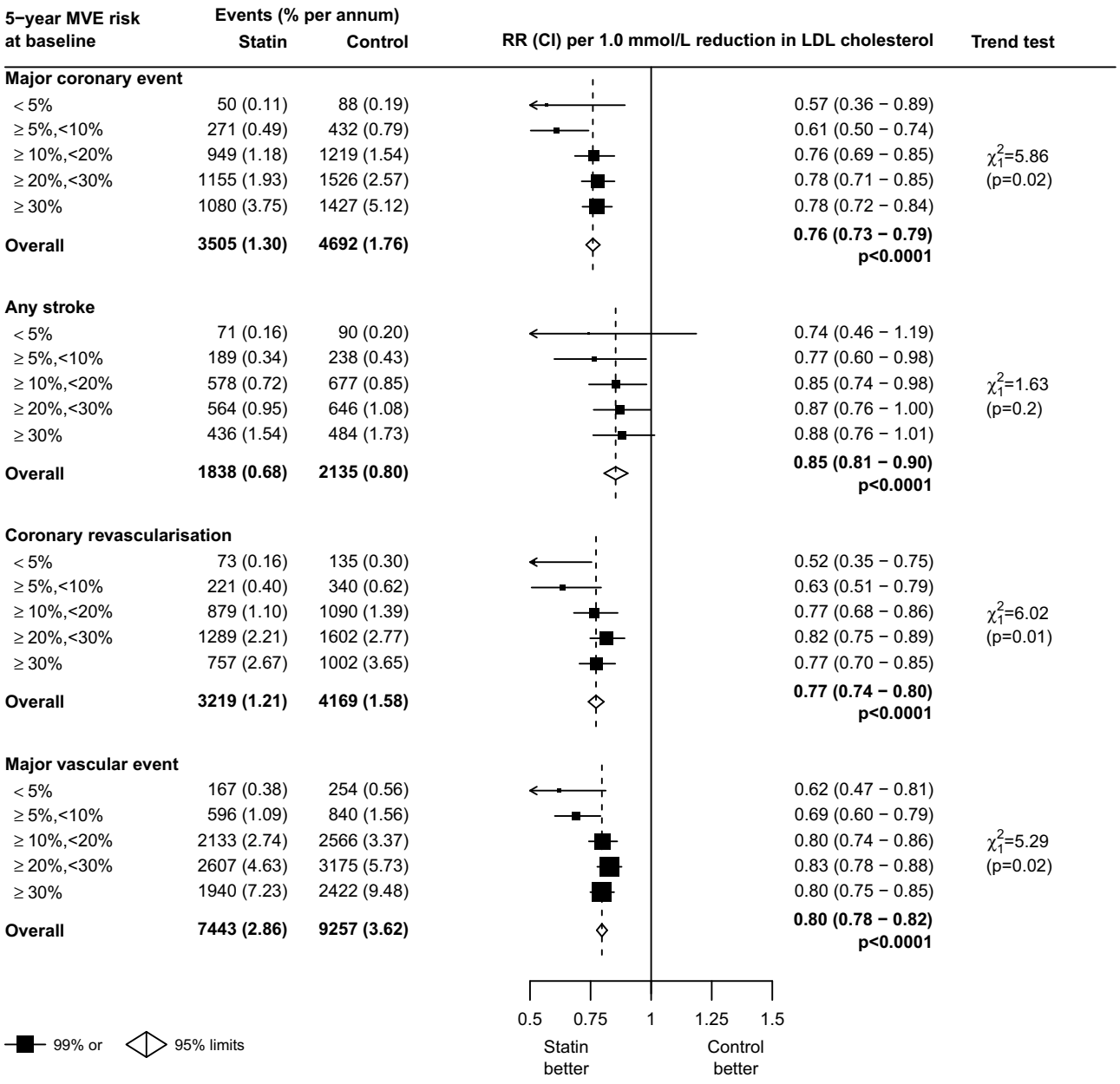
Webfigure 3: Effects on non−fatal myocardial infarctions, CHD deaths and major coronary events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk



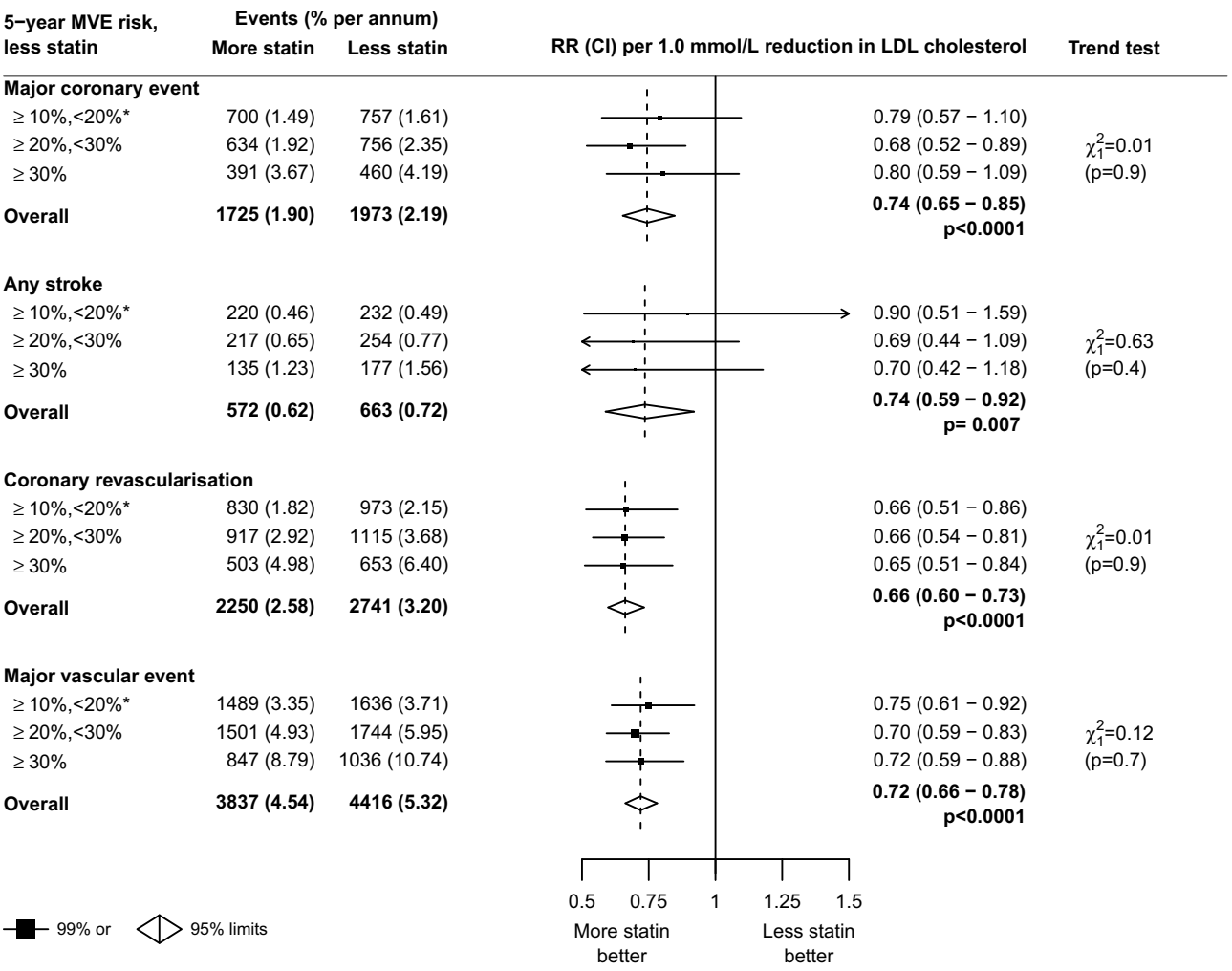
Webfigure 4: Effects on stroke subtypes per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk



Webfigure 5: Effects on major coronary events, strokes, coronary revascularisation procedures and major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk in the 22 statin vs control trials

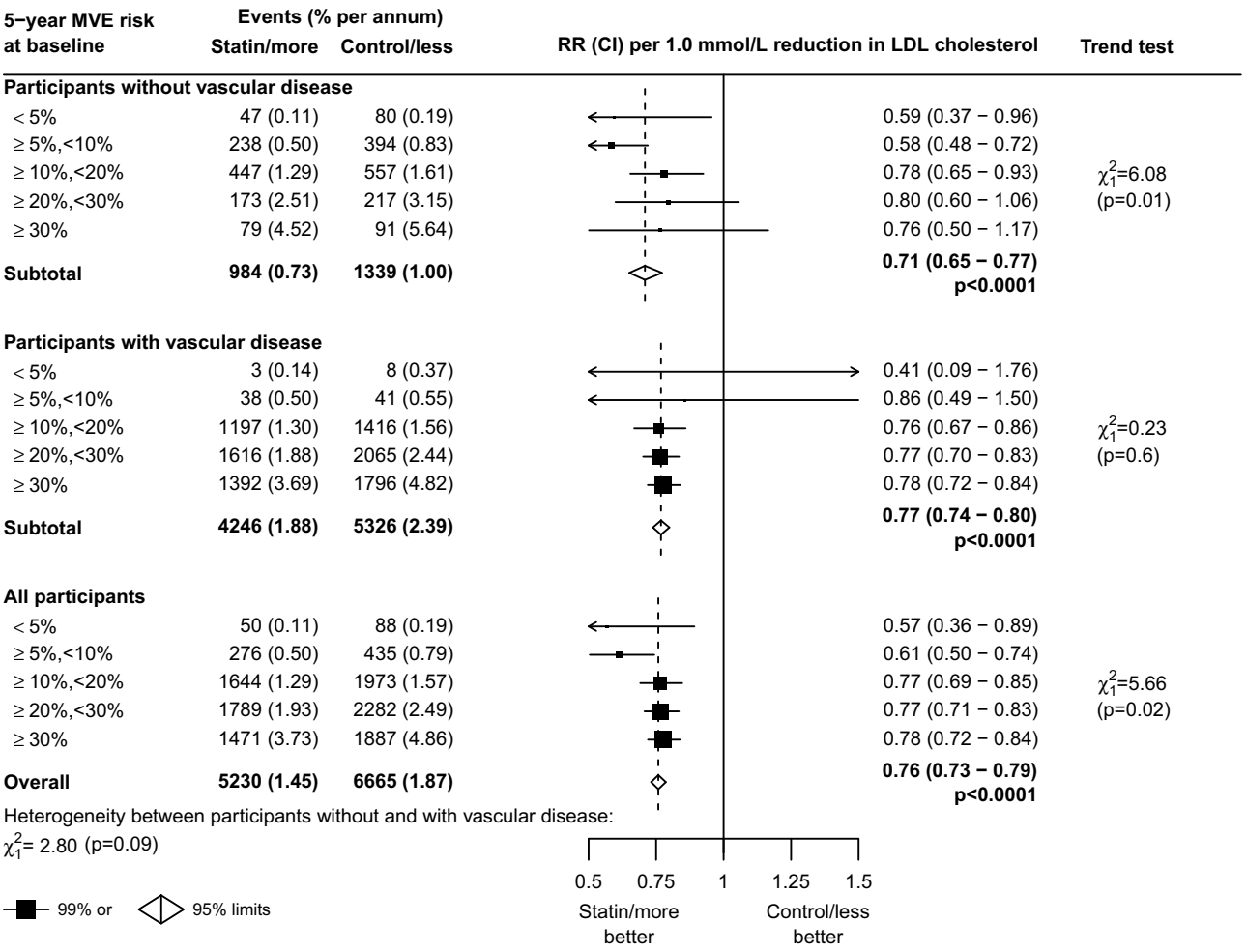


Webfigure 6: Effects on major coronary events, strokes, coronary revascularisation procedures and major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk in the 5 trials of more vs less statin

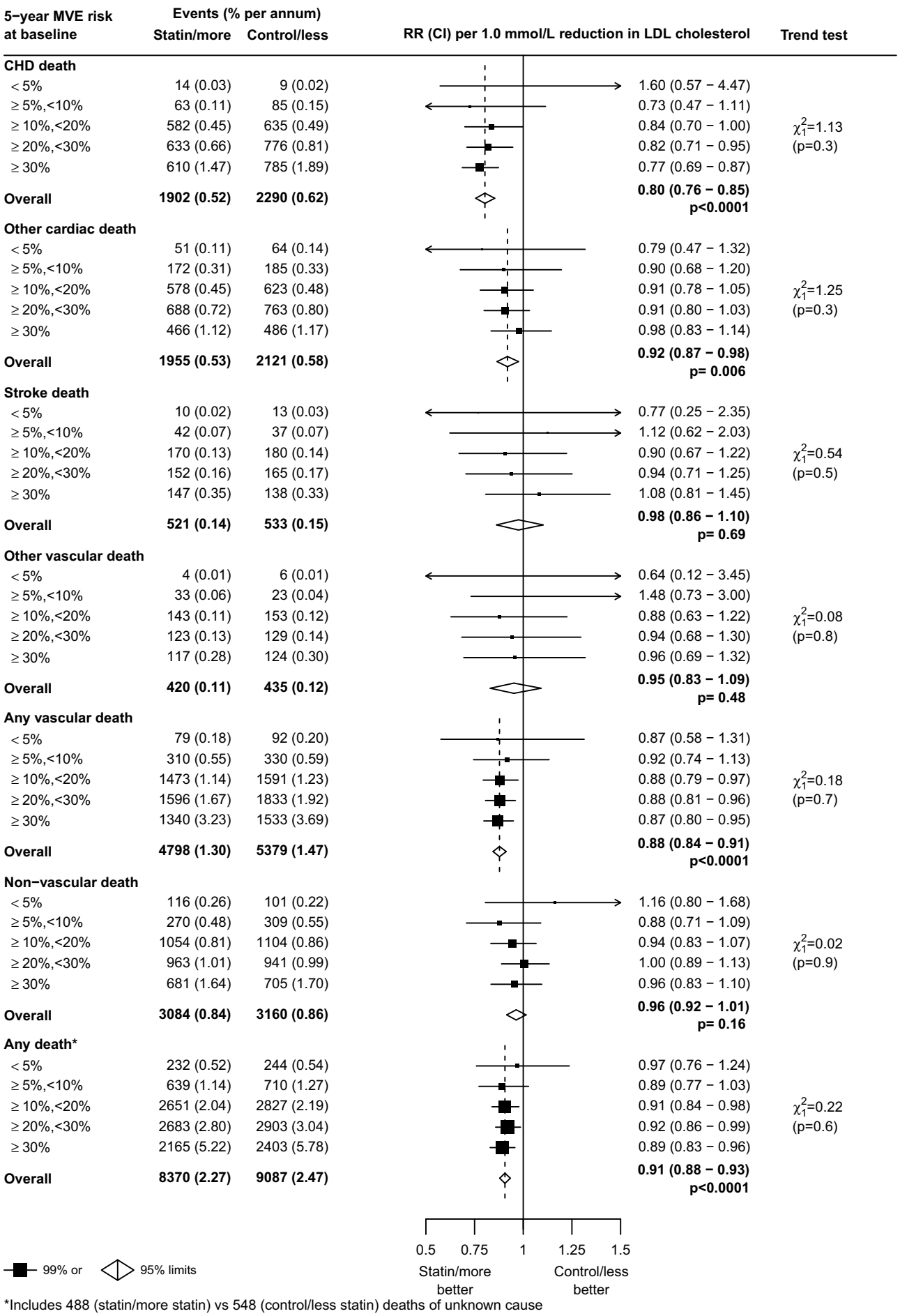


*Includes 141 participants (48 from A to Z and 93 from SEARCH) with an estimated 5−year risk of MVE less than 10%.

Webfigure 7: Effects on major coronary events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk, by history of vascular disease

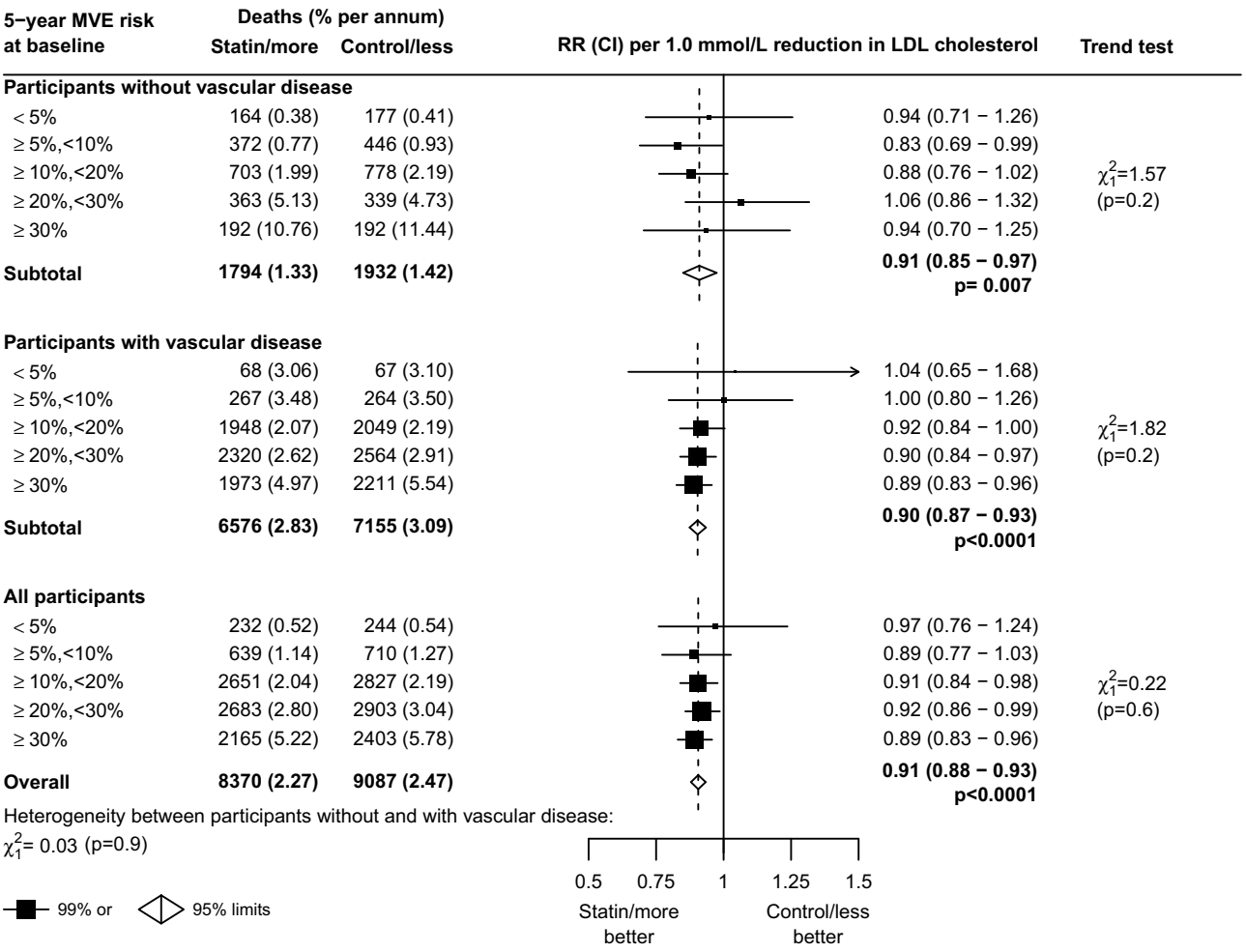


Webfigure 8: Effects on cause−specific mortality per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk



*Includes 488 (statin/more statin) vs 548 (control/less statin) deaths of unknown cause

Webfigure 9: Effects on any deaths per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk, by history of vascular disease and overall



179 (statin/more statin) vs 210 (control/less statin) deaths of unknown cause are included among participants without vascular disease.
309 (statin/more statin) vs 338 (control/less statin) deaths of unknown cause are included among participants with vascular disease.

Statistical appendix

Estimating the five year risk of major vascular event among the 174,149 participants in 27 randomised trials of statin therapy

The 5-year risk of a major vascular event (first non-fatal myocardial infarction, coronary death, stroke or coronary revascularisation procedure) was estimated using separate Cox proportional hazards models for the 67,000 patients allocated the control regimen in the 22 trials of statin versus control (model 1) and the 20,000 patients allocated the less intensive statin regimen in the 5 trials of more versus less statin (model 2). The results from these two regression models were then applied to all patients (including those in the active treatment arms), as described below.

For patient *i* in study *j* with allocated treatment *k* (where *k*=0 corresponds to the control/less statin treatment and *k*=1 corresponds to the statin/more statin treatment), the hazard function in the control/less statin group was modelled by the regression equation:

$$h_{ij0}(t) = h_0(t)exp\ (\alpha + \beta_j + \boldsymbol{\gamma}\left(\boldsymbol{x_{ij0}} - \overline{\boldsymbol{x}}_{\boldsymbol{.j0}}\right) + \boldsymbol{\delta}\left(\boldsymbol{w_{ij0}}\right) + \boldsymbol{\theta}(\boldsymbol{z_j}(t)))$$

where $h_0(t)$ is the baseline hazard function, α is an overall intercept term, β_j represents the effect of study j relative to the Heart Protection Study for model 1 or the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine for model 2 (see Webtable 1, terms C), $\boldsymbol{\gamma}$ represents a vector of log hazard ratios corresponding to the patient's set of baseline characteristics $\mathbf{x_{ij0}}$ (centred around study means $\overline{\boldsymbol{x}}_{\boldsymbol{.j0}}$ where appropriate: see Webtable 1, terms A), $\boldsymbol{\delta}$ represents a vector of log hazard ratios corresponding to interactions $\mathbf{w_{ij0}}$ between various baseline characteristics (see Webtable 1, terms B), and $\boldsymbol{\theta}$ represents a vector of log hazard ratios corresponding to trial-specific time dependent effects $\mathbf{z_j}(t)$ (defined for initial six-monthly time periods: see Webtable 1, terms D).

For each of the two regression models, the baseline characteristics $\mathbf{x_{ij}}$ and interactions $\mathbf{w_{ij}}$ were selected using backward elimination, with factors remaining in the model if they were statistically significant at the 1% level (age and sex were to be included in both models irrespective of statistical significance). The baseline characteristics included in the final models are shown in Webtable 1. The trial-specific time dependent effects $\mathbf{z_j}(t)$ were defined for initial six-monthly time periods and a backwards elimination strategy with statistical significance at 1% was employed to select the effects remaining in the models.

The Cox models provide estimates of log hazard ratios, but provide no direct estimate of the baseline hazard $h_o(t)$. However, an estimate of the cumulative hazard function $H_o(t)$ can be recovered by estimation of baseline hazard contributions at failure times using the Kalbfleisch and Prentice method and, from that, an estimate of the baseline cumulative survival $S_0(t) = \exp(-H_0(t))$ can be made.

Separating study participants according to baseline 5-year major vascular event risk

The predicted 5-year risk of a major vascular event for all patients was estimated by:

$$P_{ijk}(t) = 1 - S_0(t)^{exp\,(\alpha+\beta_j+\gamma(x_{ijk}-\bar{x}_{.j0})+\delta(w_{ijk})+\theta(z_j(t)))} \quad \text{at t=5 years}$$

Patients with missing baseline characteristics employed in the risk models were excluded from the estimation of models 1 and 2, but their values were imputed for the purpose of predicting 5-year risk of a major vascular event. Occasional missing age, gender, treatment for hypertension were imputed using study-specific mean (age) or median (gender, treatment for hypertension). Missing data for LDL-C (1.7%), HDL-C (0.7%), blood pressure (0.4%) and creatinine (1.4%) were imputed using study-specific mean values by age, gender and treatment for hypertension.

Trial participants were categorised into one of five baseline categories of 5-year risk: <5%; 5 to <10%; 10 to <20%; 20 to <30%; and 30% or larger. The proportionate and absolute effects of allocation to statin or more statin intervention on specific endpoints was then estimated separately within each of these subgroups (as described in the main statistical methods section).