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Supplementary webappendix

This webappendix 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) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010; published online November 9, 2010. DOI:10.1016/S0140-6736(10)61350-5.

Webappendix for "Efficacy and safety of intensive LDL-cholesterol-lowering therapy: a meta-analysis of data from 170,000 participants in 26 randomised trials"

Tables

Figures

Webtable 1: Baseline lipid eligibility criteria and changes in lipid profile in participating trials in mmol/L

		Baseline lipid profile (mmol/L)				Mean absolute difference at 1 year (mmol/L) §			
	Entry lipid criteria (mmol/L*)	**TC**	**LDL-C**	**HDL-C**	**TG**	**TC**	**LDL-C**	**HDL-C**	**TG**
More vs. less statin									
PROVE-IT †	TC ≤6.2 (or ≤5.2 if already on long term lipid lowering)	4.61 †	2.62 †	1.03	2.00	-0.80	-0.65	-0.03	-0.35
A to Z †	TC ≤6.5	4.01 †	2.09 †	1.03	1.86	-0.36	-0.30	-0.004	-0.11
TNT	LDL-C <3.4	4.52	2.52	1.22	1.70	-0.74	-0.62	0.001	-0.27
IDEAL †	TG ≤6.8	4.56 †	2.64 †	1.19	1.68	-0.69	-0.55	-0.04	-0.24
SEARCH	TC <3.5 for patients on lipid lowering (<4.5 if not)	4.23	2.50	1.04	1.93	-0.45	-0.39	0.02	-0.18
Subtotal (5 trials) ¶		**4.41**	**2.53**	**1.12**	**1.81**	**-0.61**	**-0.51**	**-0.01**	**-0.23**
Statin vs. control									
SSSS	TC 5.5-8 , TG ≤2.5	6.74	4.88	1.19	1.50	-1.81	-1.77	0.08	-0.27
WOSCOPS	LDL-C 4-6	7.03	4.96	1.14	1.84	-1.14	-1.07	0.05	-0.17
CARE	TC <6.2 , LDL-C 3.0-4.5 , TG <4.0	5.39	3.58	1.00	1.76	-1.12	-1.03	0.04	-0.24
Post CABG	LDL-C 3.4-4.5 , TG <3.4	5.86	4.02	1.02	1.81	-1.17	-1.07	0.02	-0.30
AFCAPS/TexCaps	TC 4.7-6.8 , LDL-C 3.4-4.9 , HDL ≤1.2 , TG ≤4.5 (LDL-C 3.2-3.3 if TC/HDL ratio >6)	5.71	3.89	0.96	1.90	-1.02	-0.94	0.04	-0.23
LIPID	TC 4-7 , TG <5.0	5.66	3.88	0.96	1.81	-1.09	-1.03	0.05	-0.16
GISSI-P	TC 5.2-6.5	5.93	3.92	1.18	1.88	-0.36	-0.35	0.01	-0.01
LIPS	TC 3.5-7.0 , TG <4.5	5.17	3.42	0.97	1.74	-0.96	-0.92	0.03	-0.14
HPS	TC ≥ 3.5	5.85	3.38	1.06	2.09	-1.68	-1.29	0.02	-0.42
PROSPER	TC 4.0-9.0 , TG <6.0	5.68	3.79	1.28	1.54	-1.07	-1.04	0.07	-0.16
ALLHAT-LLT	LDL-C 3.1-4.9(or 2.6-3.3 if known CHD) , TG<3.9	5.79	3.76	1.23	1.75	-0.64	-0.54	0.03	-0.17
ASCOT-LLA	TC ≤ 6.5	5.48	3.44	1.31	1.65	-1.18	-1.07	0.02	-0.25
ALERT	TC 4.0-9.0(or 4.0-7.0 if patient had MI >6months before randomisation)	6.45	4.14	1.34	2.21	-0.86	-0.84	0.02	-0.13
CARDS	LDL-C ≤ 4.1 , TG ≤6.8	5.35	3.03	1.40	1.94	-1.35	-1.14	-0.01	-0.36
ALLIANCE [a]	LDL-C 2.8-5.2 for patients on lipid lowering (3.4-6.5 if not)	5.86	3.80	1.05	2.24	-1.34	-1.16	-0.04	-0.30
4D [a]	LDL-C 2.1-4.9 , TG ≤11.3	5.67	3.25	0.94	2.98	-1.12	-0.89	0.05	-0.45
ASPEN [a]	LDL-C ≤ 3.6 if patients had MI or intervention procedure (≤ 4.1 if not) , TG ≤6.8	5.01	2.93	1.21	1.92	-1.14	-0.99	0.04	-0.39
MEGA [a]	TC 5.7-7.0	6.27	4.05	1.48	1.68	-0.67	-0.67	0.05	-0.11
JUPITER [a]	LDL-C ≤3.4	4.74	2.70	1.33	1.56	-1.14	-1.09	0.05	-0.23
GISSI-HF [a]	No qualifying lipid criteria	5.00	3.06	1.23	1.62	-1.03	-0.92	0.007	-0.18
AURORA [a]	No qualifying lipid criteria	4.53	2.58	1.16	1.76	-1.06	-0.99	0.04	-0.23
Subtotal (21 trials) ¶		**5.76**	**3.70**	**1.12**	**1.85**	**-1.22**	**-1.07**	**0.04**	**-0.25**

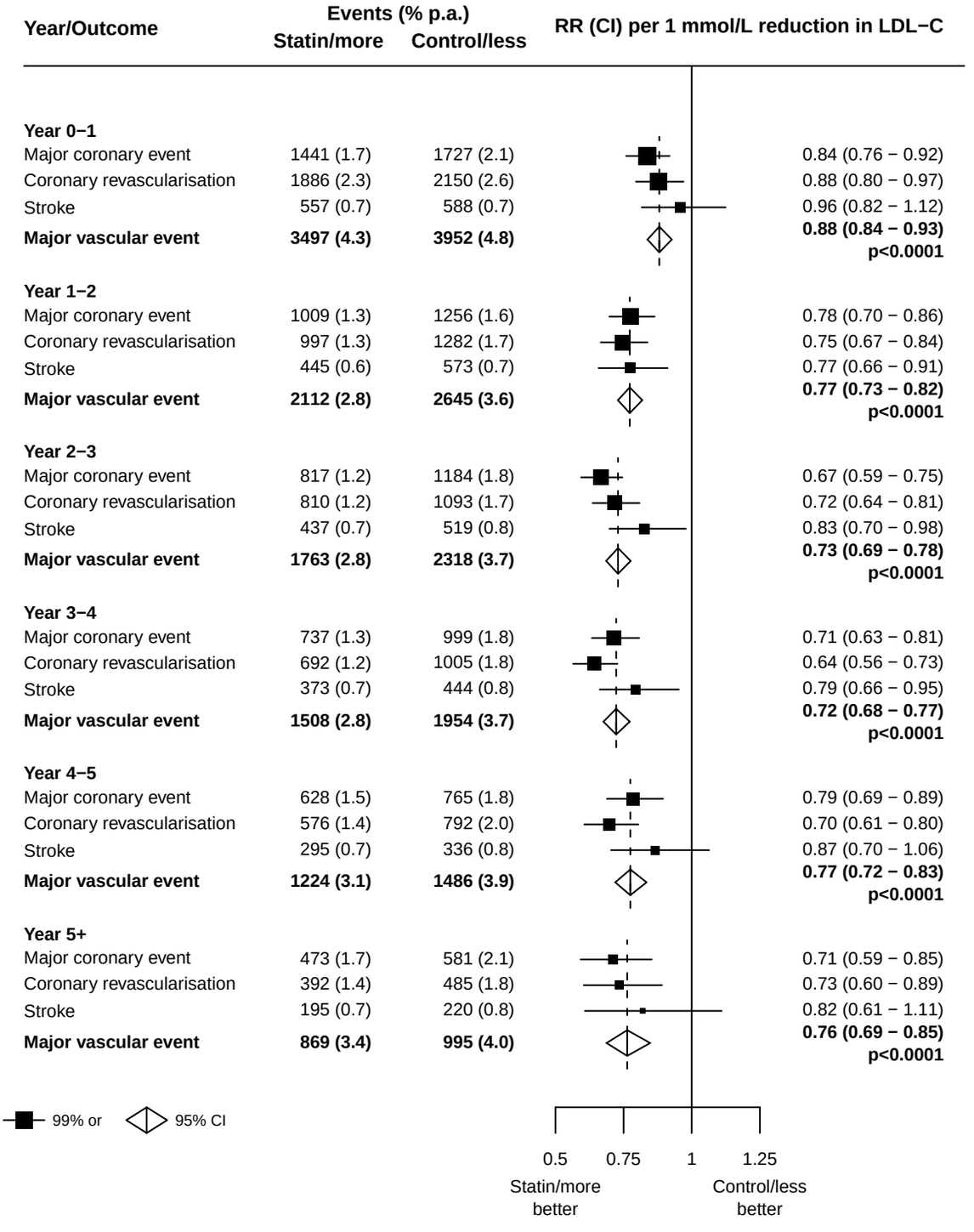
Trial abbreviations as in Table 1; TC=Total Cholesterol; LDL-C=Low density lipoprotein cholesterol; HDL-C=High density lipoprotein cholesterol; TG=Triglycerides.
* To convert values from mmol/L to mg/dL, divide TG by 0.01129 and other lipids by 0.02586.
§ In trials where the LDL-C at 1 year was missing (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-specific variances of the 'logrank' O minus E statistics for major vascular events are shown.
† These three trials did not have active run-in periods; the values shown are the estimated average on-treatment total and LDL-C levels in the standard statin group; [a] Additional statin vs. control trials included in this second cycle of analyses.

Webtable 2: Numbers of first events occuring during scheduled treatment period for every participating trial

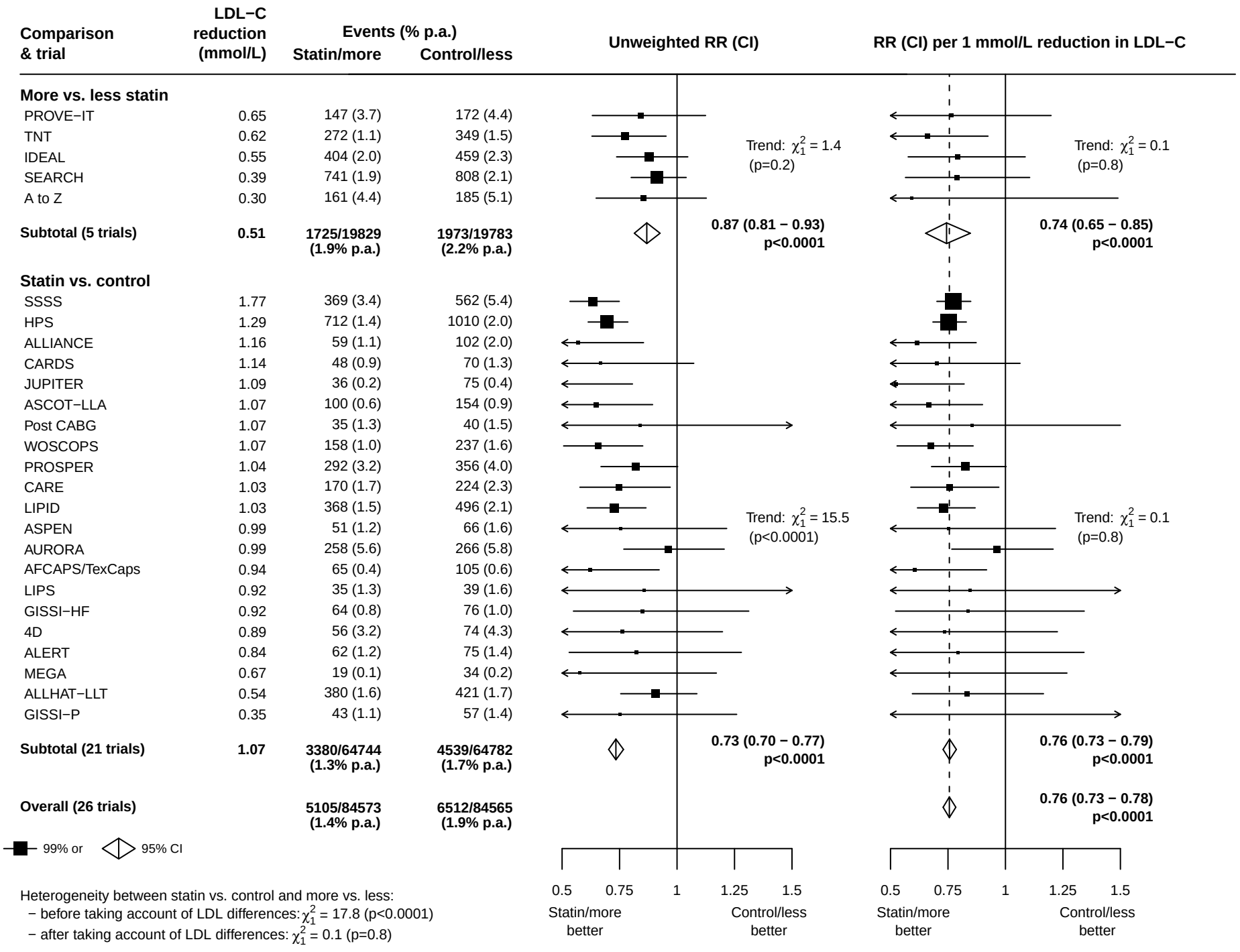
												Vascular mortality				Non-vascular mortality				
	Number of patients	Major coronary events*	Haemo-rrhagic	Definite ischaemic	Unknown	Any†	CRV	Major vascular events*	Any cancer ‡	CHD	Other Cardiac	Haemo-rrhagic stroke	Non haemorrh-agic stroke	Other vascular	Cancer	Respir-atory	Trauma	Other non vascular	Unknown	Any
More vs. less statin																				
PROVE-IT	4162	319	5	22	13	40	675	864	134	53	0	0	2	8	25	5	5	9	12	119
A to Z	4497	346	6	53	5	64	243	539	70	71	104	4	3	2	23	0	0	0	27	234
TNT	10001	621	33	226	13	272	1571	2053	684	99	129	5	25	23	160	0	24	101	0	566
IDEAL	8888	863	35	287	3	325	1322	2044	748	353	19	3	36	30	211	0	14	0	74	740
SEARCH	12064	1549	47	378	109	534	1180	2753	1302	763	142	30	94	108	512	133	26	120	6	1934
Subtotal (5 trials)	**39612**	**3698**	**126**	**966**	**143**	**1235**	**4991**	**8253**	**2938**	**1339**	**394**	**42**	**160**	**171**	**931**	**138**	**69**	**230**	**119**	**3593**
Statin vs. control																				
SSSS	4444	931	11	85	36	132	635	1351	183	300	1	7	19	16	68	0	13	14	0	438
WOSCOPS	6595	395	..	..	97	97	130	550	208	53	52	0	10	8	93	0	11	0	14	241
CARE	4159	394	8	112	8	128	685	986	307	96	119	2	12	13	94	0	12	0	28	376
Post CABG	1351	75	..	..	34	34	117	179	44	10	0	0	0	0	0	0	0	0	57	67
AFCAPS/TexCaps	6605	170	1	2	28	31	263	344	481	26	7	1	9	3	83	10	5	13	0	157
LIPID	9014	864	26	277	70	373	1290	2089	793	185	475	7	42	55	269	0	17	0	81	1131
GISSI-P	4271	100	1	28	10	39	329	439	36	26	70	0	8	4	19	0	0	8	24	159
LIPS	1677	74	..	..	..	$	331	359	73	4	29	0	3	1	30	4	2	5	7	85
HPS	20536	1722	108	682	253	1043	1238	3554	1566	850	491	47	168	181	702	204	34	144	14	2835
PROSPER	5804	648	18	179	69	266	87	926	439	216	0	1	35	40	206	0	0	0	106	604
ALLHAT-LLT	10355	801	22	154	264	440	647	1570	747	322	66	11	98	98	311	0	33	260	73	1272
ASCOT-LLA	10305	254	31	169	10	210	132	524	462	87	0	13	24	32	168	4	0	37	32	397
ALERT	2102	137	..	..	104	104	112	275	156	18	72	0	31	18	70	0	8	51	13	281
CARDS	2838	118	0	33	27	60	58	204	119	47	3	0	8	4	50	0	7	3	21	143
ALLIANCE [a]	2442	161	..	..	77	77	422	547	149	18	86	0	11	4	44	20	7	17	41	248
4D [a]	1255	130	12	79	12	103	127	306	94	69	201	8	32	8	39	0	0	210	50	617
ASPEN [a]	2410	117	6	29	37	72	98	250	127	21	43	2	8	3	38	5	4	14	0	138
MEGA [a]	8214	53	35	90	2	127	108	242	260	5	19	2	4	2	63	9	15	9	17	145
JUPITER [a]	17802	111	15	70	14	99	151	299	527	28	41	6	10	9	93	46	8	64	140	445
GISSI-HF [a]	4574	140	14	116	18	148	84	346	245	35	814	10	57	50	156	21	9	100	49	1301
AURORA [a]	2773	524	43	107	14	164	125	730	170	413	66	32	44	93	52	0	0	464	132	1296
Subtotal (21 trials)	**129526**	**7919**	**351**	**2212**	**1184**	**3747**	**7169**	**16070**	**7186**	**2829**	**2655**	**149**	**633**	**642**	**2648**	**323**	**185**	**1413**	**899**	**12376**
Total (26 trials)	**169138**	**11617**	**477**	**3178**	**1327**	**4982**	**12160**	**24323**	**10124**	**4168**	**3049**	**191**	**793**	**813**	**3579**	**461**	**254**	**1643**	**1018**	**15969**

Trial abbreviations as in Table 1.
* In the current analysis cycle, sudden death and deaths due to arrhythmia, heart failure, or unspecified cardiac causes have been recoded as 'other cardiac'; the numbers of major coronary events and major vascular events in some of the trials therefore differ slightly from those previously reported in the first CTT cycle (reference 1 of the manuscript); † Stroke subtype data available for 4670 strokes recorded in 21 trials.
‡ Excludes ICD9 codes 173 and 210-239 (unless this code given as cause of death in which case it is coded as unknown cancer death); $ LIPS only provided information on stroke death. [a] Additional statin vs. control trials included in this second cycle of analyses.

Webfigure 1: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by year

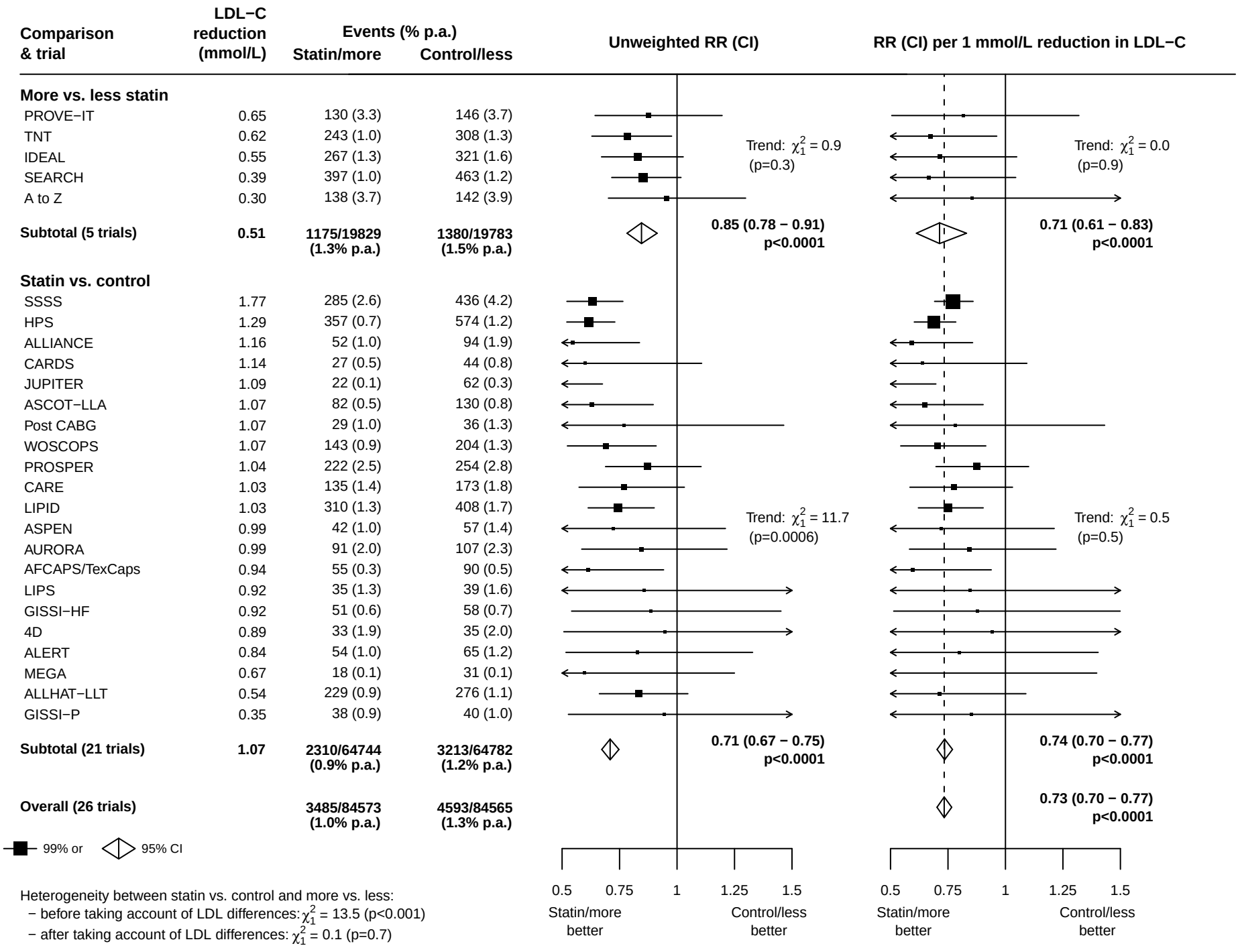


Webfigure 2: Effects on MAJOR CORONARY EVENTS in each study



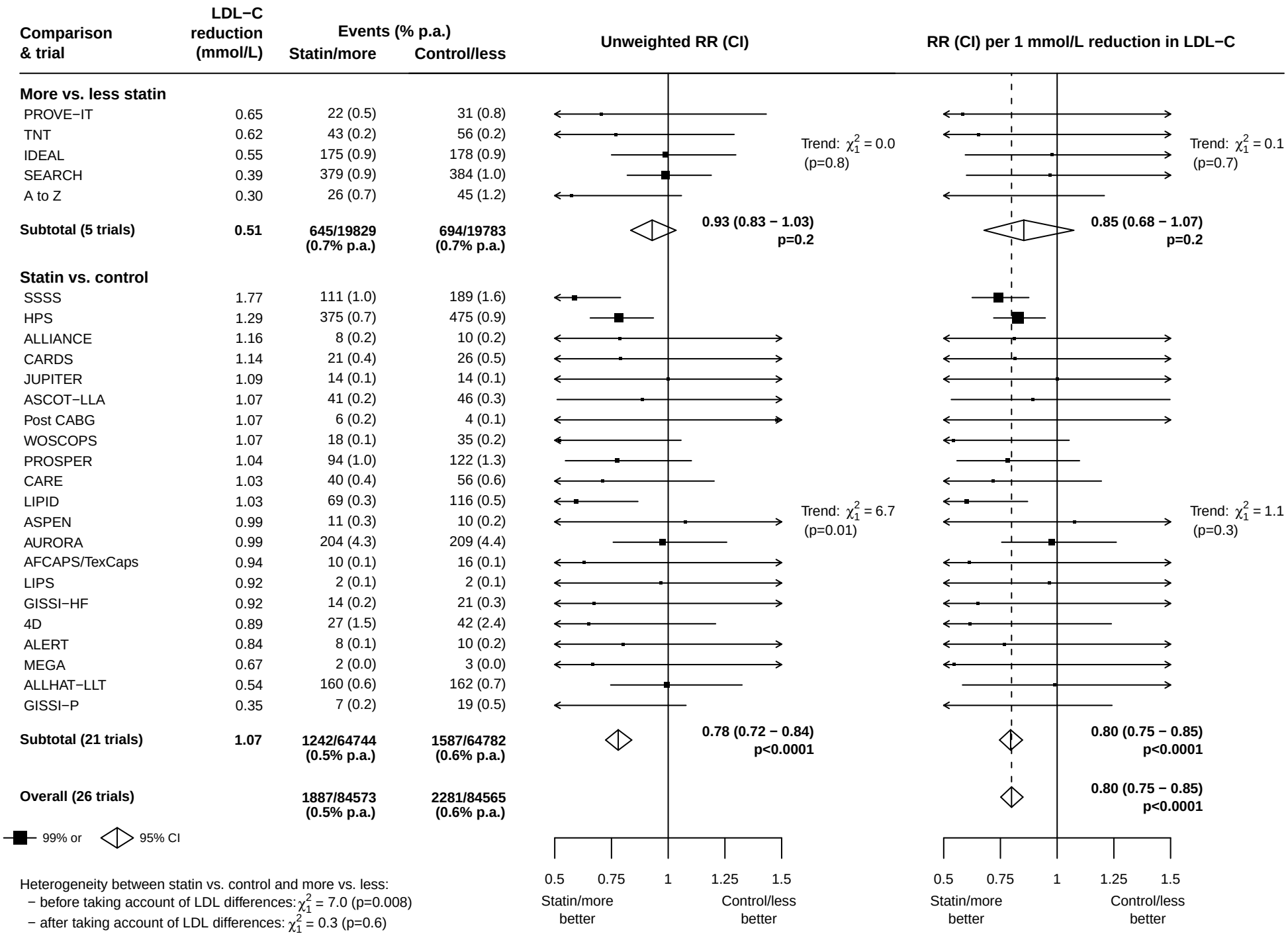
Heterogeneity between statin vs. control and more vs. less:
- before taking account of LDL differences: χ^2_1 = 17.8 (p<0.0001)
- after taking account of LDL differences: χ^2_1 = 0.1 (p=0.8)

Webfigure 3: Effects on NONFATAL MI in each study



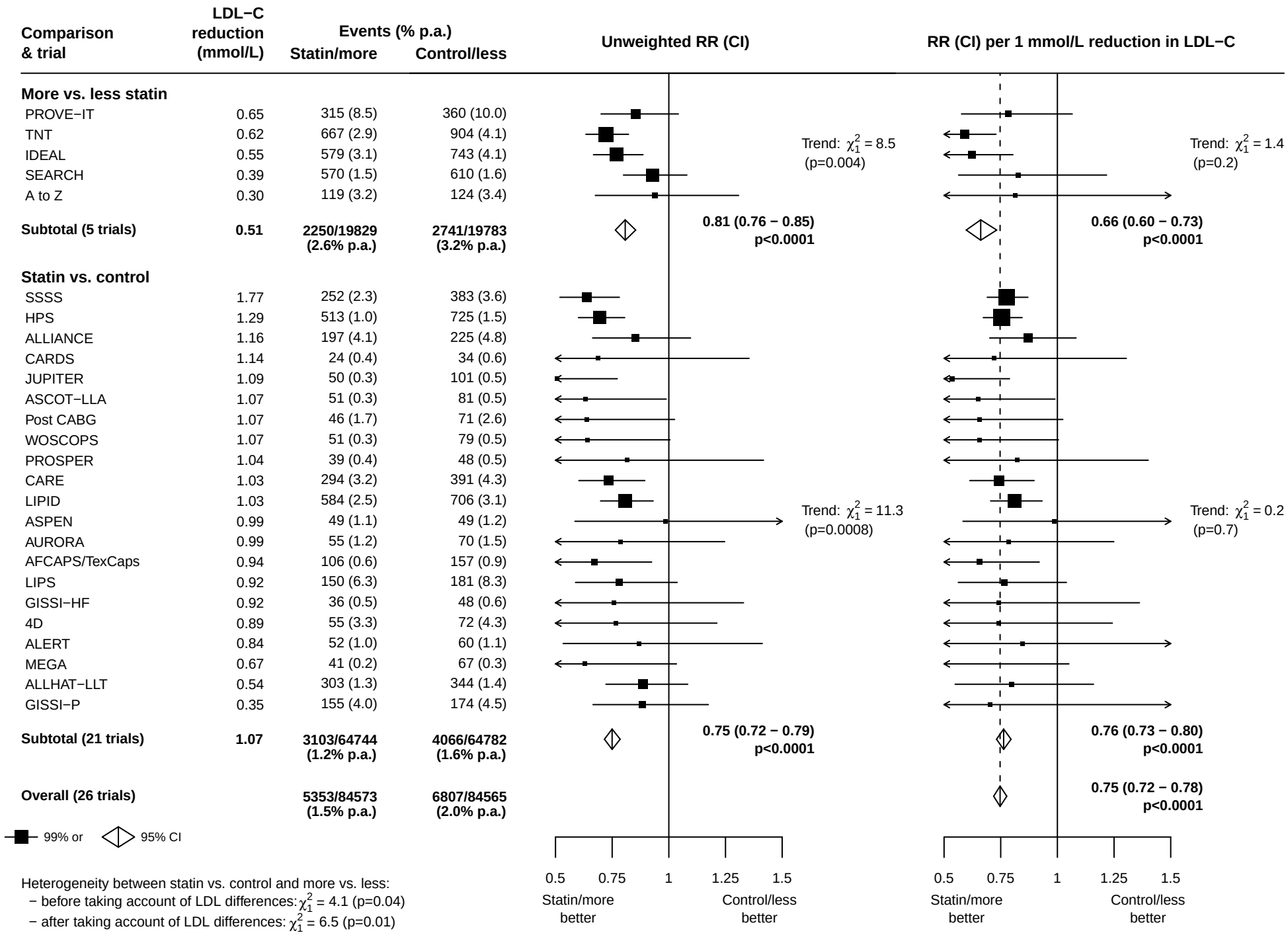
Heterogeneity between statin vs. control and more vs. less:
- before taking account of LDL differences: χ^2_1 = 13.5 (p<0.001)
- after taking account of LDL differences: χ^2_1 = 0.1 (p=0.7)

Webfigure 4: Effects on CHD DEATH in each study



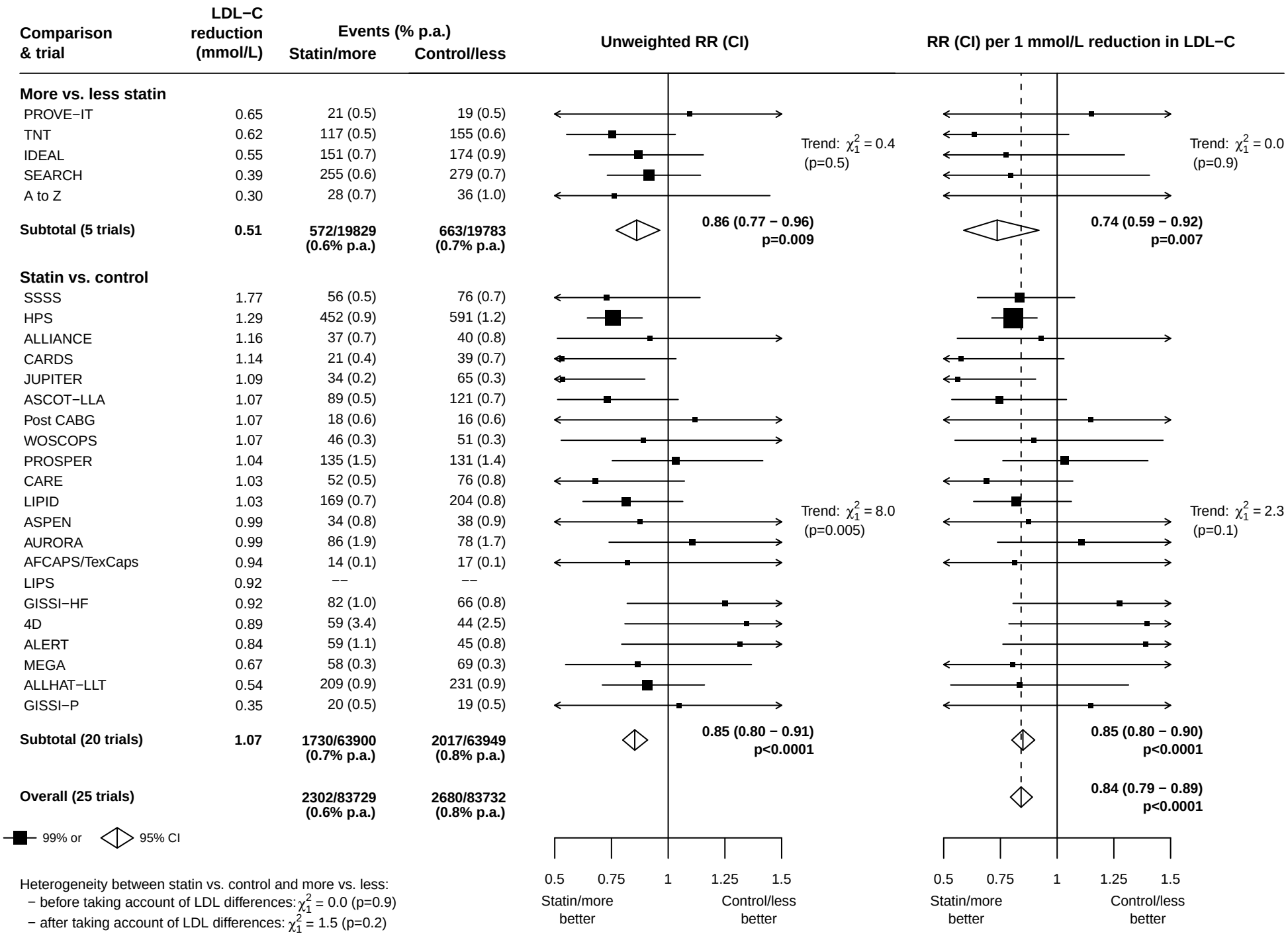
Heterogeneity between statin vs. control and more vs. less:
- before taking account of LDL differences: χ^2_1 = 7.0 (p=0.008)
- after taking account of LDL differences: χ^2_1 = 0.3 (p=0.6)

Webfigure 5: Effects on CORONARY REVASCULARISATION in each study



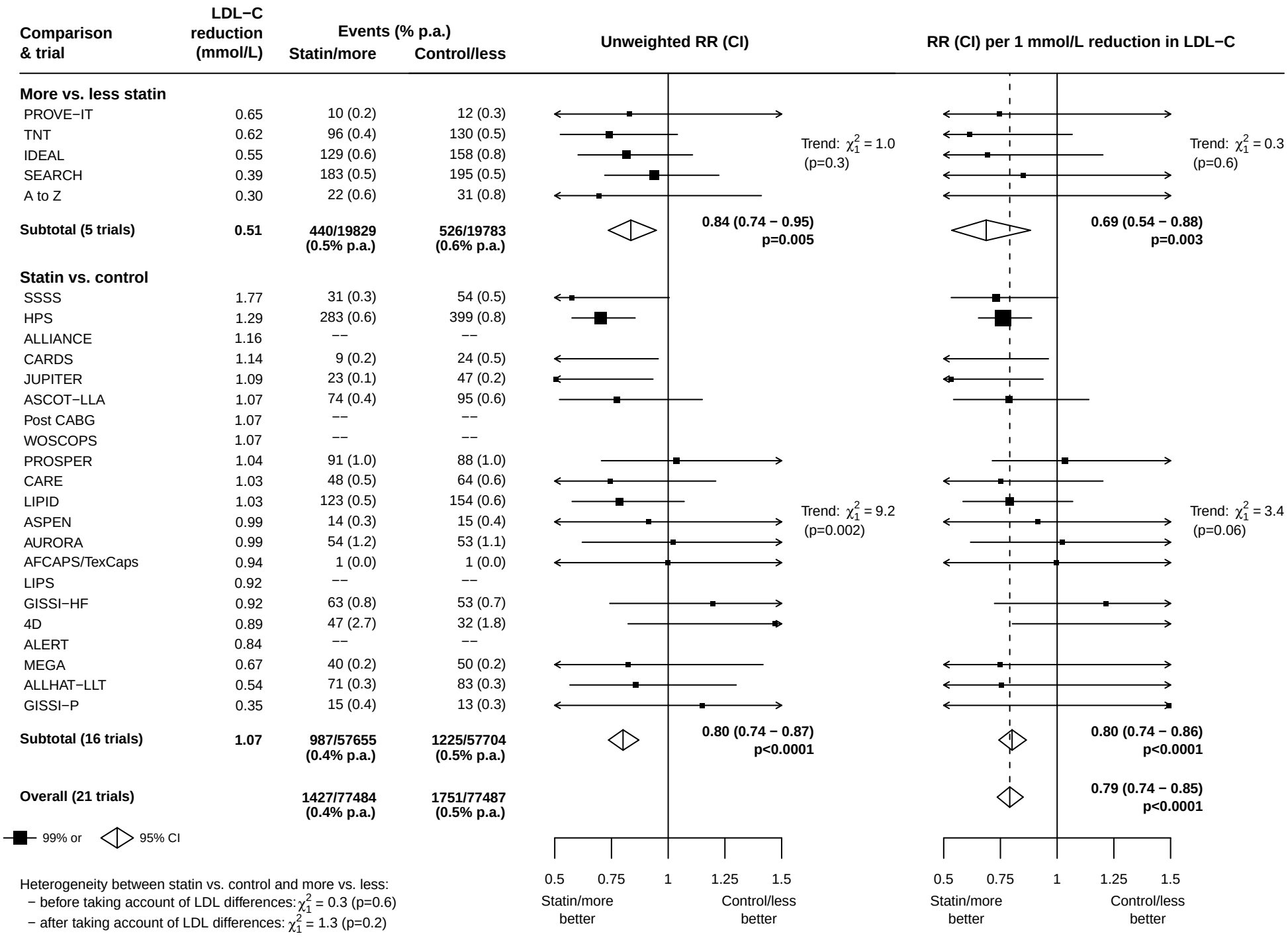
Heterogeneity between statin vs. control and more vs. less:
- before taking account of LDL differences: χ^2_1 = 4.1 (p=0.04)
- after taking account of LDL differences: χ^2_1 = 6.5 (p=0.01)

Webfigure 6: Effects on ANY STROKE in each study



Heterogeneity between statin vs. control and more vs. less:
- before taking account of LDL differences: χ^2_1 = 0.0 (p=0.9)
- after taking account of LDL differences: χ^2_1 = 1.5 (p=0.2)

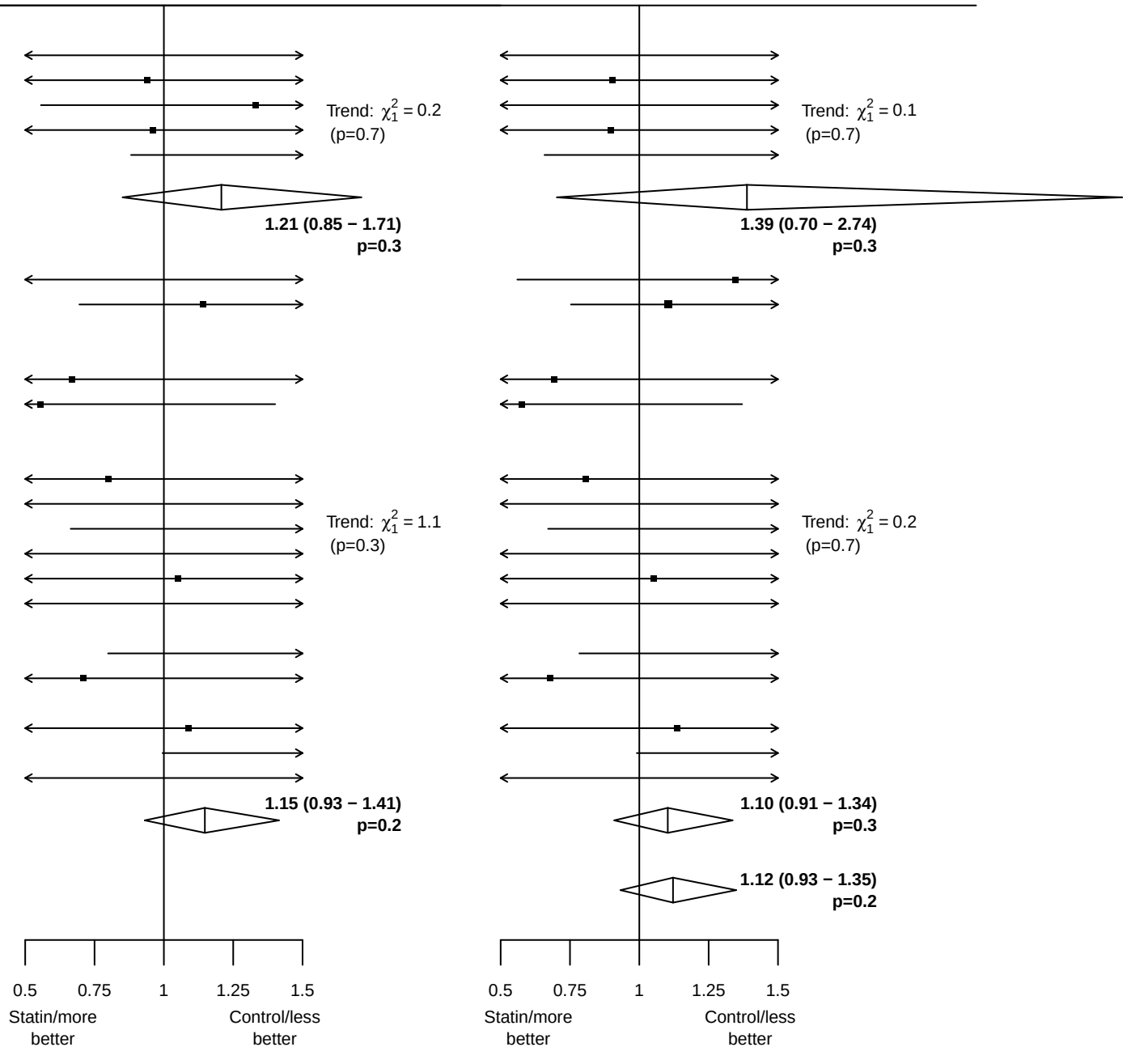
Webfigure 7: Effects on ISCHAEMIC STROKE in each study



Heterogeneity between statin vs. control and more vs. less:
- before taking account of LDL differences: χ^2_1 = 0.3 (p=0.6)
- after taking account of LDL differences: χ^2_1 = 1.3 (p=0.2)

Webfigure 8: Effects on HAEMORRHAGIC STROKE in each study

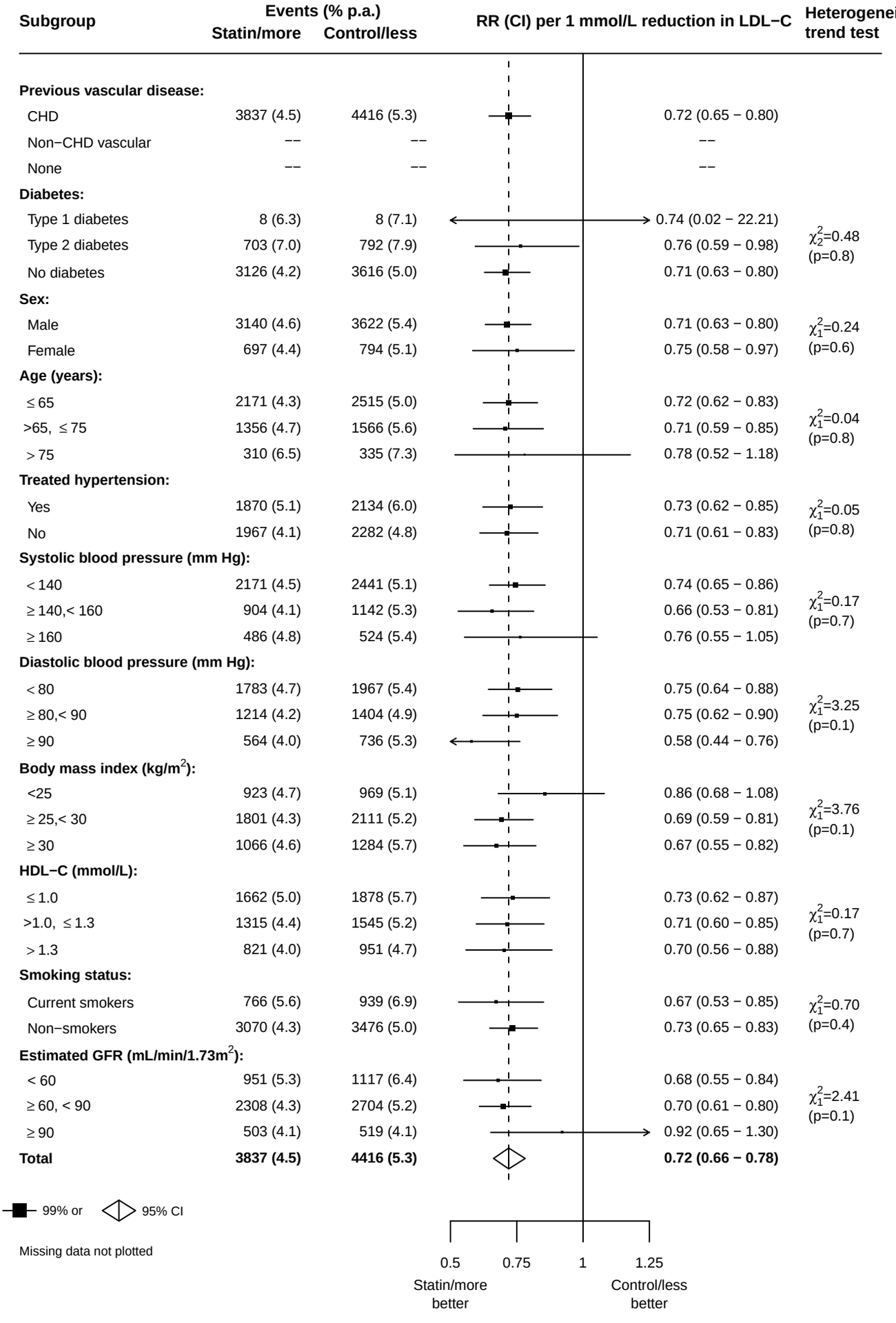
Comparison & trial	LDL−C reduction (mmol/L)	Events (% p.a.) Statin/more	Events (% p.a.) Control/less
More vs. less statin			
PROVE−IT	0.65	4 (0.1)	1 (0.0)
TNT	0.62	16 (0.1)	17 (0.1)
IDEAL	0.55	20 (0.1)	15 (0.1)
SEARCH	0.39	23 (0.1)	24 (0.1)
A to Z	0.30	6 (0.2)	0 (0.0)
Subtotal (5 trials)	**0.51**	**69/19829 (0.1% p.a.)**	**57/19783 (0.1% p.a.)**
Statin vs. control			
SSSS	1.77	7 (0.1)	4 (0.0)
HPS	1.29	58 (0.1)	50 (0.1)
ALLIANCE	1.16	−−	−−
CARDS	1.14	−−	−−
JUPITER	1.09	6 (0.0)	9 (0.0)
ASCOT−LLA	1.07	11 (0.1)	20 (0.1)
Post CABG	1.07	−−	−−
WOSCOPS	1.07	−−	−−
PROSPER	1.04	8 (0.1)	10 (0.1)
CARE	1.03	2 (0.0)	6 (0.1)
LIPID	1.03	17 (0.1)	9 (0.0)
ASPEN	0.99	4 (0.1)	2 (0.0)
AURORA	0.99	22 (0.5)	21 (0.5)
AFCAPS/TexCaps	0.94	1 (0.0)	0 (0.0)
LIPS	0.92	−−	−−
GISSI−HF	0.92	11 (0.1)	3 (0.0)
4D	0.89	5 (0.3)	7 (0.4)
ALERT	0.84	−−	−−
MEGA	0.67	18 (0.1)	17 (0.1)
ALLHAT−LLT	0.54	17 (0.1)	5 (0.0)
GISSI−P	0.35	1 (0.0)	0 (0.0)
Subtotal (15 trials)	**1.07**	**188/56227 (0.1% p.a.)**	**163/56294 (0.1% p.a.)**
Overall (20 trials)		**257/76056 (0.1% p.a.)**	**220/76077 (0.1% p.a.)**



99% or 95% CI

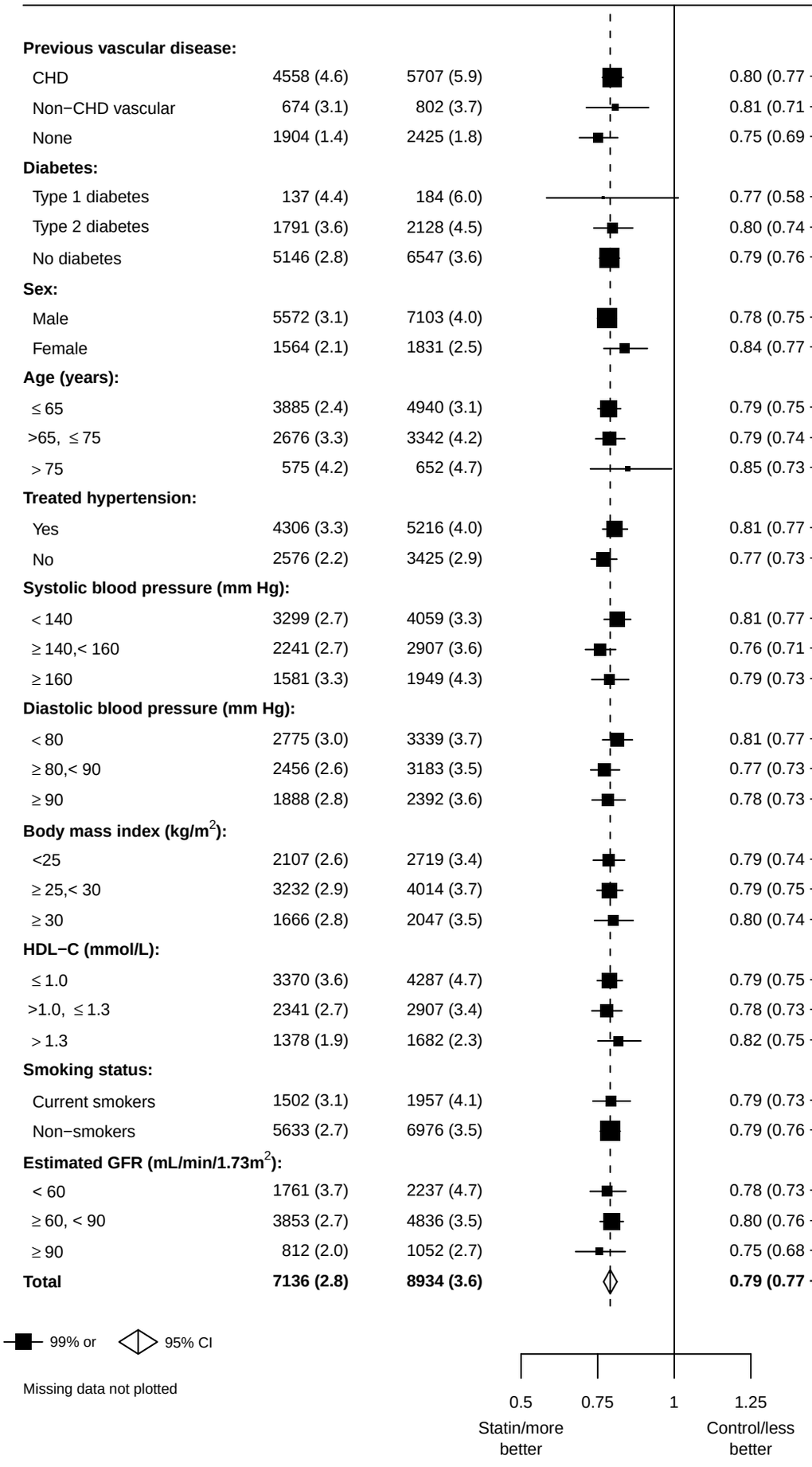
Heterogeneity between statin vs. control and more vs. less:
- before taking account of LDL differences: χ^2_1 = 0.1 (p=0.8)
- after taking account of LDL differences: χ^2_1 = 0.4 (p=0.5)

Webfigure 9: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by baseline prognostic factors in 5 more vs less trials

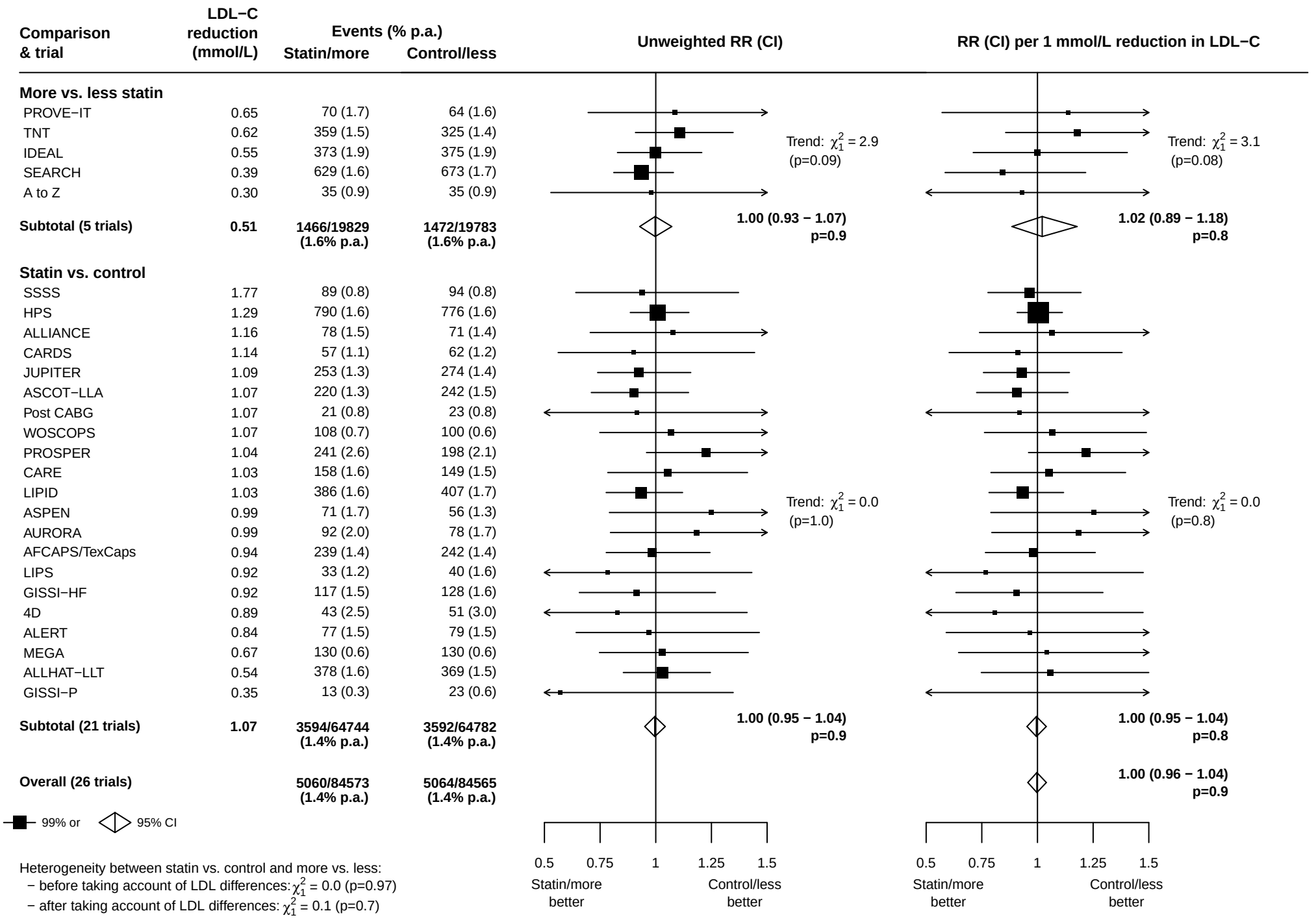


Webfigure 10: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by baseline prognostic factors in 21 statin vs control trials

Subgroup	Events (% p.a.) Statin/more	Events (% p.a.) Control/less	RR (CI) per 1 mmol/L reduction in LDL−C	Heterogeneity/ trend test
Previous vascular disease:				
CHD	4558 (4.6)	5707 (5.9)	0.80 (0.77 − 0.83)	χ^2_2=3.15 (p=0.2)
Non−CHD vascular	674 (3.1)	802 (3.7)	0.81 (0.71 − 0.92)	
None	1904 (1.4)	2425 (1.8)	0.75 (0.69 − 0.82)	
Diabetes:				
Type 1 diabetes	137 (4.4)	184 (6.0)	0.77 (0.58 − 1.01)	χ^2_2=0.21 (p=0.9)
Type 2 diabetes	1791 (3.6)	2128 (4.5)	0.80 (0.74 − 0.86)	
No diabetes	5146 (2.8)	6547 (3.6)	0.79 (0.76 − 0.82)	
Sex:				
Male	5572 (3.1)	7103 (4.0)	0.78 (0.75 − 0.81)	χ^2_1=3.93 (p=0.05)
Female	1564 (2.1)	1831 (2.5)	0.84 (0.77 − 0.91)	
Age (years):				
≤ 65	3885 (2.4)	4940 (3.1)	0.79 (0.75 − 0.83)	χ^2_1=0.68 (p=0.4)
>65, ≤ 75	2676 (3.3)	3342 (4.2)	0.79 (0.74 − 0.84)	
> 75	575 (4.2)	652 (4.7)	0.85 (0.73 − 0.99)	
Treated hypertension:				
Yes	4306 (3.3)	5216 (4.0)	0.81 (0.77 − 0.85)	χ^2_1=2.53 (p=0.1)
No	2576 (2.2)	3425 (2.9)	0.77 (0.73 − 0.81)	
Systolic blood pressure (mm Hg):				
< 140	3299 (2.7)	4059 (3.3)	0.81 (0.77 − 0.86)	χ^2_1=1.51 (p=0.2)
≥ 140,< 160	2241 (2.7)	2907 (3.6)	0.76 (0.71 − 0.81)	
≥ 160	1581 (3.3)	1949 (4.3)	0.79 (0.73 − 0.85)	
Diastolic blood pressure (mm Hg):				
< 80	2775 (3.0)	3339 (3.7)	0.81 (0.77 − 0.86)	χ^2_1=1.28 (p=0.3)
≥ 80,< 90	2456 (2.6)	3183 (3.5)	0.77 (0.73 − 0.82)	
≥ 90	1888 (2.8)	2392 (3.6)	0.78 (0.73 − 0.84)	
Body mass index (kg/m^2):				
<25	2107 (2.6)	2719 (3.4)	0.79 (0.74 − 0.84)	χ^2_1=0.22 (p=0.6)
≥ 25,< 30	3232 (2.9)	4014 (3.7)	0.79 (0.75 − 0.83)	
≥ 30	1666 (2.8)	2047 (3.5)	0.80 (0.74 − 0.87)	
HDL−C (mmol/L):				
≤ 1.0	3370 (3.6)	4287 (4.7)	0.79 (0.75 − 0.83)	χ^2_1=0.46 (p=0.5)
>1.0, ≤ 1.3	2341 (2.7)	2907 (3.4)	0.78 (0.73 − 0.83)	
> 1.3	1378 (1.9)	1682 (2.3)	0.82 (0.75 − 0.89)	
Smoking status:				
Current smokers	1502 (3.1)	1957 (4.1)	0.79 (0.73 − 0.86)	χ^2_1=0.01 (p=0.9)
Non−smokers	5633 (2.7)	6976 (3.5)	0.79 (0.76 − 0.82)	
Estimated GFR (mL/min/1.73m^2):				
< 60	1761 (3.7)	2237 (4.7)	0.78 (0.73 − 0.84)	χ^2_1=0.16 (p=0.7)
≥ 60, < 90	3853 (2.7)	4836 (3.5)	0.80 (0.76 − 0.83)	
≥ 90	812 (2.0)	1052 (2.7)	0.75 (0.68 − 0.84)	
Total	**7136 (2.8)**	**8934 (3.6)**	**0.79 (0.77 − 0.81)**	



Webfigure 11: Effects on CANCER INCIDENCE in each study



Heterogeneity between statin vs. control and more vs. less:
- before taking account of LDL differences: χ^2_1 = 0.0 (p=0.97)
- after taking account of LDL differences: χ^2_1 = 0.1 (p=0.7)

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